COMPOSITIONS AND METHODS FOR MODULATING RNA

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 62/010,417, entitled "COMPOSITIONS AND METHODS FOR MODULATING RNA STABILITY", filed June 10, 2014, of U.S. Provisional Application No. 61/898,461, entitled "COMPOSITIONS AND METHODS FOR MODULATING RNA STABILITY", filed October 31, 2013, and of U.S. Provisional Application No. 61/866,989, entitled "COMPOSITIONS AND METHODS FOR MODULATING RNA STABILITY", filed August 16, 2013, the contents of each of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to oligonucleotide based compositions, as well as methods of using oligonucleotide based compositions for modulating nucleic acids.

BACKGROUND OF THE INVENTION

A considerable portion of human diseases can be treated by selectively altering protein and/or RNA levels of disease-associated transcription units (noncoding RNAs, protein-coding RNAs or other regulatory coding or noncoding genomic regions). Methods for inhibiting the expression of genes are known in the art and include, for example, antisense, RNAi and miRNA mediated approaches. Such methods may involve blocking translation of mRNAs or causing degradation of target RNAs. However, limited approaches are available for increasing the expression of genes.

SUMMARY OF THE INVENTION

Aspects of the invention disclosed herein relate to methods and compositions useful for modulating nucleic acids. In some embodiments, methods and compositions provided herein are useful for protecting RNAs (e.g., RNA transcripts) from degradation (e.g., exonuclease mediated degradation). In some embodiments, the protected RNAs are present outside of cells. In some embodiments, the protected RNAs are present in cells. In some

embodiments, methods and compositions are provided that are useful for posttranscriptionally altering protein and/or RNA levels in a targeted manner. In some embodiments, methods disclosed herein involve reducing or preventing degradation or processing of targeted RNAs thereby elevating steady state levels of the targeted RNAs. In some embodiments, methods disclosed herein may also or alternatively involve increasing translation or increasing transcription of targeted RNAs, thereby elevating levels of RNA and/or protein levels in a targeted manner.

Aspects of the invention relate to a recognition that certain RNA degradation is mediated by exonucleases. In some embodiments, exonucleases may destroy RNA from its 3' end and/or 5' end. Without wishing to be bound by theory, in some embodiments, it is believed that one or both ends of RNA can be protected from exonuclease enzyme activity by contacting the RNA with oligonucleotides (oligos) that hybridize with the RNA at or near one or both ends, thereby increasing stability and/or levels of the RNA. The ability to increase stability and/or levels of a RNA by targeting the RNA at or near one or both ends, as disclosed herein, is surprising in part because of the presence of endonucleases (*e.g.*, in cells) capable of destroying the RNA through internal cleavage. Moreover, in some embodiments, it is surprising that a 5' targeting oligonucleotide is effective alone (*e.g.*, not in combination with a 3' targeting oligonucleotide or in the context of a pseudocircularization oligonucleotide) at stabilizing RNAs or increasing RNA levels because in cells, for example, 3' end processing exonucleases may be dominant (e.g., compared with 5' end processing exonucleases). However, in some embodiments, 3' targeting oligonucleotides are used in combination with 5' targeting oligonucleotides, or alone, to stabilize a target RNA.

In some embodiments, where a targeted RNA is protein-coding, increases in steady state levels of the RNA result in concomitant increases in levels of the encoded protein. Thus, in some embodiments, oligonucleotides (including 5'-targeting, 3'-targeting and pseudocircularization oligonucleotides) are provided herein that when delivered to cells increase protein levels of target RNAs. In some embodiments is notable that not only are target RNA levels increased but the resulting translation products are also increased. In some embodiments, this result is surprising in part because of an understanding that for translation to occur ribosomal machinery requires access to certain regions of the RNA (e.g., the 5' cap region, start codon, *etc.*) to facilitate translation.

In some embodiments, where the targeted RNA is non-coding, increases in steady state levels of the non-coding RNA result in concomitant increases activity associated with the non-coding RNA. For example, in instances where the non-coding RNA is an miRNA, increases in steady state levels of the miRNA may result in increased degradation of mRNAs targeted by the miRNA.

In some embodiments, oligonucleotides are provided with chemistries suitable for delivery, hybridization and stability within cells to target and stabilize RNA transcripts. Furthermore, in some embodiments, oligonucleotide chemistries are provided that are useful for controlling the pharmacokinetics, biodistribution, bioavailability and/or efficacy of the oligonucleotides.

In some aspects of the invention, methods are provided for stabilizing a synthetic RNA (e.g., a synthetic RNA that is to be delivered to a cell). In some embodiments, the methods involve contacting a synthetic RNA with one or more oligonucleotides that bind to a 5' region of the synthetic RNA and a 3' region of the synthetic RNA and that when bound to the synthetic RNA form a circularized product with the synthetic RNA. In some embodiments, the synthetic RNA is contacted with the one or more oligonucleotides outside of a cell. In some embodiments, the methods further involve delivering the circularized product to a cell.

In some aspects of the invention, methods are provided for increasing expression of a protein in a cell that involve delivering to a cell a circularized synthetic RNA that encodes the protein, in which synthesis of the protein in the cell is increased following delivery of the circularized RNA to the cell. In some embodiments, the circularized synthetic RNA comprises one or more modified nucleotides. In some embodiments, methods are provided that involve delivering to a cell a circularized synthetic RNA that encodes a protein, in which synthesis of the protein in the cell is increased following delivery of the circularized synthetic RNA to the cell. In some embodiments, a circularized synthetic RNA is a single-stranded covalently closed circular RNA. In some embodiments, a single-stranded covalently closed circular RNA comprises one or more modified nucleotides. In some embodiments, the circularized synthetic RNA is formed by synthesizing an RNA that has a 5' end and a 3' and ligating together the 5' and 3' ends. In some embodiments, the circularized synthetic RNA is formed by producing a synthetic RNA (*e.g.*, through *in vitro* transcription or artificial (non-natural) chemical synthesis) and contacting the synthetic RNA with one or more

oligonucleotides that bind to a 5' region of the synthetic RNA and a 3' region of the synthetic RNA, and that when bound to the synthetic RNA form a circularized product with the synthetic RNA.

In some embodiments, methods for stabilizing a synthetic RNA are provided that involve contacting a synthetic RNA with a first stabilizing oligonucleotide that targets a 5' region of the synthetic RNA and a second stabilizing oligonucleotide that targets the 3' region of the synthetic RNA under conditions in which the first stabilizing oligonucleotide and second stabilizing oligonucleotide hybridize with target sequences on the synthetic RNA. In some embodiments, the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide such that the synthetic RNA when hybridized with the first and second stabilizing oligonucleotides forms a circularized product. In some embodiments, the synthetic RNA is contacted with the first and second stabilizing oligonucleotides outside of a cell.

In some embodiments, methods of delivering a synthetic RNA to a cell are provided that involve contacting a synthetic RNA with a first stabilizing oligonucleotide that targets a 5' region of the synthetic RNA and a second stabilizing oligonucleotide that targets the 3' region of the synthetic RNA under conditions in which the first stabilizing oligonucleotide and second stabilizing oligonucleotide hybridize with target sequences on the synthetic RNA; and delivering to the cell the circularized product. In some embodiments, the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide such that the synthetic RNA, when hybridized with the first and second stabilizing oligonucleotide, forms a circularized product. In some embodiments, the first stabilizing oligonucleotide and second stabilizing oligonucleotide are covalently linked through any appropriate linker disclosed herein (e.g., an oligonucleotide linker).

Aspects of the invention relate to methods of increasing stability of an RNA transcript in a cell. In some embodiments, methods provided herein involve delivering to a cell one or more oligonucleotides disclosed herein that stabilize an RNA transcript. In some embodiments, the methods involve delivering to a cell a first stabilizing oligonucleotide that targets a 5' region of the RNA transcript and a second stabilizing oligonucleotide that targets the 3' region of the RNA transcript. In some embodiments, the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide. In some embodiments, the first stabilizing oligonucleotide comprises a region of complementarity that

is complementary with the RNA transcript at a position within 10 nucleotides of the first transcribed nucleotide at the 5' end of the RNA transcript. In some embodiments, the RNA transcript comprises a 5'-methylguanosine cap, and the first stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 10 nucleotides of the nucleotide immediately internal to the 5'-methylguanosine cap. In some embodiments, the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 250 nucleotides of the 3' end of the RNA transcript. In some embodiments, the RNA transcript comprises a 3'-poly(A) tail, and the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 100 nucleotides of the polyadenylation junction of the RNA transcript. In some embodiments, the region of complementarity of the second stabilizing oligonucleotide is immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is *in vivo*. In some embodiments, the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within the 3'-poly(a) tail. In some embodiments, the second stabilizing oligonucleotide comprises a region comprising 5 to 15 pyrimidine (e.g., thymine) nucleotides.

Further aspects of the invention relate to methods of treating a condition or disease associated with decreased levels of an RNA transcript in a subject. In some embodiments, the methods involve administering an oligonucleotide to the subject.

In some embodiments of the foregoing methods, the RNA transcript is an mRNA, non-coding RNA, long non-coding RNA, miRNA, snoRNA or any other suitable transcript.

In some embodiments, the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN, HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3.

In some embodiments, the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE, BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2,

MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST.

In some embodiments, the RNA transcript is a non-coding RNA selected from the group consisting of HOTAIR AND ANRIL.

In some embodiments, the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: FXN, EPO, KLF4, ACTB, UTRN, HBF, SMN, FOXP3, PTEN, NFE2L2, and ATP2A2.

In some aspects of the invention, an oligonucleotide is provided that comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript, in which the nucleotide at the 3'-end of the region of complementary is complementary with a nucleotide within 10 nucleotides of the transcription start site of the RNA transcript. In some embodiments, the oligonucleotide comprises nucleotides linked by at least one modified internucleoside linkage or at least one bridged nucleotide. In some embodiments, the oligonucleotide is 8 to 50 or 9 to 20 nucleotides in length.

In some aspects of the invention, an oligonucleotide is provided that comprises two regions of complementarity each of which is complementary with at least 5 contiguous nucleotides of an RNA transcript, in which the nucleotide at the 3'-end of the first region of complementary is complementary with a nucleotide within 100 nucleotides of the transcription start site of the RNA transcript and in which the second region of complementarity is complementary with a region of the RNA transcript that ends within 300 nucleotides of the 3'-end of the RNA transcript.

In some aspects of the invention, an oligonucleotide is provided that comprises the general formula 5'-X_1-X_2-3', in which X_1 comprises 5 to 20 nucleotides that have a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript, in which the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide at the transcription start site of the RNA transcript; and X_2 comprises 1 to 20 nucleotides. In some embodiments, the RNA transcript has a 7-methylguanosine cap at its 5'-end. In some embodiments, the RNA transcript has a 7-methylguanosine cap, and wherein the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide of the RNA transcript that is immediately internal to the 7-methylguanosine cap. In some embodiments, at least the first nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine. In some

embodiments, the second nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine. In some embodiments, X_2 comprises the formula 5'-Y_1-Y_2-Y_3-3', in which X_2 forms a stem-loop structure having a loop region comprising the nucleotides of Y_2 and a stem region comprising at least two contiguous nucleotides of Y_1 hybridized with at least two contiguous nucleotides of Y_3. In some embodiments, Y_1, Y_2 and Y_3 independently comprise 1 to 10 nucleotides. In some embodiments, Y_3 comprises, at a position immediately following the 3'-end of the stem region, a pyrimidine complementary with guanine. In some embodiments, Y_3 comprises 1-2 nucleotides following the 3' end of the stem region. In some embodiments, the nucleotides of Y_3 following the 3' end of the stem region are DNA nucleotides. In some embodiments, the stem region comprises 2-3 LNAs. In some embodiments, the pyrimidine complementary with guanine is cytosine. In some embodiments, the nucleotides of Y_2 comprise at least one adenine. In some embodiments, Y_2 comprises 3-4 nucleotides. In some embodiments, the nucleotides of Y_2 are DNA nucleotides. In some embodiments, Y_2 comprises 3-4 DNA nucleotides comprising at least one adenine nucleotide. It should be appreciated that one or more modified nucleotides (e.g., 2'-O-methyl, LNA nucleotides) may be present in Y_2. In some embodiments, X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides of the RNA transcript that do not overlap the region of the RNA transcript that is complementary with the region of complementarity of X_1. In some embodiments, the region of complementarity of X_2 is within 100 nucleotides of a polyadenylation junction of the RNA transcript. In some embodiments, the region of complementarity of X_2 is complementary with the RNA transcript immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript. In some embodiments, X_2 further comprises at least 2 consecutive pyrimidine nucleotides complementary with adenine nucleotides of the poly(A) tail of the RNA transcript. In some embodiments, the region of complementarity of X_2 is within the poly(a) tail. In some embodiments, the region of complementarity of X_2 comprises 5 to 15 pyrimidine (e.g., thymine) nucleotides. In some embodiments, the RNA transcript is an mRNA, non-coding RNA, long non-coding RNA, miRNA, snoRNA or any other suitable RNA transcript. In some embodiments, the RNA transcript is an mRNA transcript, and X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides in the 3'-UTR of the transcript. In some embodiments, the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN,

HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3. In some embodiments, X_1 comprises the sequence 5'-CGCCCTCCAG-3'. In some embodiments, X_2 comprises the sequence CC. In some embodiments, X_2 comprises the sequence 5'-CCAAAGGTC-3'. In some embodiments, the oligonucleotide comprises the sequence 5'-CGCCCTCCAGCCAAAGGTC-3'. In some embodiments, the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE, BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2, MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST.

In some aspects of the invention, an oligonucleotide is provided that is 10 to 50 or 9 to 50 or 9 to 20 nucleotides in length and that has a first region complementary with at least 5 consecutive nucleotides of the 5'-UTR of an mRNA transcript, and a second region complementary with at least 5 consecutive nucleotides of the 3'-UTR, poly(A) tail, or overlapping the polyadenylation junction of the mRNA transcript. In some embodiments, the first of the at least 5 consecutive nucleotides of the 5'-UTR is within 10 nucleotides of the 5'-methylguanosine cap of the mRNA transcript. In some embodiments, the second region is complementary with at least 5 consecutive nucleotides overlapping the polyadenylation junction. In some embodiments, the second region is complementary with at least 5 consecutive nucleotides of the poly(a) tail. In some embodiments, the second region comprises 5 to 15 pyrimidine (e.g., thymine) nucleotides. In some embodiments, the oligonucleotide further comprises 2-20 nucleotides that link the 5' end of the first region with the 3' end of the second region. In some embodiments, the oligonucleotide further comprises 2-20 nucleotides that link the 3' end of the first region with the 5' end of the second region. In some embodiments, the oligonucleotide is 10 to 50 or 9 to 50 or 9 to 20 nucleotides in length.

In some aspects of the invention, an oligonucleotide is provided that comprises the general formula 5'-X_1-X_2-3', in which X_1 comprises 2 to 20 pyrimidine nucleotides that form base pairs with adenine; and X_2 comprises a region of complementarity that is complementary with at least 3 contiguous nucleotides of a poly-adenylated RNA transcript, wherein the nucleotide at the 5'-end of the region of complementary of X_2 is complementary with the

nucleotide of the RNA transcript that is immediately internal to the poly-adenylation junction of the RNA transcript. In some embodiments, X_1 comprises 2 to 20 thymidines or uridines.

In some embodiments, an oligonucleotide provided herein comprises at least one modified internucleoside linkage. In some embodiments, an oligonucleotide provided herein comprises at least one modified nucleotide. In some embodiments, at least one nucleotide comprises a 2' O-methyl. In some embodiments, an oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, at least one 2'-fluoro-deoxyribonucleotides or at least one bridged nucleotide. In some embodiments, the bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide. In some embodiments, each nucleotide of the oligonucleotide is a LNA nucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides, 2'-O-methyl nucleotides, or bridged nucleotides. In some embodiments, an oligonucleotide provided herein is mixmer. In some embodiments, an oligonucleotide provided herein is morpholino.

In some aspects of the invention, an oligonucleotide is provided that comprises a nucleotide sequence as set forth in Table 3, 7, 8, or 9. In some aspects of the invention, an oligonucleotide is provided that comprises a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in Table 3, 7, 8, or 9.

In some aspects of the invention, a composition is provided that comprises a first oligonucleotide having 5 to 25 nucleotides linked through internucleoside linkages, and a second oligonucleotide having 5 to 25 nucleotides linked through internucleoside linkages, in which the first oligonucleotide is complementary with at least 5 consecutive nucleotides within 100 nucleotides of the 5'-end of an RNA transcript and in which the second oligonucleotide is complementary with at least 5 consecutive nucleotides within 100 nucleotides of the 3'-end of an RNA transcript. In some embodiments, the first oligonucleotide and second oligonucleotide are joined by a linker that is not an oligonucleotide having a sequence complementary with the RNA transcript. In some embodiments, the linker is an oligonucleotide. In some embodiments, the linker is a polypeptide.

In some aspects of the invention, compositions are provided that comprise one or more oligonucleotides disclosed herein. In some embodiments, compositions are provided that comprise a plurality of oligonucleotides, in which each of at least 75% of the

oligonucleotides comprise or consist of a nucleotide sequence as set forth in Table 3, 7, 8, or 9. In some embodiments, the oligonucleotide is complexed with a monovalent cation (e.g., Li+, Na+, K+, Cs+). In some embodiments, the oligonucleotide is in a lyophilized form. In some embodiments, the oligonucleotide is in an aqueous solution. In some embodiments, the oligonucleotide is provided, combined or mixed with a carrier (e.g., a pharmaceutically acceptable carrier). In some embodiments, the oligonucleotide is provided in a buffered solution. In some embodiments, the oligonucleotide is conjugated to a carrier (e.g., a peptide, steroid or other molecule). In some aspects of the invention, kits are provided that comprise a container housing the composition.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is an illustration depicting exemplary oligo designs for targeting 3' RNA ends. The first example shows oligos complementary to the 3' end of RNA, before the polyA-tail. The second example shows oligos complementary to the 3' end of RNA with a 5' T-stretch to hybridize to a polyA tail.

FIG. 2 is an illustration depicting exemplary oligos for targeting 5' RNA ends. The first example shows oligos complementary to the 5' end of RNA. The second example shows oligos complementary to the 5' end of RNA, the oligo having 3'overhang residues to create a RNA-oligo duplex with a recessed end. Overhang can include a combination of nucleotides including, but not limited to, C to potentially interact with a 5' methylguanosine cap and stabilize the cap further.

FIG. 3A is an illustration depicting exemplary oligos for targeting 5' RNA ends and exemplary oligos for targeting 5' and 3' RNA ends. The example shows oligos with loops to stabilize a 5' RNA cap or oligos that bind to a 5' and 3' RNA end to create a pseudo-circularized RNA.

FIG. 3B is an illustration depicting exemplary oligo-mediated RNA pseudo-circularization. The illustration shows an LNA mixmer oligo binding to the 5' and 3' regions of an exemplary RNA.

FIG. 4 is a diagram depicting Frataxin (FXN) 3' polyA sites.

FIG. 5 is a diagram depicting FXN 5' start sites.

FIG. 6 is a diagram depicting the location of the 5' and 3' oligonucleotides tested in the Examples.

FIG. 7 is a graph depicting the results of testing 3' end oligos. The screen was performed in a GM03816 FRDA patient cell line and the level of FXN mRNA was measured at 1-3 days post-transfection. Oligo concentration used for transfection was 100nM.

FIG. 8 is a graph depicting the results of testing 3' end oligos. The screen was performed in a GM03816 FRDA patient cell line and the level of FXN mRNA was measured at 1-3 days post-transfection. Oligo concentration used for transfection was 400nM.

FIG. 9 is a diagram depicting the location and sequences of FXN 3' oligos 73, 75, 76, and 77, which were shown to upregulate FXN mRNA. The oligos all contained poly-T sequences. A schematic of the binding of each oligo to the mRNA is shown.

FIG. 10 is a graph depicting the results of testing 5' end oligos. The screen was performed in a GM03816 FRDA patient cells and the level of FXN mRNA was measured at 2 days post-transfection. Oligo concentrations used for transfection were 100nM (red bars, left bar in each pair) and 400nM (blue bars, right bar in each pair). The lower response levels obtained with 400nM level may be due to the oligo concentration being too high and reducing the transfection agent availability to properly coat each oligo for delivery.

FIG. 11 is a graph depicting the results of testing 5' end oligos in combination with FXN 3' oligo 75 in GM03816 FRDA patient cells. The level of FXN mRNA was measured at 2 and 3 days post-transfection. For Oligo A/B, Oligo A targets the 5' end and OligoB targets the 3' end. Oligo concentration used for transfection was 200nM final = 100 nM oligo A + 100 nM oligo B).

FIG. 12 shows the same graph presented in FIG. 8. The boxes around bars indicate the 5' and 3' oligo pairs that were particularly effective in upregulating FXN in in GM03816 FRDA patient cells.

FIG. 13 is a diagram depicting the location and sequences of FXN 5' oligos 51, 52, 57, and 62, which were shown to upregulate FXN mRNA. The oligos all contained the motif CGCCCTCCAG. A schematic of a stem-loop structure formed by oligo 62 is shown.

FIG. 14 is an illustration depicting the predicted structure of FXN oligo 62. Nucleotides1-15 are complementary to the 5' end of one of the FXN isoforms. The predicted loop shown in nucleotides 2-8 may not exist in the cells because this portion will hybridize to the RNA and thus the loop will open up and hybridize to RNA. Nucleotides 16-24 are the artificially added loop to place the 3' most C residue in close proximity to the 5' methylguanosine cap of FXN mRNA.

FIGs. 15A and 15B are graphs depicting cytoxicity (CTG) at two days of treatment. Treatment of the FRDA patient cell line GM03816 with oligos did not result in cytotoxicity during day 2 (FIG. 15A) and 3 (FIG. 15B) of oligo treatment at 100 and 400 nM.

FIG. 16 is a set of graphs showing testing of combinations of oligos from previous experiments in the GM03816 FRDA patient cell line. The FXN mRNA levels for several of the oligos approached the levels of FXN mRNA in the GM0321B normal fibroblast cells. For Oligo A/B, Oligo A targets the 5' end and OligoB targets the 3' end. Oligo concentration used for transfection was 200nM final = 100 nM oligo A + 100 nM oligo B).

FIG. 17 is a graph depicting the levels of FXN mRNA at two and three days of treatment with oligos. Biological replicates of positive hits in previous experiments in GM03816 FRDA patient cells confirmed increased steady state FXN mRNA levels at 2-3 days. For Oligo A/B, Oligo A targets the 5' end and OligoB targets the 3' end. Oligo concentration used for transfection was 200nM final = 100 nM oligo A + 100 nM oligo B).

FIG. 18 is a graph depicting testing of oligos in GM04078 FRDA patient fibroblasts.

FIG. 19 is a graph depicting testing of oligos in a 'normal' cell line, GM0321B fibroblasts. GM0321B cells express approximately 4-fold more FXN mRNA than FRDA patient cells

FIG. 20 is a graph depicting transfection dose-response testing for 5' and 3' FXN oligo combination 62/77. Biological replicates and doses response of FXN Oligo 62/77 combination in GM03816 FRDA patient cell line showed increased steady-state FXN mRNA levels in 2-3 days. For Oligo A/B, Oligo A targets the 5' end and OligoB targets the 3' end. The transfection reagent amount was kept constant across the different concentration of oligos, which may be the cause of relatively flat response to oligo treatment. Concentrations are in nM final (i.e. 10 nM final = 5nM oligo 62 + 5nM oligo77).

FIG. 21 is a graph depicting FXN protein levels in GM03816 FRDA patient fibroblasts treated with oligos (single oligos at 100 nM) or in combination (two oligos at 200 nM final) and FXN protein levels in GM0321B normal fibroblasts.

FIG. 22 is a graph depicting levels of FXN protein with oligo treatment. FXN protein (100 nM, d3) n=2.

FIGs. 23A and 23B are graphs depicting the relative levels of mRNA with and without treatment with a combination of oligos 62 and 75 (also referred to, respectively, as oligos 385 and 398) in the presence of the de novo transcription inhibitor Actinomycin D

(ActD). FIG. 23A depicts relative levels of MYC mRNA. FIG. 22B depicts relative levels of FXN mRNA. cMyc has a relatively short half-life (~ 100 minutes) and was used as a positive control for ActD treatment.

FIG. 24 is a graph depicting oligos in GM03816 cells treated with Actinomycin D (ActD). FXN expression is depicted at 0, 2, 4 and 8 hours.

FIGs. 25A and 25B are graphs depicting FXN mRNA levels in GM15850 & GM15851 cells (FIG. 25A) or GM16209 & GM16222 (FIG. 25B) treated with combinations of 5' and 3' FXN oligos. This was a gymnotic experiment, with 10 micromolar of oligonucleotide.

FIG. 26 is a graph showing that treating cells with a combination of 5' end targeting oligos, and 3' end targeting oligos, and other FXN targeting oligos increases FXN mRNA levels.

FIG. 27 is a series of graphs showing the screening of 3' end oligos. Cells were transfected with 10 or 40 nM of an oligo and FXN mRNA was measured at 2 days post-transfection.

FIG. 28 is a series of graphs showing the screening of 3' end oligos. Cells were transfected with 10 or 40 nM of an oligo and FXN mRNA was measured at 3 days post-transfection.

FIG. 29 is a graph and a table showing the screening of 5' end oligos. Cells were transfected with 10 or 40 nM of an oligo and FXN mRNA was measured at 2 days post-transfection.

FIG. 30 is a series of graphs showing the testing of combinations of 5' and 3' end oligos. Cells were transfected with 10 or 40 nM of an oligo combination and FXN mRNA was measured at 2 days post-transfection.

FIG. 31 is a series of graphs showing the testing of combinations of 5' and 3' end oligos. Cells were transfected with 10 or 40 nM of an oligo combination and FXN mRNA was measured at 3 days post-transfection.

FIG. 32 is a graph showing that steady state levels of FXN mRNA increase over time in cells treated with combinations of 5' and 3' end oligos. Cells were transfected with 10 nM of an oligo combination and FXN mRNA was measured at 2 and 3 days post-transfection.

FIG. 33 is a graph showing that steady state levels of FXN mRNA increase over time in cells treated with combinations of 5' and 3' end oligos. Cells were transfected with 40 nM of an oligo combination and FXN mRNA was measured at 2 and 3 days post-transfection.

FIG. 34 is a graph showing the results from a testing of other oligos that target FXN, e.g., internally, close to a poly-A tail, or spanning an exon.

FIG. 35 is a graph showing that FXN mRNA levels are increased using a single oligonucleotide. Cells were transfected with 10 nM of an oligo and FXN mRNA was measured at 2 and 3 days post-transfection.

FIG. 36 is a graph showing that FXN mRNA levels are increased using a single oligonucleotide. Cells were transfected with 40 nM of an oligo and FXN mRNA was measured at 2 and 3 days post-transfection.

FIG. 37 is a graph showing that FXN mRNA levels are increased using combinations of 5' and 3' oligonucleotides. Cells were transfected with 10 or 40 nM of an oligo combination and FXN mRNA was measured at 2 and 3 days post-transfection.

FIG. 38A and 38B are graphs showing that transfection with 10 or 40 nM of an oligo is not cytoxic to the cells at day 2 (FIG. 38A) or day 3 (FIG. 38B) post-transfection.

FIG. 39A and 39B are graphs showing that FXN protein levels (FIG. 39A) and mRNA levels (FIG. 39B) are increased in cells transfected with 10 nM of an oligo. Protein and mRNA levels were measured 2 or 3 days post-transfection.

FIG. 40A and 40B are graphs showing that FXN protein levels (FIG. 40A) and mRNA levels (FIG. 40B) can be increased in cells transfected with 40 nM of an oligo. Protein and mRNA levels were measured 2 or 3 days post-transfection.

FIG. 41 is a graph depicting the expression level of KLF4 mRNA in cells treated with KLF4 5' and 3' end targeting oligos.

FIG. 42 is an image of a Western blot depicting the expression level of KLF4 protein in cells treated with KLF4 5' and 3' end targeting oligos.

FIG. 43 is a graph depicting the expression level of KLF4 mRNA in cells treated with KLF4 5' and 3' end targeting oligos, including circularized oligonucleotides targeting both 5' and 3' ends of KLF4, and individual oligonucleotides targeting 5' and 3' ends of KLF4.

FIGs. 44A and 44B are graphs depicting the expression level of PTEN mRNA at day3 in cells treated with PTEN oligos. GM04078 fibroblast cells were transfected with the oligos and lysates were collected at day3. Oligo sequences are provided in Table 9.

FIG. 45 is an image of a Western blot depicting the expression level of PTEN protein at day1 and day2 from GM04078 fibroblast cells treated with PTEN oligos PTEN-108 and PTEN-113, either alone or in combination. GM04078 fibroblast cells were transfected and lysates were collected at day1 & day2. Oligo sequences are provided in Table 9.

FIG. 46 is a graph depicting the expression level of mouse KLF4 mRNA at day3 in cells treated with KLF4 oligos. Hepa1-6 cells were transfected with the oligos and lysate was collected at day3. Oligo sequences are provided in Table 9.

FIG. 47 is an image of a Western blot depicting the expression level of mouse KLF4 protein at day3 in cells treated with pseudo-circularization oligos. Hepa1-6 cells were transfected with the oligos and lysate was collected at day3. The oligos tested were mouse KLF4-8, KLF4-9, KLF4-11, KLF4-12, KLF4-13, KLF4-14, and KLF4-15. Oligo sequences are provided in Table 9.

FIG. 48 is an image of a Western blot depicting the expression level of mouse KLF4 protein at day3 in cells treated with stability combination oligos. Hepa1-6 cells were transfected with the oligos and lysate was collected at day3. The oligos tested were mouse KLF4-1, KLF4-2, KLF4-3, KLF4-16, KLF4-17, KLF4-18, and KLF4-19, in various combinations. Oligo sequences are provided in Table 9.

FIG. 49 is a graph showing human KLF4 stability measurements in the presence of absence of circularization and individual stability oligos used alone or in combination (indicated by "/"). Oligo sequences are provided in Table 7. 47 = KLF4-47 m02, 48= KLF4-48 m02, 50= KLF4-50 m02, 51=KLF4-51 m02, 53=KLF4-53 m02.

FIG. 50 is a graph showing that 5'/3' end oligo combinations and circularization oligos can be used to increase beta actin mRNA, which is known to have a long mRNA half-life.

FIG. 51 is a graph showing human FXN mRNA upregulation in GM03816 cells treated with FXN oligos either alone or in various combinations. Concentrations are indicated as total oligo concentration (e.g. 20nM means 10nM for each oligo).

FIGs. 52 and 53 are each a photograph of a Western blot showing protein levels of premature and mature FXN induced by various FXN oligos.

FIG. 54 is a series of graphs showing FXN mRNA upregulation in GM03816 cells treated with FXN oligos either alone or in various combinations. GAPDH gapmer values

show GAPDH mRNA levels relative to FXN mRNA level. The rest of the values show FXN mRNA levels relative to GAPDH mRNA levels.

FIG. 55 a graph showing FXN mRNA upregulation in GM03816 cells treated with FXN oligos either alone or in various combinations. GAPDH gapmer values show GAPDH mRNA levels relative to FXN mRNA level. The rest of the values show FXN mRNA levels relative to GAPDH mRNA levels.

FIG. 56 provides a series of graphs showing mRNA levels of PPARGC1 and NFE2L2, candidate FXN downstream genes, in cells treated with various FXN oligos alone or in combination.

FIG. 57 is a graph showing FXN mRNA upregulation in GM03816 cells treated with FXN oligos either alone or in various combinations.

FIGs. 58A-58C are a series of graphs showing levels of FXN mRNA at day 4, day 7, and day 10, respectively, in FRDA mouse model fibroblasts treated with various FXN oligos alone or in combination.

FIGs. 59A and 59B are a series of graphs showing FXN mRNA levels in GM03816 cells treated with various FXN oligos in a dose-response study. For FIG. 59A, measurement was done at day3 and day5. For FIG. 59B, measurement was done at day5.

FIGs. 60A and 60B are a series of graphs showing levels of FXN mRNA in GM03816 cells treated with various 5' FXN oligos combined with the FXN-532 oligo.

FIG. 61 is a photograph of a Western blot showing the levels of FXN protein in GM03816 cells treated with various FXN oligos.

FIG. 62 is a graph showing levels of UTRN protein quantified from the Western blot in FIG. 64.

FIG. 63 is a photograph of a Western blot showing the levels of UTRN protein in the supernatant from cells treated with various UTRN oligos.

FIG. 64A is a graph showing levels of UTRN protein quantified from the Western blot in FIG. 64B and 64C. FIGs. 64B and 64C are each photographs of Western blots showing the levels of UTRN protein in the supernatant or pellet from cells treated with various UTRN oligos.

FIGs. 65A-65C are a series of graphs showing the level of mouse APOA1 mNRA levels in primary mouse hepatocytes treated with various APOA1 oligos.

FIG. 66 is a photograph of two Western blots showing the levels of APOA1 protein in primary mouse hepatocytes treated with various APOA1 oligos. Tubulin was used as loading control for the bottom photograph.

FIGs. 67A-67G are a series of graphs showing the level of Human Frataxin (A, B, E) or mouse Frataxin in a short arm (SA) or long arm (LA) study of oligo treatment in a mouse model of Friedreich's ataxia. FIGs. 67A-67E show heart data. FIGs. 67F&67G show liver data. FIGs. 67C and 67E show the same long-arm heart human FXN values by averaging across the 5 mice in each group (FIG. 67C) and showing values in each individual mouse in the groups (FIG. 67E). The human FXN and mouse FXN in the hearts and livers of this model were measured with QPCR and normalized to the PBS group. Each treatment group had 5 mice (n=5).

FIG. 68 shows a series of diagrams that demonstrate the potential targeting of human FXN oligos to mouse FXN. The diagrams on the left show USCS genome views of mouse FXN genomic regions corresponding to human FXN-375 (top panels) and FXN-389 (bottom panels) potential interaction locations. The boxes show the oligos' mapping position relative to the mouse genome. The panels on the right show ClustalW alignment of human oligo sequences to the mouse genome.

FIG. 69 is a series of diagrams showing oligo positions relative to mRNA-Seq signal and ribosome positioning. The signal in the top panel of each diagram shows all ribosome positioning data (including initiating and elongating ribosomes). The signal in the bottom panel of each diagram shows mRNA-Seq data. The black bars in boxes show indicated oligo localization.

FIGs. 70A and 70B are a series of graphs showing APOA1 mRNA levels in the livers of mice treated with various 5' and 3' end APOA1 oligos. For FIG. 70A, collection of livers was done at day5, 2 days after the last dose of oligos or control (PBS). For FIG. 70B, collection of livers was done at day7, 4 days after the last dose of oligos or control (PBS).

FIGs. 70 C and 70D are photographs of Western blots showing APOA1 protein levels in mice treated with various 5' and 3' end APOA1 oligos. For FIG. 70C, samples 1-5 are PBS-treated animals and samples 6-10 are from APOA1_mus -3+APOA1_mus -17 oligo-treated animals. Lane 10 blood sample, indicated by a star, contained hemolysis and therefore was omitted from analysis. For FIG. 70D, samples 1-5 are PBS-treated animals and samples 6-10 are from APOA1_mus -7+APOA1_mus -20 oligo-treated animals. The top blot

in FIG. 70D shows pre-bleeding data from all 10 animals. The bottom plot shows plasma APOA1 levels after oligo treatment. Control treated sample 4 died during the study and therefore was omitted from the blot.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

Methods and compositions disclosed herein are useful in a variety of different contexts in which is it desirable to protect RNAs from degradation, including protecting RNAs inside or outside of cells. In some embodiments, methods and compositions are provided that are useful for posttranscriptionally altering protein and/or RNA levels in cells in a targeted manner. For example, methods are provided that involve reducing or preventing degradation or processing of targeted RNAs thereby elevating steady state levels of the targeted RNAs. In some embodiments, the stability of an RNA is increased by protecting one or both ends (5' or 3' ends) of the RNA from exonuclease activity, thereby increasing stability of the RNA.

In some embodiments, methods of increasing gene expression are provided. As used herein the term, "gene expression" refers generally to the level or representation of a product of a gene in a cell, tissue or subject. It should be appreciated that a gene product may be an RNA transcript or a protein, for example. An RNA transcript may be protein coding. An RNA transcript may be non-protein coding, such as, for example, a long non-coding RNA, a long intergenic non-coding RNA, a non-coding RNA, an miRNA, a small nuclear RNA (snRNA), or other functional RNA. In some embodiments, methods of increasing gene expression may involve increasing stability of a RNA transcript, and thereby increasing levels of the RNA transcript in the cell. Methods of increasing gene expression may alternatively or in addition involve increasing transcription or translation of RNAs. In some embodiments, other mechanisms of manipulating gene expression may be involved in methods disclosed herein.

In some embodiments, methods provided herein involve delivering to a cell one or more sequence specific oligonucleotides that hybridize with an RNA transcript at or near one or both ends, thereby protecting the RNA transcript from exonuclease mediated degradation. In embodiments where the targeted RNA transcript is protein-coding, increases in steady state levels of the RNA typically result in concomitant increases in levels of the encoded

protein. In embodiments where the targeted RNA is non-coding, increases in steady state levels of the non-coding RNA typically result in concomitant increases activity associated with the non-coding RNA.

In some embodiments, approaches disclosed herein based on regulating RNA levels and/or protein levels using oligonucleotides targeting RNA transcripts by mechanisms that increase RNA stability and/or translation efficiency may have several advantages over other types of oligos or compounds, such as oligonucleotides that alter transcription levels of target RNAs using cis or noncoding based mechanisms. For example, in some embodiments, lower concentrations of oligos may be used when targeting RNA transcripts in the cytoplasm as multiple copies of the target molecules exist. In contrast, in some embodiments, oligos that target transcriptional processes may need to saturate the cytoplasm and before entering nuclei and interacting with corresponding genomic regions, of which there are only one/two copies per cell, in many cases. In some embodiments, response times may be shorter for RNA transcript targeting because RNA copies need not to be synthesized transcriptionally. In some embodiments, a continuous dose response may be easier to achieve. In some embodiments, well defined RNA transcript sequences facilitate design of oligonucleotides that target such transcripts. In some embodiments, oligonucleotide design approaches provided herein, e.g., designs having sequence overhangs, loops, and other features facilitate high oligo specificity and sensitivity compared with other types of oligonucleotides, e.g., certain oligonucleotides that target transcriptional processes.

In some embodiments, methods provided herein involve use of oligonucleotides that stabilize an RNA by hybridizing at a 5' and/or 3' region of the RNA. In some embodiments, oligonucleotides that prevent or inhibit degradation of an RNA by hybridizing with the RNA may be referred to herein as "stabilizing oligonucleotides." In some examples, such oligonucleotides hybridize with an RNA and prevent or inhibit exonuclease mediated degradation. Inhibition of exonuclease mediated degradation includes, but is not limited to, reducing the extent of degradation of a particular RNA by exonucleases. For example, an exonuclease that processes only single stranded RNA may cleave a portion of the RNA up to a region where an oligonucleotide is hybridized with the RNA because the exonuclease cannot effectively process (e.g., pass through) the duplex region. Thus, in some embodiments, using an oligonucleotide that targets a particular region of an RNA makes it possible to control the extent of degradation of the RNA by exonucleases up to that region.

For example, use of an oligonucleotide that hybridizes at an end of an RNA may reduce or eliminate degradation by an exonuclease that processes only single stranded RNAs from that end. For example, use of an oligonucleotide that hybridizes at the 5' end of an RNA may reduce or eliminate degradation by an exonuclease that processes single stranded RNAs in a 5' to 3' direction. Similarly, use of an oligonucleotide that hybridizes at the 3' end of an RNA may reduce or eliminate degradation by an exonuclease that processes single stranded RNAs in a 3' to 5' direction. In some embodiments, lower concentrations of an oligo may be used when the oligo hybridizes at both the 5' and 3' regions of the RNA. In some embodiments, an oligo that hybridizes at both the 5' and 3' regions of the RNA protects the 5' and 3' regions of the RNA from degradation (e.g., by an exonuclease). In some embodiments, an oligo that hybridizes at both the 5' and 3' regions of the RNA creates a pseudo-circular RNA (e.g., a circularized RNA with a region of the poly A tail that protrudes from the circle, see FIG. 3B). In some embodiments, a pseudo-circular RNA is translated at a higher efficiency than a non-pseudo-circular RNA.

In some embodiments, an oligonucleotide may be used that comprises multiple regions of complementarity with an RNA, such that at one region the oligonucleotide hybridizes at or near the 5' end of the RNA and at another region it hybridizes at or near the 3' end of the RNA, thereby preventing or inhibiting degradation of the RNA by exonucleases at both ends. In some embodiments, when an oligonucleotide hybridizes both at or near the 5' end of an RNA and at or near the 3' end of the RNA a circularized complex results that is protected from exonuclease mediated degradation. In some embodiments, when an oligonucleotide hybridizes both at or near the 5' end of an mRNA and at or near the 3' end of the mRNA, the circularized complex that results is protected from exonuclease mediated degradation and the mRNA in the complex retains its ability to be translated into a protein.

As used herein the term, "synthetic RNA" refers to a RNA produced through an *in vitro* transcription reaction or through artificial (non-natural) chemical synthesis. In some embodiments, a synthetic RNA is an RNA transcript. In some embodiments, a synthetic RNA encodes a protein. In some embodiments, the synthetic RNA is a functional RNA (e.g., a lncRNA, miRNA, etc.). In some embodimentst, a synthetic RNA comprises one or more modified nucleotides. In some embodiments, a synthetic RNA is up to 0.5 kilobases (kb), 1 kb, 1.5 kb, 2 kb, 2.5 kb, 3 kb, 4 kb, 5 kb, 6 kb, 7 kb, 8 kb, 9 kb, 10 kb, 15 kb, 20 kb, 25 kb, 30 kb or more in length. In some embodiments, a synthetic RNA is in a range of 0.1 kb to 1 kb,

0.5 kb to 2 kb, 0.5 kb to 10 kb, 1 kb to 5 kb, 2 kb to 5 kb, 1 kb to 10 kb, 3 kb to 10 kb, 5 kb to 15 kb, or 1 kb to 30 kb in length.

As used herein, the term "RNA transcript" refers to an RNA that has been transcribed from a nucleic acid by a polymerase enzyme. An RNA transcript may be produced inside or outside of cells. For example, an RNA transcript may be produced from a DNA template encoding the RNA transcript using an *in vitro* transcription reaction that utilizes recombination or purified polymerase enzymes. An RNA transcript may also be produced from a DNA template (e.g., chromosomal gene, an expression vector) in a cell by an RNA polymerase (e.g., RNA polymerase I, II, or III). In some embodiments, the RNA transcript is a protein coding mRNA. In some embodiments, the RNA transcript is a non-coding RNA (e.g., a tRNA, rRNA, snoRNA, miRNA, ncRNA, long-noncoding RNA, shRNA). In some embodiments, RNA transcript is up to 0.5 kilobases (kb), 1 kb, 1.5 kb, 2 kb, 2.5 kb, 3 kb, 4 kb, 5 kb, 6 kb, 7 kb, 8 kb, 9 kb, 10 kb, 15 kb, 20 kb, 25 kb, 30 kb or more in length. In some embodiments, a RNA transcript is in a range of 0.1 kb to 1 kb, 0.5 kb to 2 kb, 0.5 kb to 10 kb, 1 kb to 5 kb, 2 kb to 5 kb, 1 kb to 10 kb, 3 kb to 10 kb, 5 kb to 15 kb, or 1 kb to 30 kb in length.

In some embodiments, the RNA transcript is capped post-transcriptionally, e.g., with a 7'-methylguanosine cap. In some embodiments, the 7'-methylguanosine is added to the RNA transcript by a guanylyltransferase during transcription (e.g., before the RNA transcript is 20-50 nucleotides long.) In some embodiments, the 7 '-methylguanosine is linked to the first transcribed nucleotide through a 5'-5' triphosphate bridge. In some embodiments, the nucleotide immediately internal to the cap is an adenosine that is N6 methylated. In some embodiments, the first and second nucleotides immediately internal to the cap of the RNA transcript are not 2'-O-methylated. In some embodiments, the first nucleotide immediately internal to the cap of the RNA transcript is 2'-O-methylated. In some embodiments, the second nucleotide immediately internal to the cap of the RNA transcript is 2'-O -methylated. In some embodiments, the first and second nucleotides immediately internal to the cap of the RNA transcript are 2'-O -methylated.

In some embodiments, the RNA transcript is a non-capped transcript (e.g., a transcript produced from a mitochondrial gene). In some embodiments, the RNA transcript is a nuclear RNA that was capped but that has been decapped. In some embodiments, decapping of an RNA is catalyzed by the decapping complex, which may be composes of Dcp1 and Dcp2,

e.g., that may compete with eIF-4E to bind the cap. In some embodiments, the process of RNA decapping involves hydrolysis of the 5' cap structure on the RNA exposing a 5' monophosphate. In some embodiments, this 5' monophosphate is a substrate for the exonuclease XRN1. Accordingly, in some embodiments, an oligonucleotide that targets the 5' region of an RNA may be used to stabilize (or restore stability) to a decapped RNA, e.g., protecting it from degradation by an exonuclease such as XRN1.

In some embodiments, *in vitro* transcription (e.g., performed via a T7 RNA polymerase or other suitable polymerase) may be used to produce an RNA transcript. In some embodiments transcription may be carried out in the presence of anti-reverse cap analog (ARCA) (TriLink Cat. # N-7003). In some embodiments, transcription with ARCA results in insertion of a cap (*e.g.*, a cap analog (mCAP)) on the RNA in a desirable orientation.

In some embodiments, transcription is performed in the presence of one or more modified nucleotides (e.g., pseudouridine, 5-methylcytosine, etc.), such that the modified nucleotides are incorporated into the RNA transcript. It should be appreciated that any suitable modified nucleotide may be used, including, but not limited to, modified nucleotides that reduced immune stimulation, enhance translation and increase nuclease stability. Non-limiting examples of modified nucleotides that may be used include: 2'-amino-2'-deoxynucleotide, 2'-azido-2'-deoxynucleotide, 2'-fluoro-2'-deoxynucleotide, 2'-O-methyl-nucleotide, 2' sugar super modifier, 2'-modified thermostability enhancer, 2'-fluoro-2'-deoxyadenosine-5'-triphosphate, 2'-fluoro-2'-deoxycytidine-5'-triphosphate, 2'-fluoro-2'-deoxyguanosine-5'-triphosphate, 2'-fluoro-2'-deoxyuridine-5'-triphosphate, 2'-O-methyladenosine-5'-triphosphate, 2'-O-methylcytidine-5'-triphosphate, 2'-O-methylguanosine-5'-triphosphate, 2'-O-methyluridine-5'-triphosphate, pseudouridine-5'-triphosphate, 2'-O-methylinosine-5'-triphosphate, 2'-amino-2'-deoxycytidine-5'-triphosphate, 2'-amino-2'-deoxyuridine-5'-triphosphate, 2'-azido-2'-deoxycytidine-5'-triphosphate, 2'-azido-2'-deoxyuridine-5'-triphosphate, 2'-O-methylpseudouridine-5'-triphosphate, 2'-O-methyl-5-methyluridine-5'-triphosphate, 2'-azido-2'-deoxyadenosine-5'-triphosphate, 2'-amino-2'-deoxyadenosine-5'-triphosphate, 2'-fluoro-thymidine-5'-triphosphate, 2'-azido-2'-deoxyguanosine-5'-triphosphate, 2'-amino-2'-deoxyguanosine-5'-triphosphate, and N4-methylcytidine-5'-triphosphate. In one embodiment, RNA degradation or processing can be reduced/prevented to elevate steady state RNA and, at least for protein-coding transcripts,

protein levels. In some embodiments, a majority of degradation of RNA transcripts is done by exonucleases. In such embodiments, these enzymes start destroying RNA from either their 3' or 5' ends. By protecting the ends of the RNA transcripts from exonuclease enzyme activity, for instance, by hybridization of sequence-specific blocking oligonucleotides with proper chemistries for proper delivery, hybridization and stability within cells, RNA stability may be increase, along with protein levels for protein-coding transcripts.

In some embodiments, for the 5' end, oligonucleotides may be used that are fully/partly complementary to 10-20 nts of the RNA 5' end. In some embodiments, such oligonucleotides may have overhangs to form a hairpin (e.g., the 3' nucleotide of the oligonucleotide can be, but not limited to, a C to interact with the mRNA 5' cap's G nucleoside) to protect the RNA 5' cap. In some embodiments, all nucleotides of an oligonucleotide may be complementary to the 5' end of an RNA transcript, with or without few nucleotide overhangs to create a blunt or recessed 5'RNA-oligo duplex. In some embodiments, for the 3' end, oligonucleotides may be partly complementary to the last several nucleotides of the RNA 3' end, and optionally may have a poly(T)-stretch to protect the poly(A) tail from complete degradation (for transcripts with a poly(A)-tail). In some embodiments, similar strategies can be employed for other RNA species with different 5' and 3' sequence composition and structure (such as transcripts containing 3' poly(U) stretches or transcripts with alternate 5' structures). In some embodiments, oligonucleotides as described herein, including, for example, oligonucleotides with overhangs, may have higher specificity and sensitivity to their target RNA end regions compared to oligonucleotides designed to be perfectly complementary to RNA sequences, because the overhangs provide a destabilizing effect on mismatch regions and prefer binding in regions that are at the 5' or 3' ends of the RNAs. In some embodiments, oligonucleotides that protect the very 3' end of the poly(A) tail with a looping mechanism (*e.g.*, TTTTTTTTTTGGTTTTCC, SEQ ID NO: 458). In some embodiments, this latter approach may nonspecifically target all protein-coding transcripts. However, in some embodiments, such oligonucleotides, may be useful in combination with other target-specific oligos.

In some embodiments, methods provided herein involve the use of an oligonucleotide that comprises a region of complementarity that is complementary with the RNA transcript at a position at or near the first transcribed nucleotide of the RNA transcript. In some embodiments, an oligonucleotide (e.g., an oligonucleotide that stabilizes an RNA transcript)

comprises a region of complementarity that is complementary with the RNA transcript (e.g., with at least 5 contiguous nucleotides) at a position that begins within 100 nucleotides, within 50 nucleotides, within 30 nucleotides, within 20 nucleotides, within 10 nucleotides or within 5 nucleotides of the 5'-end of the transcript. In some embodiments, an oligonucleotide (e.g., an oligonucleotide that stabilizes an RNA transcript) comprises a region of complementarity that is complementary with the RNA transcript (e.g., with at least 5 contiguous nucleotides of the RNA transcript) at a position that begins at the 5'-end of the transcript. In some embodiments, an oligonucleotide (e.g., an oligonucleotide that stabilizes an RNA transcript) comprises a region of complementarity that is complementary with an RNA transcript at a position within a region of the 5' untranslated region (5' UTR) of the RNA transcript spanning from the transcript start site to 50, 100, 150, 200, 250, 500 or more nucleotides upstream from a translation start site (e.g., a start codon, AUG, arising in a Kozak sequence of the transcript).

In some embodiments, an RNA transcript is poly-adenylated. Polyadenylation refers to the post-transcriptional addition of a polyadenosine (poly(A)) tail to an RNA transcript. Both protein-coding and non-coding RNA transcripts may be polyadenylated. Poly(A) tails contain multiple adenosines linked together through internucleoside linkages. In some embodiments, a poly(A) tail may contain 10 to 50, 25 to 100, 50 to 200, 150 to 250 or more adenosines. In some embodiments, the process of polyadenlyation involves endonucleolytic cleavage of an RNA transcript at or near its 3'-end followed by one by one addition of multiple adenosines to the transcript by a polyadenylate polymerase, the first of which adenonsines is added to the transcript at the 3' cleavage site. Thus, often a polyadenylated RNA transcript comprises transcribed nucleotides (and possibly edited nucleotides) linked together through internucleoside linkages that are linked at the 3' end to a poly(A) tail. The location of the linkage between the transcribed nucleotides and poly(A) tail may be referred to herein as, a "polyadenylation junction." In some embodiments, endonucleolytic cleavage may occur at any one of several possible sites in an RNA transcript. In such embodiments, the sites may be determined by sequence motifs in the RNA transcript that are recognized by endonuclease machinery, thereby guiding the position of cleavage by the machinery. Thus, in some embodiments, polyadenylation can produce different RNA transcripts from a single gene, *e.g.*, RNA transcripts have different polyadenylation junctions. In some embodiments, length of a poly(A) tail may determine susceptibility of the RNA transcript to enzymatic

degradation by exonucleases with 3'-5' processing activity. In some embodiments, oligonucleotides that target an RNA transcript at or near its 3' end target a region overlapping a polyadenylation junction. In some embodiments, such oligonucleotides may have at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more nucleotides that are complementary with the transcribed portion of the transcript (5' to the junction). In some embodiments, it is advantageous to have a limited number of nucleotides (e.g., T, U) complementary to the polyA side of the junction. In some embodiments, having a limited number of nucleotides complementary to the polyA side of the junction it is advantageous because it reduces toxicity associated with cross hybridization of the oligonucleotide to the polyadenylation region of non-target RNAs in cells. In some embodiments, the oligonucleotide has only 1, 2, 3, 4, 5, or 6 nucleotides complementary to the poly A region.

In some embodiments, methods provided herein involve the use of an oligonucleotide that hybridizes with a target RNA transcript at or near its 3' end and prevents or inhibits degradation of the RNA transcript by 3'-5' exonucleases. For example, in some embodiments, RNA stabilization methods provided herein involve the use of an oligonucleotide that comprises a region of complementarity that is complementary with the RNA transcript at a position within 100 nucleotides, within 50 nucleotides, within 30 nucleotides, within 20 nucleotides, within 10 nucleotides, within 5 nucleotides of the last transcribed nucleotide of the RNA transcript. In a case where the RNA transcript is a polyadenylated transcript, the last transcribed nucleotide of the RNA transcript is the first nucleotide upstream of the polyadenylation junction. In some embodiments, RNA stabilization methods provided herein involve the use of an oligonucleotide that comprises a region of complementarity that is complementary with the RNA transcript at a position immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript. In some embodiments, RNA stabilization methods provided herein involve the use of an oligonucleotide that comprises a region of complementarity that is complementary with the RNA transcript within the poly(A) tail.

Methods for identifying transcript start sites and polyadenylation junctions are known in the art and may be used in selecting oligonucleotides that specifically bind to these regions for stabilizing RNA transcripts. In some embodiments, 3' end oligonucleotides may be designed by identifying RNA 3' ends using quantitative end analysis of poly-A tails. In some embodiments, 5' end oligonucleotides may be designed by identifying 5' start sites using Cap

analysis gene expression (CAGE). Appropriate methods are disclosed, for example, in Ozsolak *et al. Comprehensive Polyadenylation Site Maps in Yeast and Human Reveal Pervasive Alternative Polyadenylation.* Cell. Volume 143, Issue 6, 2010, Pages 1018–1029; Shiraki, T, *et al., Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage.* Proc Natl Acad Sci U S A. 100 (26): 15776–81. 2003-12-23; and Zhao, X, et al., (2011). *Systematic Clustering of Transcription Start Site Landscapes.* PLoS ONE (Public Library of Science) 6 (8): e23409, the contents of each of which are incorporated herein by reference. Other appropriate methods for identifying transcript start sites and polyadenylation junctions may also be used, including, for example, RNA-Paired-end tags (PET) (*See*, e.g., Ruan X, Ruan Y. Methods Mol Biol. 2012;809:535-62); use of standard EST databases; RACE combined with microarray or sequencing, PAS-Seq (*See*, e.g., Peter J. Shepard, et al., RNA. 2011 April; 17(4): 761–772); and 3P-Seq (*See*, e.g., Calvin H. Jan, Nature. 2011 January 6; 469(7328): 97–101; and others.

In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcript of a eukaryotic cell. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcript of a cell of a vertebrate. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcript of a cell of a mammal, e.g., a primate cell, mouse cell, rat cell, or human cell. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcript of a cardiomyocyte. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcribed in the nucleus of a cell. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcribed in a mitochondrion of a cell. In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an RNA transcript transcribed by a RNA polymerase II enzyme.

In some embodiments, an RNA transcript targeted by an oligonucleotide disclosed herein is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN, HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3. In some embodiments, the RNA transcript targeted by an oligonucleotide disclosed herein is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE,

BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2, MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST. RNA transcripts for these and other genes may be selected or identified experimentally, for example, using RNA sequencing (RNA-Seq) or other appropriate methods. RNA transcripts may also be selected based on information in public databases such as in UCSC, Ensembl and NCBI genome browsers and others. Non-limiting examples of RNA transcripts for certain genes are listed in Table 1.

Table 1: Non-limiting examples of RNA transcripts for certain genes

GENE SYMBOL	MRNA	SPECIES	GENE NAME
ABCA1	NM_013454	Mus musculus	ATP-binding cassette, sub-family A (ABC1), member 1
ABCA1	NM_005502	Homo sapiens	ATP-binding cassette, sub-family A (ABC1), member 1
ABCA4	NM_007378	Mus musculus	ATP-binding cassette, sub-family A (ABC1), member 4
ABCA4	NM_000350	Homo sapiens	ATP-binding cassette, sub-family A (ABC1), member 4
ABCB11	NM_003742	Homo sapiens	ATP-binding cassette, sub-family B (MDR/TAP), member 11
ABCB11	NM_021022	Mus musculus	ATP-binding cassette, sub-family B (MDR/TAP), member 11
ABCB4	NM_018850	Homo sapiens	ATP-binding cassette, sub-family B (MDR/TAP), member 4
ABCB4	NM_000443	Homo sapiens	ATP-binding cassette, sub-family B (MDR/TAP), member 4
ABCB4	NM_018849	Homo sapiens	ATP-binding cassette, sub-family B (MDR/TAP), member 4
ABCB4	NM_008830	Mus musculus	ATP-binding cassette, sub-family B (MDR/TAP), member 4
ABCG5	NM_022436	Homo sapiens	ATP-binding cassette, sub-family G (WHITE), member 5
ABCG5	NM_031884	Mus musculus	ATP-binding cassette, sub-family G (WHITE), member 5
ABCG8	NM_026180	Mus musculus	ATP-binding cassette, sub-family G (WHITE), member 8
ABCG8	NM_022437	Homo sapiens	ATP-binding cassette, sub-family G (WHITE), member 8
ADIPOQ	NM_009605	Mus	adiponectin, C1Q and collagen domain

GENE SYMBOL	MRNA	SPECIES	GENE NAME
		musculus	containing
ADIPOQ	NM_004797	Homo sapiens	adiponectin, C1Q and collagen domain containing
ALB	NM_000477	Homo sapiens	albumin
ALB	NM_009654	Mus musculus	albumin
APOA1	NM_000039	Homo sapiens	apolipoprotein A-I
APOA1	NM_009692	Mus musculus	apolipoprotein A-I
APOE	NM_009696	Mus musculus	apolipoprotein E
APOE	XM_001724655	Homo sapiens	hypothetical LOC100129500; apolipoprotein E
APOE	XM_001722911	Homo sapiens	hypothetical LOC100129500; apolipoprotein E
APOE	XM_001724653	Homo sapiens	hypothetical LOC100129500; apolipoprotein E
APOE	NM_000041	Homo sapiens	hypothetical LOC100129500; apolipoprotein E
APOE	XM_001722946	Homo sapiens	hypothetical LOC100129500; apolipoprotein E
ATP2A2	NM_009722	Mus musculus	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
ATP2A2	NM_001110140	Mus musculus	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
ATP2A2	NM_001135765	Homo sapiens	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
ATP2A2	NM_170665	Homo sapiens	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
ATP2A2	NM_001681	Homo sapiens	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2
BCL2L11	NM_006538	Homo sapiens	BCL2-like 11 (apoptosis facilitator)
BCL2L11	NM_207002	Homo sapiens	BCL2-like 11 (apoptosis facilitator)
BCL2L11	NM_138621	Homo sapiens	BCL2-like 11 (apoptosis facilitator)
BCL2L11	NM_207680	Mus musculus	BCL2-like 11 (apoptosis facilitator)
BCL2L11	NM_207681	Mus musculus	BCL2-like 11 (apoptosis facilitator)
BCL2L11	NM_009754	Mus musculus	BCL2-like 11 (apoptosis facilitator)

GENE SYMBOL	MRNA	SPECIES	GENE NAME
BDNF	NM_001143816	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143815	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143814	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143813	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143812	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143806	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143811	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143805	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143810	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001709	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_170735	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_170734	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_170733	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_170732	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_170731	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143809	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143807	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_001143808	Homo sapiens	brain-derived neurotrophic factor
BDNF	NM_007540	Mus musculus	brain derived neurotrophic factor
BDNF	NM_001048141	Mus musculus	brain derived neurotrophic factor
BDNF	NM_001048142	Mus musculus	brain derived neurotrophic factor
BDNF	NM_001048139	Mus musculus	brain derived neurotrophic factor
BRCA1	NM_009764	Mus musculus	breast cancer 1

GENE SYMBOL	MRNA	SPECIES	GENE NAME
BRCA1	NM_007296	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007300	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007297	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007303	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007298	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007302	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007299	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007304	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007294	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007305	Homo sapiens	breast cancer 1, early onset
BRCA1	NM_007295	Homo sapiens	breast cancer 1, early onset
CD274	NM_014143	Homo sapiens	CD274 molecule
CD274	NM_021893	Mus musculus	CD274 antigen
CEP290	NM_025114	Homo sapiens	centrosomal protein 290kDa
CEP290	NM_146009	Mus musculus	centrosomal protein 290
CFTR	NM_000492	Homo sapiens	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)
CFTR	NM_021050	Mus musculus	cystic fibrosis transmembrane conductance regulator homolog
EPO	NM_000799	Homo sapiens	erythropoietin
EPO	NM_007942	Mus musculus	erythropoietin
F7	NM_000131	Homo sapiens	coagulation factor VII (serum prothrombin conversion accelerator)
F7	NM_019616	Homo sapiens	coagulation factor VII (serum prothrombin conversion accelerator)
F7	NM_010172	Mus musculus	coagulation factor VII

GENE SYMBOL	MRNA	SPECIES	GENE NAME
F8	NM_019863	Homo sapiens	coagulation factor VIII, procoagulant component
F8	NM_000132	Homo sapiens	coagulation factor VIII, procoagulant component
F8	NM_001161373	Mus musculus	coagulation factor VIII
F8	NM_001161374	Mus musculus	coagulation factor VIII
F8	NM_007977	Mus musculus	coagulation factor VIII
FLI1	NM_002017	Homo sapiens	Friend leukemia virus integration 1
FLI1	NM_001167681	Homo sapiens	Friend leukemia virus integration 1
FLI1	NM_008026	Mus musculus	Friend leukemia integration 1
FMR1	NM_008031	Mus musculus	fragile X mental retardation syndrome 1 homolog
FMR1	NM_002024	Homo sapiens	fragile X mental retardation 1
FNDC5	NM_001171941	Homo sapiens	fibronectin type III domain containing 5
FNDC5	NM_153756	Homo sapiens	fibronectin type III domain containing 5
FNDC5	NM_001171940	Homo sapiens	fibronectin type III domain containing 5
FNDC5	NM_027402	Mus musculus	fibronectin type III domain containing 5
FOXP3	NM_054039	Mus musculus	forkhead box P3
FOXP3	NM_001114377	Homo sapiens	forkhead box P3
FOXP3	NM_014009	Homo sapiens	forkhead box P3
FXN	NM_001161706	Homo sapiens	frataxin
FXN	NM_181425	Homo sapiens	frataxin
FXN	NM_000144	Homo sapiens	frataxin
FXN	NM_008044	Mus musculus	frataxin
GCH1	NM_008102	Mus musculus	GTP cyclohydrolase 1
GCH1	NM_000161	Homo sapiens	GTP cyclohydrolase 1

GENE SYMBOL	MRNA	SPECIES	GENE NAME
GCH1	NM_001024070	Homo sapiens	GTP cyclohydrolase 1
GCH1	NM_001024071	Homo sapiens	GTP cyclohydrolase 1
GCH1	NM_001024024	Homo sapiens	GTP cyclohydrolase 1
GCK	NM_010292	Mus musculus	glucokinase
GCK	NM_000162	Homo sapiens	glucokinase (hexokinase 4)
GCK	NM_033508	Homo sapiens	glucokinase (hexokinase 4)
GCK	NM_033507	Homo sapiens	glucokinase (hexokinase 4)
GLP1R	NM_021332	Mus musculus	glucagon-like peptide 1 receptor; similar to glucagon-like peptide-1 receptor
GLP1R	XM_001471951	Mus musculus	glucagon-like peptide 1 receptor; similar to glucagon-like peptide-1 receptor
GLP1R	NM_002062	Homo sapiens	glucagon-like peptide 1 receptor
GRN	NM_002087	Homo sapiens	granulin
GRN	NM_008175	Mus musculus	granulin
HAMP	NM_021175	Homo sapiens	hepcidin antimicrobial peptide
HAMP	NM_032541	Mus musculus	hepcidin antimicrobial peptide
HBA2	NM_000517	Homo sapiens	hemoglobin, alpha 2; hemoglobin, alpha 1
HBA2	NM_000558	Homo sapiens	hemoglobin, alpha 2; hemoglobin, alpha 1
HBB	NM_000518	Homo sapiens	hemoglobin, beta
HBB	XM_921413	Mus musculus	hemoglobin beta chain complex
HBB	XM_903245	Mus musculus	hemoglobin beta chain complex
HBB	XM_921395	Mus musculus	hemoglobin beta chain complex
HBB	XM_903244	Mus musculus	hemoglobin beta chain complex
HBB	XM_903246	Mus musculus	hemoglobin beta chain complex
HBB	XM_909723	Mus musculus	hemoglobin beta chain complex

GENE SYMBOL	MRNA	SPECIES	GENE NAME
HBB	XM_921422	Mus musculus	hemoglobin beta chain complex
HBB	XM_489729	Mus musculus	hemoglobin beta chain complex
HBB	XM_903242	Mus musculus	hemoglobin beta chain complex
HBB	XM_903243	Mus musculus	hemoglobin beta chain complex
HBB	XM_921400	Mus musculus	hemoglobin beta chain complex
HBD	NM_000519	Homo sapiens	hemoglobin, delta
HBE1	NM_005330	Homo sapiens	hemoglobin, epsilon 1
HBG1	NM_000559	Homo sapiens	hemoglobin, gamma A
HBG2	NM_000184	Homo sapiens	hemoglobin, gamma G
HPRT1	NM_000194	Homo sapiens	hypoxanthine phosphoribosyltransferase 1
IDO1	NM_008324	Mus musculus	indoleamine 2,3-dioxygenase 1
IDO1	NM_002164	Homo sapiens	indoleamine 2,3-dioxygenase 1
IGF1	NM_001111284	Homo sapiens	insulin-like growth factor 1 (somatomedin C)
IGF1	NM_001111285	Homo sapiens	insulin-like growth factor 1 (somatomedin C)
IGF1	NM_001111283	Homo sapiens	insulin-like growth factor 1 (somatomedin C)
IGF1	NM_000618	Homo sapiens	insulin-like growth factor 1 (somatomedin C)
IGF1	NM_001111274	Mus musculus	insulin-like growth factor 1
IGF1	NM_010512	Mus musculus	insulin-like growth factor 1
IGF1	NM_184052	Mus musculus	insulin-like growth factor 1
IGF1	NM_001111276	Mus musculus	insulin-like growth factor 1
IGF1	NM_001111275	Mus musculus	insulin-like growth factor 1
IL10	NM_000572	Homo sapiens	interleukin 10
IL10	NM_010548	Mus musculus	interleukin 10

GENE SYMBOL	MRNA	SPECIES	GENE NAME
IL6	NM_031168	Mus musculus	interleukin 6
IL6	NM_000600	Homo sapiens	interleukin 6 (interferon, beta 2)
KCNMA1	NM_002247	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNMA1	NM_001161352	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNMA1	NM_001014797	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNMA1	NM_001161353	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNMA1	NM_010610	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, alpha member 1
KCNMB1	NM_031169	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, beta member 1
KCNMB1	NM_004137	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, beta member 1
KCNMB2	NM_028231	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, beta member 2
KCNMB2	NM_005832	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, beta member 2
KCNMB2	NM_181361	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, beta member 2
KCNMB3	NM_171829	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M beta member 3
KCNMB3	NM_171828	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M beta member 3
KCNMB3	NM_001163677	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M beta member 3
KCNMB3	NM_014407	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M beta member 3

GENE SYMBOL	MRNA	SPECIES	GENE NAME
KCNMB3	NM_171830	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M beta member 3
KCNMB3	XM_001475546	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, beta member 3
KCNMB3	XM_912348	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, beta member 3
KCNMB4	NM_021452	Mus musculus	potassium large conductance calcium-activated channel, subfamily M, beta member 4
KCNMB4	NM_014505	Homo sapiens	potassium large conductance calcium-activated channel, subfamily M, beta member 4
KLF1	NM_010635	Mus musculus	Kruppel-like factor 1 (erythroid)
KLF1	NM_006563	Homo sapiens	Kruppel-like factor 1 (erythroid)
KLF4	NM_010637	Mus musculus	Kruppel-like factor 4 (gut)
KLF4	NM_004235	Homo sapiens	Kruppel-like factor 4 (gut)
LAMA1	NM_005559.3	Homo sapiens	laminin, alpha 1
LAMA1	NM_008480.2	Mus musculus	laminin, alpha 1
LDLR	NM_000527	Homo sapiens	low density lipoprotein receptor
LDLR	NM_010700	Mus musculus	low density lipoprotein receptor
MBNL1	NM_021038.3, NM_020007.3, NM_207293.1, NM_207294.1, NM_207295.1, NM_207296.1, NM_207297.1	Homo sapiens	muscleblind-like splicing regulator 1
MBNL1	NM_001253708.1, NM_001253709.1, NM_001253710.1, NM_001253711.1, NM_001253713.1, NM_020007.3	Mus musculus	muscleblind-like 1 (Drosophila)
MECP2	NM_010788	Mus musculus	methyl CpG binding protein 2

GENE SYMBOL	MRNA	SPECIES	GENE NAME
MECP2	NM_001081979	Mus musculus	methyl CpG binding protein 2
MECP2	NM_001110792	Homo sapiens	methyl CpG binding protein 2 (Rett syndrome)
MECP2	NM_004992	Homo sapiens	methyl CpG binding protein 2 (Rett syndrome)
MERTK	NM_006343.2	Homo sapiens	MER proto-oncogene, tyrosine kinase
MERTK	NM_008587.1	Mus musculus	c-mer proto-oncogene tyrosine kinase
MSX2	NM_013601	Mus musculus	similar to homeobox protein; homeobox, msh-like 2
MSX2	XM_001475886	Mus musculus	similar to homeobox protein; homeobox, msh-like 2
MSX2	NM_002449	Homo sapiens	msh homeobox 2
MYBPC3	NM_008653	Mus musculus	myosin binding protein C, cardiac
MYBPC3	NM_000256	Homo sapiens	myosin binding protein C, cardiac
NANOG	NM_024865	Homo sapiens	Nanog homeobox pseudogene 8; Nanog homeobox
NANOG	XM_001471588	Mus musculus	similar to Nanog homeobox; Nanog homeobox
NANOG	NM_028016	Mus musculus	similar to Nanog homeobox; Nanog homeobox
NANOG	NM_001080945	Mus musculus	similar to Nanog homeobox; Nanog homeobox
NF1	NM_000267	Homo sapiens	neurofibromin 1
NF1	NM_001042492	Homo sapiens	neurofibromin 1
NF1	NM_001128147	Homo sapiens	neurofibromin 1
NF1	NM_010897	Mus musculus	neurofibromatosis 1
NKX2-1	NM_001079668	Homo sapiens	NK2 homeobox 1
NKX2-1	NM_003317	Homo sapiens	NK2 homeobox 1
NKX2-1	XM_002344771	Homo sapiens	NK2 homeobox 1
NKX2-1	NM_009385	Mus musculus	NK2 homeobox 1
NKX2-1	NM_001146198	Mus musculus	NK2 homeobox 1

GENE SYMBOL	MRNA	SPECIES	GENE NAME
PAH	NM_008777	Mus musculus	phenylalanine hydroxylase
PAH	NM_000277	Homo sapiens	phenylalanine hydroxylase
PTEN	NM_000314	Homo sapiens	phosphatase and tensin homolog; phosphatase and tensin homolog pseudogene 1
PTEN	NM_177096	Mus musculus	phosphatase and tensin homolog
PTEN	NM_008960	Mus musculus	phosphatase and tensin homolog
PTGS2	NM_011198	Mus musculus	prostaglandin-endoperoxide synthase 2
PTGS2	NM_000963	Homo sapiens	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)
RB1	NM_009029	Mus musculus	retinoblastoma 1
RB1	NM_000321	Homo sapiens	retinoblastoma 1
RPS14	NM_020600	Mus musculus	predicted gene 6204; ribosomal protein S14
RPS14	NM_001025071	Homo sapiens	ribosomal protein S14
RPS14	NM_005617	Homo sapiens	ribosomal protein S14
RPS14	NM_001025070	Homo sapiens	ribosomal protein S14
RPS19	XM_204069	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_991053	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_905004	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072

GENE SYMBOL	MRNA	SPECIES	GENE NAME
RPS19	XM_001005575	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	NM_023133	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_994263	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_001481027	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_913504	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_001479631	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_902221	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19; predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	XM_893968	Mus musculus	predicted gene 4327; predicted gene 8683; similar to 40S ribosomal protein S19; predicted gene 4510; predicted gene 13143; predicted gene 9646; ribosomal protein S19;

GENE SYMBOL	MRNA	SPECIES	GENE NAME
			predicted gene 9091; predicted gene 6636; predicted gene 14072
RPS19	NM_001022	Homo sapiens	ribosomal protein S19 pseudogene 3; ribosomal protein S19
SCARB1	NM_016741	Mus musculus	scavenger receptor class B, member 1
SCARB1	NM_001082959	Homo sapiens	scavenger receptor class B, member 1
SCARB1	NM_005505	Homo sapiens	scavenger receptor class B, member 1
SERPINF1	NM_011340	Mus musculus	serine (or cysteine) peptidase inhibitor, clade F, member 1
SERPINF1	NM_002615	Homo sapiens	serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 1
SIRT1	NM_001159590	Mus musculus	sirtuin 1 (silent mating type information regulation 2, homolog) 1 (S. cerevisiae)
SIRT1	NM_019812	Mus musculus	sirtuin 1 (silent mating type information regulation 2, homolog) 1 (S. cerevisiae)
SIRT1	NM_001159589	Mus musculus	sirtuin 1 (silent mating type information regulation 2, homolog) 1 (S. cerevisiae)
SIRT1	NM_012238	Homo sapiens	sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae)
SIRT1	NM_001142498	Homo sapiens	sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae)
SIRT6	NM_016539	Homo sapiens	sirtuin (silent mating type information regulation 2 homolog) 6 (S. cerevisiae)
SIRT6	NM_001163430	Mus musculus	sirtuin 6 (silent mating type information regulation 2, homolog) 6 (S. cerevisiae)
SIRT6	NM_181586	Mus musculus	sirtuin 6 (silent mating type information regulation 2, homolog) 6 (S. cerevisiae)
SMAD7	NM_005904	Homo sapiens	SMAD family member 7
SMAD7	NM_001042660	Mus musculus	MAD homolog 7 (Drosophila)
SMN1	NM_000344.3	Homo sapiens	Survival Motor Neuron 1
SMN1	NM_022874.2	Homo sapiens	Survival Motor Neuron 1
SMN2	NM_017411.3 NM_022875.2 NM_022876.2 NM_022877.2	Homo sapiens	Survival Motor Neuron 2
SSPN	NM_001135823.1, NM_005086.4	Homo sapiens	sarcospan

GENE SYMBOL	MRNA	SPECIES	GENE NAME
SSPN	NM_010656.2	Homo sapiens	sarcospan
ST7	NM_021908	Homo sapiens	suppression of tumorigenicity 7
ST7	NM_018412	Homo sapiens	suppression of tumorigenicity 7
STAT3	NM_213660	Mus musculus	similar to Stat3B; signal transducer and activator of transcription 3
STAT3	XM_001474017	Mus musculus	similar to Stat3B; signal transducer and activator of transcription 3
STAT3	NM_213659	Mus musculus	similar to Stat3B; signal transducer and activator of transcription 3
STAT3	NM_011486	Mus musculus	similar to Stat3B; signal transducer and activator of transcription 3
STAT3	NM_213662	Homo sapiens	signal transducer and activator of transcription 3 (acute-phase response factor)
STAT3	NM_003150	Homo sapiens	signal transducer and activator of transcription 3 (acute-phase response factor)
STAT3	NM_139276	Homo sapiens	signal transducer and activator of transcription 3 (acute-phase response factor)
UTRN	NM_007124	Homo sapiens	utrophin
UTRN	NM_011682	Mus musculus	utrophin
NFE2L2	NM_001145412.2, NM_001145413.2, NM_006164.4	Homo sapiens	nuclear factor, erythroid 2-like 2
NFE2L2	NM_010902.3	Mus musculus	nuclear factor, erythroid 2-like 2
ACTB	NM_001101.3	Homo sapiens	actin, beta
ACTB	NM_007393.3	Mus musculus	actin, beta
ANRIL	NR_003529.3, NR_047532.1, NR_047533.1, NR_047534.1, NR_047535.1, NR_047536.1, NR_047538.1, NR_047539.1, NR_047540.1, NR_047541.1, NR_047542.1, NR_047543.1	Homo sapiens	CDKN2B antisense RNA 1 (also called CDKN2B)

GENE SYMBOL	MRNA	SPECIES	GENE NAME
HOTAIR	NR_003716.3, NR_047517.1, NR_047518.1	Homo sapiens	HOX transcript antisense RNA
HOTAIR	NR_047528.1	Mus musculus	HOX transcript antisense RNA
DINO	JX993265	Homo sapiens	Damage Induced NOncoding
DINO	JX993266	Mus musculus	Damage Induced NOncoding
HOTTIP	NR_037843.3	Homo sapiens	HOXA distal transcript antisense RNA
HOTTIP	NR_110441.1, NR_110442.1	Mus musculus	Hoxa distal transcript antisense RNA
NEST	NR_104124.1	Homo sapiens	Homo sapiens IFNG antisense RNA 1 (IFNG-AS1), transcript variant 1, long non-coding RNA.
NEST	NR_104123.1	Mus musculus	Theiler's murine encephalomyelitis virus persistence candidate gene 1

Oligonucleotides

Oligonucleotides provided herein are useful for stabilizing RNAs by inhibiting or preventing degradation of the RNAs (e.g., degradation mediated by exonucleases). Such oligonucleotides may be referred to as "stabilizing oligonucleotides". In some embodiments, oligonucleotides hybridize at a 5' and/or 3' region of the RNA resulting in duplex regions that stabilize the RNA by preventing degradation by exonucleotides having single strand processing activity.

In some embodiments, oligonucleotides are provided having a region complementary with at least 5 consecutive nucleotides of a 5' region of an RNA transcript. In some embodiments, oligonucleotides are provided having a region complementary with at least 5 consecutive nucleotides of a 3'-region of an RNA transcript. In some embodiments, oligonucleotides are provided having a first region complementary with at least 5 consecutive nucleotides of a 5' region of an RNA transcript, and a second region complementary with at least 5 consecutive nucleotides of a 3'-region of an RNA transcript.

In some embodiments, oligonucleotides are provided having a region complementary with at least 5 consecutive nucleotides of the 5'-UTR of an mRNA transcript. In some embodiments, oligonucleotides are provided having a region complementary with at least 5 consecutive nucleotides of the 3'-UTR, poly(A) tail, or overlapping the polyadenylation junction of the mRNA transcript. In some embodiments, oligonucleotides are provided having a first region complementary with at least 5 consecutive nucleotides of the 5'-UTR of an mRNA transcript, and a second region complementary with at least 5 consecutive nucleotides of the 3'-UTR, poly(A) tail, or overlapping the polyadenylation junction of the mRNA transcript.

In some embodiments, oligonucleotides are provided that have a region of complementarity that is complementary to an RNA transcript in proximity to the 5'-end of the RNA transcript. In such embodiments, the nucleotide at the 3'-end of the region of complementarity of the oligonucleotides may be complementary with the RNA transcript at a position that is within 10 nucleotides, within 20 nucleotides, within 30 nucleotides, within 40 nucleotides, within 50 nucleotides, or within 100 nucleotides, within 200 nucleotides, within 300 nucleotides, within 400 nucleotides or more of the transcription start site of the RNA transcript.

In some embodiments, oligonucleotides are provided that have a region of complementarity that is complementary to an RNA transcript in proximity to the 3'-end of the RNA transcript. In such embodiments, the nucleotide at the 3'-end and/or 5' end of the region of complementarity may be complementary with the RNA transcript at a position that is within 10 nucleotides, within 20 nucleotides, within 30 nucleotides, within 40 nucleotides, within 50 nucleotides, within 100 nucleotides, within 200 nucleotides, within 300 nucleotides, within 400 nucleotides or more of the 3'-end of the RNA transcript. In some embodiments, if the target RNA transcript is polyadenylated, the nucleotide at the 3'-end of the region of complementarity of the oligonucleotide may be complementary with the RNA transcript at a position that is within 10 nucleotides, within 20 nucleotides, within 30 nucleotides, within 40 nucleotides, within 50 nucleotides, within 100 nucleotides, within 200 nucleotides, within 300 nucleotides, within 400 nucleotides or more of polyadenylation junction. In some embodiments, an oligonucleotide that targets a 3' region of an RNA

comprises a region of complementarity that is a stretch of pyrimidines (e.g., 4 to 10 or 5 to 15 thymine nucleotides) complementary with adenines.

In some embodiments, combinations of 5' targeting and 3' targeting oligonucleotides are contacted with a target RNA. In some embodiments, the 5' targeting and 3' targeting oligonucleotides a linked together via a linker (e.g., a stretch of nucleotides non-complementary with the target RNA). In some embodiments, the region of complementarity of the 5' targeting oligonucleotide is complementary to a region in the target RNA that is at least 2, 5, 10, 20, 50, 100, 500, 1000, 5000, 10000 nucleotides upstream from the region of the target RNA that is complementary to the region of complementarity of the 3' end targeting oligonucleotide.

In some embodiments, oligonucleotides are provided that have the general formula 5'-X_1-X_2-3', in which X_1 has a region of complementarity that is complementary with an RNA transcript (*e.g.*, with at least 5 contiguous nucleotides of the RNA transcript). In some embodiments, the nucleotide at the 3'-end of the region of complementary of X_1 may be complementary with a nucleotide in proximity to the transcription start site of the RNA transcript. In some embodiments, the nucleotide at the 3'-end of the region of complementary of X_1 may be complementary with a nucleotide that is present within 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides of the transcription start site of the RNA transcript. In some embodiments, the nucleotide at the 3'-end of the region of complementary of X_1 may be complementary with the nucleotide at the transcription start site of the RNA transcript.

In some embodiments, X_1 comprises 5 to 10 nucleotides, 5 to 15 nucleotides, 5 to 25 nucleotides, 10 to 25 nucleotides, 5 to 20 nucleotides, or 15 to 30 nucleotides. In some embodiments, X_1 comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more nucleotides. In some embodiments, the region of complementarity of X_1 may be complementary with at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 contiguous nucleotides of the RNA transcript. In some embodiments, the region of complementarity of X_1 may be complementary with 4, 5, 6, 7, 8, 9, 10, 11,12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous nucleotides of the RNA transcript.

In some embodiments, X_2 is absent. In some embodiments, X_2 comprises 1 to 10, 1 to 20 nucleotides, 1 to 25 nucleotides, 5 to 20 nucleotides, 5 to 30 nucleotides, 5 to 40 nucleotides, or 5 to 50 nucleotides. In some embodiments, X_2 comprises 5, 6, 7, 8, 9, 10, 11, 12. 13. 14. 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50 or more nucleotides. In some

embodiments, X_2 comprises a region of complementarity complementary with at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 contiguous nucleotides of the RNA transcript. In some embodiments, X_2 comprises a region of complementarity complementary with 4, 5, 6, 7, 8, 9, 10, 11,12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous nucleotides of the RNA transcript.

In some embodiments, the RNA transcript has a 7-methylguanosine cap at its 5'-end. In some embodiments, the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide of the RNA transcript that is immediately internal to the 7-methylguanosine cap or in proximity to the cap (*e.g.*, with 10 nucleotides of the cap). In some embodiments, at least the first nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine (*e.g.*, a cytosine or analogue thereof). In some embodiments, the first and second nucleotides at the 5'-end of X_2 are pyrimidines complementary with guanine. Thus, in some embodiments, at least one nucleotide at the 5'-end of X_2 is a pyrimidine that may form stabilizing hydrogen bonds with the 7-methylguanosine of the cap.

In some embodiments, X_2 forms a stem-loop structure. In some embodiments, X_2 comprises the formula 5'-Y_1-Y_2-Y_3-3', in which X_2 forms a stem-loop structure having a loop region comprising the nucleotides of Y_2 and a stem region comprising at least two contiguous nucleotides of Y_1 hybridized with at least two contiguous nucleotides of Y_3. In some embodiments, the stem region comprises 1-6, 1-5, 2-5, 1-4, 2-4 or 2-3 nucleotides. In some embodiments, the stem region comprises LNA nucleotides. In some embodiments, the stem region comprises 1-6, 1-5, 2-5, 1-4, 2-4 or 2-3 LNA nucleotides. In some embodiments, Y_1 and Y_3 independently comprise 2 to 10 nucleotides, 2 to 20 nucleotides, 2 to 25 nucleotides, or 5 to 20 nucleotides. In some embodiments, Y_1 and Y_3 independently comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25 or more nucleotides. In some embodiments, Y_2 comprises 3 to 10 nucleotides, 3 to 15 nucleotides, 3 to 25 nucleotides, or 5 to 20 nucleotides. In some embodiments, Y_2 comprises 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25 or more nucleotides. In some embodiments, Y_2 comprises 2-8, 2-7, 2-6, 2-5, 3-8, 3-7, 3-6, 3-5 or 3-4 nucleotides. In some embodiments, Y_2 comprises at least one DNA nucleotide. In some embodiments, the nucleotides of Y_2 comprise at least one (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25 or more adenines). In some embodiments, Y_3 comprises 1-5, 1-4, 1-3 or 1-2 nucleotides following the 3' end of

the stem region. In some embodiments, the nucleotides of Y_3 following the 3' end of the stem region are DNA nucleotides. In some embodiments, Y_3 comprises a pyrimidine complementary with guanine (e.g., cytosine or an analogue thereof). In some embodiments, Y_3 comprises one or more (*e.g.*, two) pyrimidines complementary with guanine at a position following the 3'-end of the stem region (*e.g.*, 1, 2, 3 or more nucleotide after the 3'-end of the stem region). Thus, in embodiments where the RNA transcript is capped, Y_3 may have a pyrimidine that forms stabilizing hydrogen bonds with the 7-methylguanosine of the cap.

In some embodiments, X_1 and X_2 are complementary with non-overlapping regions of the RNA transcript. In some embodiments, X_1 comprises a region complementary with a 5' region of the RNA transcript and X_2 comprises a region complementary with a 3' region of the RNA transcript. For example, if the RNA transcript is polyadenylated, X_2 may comprise a region of complementarity that is complementary with the RNA transcript at a region within 100 nucleotides, within 50 nucleotides, within 25 nucleotides or within 10 nucleotides of the polyadenylation junction of the RNA transcript. In some embodiments, X_2 comprises a region of complementarity that is complementary with the RNA transcript immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript. In some embodiments, X_2 comprises at least 2 consecutive pyrimidine nucleotides (e.g., 5 to 15 pyrimidine nucleotides) complementary with adenine nucleotides of the poly(A) tail of the RNA transcript.

In some embodiments, oligonucleotides are provided that comprise the general formula 5'-X_1-X_2-3', in which X_1 comprises at least 2 nucleotides that form base pairs with adenine (e.g., thymidines or uridines or analogues thereof); and X_2 comprises a region of complementarity that is complementary with at least 3 contiguous nucleotides of a poly-adenylated RNA transcript, wherein the nucleotide at the 5'-end of the region of complementary of X_2 is complementary with the nucleotide of the RNA transcript that is immediately internal to the poly-adenylation junction of the RNA transcript. In such embodiments, X_1 may comprises 2 to 10, 2 to 20, 5 to 15 or 5 to 25 nucleotides and X_2 may independently comprises 2 to 10, 2 to 20, 5 to 15 or 5 to 25 nucleotides.

In some embodiments, compositions are provided that comprise a first oligonucleotide comprising at least 5 nucleotides (*e.g.*, of 5 to 25 nucleotides) linked through internucleoside linkages, and a second oligonucleotide comprising at least 5 nucleotides (*e.g.*,

of 5 to 25 nucleotides) linked through internucleoside linkages, in which the the first oligonucleotide is complementary with at least 5 consecutive nucleotides in proximity to the 5'-end of an RNA transcript and the second oligonucleotide is complementary with at least 5 consecutive nucleotides in proximity to the 3'-end of an RNA transcript. In some embodiments, the 5' end of the first oligonucleotide is linked with the 3' end of the second oligonucleotide. In some embodiments, the 3' end of the first oligonucleotide is linked with the 5' end of the second oligonucleotide. In some embodiments, the 5' end of the first oligonucleotide is linked with the 5' end of the second oligonucleotide. In some embodiments, the 3' end of the first oligonucleotide is linked with the 3' end of the second oligonucleotide.

In some embodiments, the first oligonucleotide and second oligonucleotide are joined by a linker. The term "linker" generally refers to a chemical moiety that is capable of covalently linking two or more oligonucleotides. In some embodiments, a linker is resistant to cleavage in certain biological contexts, such as in a mammalian cell extract, such as an endosomal extract. However, in some embodiments, at least one bond comprised or contained within the linker is capable of being cleaved (e.g., in a biological context, such as in a mammalian extract, such as an endosomal extract), such that at least two oligonucleotides are no longer covalently linked to one another after bond cleavage. In some embodiments, the linker is not an oligonucleotide having a sequence complementary with the RNA transcript. In some embodiments, the linker is an oligonucleotide (*e.g.*, 2-8 thymines). In some embodiments, the linker is a polypeptide. Other appropriate linkers may also be used, including, for example, linkers disclosed in International Patent Application Publication WO 2013/040429 A1, published on March 21, 2013, and entitled MULTIMERIC ANTISENSE OLIGONUCLEOTIDES. The contents of this publication relating to linkers are incorporated herein by reference in their entirety.

An oligonucleotide may have a region of complementarity with a target RNA transcript (e.g., a mammalin mRNA transcript) that has less than a threshold level of complementarity with every sequence of nucleotides, of equivalent length, of an off-target RNA transcript. For example, an oligonucleotide may be designed to ensure that it does not have a sequence that targets RNA transcripts in a cell other than the target RNA transcript.

The threshold level of sequence identity may be 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99% or 100% sequence identity.

An oligonucleotide may be complementary to RNA transcripts encoded by homologues of a gene across different species (*e.g.*, a mouse, rat, rabbit, goat, monkey, *etc.*) In some embodiments, oligonucleotides having these characteristics may be tested *in vivo* or *in vitro* for efficacy in multiple species (*e.g.*, human and mouse). This approach also facilitates development of clinical candidates for treating human disease by selecting a species in which an appropriate animal exists for the disease.

In some embodiments, the region of complementarity of an oligonucleotide is complementary with at least 8 to 15, 8 to 30, 8 to 40, or 10 to 50, or 5 to 50, or 5 to 40 bases, *e.g.*, 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 consecutive nucleotides of a target RNA. In some embodiments, the region of complementarity is complementary with at least 8 consecutive nucleotides of a target RNA.

Complementary, as the term is used in the art, refers to the capacity for precise pairing between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at a corresponding position of a target RNA, then the nucleotide of the oligonucleotide and the nucleotide of the target RNA are complementary to each other at that position. The oligonucleotide and target RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides that can hydrogen bond with each other through their bases. Thus, "complementary" is a term which is used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and target RNA. For example, if a base at one position of an oligonucleotide is capable of hydrogen bonding with a base at the corresponding position of a target RNA, then the bases are considered to be complementary to each other at that position. 100% complementarity is not required.

An oligonucleotide may be at least 80% complementary to (optionally one of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% complementary to) the consecutive nucleotides of a target RNA. In some embodiments an oligonucleotide may contain 1, 2 or 3 base mismatches compared to the portion of the consecutive nucleotides of

the target RNA. In some embodiments an oligonucleotide may have up to 3 mismatches over 15 bases, or up to 2 mismatches over 10 bases.

In some embodiments, a complementary nucleic acid sequence need not be 100% complementary to that of its target to be specifically hybridizable. In some embodiments, an oligonucleotide for purposes of the present disclosure is specifically hybridizable with a target RNA when hybridization of the oligonucleotide to the target RNA prevents or inhibits degradation of the target RNA, and when there is a sufficient degree of complementarity to avoid non-specific binding of the sequence to non-target sequences under conditions in which avoidance of non-specific binding is desired, *e.g.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the assays are performed under suitable conditions of stringency.

In some embodiments, an oligonucleotide is 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 60, 70, 80 or more nucleotides in length. In some embodiments, the oligonucleotide is 8 to 50, 10 to 30, 9 to 20, 15 to 30 or 8 to 80 nucleotides in length.

Base pairings may include both canonical Watson-Crick base pairing and non-Watson-Crick base pairing (*e.g.*, Wobble base pairing and Hoogsteen base pairing). It is understood that for complementary base pairings, adenosine-type bases (A) are complementary to thymidine-type bases (T) or uracil-type bases (U), that cytosine-type bases (C) are complementary to guanosine-type bases (G), and that universal bases such as 3-nitropyrrole or 5-nitroindole can hybridize to and are considered complementary to any A, C, U, or T. Inosine (I) has also been considered in the art to be a universal base and is considered complementary to any A, C, U or T.

In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) or uridine (U) nucleotides (or a modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be replaced with any other nucleotide suitable for base pairing (e.g., via a Watson-Crick base pair) with an adenosine nucleotide. In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) or uridine (U) nucleotides (or a modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a different pyrimidine nucleotide or vice versa. In some embodiments, any one or more thymidine (T) nucleotides (or modified

nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a uridine (U) nucleotide (or a modified nucleotide thereof) or vice versa.

In some embodiments, an oligonucleotide may have a sequence that does not contain guanosine nucleotide stretches (*e.g.*, 3 or more, 4 or more, 5 or more, 6 or more consecutive guanosine nucleotides). In some embodiments, oligonucleotides having guanosine nucleotide stretches have increased non-specific binding and/or off-target effects, compared with oligonucleotides that do not have guanosine nucleotide stretches. Contiguous runs of three or more Gs or Cs may not be preferable in some embodiments. Accordingly, in some embodiments, the oligonucleotide does not comprise a stretch of three or more guanosine nucleotides.

An oligonucleotide may have a sequence that is has greater than 30% G-C content, greater than 40% G-C content, greater than 50% G-C content, greater than 60% G-C content, greater than 70% G-C content, or greater than 80% G-C content. An oligonucleotide may have a sequence that has up to 100% G-C content, up to 95% G-C content, up to 90% G-C content, or up to 80% G-C content. In some embodiments, GC content of an oligonucleotide is preferably between about 30-60 %.

It is to be understood that any oligonucleotide provided herein can be excluded.

In some embodiments, it has been found that oligonucleotides disclosed herein may increase stability of a target RNA by at least about 50% (i.e. 150% of normal or 1.5 fold), or by about 2 fold to about 5 fold. In some embodiments, stability (e.g., stability in a cell) may be increased by at least about 15 fold, 20 fold, 30 fold, 40 fold, 50 fold or 100 fold, or any range between any of the foregoing numbers. In some embodiments, increased mRNA stability has been shown to correlate to increased protein expression. Similarly, in some embodiments, increased stability of non-coding positively correlates with increased activity of the RNA.

It is understood that any reference to uses of oligonucleotides or other molecules throughout the description contemplates use of the oligonucleotides or other molecules in preparation of a pharmaceutical composition or medicament for use in the treatment of condition or a disease associated with decreased levels or activity of a RNA transcript. Thus, as one nonlimiting example, this aspect of the invention includes use of oligonucleotides or other molecules in the preparation of a medicament for use in the treatment of disease,

wherein the treatment involves posttranscriptionally altering protein and/or RNA levels in a targeted manner.

Oligonucleotide Modifications

In some embodiments, oligonucleotides are provided with chemistries suitable for delivery, hybridization and stability within cells to target and stabilize RNA transcripts. Furthermore, in some embodiments, oligonucleotide chemistries are provided that are useful for controlling the pharmacokinetics, biodistribution, bioavailability and/or efficacy of the oligonucleotides. Accordingly, oligonucleotides described herein may be modified, *e.g.*, comprise a modified sugar moiety, a modified internucleoside linkage, a modified nucleotide and/or combinations thereof. In addition, the oligonucleotides may exhibit one or more of the following properties: do not induce substantial cleavage or degradation of the target RNA; do not cause substantially complete cleavage or degradation of the target RNA; do not activate the RNAse H pathway; do not activate RISC; do not recruit any Argonaute family protein; are not cleaved by Dicer; do not mediate alternative splicing; are not immune stimulatory; are nuclease resistant; have improved cell uptake compared to unmodified oligonucleotides; are not toxic to cells or mammals; and may have improved endosomal exit.

Oligonucleotides that are designed to interact with RNA to modulate gene expression are a distinct subset of base sequences from those that are designed to bind a DNA target (*e.g.*, are complementary to the underlying genomic DNA sequence from which the RNA is transcribed).

Any of the oligonucleotides disclosed herein may be linked to one or more other oligonucleotides disclosed herein by a linker, *e.g.*, a cleavable linker.

Oligonucleotides of the invention can be stabilized against nucleolytic degradation such as by the incorporation of a modification, *e.g.*, a nucleotide modification. For example, nucleic acid sequences of the invention include a phosphorothioate at least the first, second, or third internucleotide linkage at the 5' or 3' end of the nucleotide sequence. As another example, the nucleic acid sequence can include a 2'-modified nucleotide, *e.g.*, a 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O--N-methylacetamido (2'-O--NMA). As another example, the nucleic acid sequence can include at least one 2'-O-methyl-modified

nucleotide, and in some embodiments, all of the nucleotides include a 2'-O-methyl modification. In some embodiments, the nucleic acids are "locked," i.e., comprise nucleic acid analogues in which the ribose ring is "locked" by a methylene bridge connecting the 2'-O atom and the 4'-C atom.

Any of the modified chemistries or formats of oligonucleotides described herein can be combined with each other, and that one, two, three, four, five, or more different types of modifications can be included within the same molecule.

In some embodiments, the oligonucleotide may comprise at least one ribonucleotide, at least one deoxyribonucleotide, and/or at least one bridged nucleotide. In some embodiments, the oligonucleotide may comprise a bridged nucleotide, such as a locked nucleic acid (LNA) nucleotide, a constrained ethyl (cEt) nucleotide, or an ethylene bridged nucleic acid (ENA) nucleotide. Examples of such nucleotides are disclosed herein and known in the art. In some embodiments, the oligonucleotide comprises a nucleotide analog disclosed in one of the following United States Patent or Patent Application Publications: US 7,399,845, US 7,741,457, US 8,022,193, US 7,569,686, US 7,335,765, US 7,314,923, US 7,335,765, and US 7,816,333, US 20110009471, the entire contents of each of which are incorporated herein by reference for all purposes. The oligonucleotide may have one or more 2' O-methyl nucleotides. The oligonucleotide may consist entirely of 2' O-methyl nucleotides.

Often an oligonucleotide has one or more nucleotide analogues. For example, an oligonucleotide may have at least one nucleotide analogue that results in an increase in T_m of the oligonucleotide in a range of 1°C, 2 °C, 3°C, 4 °C, or 5°C compared with an oligonucleotide that does not have the at least one nucleotide analogue. An oligonucleotide may have a plurality of nucleotide analogues that results in a total increase in T_m of the oligonucleotide in a range of 2 °C, 3 °C, 4 °C, 5 °C, 6 °C, 7 °C, 8 °C, 9 °C, 10 °C, 15 °C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C or more compared with an oligonucleotide that does not have the nucleotide analogue.

The oligonucleotide may be of up to 50 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30, 2 to 40, 2 to 45, or more nucleotides of the oligonucleotide are nucleotide analogues. The oligonucleotide may be of 8 to 30 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30 nucleotides of the oligonucleotide are nucleotide analogues.

The oligonucleotide may be of 8 to 15 nucleotides in length in which 2 to 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11, 2 to 12, 2 to 13, 2 to 14 nucleotides of the oligonucleotide are nucleotide analogues. Optionally, the oligonucleotides may have every nucleotide except 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides modified.

The oligonucleotide may consist entirely of bridged nucleotides (*e.g.*, LNA nucleotides, cEt nucleotides, ENA nucleotides). The oligonucleotide may comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and 2'-O-methyl nucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and ENA nucleotide analogues. The oligonucleotide may comprise alternating deoxyribonucleotides and LNA nucleotides. The oligonucleotide may comprise alternating LNA nucleotides and 2'-O-methyl nucleotides. The oligonucleotide may have a 5' nucleotide that is a bridged nucleotide (*e.g.*, a LNA nucleotide, cEt nucleotide, ENA nucleotide). The oligonucleotide may have a 5' nucleotide that is a deoxyribonucleotide.

The oligonucleotide may comprise deoxyribonucleotides flanked by at least one bridged nucleotide (*e.g.*, a LNA nucleotide, cEt nucleotide, ENA nucleotide) on each of the 5' and 3' ends of the deoxyribonucleotides. The oligonucleotide may comprise deoxyribonucleotides flanked by 1, 2, 3, 4, 5, 6, 7, 8 or more bridged nucleotides (*e.g.*, LNA nucleotides, cEt nucleotides, ENA nucleotides) on each of the 5' and 3' ends of the deoxyribonucleotides. The 3' position of the oligonucleotide may have a 3' hydroxyl group. The 3' position of the oligonucleotide may have a 3' thiophosphate.

The oligonucleotide may be conjugated with a label. For example, the oligonucleotide may be conjugated with a biotin moiety, cholesterol, Vitamin A, folate, sigma receptor ligands, aptamers, peptides, such as CPP, hydrophobic molecules, such as lipids, ligands of the asialoglycoprotein receptor (ASGPR), such as GalNac, or dynamic polyconjugates and variants thereof at its 5' or 3' end.

Preferably an oligonucleotide comprises one or more modifications comprising: a modified sugar moiety, and/or a modified internucleoside linkage, and/or a modified nucleotide and/or combinations thereof. It is not necessary for all positions in a given oligonucleotide to be uniformly modified, and in fact more than one of the modifications described herein may be incorporated in a single oligonucleotide or even at within a single nucleoside within an oligonucleotide.

In some embodiments, the oligonucleotides are chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the target) and a region that is a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. Chimeric oligonucleotides of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures comprise, but are not limited to, US patent nos. 5,013,830; 5,149,797; 5, 220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference.

In some embodiments, an oligonucleotide comprises at least one nucleotide modified at the 2' position of the sugar, most preferably a 2'-O-alkyl, 2'-O-alkyl-O-alkyl or 2'-fluoro-modified nucleotide. In other preferred embodiments, RNA modifications include 2'-fluoro, 2'-amino and 2' O-methyl modifications on the ribose of pyrimidines, abasic residues or an inverted base at the 3' end of the RNA. Such modifications are routinely incorporated into oligonucleotides and these oligonucleotides have been shown to have a higher Tm (i.e., higher target binding affinity) than 2'-deoxyoligonucleotides against a given target.

A number of nucleotide and nucleoside modifications have been shown to make the oligonucleotide into which they are incorporated more resistant to nuclease digestion than the native oligodeoxynucleotide; these modified oligos survive intact for a longer time than unmodified oligonucleotides. Specific examples of modified oligonucleotides include those comprising modified backbones, for example, phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. In some embodiments, oligonucleotides may have phosphorothioate backbones; heteroatom backbones, such as methylene(methylimino) or MMI backbones; amide backbones (see De Mesmaeker et al. Ace. Chem. Res. 1995, 28:366-374); morpholino backbones (see Summerton and Weller, U.S. Pat. No. 5,034,506); or peptide nucleic acid (PNA) backbones (wherein the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the nucleotides being bound directly

or indirectly to the aza nitrogen atoms of the polyamide backbone, see Nielsen et al., Science 1991, 254, 1497). Phosphorus-containing linkages include, but are not limited to, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates comprising 3'alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates comprising 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'; see US patent nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5, 177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455, 233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563, 253; 5,571,799; 5,587,361; and 5,625,050.

Morpholino-based oligomeric compounds are described in Dwaine A. Braasch and David R. Corey, Biochemistry, 2002, 41(14), 4503-4510); Genesis, volume 30, issue 3, 2001; Heasman, J., Dev. Biol., 2002, 243, 209-214; Nasevicius et al., Nat. Genet., 2000, 26, 216-220; Lacerra et al., Proc. Natl. Acad. Sci., 2000, 97, 9591-9596; and U.S. Pat. No. 5,034,506, issued Jul. 23, 1991. In some embodiments, the morpholino-based oligomeric compound is a phosphorodiamidate morpholino oligomer (PMO) (*e.g.*, as described in Iverson, Curr. Opin. Mol. Ther., 3:235-238, 2001; and Wang et al., J. Gene Med., 12:354-364, 2010; the disclosures of which are incorporated herein by reference in their entireties).

Cyclohexenyl nucleic acid oligonucleotide mimetics are described in Wang et al., J. Am. Chem. Soc., 2000, 122, 8595-8602.

Modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These comprise those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S

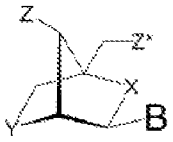
and CH2 component parts; see US patent nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264, 562; 5, 264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596, 086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623, 070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

Modified oligonucleotides are also known that include oligonucleotides that are based on or constructed from arabinonucleotide or modified arabinonucleotide residues. Arabinonucleosides are stereoisomers of ribonucleosides, differing only in the configuration at the 2'-position of the sugar ring. In some embodiments, a 2'-arabino modification is 2'-F arabino. In some embodiments, the modified oligonucleotide is 2'-fluoro-D-arabinonucleic acid (FANA) (as described in, for example, Lon et al., Biochem., 41:3457-3467, 2002 and Min et al., Bioorg. Med. Chem. Lett., 12:2651-2654, 2002; the disclosures of which are incorporated herein by reference in their entireties). Similar modifications can also be made at other positions on the sugar, particularly the 3' position of the sugar on a 3' terminal nucleoside or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide.

PCT Publication No. WO 99/67378 discloses arabinonucleic acids (ANA) oligomers and their analogues for improved sequence specific inhibition of gene expression via association to complementary messenger RNA.

Other preferred modifications include ethylene-bridged nucleic acids (ENAs) (*e.g.*, International Patent Publication No. WO 2005/042777, Morita et al., Nucleic Acid Res., Suppl 1:241-242, 2001; Surono et al., Hum. Gene Ther., 15:749-757, 2004; Koizumi, Curr. Opin. Mol. Ther., 8:144-149, 2006 and Horie et al., Nucleic Acids Symp. Ser (Oxf), 49:171-172, 2005; the disclosures of which are incorporated herein by reference in their entireties). Preferred ENAs include, but are not limited to, 2'-O,4'-C-ethylene-bridged nucleic acids.

Examples of LNAs are described in WO/2008/043753 and include compounds of the following general formula.



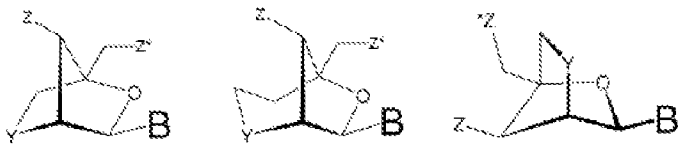
where X and Y are independently selected among the groups -O-,

-S-, -N(H)-, N(R)-, -CH_2- or -CH- (if part of a double bond),

-CH_2-O-, -CH_2-S-, -CH_2-N(H)-, -CH_2-N(R)-, -CH_2-CH_2- or -CH_2-CH- (if part of a double bond),

-CH=CH-, where R is selected from hydrogen and C_{1-4}-alkyl; Z and Z* are independently selected among an internucleoside linkage, a terminal group or a protecting group; B constitutes a natural or non-natural nucleotide base moiety; and the asymmetric groups may be found in either orientation.

Preferably, the LNA used in the oligonucleotides described herein comprises at least one LNA unit according any of the formulas

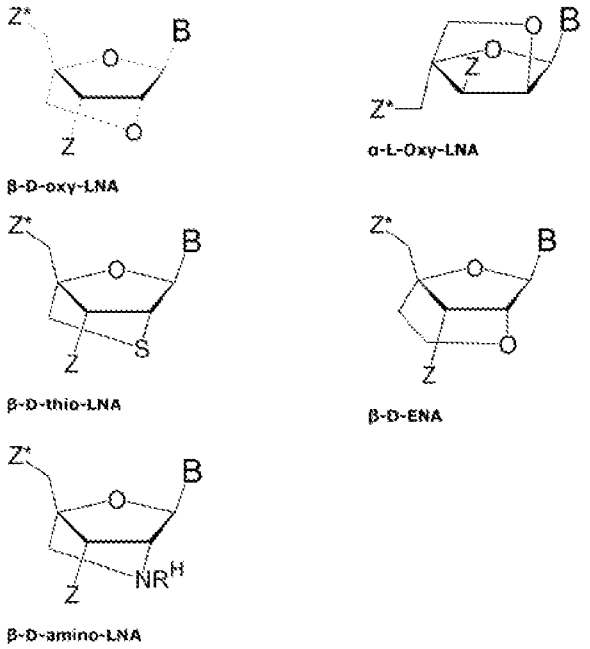


wherein Y is -O-, -S-, -NH-, or N(R^H); Z and Z* are independently selected among an internucleoside linkage, a terminal group or a protecting group; B constitutes a natural or non-natural nucleotide base moiety, and RH is selected from hydrogen and C_{1-4}-alkyl.

In some embodiments, the Locked Nucleic Acid (LNA) used in the oligonucleotides described herein comprises at least one Locked Nucleic Acid (LNA) unit according any of the formulas shown in Scheme 2 of PCT/DK2006/000512.

In some embodiments, the LNA used in the oligomer of the invention comprises internucleoside linkages selected from -0-P(O)$_2$-O-, -O-P(O,S)-O-, -0-P(S)$_2$-O-, -S-P(O)$_2$-O-, -S-P(O,S)-O-, -S-P(S)$_2$-O-, -0-P(O)$_2$-S-, -O-P(O,S)-S-, -S-P(O)$_2$-S-, -O-PO(R^H)-O-, O-PO(OCH_3)-O-, -O-PO(NR^H)-O-, -0-PO(OCH_2CH_2S-R)-O-, -O-PO(BH_3)-O-, -O-PO(NHR^H)-O-, -O-P(O)$_2$-NR^H-, -NR^H-P(O)$_2$-O-, -NR^H-CO-O-, where R^H is selected from hydrogen and C_{1-4}-alkyl.

Other examples of LNA units are shown below:



The term "thio-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from S or -CH_2-S-. Thio-LNA can be in both beta-D and alpha-L-configuration.

The term "amino-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from -N(H)-, N(R)-, CH_2-N(H)-, and -CH_2-N(R)- where R is selected from hydrogen and C_{1-4}-alkyl. Amino-LNA can be in both beta-D and alpha-L-configuration.

The term "oxy-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above represents -O- or -CH_2-O-. Oxy-LNA can be in both beta-D and alpha-L-configuration.

The term "ena-LNA" comprises a locked nucleotide in which Y in the general formula above is -CH_2-O- (where the oxygen atom of -CH_2-O- is attached to the 2'-position relative to the base B).

LNAs are described in additional detail herein.

One or more substituted sugar moieties can also be included, *e.g.*, one of the following at the 2' position: OH, SH, SCH_3, F, OCN, OCH_3 OCH_3, OCH_3 $O(CH_2)n$ CH_3, $O(CH_2)n$ NH_2 or $O(CH_2)n$ CH_3 where n is from 1 to about 10; C1 to C10 lower alkyl,

alkoxyalkoxy, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF_3 ; OCF_3; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; $SOCH_3$; SO_2 CH_3; ONO_2; NO_2; N_3; NH2; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy [2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl)] (Martin et al, HeIv. Chim. Acta, 1995, 78, 486). Other preferred modifications include 2'-methoxy (2'-O-CH_3), 2'-propoxy (2'-OCH_2 CH_2CH_3) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

Oligonucleotides can also include, additionally or alternatively, nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U). Modified nucleobases include nucleobases found only infrequently or transiently in natural nucleic acids, *e.g.*, hypoxanthine, 6-methyladenine, 5-Me pyrimidines, particularly 5-methylcytosine (also referred to as 5-methyl-2' deoxycytosine and often referred to in the art as 5-Me-C), 5-hydroxymethylcytosine (HMC), glycosyl HMC and gentobiosyl HMC, isocytosine, pseudoisocytosine, as well as synthetic nucleobases, *e.g.*, 2-aminoadenine, 2- (methylamino)adenine, 2-(imidazolylalkyl)adenine, 2-(aminoalklyamino)adenine or other heterosubstituted alkyladenines, 2-thiouracil, 2-thiothymine, 5-bromouracil, 5-hydroxymethyluracil, 5-propynyluracil, 8-azaguanine, 7-deazaguanine, N6 (6-aminohexyl)adenine, 6-aminopurine, 2-aminopurine, 2-chloro-6-aminopurine and 2,6-diaminopurine or other diaminopurines. See, *e.g.*, Kornberg, "DNA Replication," W. H. Freeman & Co., San Francisco, 1980, pp75-77; and Gebeyehu, G., et al. Nucl. Acids Res., 15:4513 (1987)). A "universal" base known in the art, *e.g.*, inosine, can also be included. 5-Me-C substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C. (Sanghvi, in Crooke, and Lebleu, eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and may be used as base substitutions.

It is not necessary for all positions in a given oligonucleotide to be uniformly modified, and in fact more than one of the modifications described herein may be incorporated in a single oligonucleotide or even at within a single nucleoside within an oligonucleotide.

In some embodiments, both a sugar and an internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, for example, an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, US patent nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al, Science, 1991, 254, 1497-1500.

Oligonucleotides can also include one or more nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases comprise the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases comprise other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudo-uracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8- thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5- bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylquanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3- deazaguanine and 3-deazaadenine.

Further, nucleobases comprise those disclosed in United States Patent No. 3,687,808, those disclosed in “The Concise Encyclopedia of Polymer Science And Engineering”, pages 858-859, Kroschwitz, ed. John Wiley & Sons, 1990;, those disclosed by Englisch et al.,

Angewandle Chemie, International Edition, 1991, 30, page 613, and those disclosed by Sanghvi, Chapter 15, Antisense Research and Applications," pages 289- 302, Crooke, and Lebleu, eds., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, comprising 2-aminopropyladenine, 5-propynyluracil and 5- propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2<0>C (Sanghvi, et al., eds, "Antisense Research and Applications," CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Modified nucleobases are described in US patent nos. 3,687,808, as well as 4,845,205; 5,130,302; 5,134,066; 5,175, 273; 5, 367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,596,091; 5,614,617; 5,750,692, and 5,681,941, each of which is herein incorporated by reference.

In some embodiments, the oligonucleotides are chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the oligonucleotide. For example, one or more oligonucleotides, of the same or different types, can be conjugated to each other; or oligonucleotides can be conjugated to targeting moieties with enhanced specificity for a cell type or tissue type. Such moieties include, but are not limited to, lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Let., 1994, 4, 1053-1060), a thioether, *e.g.*, hexyl-S- tritylthiol (Manoharan et al, Ann. N. Y. Acad. Sci., 1992, 660, 306-309; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49- 54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl- rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Mancharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-t oxycholesterol

moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937). See also US patent nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552, 538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486, 603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762, 779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082, 830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5, 245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391, 723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5, 565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599, 928 and 5,688,941, each of which is herein incorporated by reference.

These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterols, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application No. PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, which are incorporated herein by reference. Conjugate moieties include, but are not limited to, lipid moieties such as a cholesterol moiety, cholic acid, a thioether, *e.g.*, hexyl-5-tritylthiol, a thiocholesterol, an aliphatic chain, *e.g.*, dodecandiol or undecyl residues, a phospholipid, *e.g.*, di-hexadecyl-rac- glycerol or triethylammonium l,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxy cholesterol moiety. See, *e.g.*, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582;

4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941.

In some embodiments, oligonucleotide modification include modification of the 5' or 3' end of the oligonucleotide. In some embodiments, the 3' end of the oligonucleotide comprises a hydroxyl group or a thiophosphate. It should be appreciated that additional molecules (*e.g.* a biotin moiety or a fluorophor) can be conjugated to the 5' or 3' end of an oligonucleotide. In some embodiments, an oligonucleotide comprises a biotin moiety conjugated to the 5' nucleotide.

In some embodiments, an oligonucleotide comprises locked nucleic acids (LNA), ENA modified nucleotides, 2'-O-methyl nucleotides, or 2'-fluoro-deoxyribonucleotides. In some embodiments, an oligonucleotide comprises alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. In some embodiments, an oligonucleotide comprises alternating deoxyribonucleotides and 2'-O-methyl nucleotides. In some embodiments, an oligonucleotide comprises alternating deoxyribonucleotides and ENA modified nucleotides. In some embodiments, an oligonucleotide comprises alternating deoxyribonucleotides and locked nucleic acid nucleotides. In some embodiments, an oligonucleotide comprises alternating locked nucleic acid nucleotides and 2'-O-methyl nucleotides.

In some embodiments, the 5' nucleotide of the oligonucleotide is a deoxyribonucleotide. In some embodiments, the 5' nucleotide of the oligonucleotide is a locked nucleic acid nucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one locked nucleic acid nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides. In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group or a 3' thiophosphate.

In some embodiments, an oligonucleotide comprises phosphorothioate internucleotide linkages. In some embodiments, an oligonucleotide comprises phosphorothioate internucleotide linkages between at least two nucleotides. In some embodiments, an oligonucleotide comprises phosphorothioate internucleotide linkages between all nucleotides.

It should be appreciated that an oligonucleotide can have any combination of modifications as described herein.

The oligonucleotide may comprise a nucleotide sequence having one or more of the following modification patterns.

(a) (X)Xxxxxx, (X)xXxxxx, (X)xxXxxx, (X)xxxXxx, (X)xxxxXx and (X)xxxxxX,

(b) (X)XXxxxx, (X)XxXxxx, (X)XxxXxx, (X)XxxxXx, (X)XxxxxX, (X)xXXxxx, (X)xXxXxx, (X)xXxxXx, (X)xXxxxX, (X)xxXXxx, (X)xxXxXx, (X)xxXxxX, (X)xxxXXx, (X)xxxXxX and (X)xxxxXX,

(c) (X)XXXxxx, (X)xXXXxx, (X)xxXXXx, (X)xxxXXX, (X)XXxXxx, (X)XXxxXx, (X)XXxxxX, (X)xXXxXx, (X)xXXxxX, (X)xxXXxX, (X)XxXXxx, (X)XxxXXx (X)XxxxXX, (X)xXxXXx, (X)xXxxXX, (X)xxXxXX, (X)xXxXxX and (X)XxXxXx,

(d) (X)xxXXX, (X)xXxXXX, (X)xXXxXX, (X)xXXXxX, (X)xXXXXx, (X)XxxXXXX, (X)XxXxXX, (X)XxXXxX, (X)XxXXx, (X)XXxxXX, (X)XXxXxX, (X)XXxXXx, (X)XXXxxX, (X)XXXxXx, and (X)XXXXxx,

(e) (X)xXXXXX, (X)XxXXXX, (X)XXxXXX, (X)XXXxXX, (X)XXXXxX and (X)XXXXXx, and

(f) XXXXXX, XxXXXXX, XXxXXXX, XXXxXXX, XXXXxXX, XXXXXxX and XXXXXXx, in which "X" denotes a nucleotide analogue, (X) denotes an optional nucleotide analogue, and "x" denotes a DNA or RNA nucleotide unit. Each of the above listed patterns may appear one or more times within an oligonucleotide, alone or in combination with any of the other disclosed modification patterns.

Methods for Modulating Gene Expression

In one aspect, the invention relates to methods for modulating (e.g., increasing) stability of RNA transcripts in cells. The cells can be *in vitro*, *ex vivo*, or *in vivo*. The cells can be in a subject who has a disease resulting from reduced expression or activity of the RNA transcript or its corresponding protein product in the case of mRNAs. In some embodiments, methods for modulating stability of RNA transcripts in cells comprise delivering to the cell an oligonucleotide that targets the RNA and prevents or inhibits its degradation by exonucleases. In some embodiments, delivery of an oligonucleotide to the cell results in an increase in stability of a target RNA that is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200% or more greater than a level of stability of the target RNA in a control cell. An appropriate control cell may be a cell to which an

oligonucleotide has not been delivered or to which a negative control has been delivered (*e.g.*, a scrambled oligo, a carrier, *etc.*).

Another aspect of the invention provides methods of treating a disease or condition associated with low levels of a particular RNA in a subject. Accordingly, in some embodiments, methods are provided that comprise administering to a subject (*e.g.* a human) a composition comprising an oligonucleotide as described herein to increase mRNA stability in cells of the subject for purposes of increasing protein levels. In some embodiments, the increase in protein levels is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, or more, higher than the amount of a protein in the subject (e.g., in a cell or tissue of the subject) before administering or in a control subject which has not been administered the oligonucleotide or that has been administered a negative control (*e.g.*, a scrambled oligo, a carrier, *etc.*). In some embodiments, methods are provided that comprise administering to a subject (*e.g.* a human) a composition comprising an oligonucleotide as described herein to increase stability of non-coding RNAs in cells of the subject for purposes of increasing activity of those non-coding RNAs.

A subject can include a non-human mammal, *e.g.* mouse, rat, guinea pig, rabbit, cat, dog, goat, cow, or horse. In preferred embodiments, a subject is a human. Oligonucleotides may be employed as therapeutic moieties in the treatment of disease states in animals, including humans. Oligonucleotides can be useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

For therapeutics, an animal, preferably a human, suspected of having a disease associated with low levels of an RNA or protein is treated by administering oligonucleotide in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of an oligonucleotide as described herein. Table 1 listed examples examples of diseases or conditions that may be treated by targeting mRNA transcripts with stabilizing oligonucleotides. In some embodiments, cells used in the methods disclosed herein may, for example, be cells obtained from a subject having one or more of the conditions listed in Table 1, or from a subject that is a disease model of one or more of the conditions listed in Table 1.

Table 1: Examples of diseases or conditions treatable with oligonucleotides targeting associated mRNA.

Gene	Disease or conditions
FXN	Friedreich's Ataxia
SMN	Spinal muscular atrophy (SMA) types I-IV
UTRN	Muscular dystrophy (MD) (e.g., Duchenne's muscular dystrophy, Becker's muscular dystrophy, myotonic dystrophy)
HEMOGLOBIN	Anemia, microcytic anemia, sickle cell anemia and/or thalassemia (e.g., alpha-thalassemia, beta-thalaseemia, delta-thalessemia), beta-thalaseemia (e.g., thalassemia minor/intermedia/major)
ATP2A2	Cardiac conditions (e.g., congenital heart disease, aortic aneurysms, aortic dissections, arrhythmia, cardiomyopathy, and congestive heart failure), Darier-White disease and Acrokeratosis verruciformi
APOA1 / ABCA1	Dyslipidemia (e.g. Hyperlipidemia) and atherosclerosis (e.g. coronary artery disease (CAD) and myocardial infarction (MI))
PTEN	Cancer, such as, leukemias, lymphomas, myelomas, carcinomas, metastatic carcinomas, sarcomas, adenomas, nervous system cancers and

Gene	Disease or conditions
	genito-urinary cancers. In some embodiments, the cancer is adult and pediatric acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, anal cancer, cancer of the appendix, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, fibrous histiocytoma, brain cancer, brain stem glioma, cerebellar astrocytoma, malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, hypothalamic glioma, breast cancer, male breast cancer, bronchial adenomas, Burkitt lymphoma, carcinoid tumor, carcinoma of unknown origin, central nervous system lymphoma, cerebellar astrocytoma, malignant glioma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, ependymoma, esophageal cancer, Ewing family tumors, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric cancer, gastrointestinal stromal tumor, extracranial germ cell tumor, extragonadal germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, islet cell tumors, Kaposi sarcoma, kidney cancer, renal cell cancer, laryngeal cancer, lip and oral cavity cancer, small cell lung cancer, non-small cell lung cancer, primary central nervous system lymphoma, Waldenstrom macroglobulinema, malignant fibrous histiocytoma, medulloblastoma, melanoma, Merkel cell carcinoma, malignant mesothelioma, squamous neck cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myeloproliferative disorders, chronic myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary cancer, plasma cell neoplasms, pleuropulmonary blastoma, prostate cancer, rectal cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, uterine sarcoma, Sezary syndrome, non-melanoma skin cancer, small intestine cancer, squamous cell carcinoma, squamous neck cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer, trophoblastic tumors, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Wilms tumor
BDNF	Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's Disease (AD), and Parkinson's Disease (PD), Neurodegeneration

Gene	Disease or conditions
MECP2	Rett Syndrome, MECP2-related severe neonatal encephalopathy, Angelman syndrome, or PPM-X syndrome
FOXP3	Diseases or disorders associated with aberrant immune cell (e.g., T cell) activation, e.g., autoimmune or inflammatory diseases or disorders. Examples of autoimmune diseases and disorders that may be treated according to the methods disclosed herein include, but are not limited to, Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune dysautonomia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticaria, Axonal & neuronal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, inflammatory bowel disease (e.g., Crohn's disease or Ulcerative colitis), Cogans syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Experimental allergic encephalomyelitis, Evans syndrome, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inclusion body myositis, Interstitial cystitis, IPEX (Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-linked) syndrome, Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), systemic lupus erythematosus (SLE), chronic Lyme disease, Meniere's disease, Microscopic polyangiitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy,

Gene	Disease or conditions
	Neuromyelitis optica (Devic's), Neutropenia ,Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, Transverse myelitis, Type 1 diabetes, Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, and Wegener's granulomatosis (also called Granulomatosis with Polyangiitis (GPA)). Further examples of autoimmune disease or disorder include inflammatory bowel disease (e.g., Crohn's disease or Ulcerative colitis), IPEX syndrome, Multiple sclerosis, Psoriasis, Rheumatoid arthritis, SLE or Type 1 diabetes. Examples of inflammatory diseases or disorders that may be treated according to the methods disclosed herein include, but are not limited to, Acne Vulgaris, Appendicitis, Arthritis, Asthma, Atherosclerosis, Allergies (Type 1 Hypersensitivity), Bursitis, Colitis, Chronic Prostatitis, Cystitis, Dermatitis, Glomerulonephritis, Inflammatory Bowel Disease, Inflammatory Myopathy (e.g., Polymyositis, Dermatomyositis, or Inclusion-body Myositis), Inflammatory Lung Disease, Interstitial Cystitis, Meningitis, Pelvic Inflammatory Disease, Phlebitis, Psoriasis, Reperfusion Injury, Rheumatoid Arthritis, Sarcoidosis, Tendonitis, Tonsilitis, Transplant Rejection, and Vasculitis. In some embodiments, the inflammatory disease or disorder is asthma.

Formulation, Delivery, And Dosing

The oligonucleotides described herein can be formulated for administration to a subject for treating a condition associated with decreased levels of expression of gene or instability or low stability of an RNA transcript that results in decreased levels of expression

of a gene (e.g., decreased protein levels or decreased levels of functional RNAs, such as miRNAs, snoRNAs, lncRNAs, etc.). It should be understood that the formulations, compositions and methods can be practiced with any of the oligonucleotides disclosed herein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient (*e.g.*, an oligonucleotide or compound of the invention) which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration, *e.g.*, intradermal or inhalation. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect, *e.g.* tumor regression.

Pharmaceutical formulations of this invention can be prepared according to any method known to the art for the manufacture of pharmaceuticals. Such formulations can contain sweetening agents, flavoring agents, coloring agents and preserving agents. A formulation can be admixtured with nontoxic pharmaceutically acceptable excipients which are suitable for manufacture. Formulations may comprise one or more diluents, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, lyophilized powders, sprays, creams, lotions, controlled release formulations, tablets, pills, gels, on patches, in implants, etc.

A formulated oligonucleotide composition can assume a variety of states. In some examples, the composition is at least partially crystalline, uniformly crystalline, and/or anhydrous (*e.g.*, less than 80, 50, 30, 20, or 10% water). In another example, an oligonucleotide is in an aqueous phase, *e.g.*, in a solution that includes water. The aqueous phase or the crystalline compositions can, *e.g.*, be incorporated into a delivery vehicle, *e.g.*, a liposome (particularly for the aqueous phase) or a particle (*e.g.*, a microparticle as can be appropriate for a crystalline composition). Generally, an oligonucleotide composition is formulated in a manner that is compatible with the intended method of administration.

In some embodiments, the composition is prepared by at least one of the following methods: spray drying, lyophilization, vacuum drying, evaporation, fluid bed drying, or a combination of these techniques; or sonication with a lipid, freeze-drying, condensation and other self-assembly.

An oligonucleotide preparation can be formulated or administered (together or separately) in combination with another agent, *e.g.*, another therapeutic agent or an agent that stabilizes an oligonucleotide, *e.g.*, a protein that complexes with oligonucleotide. Still other agents include chelators, *e.g.*, EDTA (*e.g.*, to remove divalent cations such as Mg^{2+}), salts, RNAse inhibitors (*e.g.*, a broad specificity RNAse inhibitor such as RNAsin) and so forth.

In one embodiment, an oligonucleotide preparation includes another oligonucleotide, *e.g.*, a second oligonucleotide that modulates expression of a second gene or a second oligonucleotide that modulates expression of the first gene. Still other preparation can include at least 3, 5, ten, twenty, fifty, or a hundred or more different oligonucleotide species. Such oligonucleotides can mediated gene expression with respect to a similar number of different genes. In one embodiment, an oligonucleotide preparation includes at least a second therapeutic agent (*e.g.*, an agent other than an oligonucleotide).

Any of the formulations, excipients, vehicles, *etc*. disclosed herein may be adapted or used to facilitate delivery of synthetic RNAs (e.g., circularized synthetic RNAs) to a cell. Formulations, excipients, vehicles, *etc*. disclosed herein may be adapted or used to facilitate delivery of a synthetic RNA to a cell *in vitro* or *in vivo*. For example, a synthetic RNA (e.g., a circularized synthetic RNA) may be formulated with a nanoparticle, poly(lactic-co-glycolic acid) (PLGA) microsphere, lipidoid, lipoplex, liposome, polymer, carbohydrate (including simple sugars), cationic lipid, a fibrin gel, a fibrin hydrogel, a fibrin glue, a fibrin sealant, fibrinogen, thrombin, rapidly eliminated lipid nanoparticles (reLNPs) and combinations thereof. In some embodiments, a synthetic RNA may be delivered to a cell gymnotically. In some embodiments, oligonucleotides or synthetic RNAs may be conjugated with factors that facilitate delivery to cells. In some embodiments, a synthetic RNA or oligonucleotide used to circularize a synthetic RNA is conjugated with a carbohydrate, such as GalNac, or other targeting moiety.

Route of Delivery

A composition that includes an oligonucleotide can be delivered to a subject by a variety of routes. Exemplary routes include: intravenous, intradermal, topical, rectal, parenteral, anal, intravaginal, intranasal, pulmonary, ocular. The term "therapeutically effective amount" is the amount of oligonucleotide present in the composition that is needed to provide the desired level of gene expression (*e.g.*, by stabilizing RNA transcripts) in the

subject to be treated to give the anticipated physiological response. The term "physiologically effective amount" is that amount delivered to a subject to give the desired palliative or curative effect. The term "pharmaceutically acceptable carrier" means that the carrier can be administered to a subject with no significant adverse toxicological effects to the subject.

An oligonucleotide molecules of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of oligonucleotide and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), oral or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For example, to target muscle cells, intramuscular injection into the muscles of interest would be a logical choice. Lung cells might be targeted by administering an oligonucleotide in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with an oligonucleotide and mechanically introducing the oligonucleotide.

Topical administration refers to the delivery to a subject by contacting the formulation directly to a surface of the subject. The most common form of topical delivery is to the skin, but a composition disclosed herein can also be directly applied to other surfaces of the body, *e.g.*, to the eye, a mucous membrane, to surfaces of a body cavity or to an internal surface. As mentioned above, the most common topical delivery is to the skin. The term encompasses several routes of administration including, but not limited to, topical and transdermal. These modes of administration typically include penetration of the skin's permeability barrier and

efficient delivery to the target tissue or stratum. Topical administration can be used as a means to penetrate the epidermis and dermis and ultimately achieve systemic delivery of the composition. Topical administration can also be used as a means to selectively deliver oligonucleotides to the epidermis or dermis of a subject, or to specific strata thereof, or to an underlying tissue.

Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

Transdermal delivery is a valuable route for the administration of lipid soluble therapeutics. The dermis is more permeable than the epidermis and therefore absorption is much more rapid through abraded, burned or denuded skin. Inflammation and other physiologic conditions that increase blood flow to the skin also enhance transdermal adsorption. Absorption via this route may be enhanced by the use of an oily vehicle (inunction) or through the use of one or more penetration enhancers. Other effective ways to deliver a composition disclosed herein via the transdermal route include hydration of the skin and the use of controlled release topical patches. The transdermal route provides a potentially effective means to deliver a composition disclosed herein for systemic and/or local therapy. In addition, iontophoresis (transfer of ionic solutes through biological membranes under the influence of an electric field), phonophoresis or sonophoresis (use of ultrasound to enhance the absorption of various therapeutic agents across biological membranes, notably the skin and the cornea), and optimization of vehicle characteristics relative to dose position and retention at the site of administration may be useful methods for enhancing the transport of topically applied compositions across skin and mucosal sites.

Both the oral and nasal membranes offer advantages over other routes of administration. For example, oligonucleotides administered through these membranes may have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the oligonucleotides to the hostile gastrointestinal (GI) environment. Additional advantages include easy access to the membrane sites so that the oligonucleotide can be applied, localized and removed easily.

In oral delivery, compositions can be targeted to a surface of the oral cavity, *e.g.*, to sublingual mucosa which includes the membrane of ventral surface of the tongue and the

floor of the mouth or the buccal mucosa which constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many agents. Further, the sublingual mucosa is convenient, acceptable and easily accessible.

A pharmaceutical composition of oligonucleotide may also be administered to the buccal cavity of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a mixed micellar pharmaceutical formulation as described above and a propellant. In one embodiment, the dispenser is first shaken prior to spraying the pharmaceutical formulation and propellant into the buccal cavity.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, slurries, emulsions, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added.

Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, intrathecal or intraventricular administration. In some embodiments, parental administration involves administration directly to the site of disease (*e.g.* injection into a tumor).

Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

Any of the oligonucleotides described herein can be administered to ocular tissue. For example, the compositions can be applied to the surface of the eye or nearby tissue, *e.g.*, the inside of the eyelid. For ocular administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid, chondroitin sulfate,

hydroxypropyl methylcellulose or poly(vinyl alcohol), preservatives such as sorbic acid, EDTA or benzylchronium chloride, and the usual quantities of diluents and/or carriers. An oligonucleotide can also be administered to the interior of the eye, and can be introduced by a needle or other delivery device which can introduce it to a selected area or structure.

Pulmonary delivery compositions can be delivered by inhalation by the patient of a dispersion so that the composition, preferably oligonucleotides, within the dispersion can reach the lung where it can be readily absorbed through the alveolar region directly into blood circulation. Pulmonary delivery can be effective both for systemic delivery and for localized delivery to treat diseases of the lungs.

Pulmonary delivery can be achieved by different approaches, including the use of nebulized, aerosolized, micellular and dry powder-based formulations. Delivery can be achieved with liquid nebulizers, aerosol-based inhalers, and dry powder dispersion devices. Metered-dose devices are preferred. One of the benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self-contained. Dry powder dispersion devices, for example, deliver agents that may be readily formulated as dry powders. An oligonucleotide composition may be stably stored as lyophilized or spray-dried powders by itself or in combination with suitable powder carriers. The delivery of a composition for inhalation can be mediated by a dosing timing element which can include a timer, a dose counter, time measuring device, or a time indicator which when incorporated into the device enables dose tracking, compliance monitoring, and/or dose triggering to a patient during administration of the aerosol medicament.

The term "powder" means a composition that consists of finely dispersed solid particles that are free flowing and capable of being readily dispersed in an inhalation device and subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the alveoli. Thus, the powder is said to be "respirable." Preferably the average particle size is less than about 10 μm in diameter preferably with a relatively uniform spheroidal shape distribution. More preferably the diameter is less than about 7.5 μ m and most preferably less than about 5.0 μ m. Usually the particle size distribution is between about 0.1 μ m and about 5 μ m in diameter, particularly about 0.3 μ m to about 5 μ m.

The term "dry" means that the composition has a moisture content below about 10% by weight (% w) water, usually below about 5% w and preferably less it than about 3% w. A

dry composition can be such that the particles are readily dispersible in an inhalation device to form an aerosol.

The types of pharmaceutical excipients that are useful as carrier include stabilizers such as human serum albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers; salts such as sodium chloride; and the like. These carriers may be in a crystalline or amorphous form or may be a mixture of the two.

Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred. Pulmonary administration of a micellar oligonucleotide formulation may be achieved through metered dose spray devices with propellants such as tetrafluoroethane, heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants.

Exemplary devices include devices which are introduced into the vasculature, *e.g.*, devices inserted into the lumen of a vascular tissue, or which devices themselves form a part of the vasculature, including stents, catheters, heart valves, and other vascular devices. These devices, *e.g.*, catheters or stents, can be placed in the vasculature of the lung, heart, or leg.

Other devices include non-vascular devices, *e.g.*, devices implanted in the peritoneum, or in organ or glandular tissue, *e.g.*, artificial organs. The device can release a therapeutic substance in addition to an oligonucleotide, *e.g.*, a device can release insulin.

In one embodiment, unit doses or measured doses of a composition that includes oligonucleotide are dispensed by an implanted device. The device can include a sensor that monitors a parameter within a subject. For example, the device can include pump, *e.g.*, and, optionally, associated electronics.

Tissue, *e.g.*, cells or organs can be treated with an oligonucleotide, ex vivo and then administered or implanted in a subject. The tissue can be autologous, allogeneic, or xenogeneic tissue. *E.g.*, tissue can be treated to reduce graft v. host disease . In other embodiments, the tissue is allogeneic and the tissue is treated to treat a disorder characterized by unwanted gene expression in that tissue. *E.g.*, tissue, *e.g.*, hematopoietic cells, *e.g.*, bone marrow hematopoietic cells, can be treated to inhibit unwanted cell proliferation. Introduction of treated tissue, whether autologous or transplant, can be combined with other therapies. In some implementations, an oligonucleotide treated cells are insulated from other cells, *e.g.*, by a semi-permeable porous barrier that prevents the cells from leaving the

implant, but enables molecules from the body to reach the cells and molecules produced by the cells to enter the body. In one embodiment, the porous barrier is formed from alginate.

In one embodiment, a contraceptive device is coated with or contains an oligonucleotide. Exemplary devices include condoms, diaphragms, IUD (implantable uterine devices, sponges, vaginal sheaths, and birth control devices.

Dosage

In one aspect, the invention features a method of administering an oligonucleotide (e.g., as a compound or as a component of a composition) to a subject (*e.g.*, a human subject). In one embodiment, the unit dose is between about 10 mg and 25 mg per kg of bodyweight. In one embodiment, the unit dose is between about 1 mg and 100 mg per kg of bodyweight. In one embodiment, the unit dose is between about 0.1 mg and 500 mg per kg of bodyweight. In some embodiments, the unit dose is more than 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 2, 5, 10, 25, 50 or 100 mg per kg of bodyweight.

The defined amount can be an amount effective to treat or prevent a disease or disorder, *e.g.*, a disease or disorder associated with low levels of an RNA or protein. The unit dose, for example, can be administered by injection (*e.g.*, intravenous or intramuscular), an inhaled dose, or a topical application.

In some embodiments, the unit dose is administered daily. In some embodiments, less frequently than once a day, *e.g.*, less than every 2, 4, 8 or 30 days. In another embodiment, the unit dose is not administered with a frequency (*e.g.*, not a regular frequency). For example, the unit dose may be administered a single time. In some embodiments, the unit dose is administered more than once a day, *e.g.*, once an hour, two hours, four hours, eight hours, twelve hours, etc.

In one embodiment, a subject is administered an initial dose and one or more maintenance doses of an oligonucleotide. The maintenance dose or doses are generally lower than the initial dose, *e.g.*, one-half less of the initial dose. A maintenance regimen can include treating the subject with a dose or doses ranging from 0.0001 to 100 mg/kg of body weight per day, *e.g.*, 100, 10, 1, 0.1, 0.01, 0.001, or 0.0001 mg per kg of bodyweight per day. The maintenance doses may be administered no more than once every 1, 5, 10, or 30 days. Further, the treatment regimen may last for a period of time which will vary depending upon the nature of the particular disease, its severity and the overall condition of the patient. In

some embodiments the dosage may be delivered no more than once per day, *e.g.*, no more than once per 24, 36, 48, or more hours, *e.g.*, no more than once for every 5 or 8 days. Following treatment, the patient can be monitored for changes in his condition and for alleviation of the symptoms of the disease state. The dosage of the oligonucleotide may either be increased in the event the patient does not respond significantly to current dosage levels, or the dose may be decreased if an alleviation of the symptoms of the disease state is observed, if the disease state has been ablated, or if undesired side-effects are observed.

The effective dose can be administered in a single dose or in two or more doses, as desired or considered appropriate under the specific circumstances. If desired to facilitate repeated or frequent infusions, implantation of a delivery device, *e.g.*, a pump, semi-permanent stent (*e.g.*, intravenous, intraperitoneal, intracisternal or intracapsular), or reservoir may be advisable.

In some cases, a patient is treated with an oligonucleotide in conjunction with other therapeutic modalities.

Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the compound of the invention is administered in maintenance doses, ranging from 0.0001 mg to 100 mg per kg of body weight.

The concentration of an oligonucleotide composition is an amount sufficient to be effective in treating or preventing a disorder or to regulate a physiological condition in humans. The concentration or amount of oligonucleotide administered will depend on the parameters determined for the agent and the method of administration, *e.g.* nasal, buccal, pulmonary. For example, nasal formulations may tend to require much lower concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

Certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an oligonucleotide can include a single treatment or, preferably, can include a series of treatments. It will also be appreciated that the effective dosage of an oligonucleotide used for treatment may increase or decrease over the

course of a particular treatment. For example, the subject can be monitored after administering an oligonucleotide composition. Based on information from the monitoring, an additional amount of an oligonucleotide composition can be administered.

Dosing is dependent on severity and responsiveness of the disease condition to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of disease state is achieved. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual compounds, and can generally be estimated based on EC50s found to be effective in *in vitro* and *in vivo* animal models.

In one embodiment, the administration of an oligonucleotide composition is parenteral, *e.g.* intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The composition can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

Kits

In certain aspects of the invention, kits are provided, comprising a container housing a composition comprising an oligonucleotide. In some embodiments, the composition is a pharmaceutical composition comprising an oligonucleotide and a pharmaceutically acceptable carrier. In some embodiments, the individual components of the pharmaceutical composition may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical composition separately in two or more containers, *e.g.*, one container for oligonucleotides, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

EXAMPLES

Example 1. Oligonucleotide for targeting 5' and 3' ends of RNAs

Several exemplary oligonucleotide design schemes are contemplated herein for increasing mRNA stability. With regard to oligonucleotides targeting the 3' end of an RNA, at least two exemplary design schemes are contemplated. As a first scheme, an oligo nucleotide is designed to be complementary to the 3' end of an RNA, before the poly-A tail (FIG. 1). As a second scheme, an oligonucleotide is designed to be complementary to the 3' end of RNA with a 5' poly-T region that hybridizes to a poly-A tail (FIG. 1).

With regard to oligonucleotides targeting the 5' end of an RNA, at least three exemplary design schemes are contemplated. For scheme one, an oligonucleotide is designed to be complementary to the 5' end of RNA (FIG. 2). For scheme two, an oligonucleotide is designed to be complementary to the 5' end of RNA and has a 3'overhang to create a RNA-oligo duplex with a recessed end. In this example, the overhang is one or more C nucleotides, e.g., two Cs, which can potentially interact with a 5' methylguanosine cap and stabilize the cap further (FIG. 2). The overhang could also potentially be another type of nucleotide, and is not limited to C. For scheme 3, an oligonucleotide is designed to include a loop region to stabilize 5' RNA cap.

An oligonucleotide designed as described in Example 1 may be tested for its ability to upregulate RNA by increasing mRNA stability using the methods outlined in Example 2.

Example 2: Oligos for targeting the 5' and 3' end of Frataxin

MATERIALS AND METHODS:

Real Time PCR

RNA analysis, cDNA synthesis and QRT-PCR was done with Life Technologies Cells-to-Ct kit and StepOne Plus instrument. Baseline levels were also determined for mRNA of various housekeeping genes which are constitutively expressed. A "control" housekeeping gene with approximately the same level of baseline expression as the target gene was chosen for comparison purposes

Western Blot

Western blots were performed as previously described. KLF4 antibody (Cell Signaling 4038S) was used at 1:1000 dilution. The images were taken on a UVP ChemicDoc-It instrument using fluorescently-labeled anti-rabbit antibodies.

ELISA

ELISA assays were performed using the Abcam Frataxin ELISA kit (ab115346) following manufacturer's instructions.

Cell lines

Cells were cultured using conditions known in the art. Details of the cell lines used in the experiments described herein are provided in Table 2.

Table 2: Cells

Cell lines	Clinically affected	Cell type	# of GAA repeats	Notes
GM15850	Y	B-lymphoblast	650 & 1030	13yr old white male, brother to GM15851
GM15851	N	B-lymphoblast	<20 for both	14yr old white male, brother to GM15850
GM16209	Y	B-lymphoblast	800 for both	41yr old white female, half-sister to GM16222
GM16222	N	B-lymphoblast	830 & <20	59yr old white female, half-sister to GM16209
GM03816	Y	Fibroblast	330/380	36yr old white female, sister to GM04078
GM03816	Y	Fibroblast	541-420	30yr old white male, brother to GM03816
GM0321B	N	Fibroblast	Not applicable	Healthy 40yr old female

Actinomycin D treatment

Actinomycin D (Life Technologies) was added to cell culture media at 10 microgram/ml concentration and incubated. RNA isolation was done using Trizol (Sigma) following manufacturer's instructions. FXN and c-Myc probes were purchased from Life Technologies.

Oligonucleotide design

Oligonucleotides were designed to target the 5' and 3' ends of FXN mRNA. The 3' end oligonucleotides were designed by identifying putative mRNA 3' ends using quantitative end analysis of poly-A tails as described previously (see, e.g., Ozsolak et al. Comprehensive Polyadenylation Site Maps in Yeast and Human Reveal Pervasive Alternative Polyadenylation. Cell. Volume 143, Issue 6, 2010, Pages 1018–1029). FIG. 4 shows the identified poly-A sites. The 5' end oligonucleotides were designed by identifying potential 5' start sites using Cap analysis gene expression (CAGE) as previously described (see, e.g., Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage. Proc Natl Acad Sci U S A. 100 (26): 15776–81. 2003-12-23 and Zhao, Xiaobei (2011). "Systematic Clustering of Transcription Start Site Landscapes". PLoS ONE (Public Library of Science) 6 (8): e23409). FIG. 5 shows the identified 5' start sites. FIG. 6 provides the location of the designed 5' and 3' end oligonucleotides.

The oligonucleotide positions of certain designed oligonucleotides relative to mRNA-Seq signals and ribosome positioning was also calculated using public data sets (Guo, H., Ingolia, N. T., Weissman, J. S., & Bartel, D. P. (2010). Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature, 466(7308), 835-40. doi:10.1038/nature09267). The oligonucleotide positions relative to these data sets are shown in FIG. 69.

The sequence and structure of each oligonucleotide is shown in Table 3. Table 5 provides a description of the nucleotide analogs, modifications and intranucleotide linkages used for certain oligonucleotides tested and described in Tables 3, 7,8 9, 10, 11, and 12. Certain oligos in Table 3 and Table 4 have two oligo names the "Oligo Name" and the "Alternative Oligo Name", which are used interchangeably herein and are to be understood to refer to the same oligo.

Table 3: Oligonucleotides targeting 5' and 3' ends of FXN

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
1	Oligo48	FXN-371	TGACCCAAGGGAGAC	5'-End	FXN	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dC-Sup
2	Oligo49	FXN-372	TGGCCACTGGCCGCA	5'-End	FXN	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dA-Sup
3	Oligo50	FXN-373	CGGCGACCCCTGGTG	5'-End	FXN	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dG-Sup
4	Oligo51	FXN-374	CGCCCTCCAGCGCTG	5'-End	FXN	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dG-Sup
5	Oligo52	FXN-375	CGCTCCGCCCTCCAG	5'-End	FXN	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dG-Sup
6	Oligo53	FXN-376	TGACCCAAGGGAGACCC	5'-End	FXN	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dCs;lnaCs;dC-Sup
7	Oligo54	FXN-377	TGGCCACTGGCCGCACC	5'-End	FXN	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaCs;dC-Sup
8	Oligo55	FXN-378	CGGCGACCCCTGGTGCC	5'-End	FXN	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaCs;dC-Sup
9	Oligo56	FXN-379	CGCCCTCCAGCGCTGCC	5'-End	FXN	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaCs;dC-Sup
10	Oligo57	FXN-380	CGCTCCGCCCTCCAGCC	5'-End	FXN	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaCs;dC-Sup
11	Oligo58	FXN-381	TGACCCAAGGGAGACGGAAACCAC	5'-End	FXN	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dCs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
12	Oligo59	FXN-382	TGGCCACTGGCCGCAGGAAACCAC	5'-End	FXN	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup

13	Oligo60	FXN-383	CGGCGACCCTGGTGGGAAACCTC	5'-End	FXN	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dTs;lnaC-Sup
14	Oligo61	FXN-384	CGCCCTCCAGCGCTGGGAAACCTC	5'-End	FXN	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dTs;lnaC-Sup
15	Oligo62	FXN-385	CGCTCCGCCCTCCAGCCAAAGGTC	5'-End	FXN	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaCs;dCs;dAs;dAs;dAs;dGs;lnaGs;dTs;lnaC-Sup
16	Oligo63	FXN-386	GGTTTTTAAGGCTTT	3'-End	FXN	human	dGs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaGs;dGs;lnaCs;dTs;lnaTs;dT-Sup
17	Oligo64	FXN-387	GGGGTCTTGGCCTGA	3'-End	FXN	human	dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dGs;lnaGs;dCs;lnaCs;dTs;lnaGs;dA-Sup
18	Oligo65	FXN-388	CATAATGAAGCTGGG	3'-End	FXN	human	dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup
19	Oligo66	FXN-389	AGGAGGCAACACATT	3'-End	FXN	human	dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dT-Sup
20	Oligo67	FXN-390	ATTATTTTGCTTTTT	3'-End	FXN	human	dAs;lnaTs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dGs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
21	Oligo68	FXN-391	CATTTTCCCTCCTGG	3'-End	FXN	human	dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaGs;dG-Sup
22	Oligo69	FXN-392	GTAGGCTACCCTTTA	3'-End	FXN	human	dGs;lnaTs;dAs;lnaGs;dGs;lnaCs;dTs;lnaAs;dCs;lnaCs;dCs;lnaTs;dTs;lnaTs;dA-Sup
23	Oligo70	FXN-393	GAGGCTTGTTGCTTT	3'-End	FXN	human	dGs;lnaAs;dGs;lnaGs;dCs;lnaTs;dTs;lnaGs;dTs;lnaTs;dGs;lnaCs;dTs;lnaTs;dT-Sup
24	Oligo71	FXN-394	CATGTATGATGTTAT	3'-End	FXN	human	dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dTs;lnaGs;dAs;lnaTs;dGs;lnaTs;dTs;lnaAs;dT-Sup
25	Oligo72	FXN-395	TTTTTGGTTTTTAAGGCTTT	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaAs;dGs;lnaGs;dCs;lnaTs;dTs;lnaT-Sup
26	Oligo73	FXN-396	TTTTTGGGGTCTTGGCCTGA	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaGs;dGs;lnaTs;dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaTs;dGs;lnaA-Sup

27	Oligo74	FXN-397	TTTTTCAT AATGAAG CTGGG	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dAs;lnaAs;dTs;lnaGs;dAs;lnaAs;dGs;lnaCs;dTs;lnaGs;dGs;lnaG-Sup
28	Oligo75	FXN-398	TTTTTAGG AGGCAAC ACATT	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dTs;lnaT-Sup
29	Oligo76	FXN-399	TTTTTATT ATTTTGCT TTTT	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dCs;lnaTs;dTs;lnaTs;dTs;lnaT-Sup
30	Oligo77	FXN-400	TTTTTCAT TTCCCTC CTGG	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaTs;dGs;lnaG-Sup
31	Oligo78	FXN-401	TTTTTGTA GGCTACC CTTTA	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaAs;dGs;lnaGs;dCs;lnaTs;dAs;lnaCs;dCs;lnaCs;dTs;lnaTs;dTs;lnaA-Sup
32	Oligo79	FXN-402	TTTTTGAG GCTTGTT GCTTT	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dAs;lnaGs;dGs;lnaCs;dTs;lnaTs;dGs;lnaTs;dTs;lnaGs;dCs;lnaTs;dTs;lnaT-Sup
33	Oligo80	FXN-403	TTTTTCAT GTATGAT GTTAT	3'-End	FXN	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaTs;dGs;lnaAs;dTs;lnaGs;dTs;lnaTs;dAs;lnaT-Sup

Table 4: Other oligonucleotides targeting FXN

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
34	Oligo1	FXN-324	CGGCGCC CGAGAGT CCACAT	Internal	FXN	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaCs;dCs;lnaCs;dGs;lnaAs;dGs;lnaAs;dGs;lnaTs;dCs;lnaCs;dAs;lnaCs;dAs;lnaT-Sup
35	Oligo2	FXN-325	CCAGGAG GCCGGCT ACTGCG	Internal	FXN	human	dCs;lnaCs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaCs;dGs;lnaGs;dCs;lnaTs;dAs;lnaCs;dTs;lnaGs;dCs;lnaG-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
36	Oligo3	FXN-326	CTGGGCT GGGCTGG GTGACG	Internal	FXN	human	dCs;lnaTs;dGs;lnaG s;dGs;lnaCs;dTs;lna Gs;dGs;lnaGs;dCs;l naTs;dGs;lnaGs;dG s;lnaTs;dGs;lnaAs;d Cs;lnaG-Sup
37	Oligo4	FXN-327	ACCCGGG TGAGGGT CTGGGC	Internal	FXN	human	dAs;lnaCs;dCs;lnaC s;dGs;lnaGs;dGs;ln aTs;dGs;lnaAs;dGs;l naGs;dGs;lnaTs;dCs ;lnaTs;dGs;lnaGs;d Gs;lnaC-Sup
38	Oligo5	FXN-328	CCAACTCT GCCGGCC GCGGG	Internal	FXN	human	dCs;lnaCs;dAs;lnaA s;dCs;lnaTs;dCs;lna Ts;dGs;lnaCs;dCs;ln aGs;dGs;lnaCs;dCs;l naGs;dCs;lnaGs;dG s;lnaG-Sup
39	Oligo6	FXN-329	ACGGCGG CCGCAGA GTGGGG	Internal	FXN	human	dAs;lnaCs;dGs;lnaG s;dCs;lnaGs;dGs;lna Cs;dCs;lnaGs;dCs;ln aAs;dGs;lnaAs;dGs; lnaTs;dGs;lnaGs;dG s;lnaG-Sup
40	Oligo7	FXN-330	TCGATGT CGGTGCG CAGGCC	Internal	FXN	human	dTs;lnaCs;dGs;lnaA s;dTs;lnaGs;dTs;lna Cs;dGs;lnaGs;dTs;ln aGs;dCs;lnaGs;dCs;l naAs;dGs;lnaGs;dC s;lnaC-Sup
41	Oligo8	FXN-331	GGCGGGG CGTGCAG GTCGCA	Internal	FXN	human	dGs;lnaGs;dCs;lnaG s;dGs;lnaGs;dGs;ln aCs;dGs;lnaTs;dGs;l naCs;dAs;lnaGs;dG s;lnaTs;dCs;lnaGs;d Cs;lnaA-Sup
42	Oligo9	FXN-332	ACGTTGG TTCGAACT TGCGC	Internal	FXN	human	dAs;lnaCs;dGs;lnaT s;dTs;lnaGs;dGs;lna Ts;dTs;lnaCs;dGs;ln aAs;dAs;lnaCs;dTs;l naTs;dGs;lnaCs;dGs ;lnaC-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
43	Oligo10	FXN-333	TTCCAAATCTGGTTGAGGCC	Internal	FXN	human	dTs;lnaTs;dCs;lnaCs;dAs;lnaAs;dAs;lnaTs;dCs;lnaTs;dGs;lnaGs;dTs;lnaTs;dGs;lnaAs;dGs;lnaGs;dCs;lnaC-Sup
44	Oligo11	FXN-334	AGACACTCTGCTTTTTGACA	Internal	FXN	human	dAs;lnaGs;dAs;lnaCs;dAs;lnaCs;dTs;lnaCs;dTs;lnaGs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaAs;dCs;lnaA-Sup
45	Oligo12	FXN-335	TTTCCTCAAATTCATCAAAT	Internal	FXN	human	dTs;lnaTs;dTs;lnaCs;dCs;lnaTs;dCs;lnaAs;dAs;lnaAs;dTs;lnaTs;dCs;lnaAs;dTs;lnaCs;dAs;lnaAs;dAs;lnaT-Sup
46	Oligo13	FXN-336	GGGTGGCCCAAAGTTCCAGA	Internal	FXN	human	dGs;lnaGs;dGs;lnaTs;dGs;lnaGs;dCs;lnaCs;dCs;lnaAs;dAs;lnaAs;dGs;lnaTs;dTs;lnaCs;dCs;lnaAs;dGs;lnaA-Sup
47	Oligo14	FXN-337	TGGTCTCATCTAGAGAGCCT	Internal	FXN	human	dTs;lnaGs;dGs;lnaTs;dCs;lnaTs;dCs;lnaAs;dTs;lnaCs;dTs;lnaAs;dGs;lnaAs;dGs;lnaAs;dGs;lnaCs;dCs;lnaT-Sup
48	Oligo15	FXN-338	CTCTGCTAGTCTTTCATAGG	Internal	FXN	human	dCs;lnaTs;dCs;lnaTs;dGs;lnaCs;dTs;lnaAs;dGs;lnaTs;dCs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dGs;lnaG-Sup
49	Oligo16	FXN-339	GCTAAAGAGTCCAGCGTTTC	Internal	FXN	human	dGs;lnaCs;dTs;lnaAs;dAs;lnaAs;dGs;lnaAs;dGs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dTs;lnaTs;dTs;lnaC-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
50	Oligo17	FXN-340	GCAAGGTCTTCAAAAAACTCT	Internal	FXN	human	dGs;lnaCs;dAs;lnaAs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dCs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaCs;dTs;lnaCs;dT-Sup
51	Oligo18	FXN-341	CTCAAACGTGTATGGCTTGTCT	Internal	FXN	human	dCs;lnaTs;dCs;lnaAs;dAs;lnaAs;dCs;lnaGs;dTs;lnaGs;dTs;lnaAs;dTs;lnaGs;dGs;lnaCs;dTs;lnaTs;dGs;lnaTs;dCs;lnaT-Sup
52	Oligo19	FXN-342	CCCAAAGGAGACATCATAGTC	Internal	FXN	human	dCs;lnaCs;dCs;lnaAs;dAs;lnaAs;dGs;lnaGs;dAs;lnaGs;dAs;lnaCs;dAs;lnaTs;dCs;lnaAs;dTs;lnaAs;dGs;lnaTs;dC-Sup
53	Oligo20	FXN-343	CAGTTTGACAGTTAAGACACCACT	Internal	FXN	human	dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dGs;lnaAs;dCs;lnaAs;dGs;lnaTs;dTs;lnaAs;dAs;lnaGs;dAs;lnaCs;dAs;lnaCs;dCs;lnaAs;dCs;lnaT-Sup
54	Oligo21	FXN-344	ATAGGTTCCTAGATCTCCACC	Internal	FXN	human	dAs;lnaTs;dAs;lnaGs;dGs;lnaTs;dTs;lnaCs;dCs;lnaTs;dAs;lnaGs;dAs;lnaTs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dC-Sup
55	Oligo22	FXN-345	GGCGTCTGCTTGTTGATCAC	Internal	FXN	human	dGs;lnaGs;dCs;lnaGs;dTs;lnaCs;dTs;lnaGs;dCs;lnaTs;dTs;lnaGs;dTs;lnaTs;dGs;lnaAs;dTs;lnaCs;dAs;lnaC-Sup
56	Oligo23	FXN-346	AAGATAGCCAGATTTGCTTGTTT	Internal	FXN	human	dAs;lnaAs;dGs;lnaAs;dTs;lnaAs;dGs;lnaCs;dCs;lnaAs;dGs;lnaAs;dTs;lnaTs;dTs;lnaGs;dCs;lnaTs;dTs;lnaGs;dTs;lnaTs;dT-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
57	Oligo24	FXN-347	GGTCCAC TACATACC TGGATGG AG	Internal	FXN	human	dGs;lnaGs;dTs;lnaC s;dCs;lnaAs;dCs;lna Ts;dAs;lnaCs;dAs;ln aTs;dAs;lnaCs;dCs;l naTs;dGs;lnaGs;dAs ;lnaTs;dGs;lnaGs;d As;lnaG-Sup
58	Oligo25	FXN-348	CCCAGTC CAGTCAT AACGCTT	Internal	FXN	human	dCs;lnaCs;dCs;lnaA s;dGs;lnaTs;dCs;lna Cs;dAs;lnaGs;dTs;ln aCs;dAs;lnaTs;dAs;l naAs;dCs;lnaGs;dCs ;lnaTs;dT-Sup
59	Oligo26	FXN-349	CGTGGGA GTACACC CAGTTTTT	Internal	FXN	human	dCs;lnaGs;dTs;lnaG s;dGs;lnaGs;dAs;lna Gs;dTs;lnaAs;dCs;ln aAs;dCs;lnaCs;dCs;l naAs;dGs;lnaTs;dTs ;lnaTs;dTs;lnaT-Sup
60	Oligo27	FXN-350	CATGGAG GGACACG CCGT	Internal	FXN	human	dCs;lnaAs;dTs;lnaG s;dGs;lnaAs;dGs;lna Gs;dGs;lnaAs;dCs;l naAs;dCs;lnaGs;dCs ;lnaCs;dGs;lnaT-Sup
61	Oligo28	FXN-351	GTGAGCT CTGCGGC CAGCAGC T	Internal	FXN	human	dGs;lnaTs;dGs;lnaA s;dGs;lnaCs;dTs;lna Cs;dTs;lnaGs;dCs;ln aGs;dGs;lnaCs;dCs;l naAs;dGs;lnaCs;dAs ;lnaGs;dCs;lnaT-Sup
62	Oligo29	FXN-352	AGTTTGG TTTTTAAG GCTTTA	Internal	FXN	human	dAs;lnaGs;dTs;lnaT s;dTs;lnaGs;dGs;lna Ts;dTs;lnaTs;dTs;ln aTs;dAs;lnaAs;dGs;l naGs;dCs;lnaTs;dTs ;lnaTs;dA-Sup
63	Oligo30	FXN-353	TAGGCCA AGGAAGA CAAGTCC	Internal	FXN	human	dTs;lnaAs;dGs;lnaG s;dCs;lnaCs;dAs;lna As;dGs;lnaGs;dAs;l naAs;dGs;lnaAs;dCs ;lnaAs;dAs;lnaGs;d Ts;lnaCs;dC-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
64	Oligo31	FXN-354	TCAAGCA TCTTTTCC GGAA	Internal	FXN	human	dTs;lnaCs;dAs;lnaA s;dGs;lnaCs;dAs;lna Ts;dCs;lnaTs;dTs;ln aTs;dTs;lnaCs;dCs;l naGs;dGs;lnaAs;dA-Sup
65	Oligo32	FXN-355	TCCTTAAA ACGGGGC TGGGCA	Internal	FXN	human	dTs;lnaCs;dCs;lnaTs ;dTs;lnaAs;dAs;lnaA s;dAs;lnaCs;dGs;lna Gs;dGs;lnaGs;dCs;l naTs;dGs;lnaGs;dG s;lnaCs;dA-Sup
66	Oligo33	FXN-356	TTGGCCT GATAGCT TTTAATG	Internal	FXN	human	dTs;lnaTs;dGs;lnaG s;dCs;lnaCs;dTs;lna Gs;dAs;lnaTs;dAs;ln aGs;dCs;lnaTs;dTs;l naTs;dTs;lnaAs;dAs ;lnaTs;dG-Sup
67	Oligo34	FXN-357	CCTCAGCT GCATAAT GAAGCTG GGGTC	Internal	FXN	human	dCs;lnaCs;dTs;lnaCs ;dAs;lnaGs;dCs;lnaT s;dGs;lnaCs;dAs;lna Ts;dAs;lnaAs;dTs;ln aGs;dAs;lnaAs;dGs; lnaCs;dTs;lnaGs;dG s;lnaGs;dGs;lnaTs;d C-Sup
68	Oligo35	FXN-358	AACAACA ACAACAA CAAAAAA CAGA	Internal	FXN	human	dAs;lnaAs;dCs;lnaA s;dAs;lnaCs;dAs;lna As;dCs;lnaAs;dAs;ln aCs;dAs;lnaAs;dCs;l naAs;dAs;lnaAs;dAs ;lnaAs;dAs;lnaCs;d As;lnaGs;dA-Sup
69	Oligo36	FXN-359	CCTCAAA AGCAGGA ATAAAAA AAATA	Internal	FXN	human	dCs;lnaCs;dTs;lnaCs ;dAs;lnaAs;dAs;lna As;dGs;lnaCs;dAs;ln aGs;dGs;lnaAs;dAs; lnaTs;dAs;lnaAs;dA s;lnaAs;dAs;lnaAs;d As;lnaAs;dTs;lnaA-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
70	Oligo37	FXN-360	GCTGTGACACATAGCCCAACTGT	Internal	FXN	human	dGs;lnaCs;dTs;lnaGs;dTs;lnaGs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dAs;lnaGs;dCs;lnaCs;dCs;lnaAs;dAs;lnaCs;dTs;lnaGs;dT-Sup
71	Oligo38	FXN-361	GGAGGCAACACATTCTTTCTACAGA	Internal	FXN	human	dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dTs;lnaTs;dCs;lnaTs;dTs;lnaTs;dCs;lnaTs;dAs;lnaCs;dAs;lnaGs;dA-Sup
72	Oligo39	FXN-362	CTATTAATATTACTG	Intron	FXN	human	dCs;lnaTs;dAs;lnaTs;dTs;lnaAs;dAs;lnaTs;dAs;lnaTs;dTs;lnaAs;dCs;lnaTs;dG-Sup
73	Oligo40	FXN-363	CATTATGTGTATGTAT	Intron	FXN	human	dCs;lnaAs;dTs;lnaTs;dAs;lnaTs;dGs;lnaTs;dGs;lnaTs;dAs;lnaTs;dGs;lnaTs;dAs;lnaT-Sup
74	Oligo41	FXN-364	TTTATCTATGTTATT	Intron	FXN	human	dTs;lnaTs;dTs;lnaAs;dTs;lnaCs;dTs;lnaAs;dTs;lnaGs;dTs;lnaTs;dAs;lnaTs;dT-Sup
75	Oligo42	FXN-365	CTAATTTGAAGTTCT	Intron	FXN	human	dCs;lnaTs;dAs;lnaAs;dTs;lnaTs;dTs;lnaGs;dAs;lnaAs;dGs;lnaTs;dTs;lnaCs;dT-Sup
76	Oligo43	FXN-366	TTCGAACTTGCGCGG	Exon Spanning	FXN	human	dTs;lnaTs;dCs;lnaGs;dAs;lnaAs;dCs;lnaTs;dTs;lnaGs;dCs;lnaGs;dCs;lnaGs;dG-Sup
77	Oligo44	FXN-367	TAGAGAGCCTGGGT	Exon Spanning	FXN	human	dTs;lnaAs;dGs;lnaAs;dGs;lnaAs;dGs;lnaCs;dCs;lnaTs;dGs;lnaGs;dGs;lnaT-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
78	Oligo45	FXN-368	ACACCAC TCCCAAA G	Exon Spanning	FXN	human	dAs;lnaCs;dAs;lnaC s;dCs;lnaAs;dCs;lna Ts;dCs;lnaCs;dCs;ln aAs;dAs;lnaAs;dG-Sup
79	Oligo46	FXN-369	AGGTCCA CTACATAC	Exon Spanning	FXN	human	dAs;lnaGs;dGs;lnaT s;dCs;lnaCs;dAs;lna Cs;dTs;lnaAs;dCs;ln aAs;dTs;lnaAs;dC-Sup
80	Oligo47	FXN-370	CGTTAAC CTGGATG G	Exon Spanning	FXN	human	dCs;lnaGs;dTs;lnaT s;dAs;lnaAs;dCs;lna Cs;dTs;lnaGs;dGs;ln aAs;dTs;lnaGs;dG-Sup
81	Oligo81	FXN-404	AAAGCCT TAAAAAC C	Antisens e	FXN	human	dAs;lnaAs;dAs;lnaG s;dCs;lnaCs;dTs;lna Ts;dAs;lnaAs;dAs;ln aAs;dAs;lnaCs;dC-Sup
82	Oligo82	FXN-405	TCAGGCC AAGACCC C	Antisens e	FXN	human	dTs;lnaCs;dAs;lnaG s;dGs;lnaCs;dCs;lna As;dAs;lnaGs;dAs;l naCs;dCs;lnaCs;dC-Sup
83	Oligo83	FXN-406	CCCAGCTT CATTATG	Antisens e	FXN	human	dCs;lnaCs;dCs;lnaA s;dGs;lnaCs;dTs;lna Ts;dCs;lnaAs;dTs;ln aTs;dAs;lnaTs;dG-Sup
84	Oligo84	FXN-407	AATGTGT TGCCTCCT	Antisens e	FXN	human	dAs;lnaAs;dTs;lnaG s;dTs;lnaGs;dTs;lna Ts;dGs;lnaCs;dCs;ln aTs;dCs;lnaCs;dT-Sup
85	Oligo85	FXN-408	AAAAAGC AAAATAA T	Antisens e	FXN	human	dAs;lnaAs;dAs;lnaA s;dAs;lnaGs;dCs;lna As;dAs;lnaAs;dAs;ln aTs;dAs;lnaAs;dT-Sup
86	Oligo86	FXN-409	CCAGGAG GGAAAAT G	Antisens e	FXN	human	dCs;lnaCs;dAs;lnaG s;dGs;lnaAs;dGs;lna Gs;dGs;lnaAs;dAs;l naAs;dAs;lnaTs;dG-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
87	Oligo87	FXN-410	TAAAGGGTAGCCTAC	Antisense	FXN	human	dTs;lnaAs;dAs;lnaAs;dGs;lnaGs;dGs;lnaTs;dAs;lnaGs;dCs;lnaCs;dTs;lnaAs;dC-Sup
88	Oligo88	FXN-411	AAAGCAACAAGCCTC	Antisense	FXN	human	dAs;lnaAs;dAs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaAs;dGs;lnaCs;dCs;lnaTs;dC-Sup
89	Oligo89	FXN-412	ATAACATCATACATG	Antisense	FXN	human	dAs;lnaTs;dAs;lnaAs;dCs;lnaAs;dTs;lnaCs;dAs;lnaTs;dAs;lnaCs;dAs;lnaTs;dG-Sup
90	Oligo90	FXN-413	GATACTATCTTCCTC	Antisense	FXN	human	dGs;lnaAs;dTs;lnaAs;dCs;lnaTs;dAs;lnaTs;dCs;lnaTs;dTs;lnaCs;dCs;lnaTs;dC-Sup
91	Oligo91	FXN-414	ATGGGGGACGGGGCA	Antisense	FXN	human	dAs;lnaTs;dGs;lnaGs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dA-Sup
92	Oligo92	FXN-415	GGTTGAGACTGGGTG	Antisense	FXN	human	dGs;lnaGs;dTs;lnaTs;dGs;lnaAs;dGs;lnaAs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dG-Sup
93	Oligo93	FXN-416	AGACTGAAGAGGTGC	Antisense	FXN	human	dAs;lnaGs;dAs;lnaCs;dTs;lnaGs;dAs;lnaAs;dGs;lnaAs;dGs;lnaGs;dTs;lnaGs;dC-Sup
94	Oligo94	FXN-417	CGGGACGGCTGTGTT	Antisense	FXN	human	dCs;lnaGs;dGs;lnaGs;dAs;lnaCs;dGs;lnaGs;dCs;lnaTs;dGs;lnaTs;dGs;lnaTs;dT-Sup
95	Oligo95	FXN-418	TCTGTGTGGGCAGCA	Antisense	FXN	human	dTs;lnaCs;dTs;lnaGs;dTs;lnaGs;dTs;lnaGs;dGs;lnaGs;dCs;lnaAs;dGs;lnaCs;dA-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
96	Oligo96	FXN-419	AAAGCCTTAAAAACC	Antisense	FXN	human	lnaAs;lnaAs;lnaAs;dGs;dCs;dCs;dTs;dTs;dAs;dAs;dAs;dAs;lnaAs;lnaCs;lnaC-Sup
97	Oligo97	FXN-420	TCAGGCCAAGACCCC	Antisense	FXN	human	lnaTs;lnaCs;lnaAs;dGs;dGs;dCs;dCs;dAs;dAs;dGs;dAs;dCs;lnaCs;lnaCs;lnaC-Sup
98	Oligo98	FXN-421	CCCAGCTTCATTATG	Antisense	FXN	human	lnaCs;lnaCs;lnaCs;dAs;dGs;dCs;dTs;dTs;dCs;dAs;dTs;dTs;lnaAs;lnaTs;lnaG-Sup
99	Oligo99	FXN-422	AATGTGTTGCCTCCT	Antisense	FXN	human	lnaAs;lnaAs;lnaTs;dGs;dTs;dGs;dTs;dTs;dGs;dCs;dCs;dTs;lnaCs;lnaCs;lnaT-Sup
100	Oligo100	FXN-423	AAAAAGCAAAATAAT	Antisense	FXN	human	lnaAs;lnaAs;lnaAs;dAs;dAs;dGs;dCs;dAs;dAs;dAs;dAs;dTs;lnaAs;lnaAs;lnaT-Sup
101	Oligo101	FXN-424	CCAGGAGGGAAAATG	Antisense	FXN	human	lnaCs;lnaCs;lnaAs;dGs;dGs;dAs;dGs;dGs;dGs;dAs;dAs;dAs;lnaAs;lnaTs;lnaG-Sup
102	Oligo102	FXN-425	TAAAGGGTAGCCTAC	Antisense	FXN	human	lnaTs;lnaAs;lnaAs;dAs;dGs;dGs;dGs;dTs;dAs;dGs;dCs;dCs;lnaTs;lnaAs;lnaC-Sup
103	Oligo103	FXN-426	AAAGCAACAAGCCTC	Antisense	FXN	human	lnaAs;lnaAs;lnaAs;dGs;dCs;dAs;dAs;dCs;dAs;dAs;dGs;dCs;lnaCs;lnaTs;lnaC-Sup
104	Oligo104	FXN-427	ATAACATCATACATG	Antisense	FXN	human	lnaAs;lnaTs;lnaAs;dAs;dCs;dAs;dTs;dCs;dAs;dTs;dAs;dCs;lnaAs;lnaTs;lnaG-Sup

SEQ ID NO	Oligo Name	Alternative Oligo Name	Base Sequence	Targeting Region	Gene Name	Organism	Formatted Sequence
105	Oligo105	FXN-428	GATACTATCTTCCTC	Antisense	FXN	human	lnaGs;lnaAs;lnaTs;dAs;dCs;dTs;dAs;dTs;dCs;dTs;dTs;dCs;lnaCs;lnaTs;lnaC-Sup
106	Oligo106	FXN-429	ATGGGGGACGGGGCA	Antisense	FXN	human	lnaAs;lnaTs;lnaGs;dGs;dGs;dGs;dGs;dAs;dCs;dGs;dGs;dGs;lnaGs;lnaCs;lnaA-Sup
107	Oligo107	FXN-430	GGTTGAGACTGGGTG	Antisense	FXN	human	lnaGs;lnaGs;lnaTs;dTs;dGs;dAs;dGs;dAs;dCs;dTs;dGs;dGs;lnaGs;lnaTs;lnaG-Sup
108	Oligo108	FXN-431	AGACTGAAGAGGTGC	Antisense	FXN	human	lnaAs;lnaGs;lnaAs;dCs;dTs;dGs;dAs;dAs;dGs;dAs;dGs;dGs;lnaTs;lnaGs;lnaC-Sup
109	Oligo109	FXN-432	CGGGACGGCTGTGTT	Antisense	FXN	human	lnaCs;lnaGs;lnaGs;dGs;dAs;dCs;dGs;dGs;dCs;dTs;dGs;dTs;lnaGs;lnaTs;lnaT-Sup
110	Oligo110	FXN-433	TCTGTGTGGGCAGCA	Antisense	FXN	human	lnaTs;lnaCs;lnaTs;dGs;dTs;dGs;dTs;dGs;dGs;dGs;dCs;dAs;lnaGs;lnaCs;lnaA-Sup
111	Oligo111	FXN-115	GAAGAAGAAGAAGAA	Antisense	FXN	human	lnaGs;lnaAs;lnaAs;dGs;dAs;dAs;dGs;dAs;dAs;dGs;dAs;dAs;lnaGs;lnaAs;lnaA-Sup
112	Oligo112	FXN-117	TTCTTCTTCTTCTTC	Antisense	FXN	human	lnaTs;lnaTs;lnaCs;dTs;dTs;dCs;dTs;dTs;dCs;dTs;dTs;dCs;lnaTs;lnaTs;lnaC-Sup

Table 5: Oligonucleotide modifications

Symbol	Feature Description
bio	5' biotin
dAs	DNA w/3' thiophosphate

Symbol	Feature Description
dCs	DNA w/3' thiophosphate
dGs	DNA w/3' thiophosphate
dTs	DNA w/3' thiophosphate
dG	DNA
enaAs	ENA w/3' thiophosphate
enaCs	ENA w/3' thiophosphate
enaGs	ENA w/3' thiophosphate
enaTs	ENA w/3' thiophosphate
fluAs	2'-fluoro w/3' thiophosphate
fluCs	2'-fluoro w/3' thiophosphate
fluGs	2'-fluoro w/3' thiophosphate
fluUs	2'-fluoro w/3' thiophosphate
lnaAs	LNA w/3' thiophosphate
lnaCs	LNA w/3' thiophosphate
lnaGs	LNA w/3' thiophosphate
lnaTs	LNA w/3' thiophosphate
omeAs	2'-OMe w/3' thiophosphate
omeCs	2'-OMe w/3' thiophosphate
omeGs	2'-OMe w/3' thiophosphate
omeTs	2'-OMe w/3' thiophosphate
lnaAs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaCs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaGs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaTs-Sup	LNA w/3' thiophosphate at 3' terminus
lnaA-Sup	LNA w/3' OH at 3' terminus
lnaC-Sup	LNA w/3' OH at 3' terminus
lnaG-Sup	LNA w/3' OH at 3' terminus
lnaT-Sup	LNA w/3' OH at 3' terminus
omeA-Sup	2'-OMe w/3' OH at 3' terminus
omeC-Sup	2'-OMe w/3' OH at 3' terminus

Symbol	Feature Description
omeG-Sup	2'-OMe w/3' OH at 3' terminus
omeU-Sup	2'-OMe w/3' OH at 3' terminus
dAs-Sup	DNA w/3' thiophosphate at 3' terminus
dCs-Sup	DNA w/3' thiophosphate at 3' terminus
dGs-Sup	DNA w/3' thiophosphate at 3' terminus
dTs-Sup	DNA w/3' thiophosphate at 3' terminus
dA-Sup	DNA w/3' OH at 3' terminus
dC-Sup	DNA w/3' OH at 3' terminus
dG-Sup	DNA w/3' OH at 3' terminus
dT-Sup	DNA w/3' OH at 3' terminus

***In vitro* transfection of cells with oligonucleotides**

Cells were seeded into each well of 24-well plates at a density of 25,000 cells per 500uL and transfections were performed with Lipofectamine and the single stranded oligonucleotides. Control wells contained Lipofectamine alone. At time points post-transfection, approximately 200 uL of cell culture supernatants were stored at -80 C for ELISA or Western blot analysis and RNA was harvested from another aliquot of cells and quantitative PCR was carried out as outlined above. The percent induction of target mRNA expression by each oligonucleotide was determined by normalizing mRNA levels in the presence of the oligonucleotide to the mRNA levels in the presence of control (Lipofectamine alone).

As a control, the oligos were tested for cytotoxic effects. It was determined that cell transfected with oligos did not demonstrate cytotoxicity at either 100 or 400 nM oligo concentrations (FIG. 15).

RESULTS:

In vitro delivery of single stranded oligonucleotides that target the 5' and 3' end of FXN mRNA upregulated FXN expression

FXN was chosen as an exemplary target for RNA stabilization because FXN is a housekeeping gene that is challenging to upregulate. Oligonucleotides were designed against the putative 5' and 3' ends of FXN mRNA using the methods described above. The 3' and 5' oligos were first tested separately and then in combination.

The 3' and 5' oligos were initially screened in a cell line from a patient having Friedreich's Ataxia (Cell line GM03816). FIGs. 7 and 8 show the results from transfecting the cell line with FXN 3' end targeting oligonucleotides, demonstrating that several 3' oligos were capable of upregulating FXN mRNA. Oligos 73, 75, 76, and 77 were shown to upregulate FXN mRNA to the greatest extent. Upon examination of the sequences of these four oligos, it was determined that oligos 73, 75, 76, and 77 contained poly-T sequences (FIG. 9). It was hypothesized that these oligos bound to the 3' most end before the poly A tail, thus protecting the 3' end from degradation. These results demonstrate that oligos designed to target the 3' end can upregulate FXN expression. These results also suggest that oligos that target the 3'-most end directly adjacent to or overlapping with a poly-A tail can upregulate mRNA levels.

FIG. 10 shows the results from transfecting the GM03816 cell line with FXN 5' end targeting oligonucleotides, demonstrating that several 5' oligos are capable of upregulating FXN mRNA expression. FIGS. 11 and 12 show the results of screening FXN 5' end oligos in combination with FXN 3' oligo 75 in the GM03816 cell line. The combination of oligos 51 and 75, 52 and 75, 57 and 75, and 62 and 75 showed the highest upregulation of FXN mRNA expression. Upon examination of the sequences of the 5' oligos, it was determined that oligos 51, 52, 57, and 62 all contained the motif CGCCCTCCAG, which mapped to a putatitive 5' start site for a FXN mRNA isoform (FIG. 13). It was hypothesized that the oligos bound at the 5'-most end of the FXN mRNA, thus protecting the 5' end from degradation. Oligo 62 contained a very long overhang sequence beyond the motif, which was hypothesized to form a loop structure that further protected the 5'-end by interacting with the 5' methylguanosine cap (FIG. 14). These results suggest that targeting of the 5'-most end of an mRNA (which may be adjacent to a 5' methylguanosine cap) is effective for upregulating mRNA.

Next, a screening of the combination of positive oligo hits from previous 5' and 3' experiments was performed in the GM03816 FRDA patient cell line. It was determined that the FXN mRNA levels for several of the oligo combinations tested approached the levels of

FXN mRNA in the GM0321B normal fibroblast cells, indicating that these oligo combinations were capable of upregulating FXN mRNA (FIG. 16). The levels of FXN mRNA at two and three days post transfection were then measured and it was confirmed that an increased steady state FXN mRNA levels was observed at 2 and 3 days post transfection (FIG. 17). The positive hits were then validated and shown to be effective in a second cell line, GM04078 FRDA patient fibroblasts (FIG. 18). Lastly a validation of the hits was performed in a 'normal' cell line, GM0321B fibroblasts. It was found that the oligos could upregulate FXN mRNA even in a normal cell line (FIG. 19). Together, these results suggest that combinations of 5' and 3' targeting oligos are capable of upregulating FXN expression and that these combinations can be, in some instances, more effective than the use of 5' or 3' oligos alone.

An exemplary 5' and 3' oligo combination, oligo 62 and oligo 77, was chosen for further optimization. All concentrations were shown to upregulate FXN in the GM03816 FRDA patient cell line and showed an increased steady-state of FXN mRNA levels at 2-3 days post transfection (FIG. 20). These results suggest that the oligos are effective over a wide range of concentrations, from 10 nM to 400 nM.

Next the effects of individual oligos and combinations of oligos on protein levels of FXN were investigated. GM03816 FRDA patient fibroblasts were treated with single oligos at 100 nM or two oligos at 200 nM final and the level of FXN protein was measured. Several single oligos and combinations of oligos were shown to upregulate FXN protein expression to some degree. The treatment with the combinations of oligos 52 and 75, oligos 64 and 52, oligos 51 and 76, oligos 52 and 76, oligos 62 and 77, and oligos 62 and 76, caused significant upregulation of FXN protein at day 3 post transfection (FIGs. 21 and 22). These results suggest that 5' and 3' targeting oligos are capable of upregulating FXN protein levels.

Next, the stability of FXN mRNA in the presence of different oligos was measured. It was hypothesized that the oligos were increasing FXN mRNA stability, rather than increasing the transcription of the FXN mRNA. To test this, cells were transfected with oligos in the presence of the transcription inhibitor Actinomycin D (ActD). The oligo combinations 62 and 75, 52 and 75, and 57 and 75 had higher levels of FXN mRNA in the presence of ActD, indicating that FXN mRNA was more stable in cells treated with the oligo combinations (FIGs. 23 and 24) than untreated cells.

Lastly, several oligo combinations were tested in additional cell lines. One set of cell lines was obtained from a patient with Friedreich's ataxia (cell line GM15850) and from their unaffected sibling (cell line GM15851). The other cell lines were obtained from a patient with Friedreich's ataxia (cell line GM16209) and from their unaffected half-sibling (cell line GM16222). It was found that treatment with the combination of oligos 52 and 76, the combination of oligos 57 and 76, and the combination of oligos 62 and 76 significantly upregulated FXN mRNA levels (FIG. 25). In the GM15850 cell line, the levels of FXN mRNA in cells treated with either oligos 52 and 76 or oligos 57 and 76 approached the levels of the FXN mRNA in cells from the unaffected sibling. These results further indicate the efficacy of 5' and 3' end targeting oligonucleotides in upregulating FXN mRNA.

Overall, these results show that 5' and 3' end targeting oligos are effective for upregulating mRNA and protein expression and that this upregulation of expression is likely through stabilization of the mRNA.

As an additional experiment, the 5' and 3' end targeting oligos were further combined with other oligos specific for sequences within the FXN gene (Table 6). The upregulation of the 5' and 3' oligos was further enhanced upon addition of subsets of these other oligos, suggesting that providing oligos that target multiple regions of an RNA or gene locus, e.g., a 5' targeting oligo, a 3' targeting oligo, and an internal targeting oligo, may be an additional method for upregulating mRNA expression levels (FIG. 26).

Table 6: Other targeting FXN

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Organism	Formatted Sequence
113	324	CGGCGCCCGAGAG TCCACAT	FXN	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaCs;dCs;lnaCs;dGs;lnaAs;dGs;lnaAs;dGs;lnaTs;dCs;lnaCs;dAs;lnaCs;dAs;lnaT-Sup
114	329	ACGGCGGCCGCAG AGTGGGG	FXN	human	dAs;lnaCs;dGs;lnaGs;dCs;lnaGs;dGs;lnaCs;dCs;lnaGs;dCs;lnaAs;dGs;lnaAs;dGs;lnaTs;dGs;lnaGs;dGs;lnaG-Sup
115	359	CCTCAAAAGCAGGA ATAAAAAAAATA	FXN	human	dCs;lnaCs;dTs;lnaCs;dAs;lnaAs;dAs;lnaAs;dGs;lnaCs;dAs;lnaGs;dGs;lnaAs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaAs;dTs;lnaA-Sup

116	414	ATGGGGGACGGGGCA	FXN	human	dAs;lnaTs;dGs;lnaGs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dA-Sup
117	415	GGTTGAGACTGGGTG	FXN	human	dGs;lnaGs;dTs;lnaTs;dGs;lnaAs;dGs;lnaAs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dG-Sup
118	429	ATGGGGGACGGGGCA	FXN	human	dAs;lnaTs;dGs;lnaGs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dA-Sup

Example 3. Further oligonucleotide experiments related to FXN

The experiments conducted in Example 3 utilized the same methods as Example 2, except that the oligonucleotide concentrations used were 10 and 40 nm. Transfection with 10 or 40 nM of an oligo was found to not be cytoxic to the cells at day 2 and day 3 post-transfection (FIG. 38).

3' and 5' end targeting oligos were screened at 10 and 40 nM concentrations and FXN mRNA was measured at 2 and 3 days post-transfection. A subset of oligos were found to be capable of upregulating FXN mRNA at doses of 10 or 40 nM (FIGS. 27-29).

A screening of combinations of 5' and 3' end oligos was also performed at 10 and 40 nM concentrations and FXN mRNA was measured at 2 and 3 days post-transfection. A subset of oligo combinations were found to be capable of upregulating FXN mRNA at doses of 10 or 40 nM (FIGs. 30-33).

Other oligos that target FXN, e.g., internally, close to a poly-A tail, or spanning an exon, were also found to be capable of upregulating FXN mRNA at doses of 10 or 40 nM (FIG. 34).

Additional experiments were performed to further demonstrate that FXN mRNA levels can be increased using a single oligonucleotide or combinations of oligonucleotides at 10 and 40 nM concentrations (FIGs. 35-37).

Next, 5' and 3' end targeting oligos were tested individually for their capability to upregulate FXN protein levels at 10 and 40 nM concentrations. It was determined that a subset of oligos were capable of upregulating FXN protein levels at 2 and 3 days post-transfection at 10 and 40 nM concentrations (FIGs. 39 and 40). The results indicate that 5' and 3' targeting oligos, and combinations thereof, are capable to upregulating FXN mRNA and protein even at concentrations as low as 10 nM.

Example 4. Further oligonucleotides for increasing mRNA stability

Several additional oligonucleotides were designed to target the 5' end of an RNA, the 3' end of an RNA, or target both the 5' end and 3' end of an RNA ("bridging oligos"). These oligos are shown in Table 7.

Oligonucleotides specific for KLF4 were tested by treating cells with each oligo. Several KLF4 oligos were able to upregulate KLF4 mRNA levels in the treated cells (FIG. 41). A subset of the KLF4 oligos were also able to upregulate KLF4 protein levels in the treated cells (FIG. 42). These results show that 5' and 3' targeting oligos were able to upregulate mRNA and protein levels for KLF4, demonstrating that 5' and 3' targeting oligos are generally useful for upregulating expression of an RNA (and also the corresponding protein).

In addition, expression levels of KLF4 mRNA were evaluated in cells treated with KLF4 5' and 3' end targeting oligos, including circularized oligonucleotides targeting both 5' and 3' ends of KLF4, and individual oligonucleotides targeting 5' and 3' ends of KLF4. Results are shown in FIG. 43.

KLF4 5' and 3' end oligos were transfected to Hep3B cells at 30nM concentration using RNAimax. RNA analysis was done with Cells-to-Ct kit (Life Technologies) using KLF4 and ACTIN (housekeeper control) primers purchased from Life Technologies. Western for KLF4 protein was done with KLF4 rabbit (Cell Signaling 4038S).

Table 7: Oligonucleotides designed to target 5' and 3' ends of RNAs

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
119	FXN-437 m02	TGACCCAAGGGAGACTT TTTGGTTTTTAAGGCTTT	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaGs;dTs;lnaT s;dTs;lnaTs;dTs;lnaAs;dA s;lnaGs;dGs;lnaCs;dTs;ln aTs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
120	FXN-438 m02	TGGCCACTGGCCGCATT TTTGGTTTTTAAGGCTTT	FXN	5′ and 3′	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaGs;dTs;lnaT s;dTs;lnaTs;dTs;lnaAs;dA s;lnaGs;dGs;lnaCs;dTs;ln aTs;dT-Sup
121	FXN-439 m02	CGGCGACCCCTGGTGTT TTTGGTTTTTAAGGCTTT	FXN	5′ and 3′	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dGs;lnaGs;dTs;lnaTs; dTs;lnaTs;dTs;lnaAs;dAs; lnaGs;dGs;lnaCs;dTs;lnaT s;dT-Sup
122	FXN-440 m02	CGCCCTCCAGCGCTGTT TTTGGTTTTTAAGGCTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs; lnaTs;dCs;lnaCs;dAs;lnaG s;dCs;lnaGs;dCs;lnaTs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaGs;dTs;lnaTs;d Ts;lnaTs;dTs;lnaAs;dAs;l naGs;dGs;lnaCs;dTs;lnaT s;dT-Sup
123	FXN-441 m02	CGCTCCGCCCTCCAGTTT TTGGTTTTTAAGGCTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaGs;dTs;lnaTs;d Ts;lnaTs;dTs;lnaAs;dAs;l naGs;dGs;lnaCs;dTs;lnaT s;dT-Sup
124	FXN-442 m02	TGACCCAAGGGAGACTT TTTGGGGTCTTGGCCTG A	FXN	5′ and 3′	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaGs;dGs;lnaG s;dTs;lnaCs;dTs;lnaTs;dG s;lnaGs;dCs;lnaCs;dTs;ln aGs;dA-Sup
125	FXN-443 m02	TGGCCACTGGCCGCATT TTTGGGGTCTTGGCCTG A	FXN	5′ and 3′	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaGs;dGs;lnaG s;dTs;lnaCs;dTs;lnaTs;dG s;lnaGs;dCs;lnaCs;dTs;ln aGs;dA-Sup

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126	FXN-444 m02	CGGCGACCCCTGGTGTTTTTGGGGTCTTGGCCTGA	FXN	5′ and 3′	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dGs;lnaGs;dCs;lnaCs;dTs;lnaGs;dA-Sup
127	FXN-445 m02	CGCCCTCCAGCGCTGTTTTTGGGGTCTTGGCCTGA	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dGs;lnaGs;dCs;lnaCs;dTs;lnaGs;dA-Sup
128	FXN-446 m02	CGCTCCGCCCTCCAGTTTTTGGGGTCTTGGCCTGA	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dGs;lnaGs;dCs;lnaCs;dTs;lnaGs;dA-Sup
129	FXN-447 m02	TGACCCAAGGGAGACTTTTTCATAATGAAGCTGGG	FXN	5′ and 3′	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup
130	FXN-448 m02	TGGCCACTGGCCGCATTTTTCATAATGAAGCTGGG	FXN	5′ and 3′	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup
131	FXN-449 m02	CGGCGACCCCTGGTGTTTTTCATAATGAAGCTGGG	FXN	5′ and 3′	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
132	FXN-450 m02	CGCCCTCCAGCGCTGTTTTTCATAATGAAGCTGGG	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup
133	FXN-451 m02	CGCTCCGCCCTCCAGTTTTTCATAATGAAGCTGGG	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dGs;lnaGs;dG-Sup
134	FXN-452 m02	TGACCCAAGGGAGACTTTTTAGGAGGCAACACATT	FXN	5′ and 3′	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dT-Sup
135	FXN-453 m02	TGGCCACTGGCCGCATTTTTAGGAGGCAACACATT	FXN	5′ and 3′	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dT-Sup
136	FXN-454 m02	CGGCGACCCCTGGTGTTTTTAGGAGGCAACACATT	FXN	5′ and 3′	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dT-Sup
137	FXN-455 m02	CGCCCTCCAGCGCTGTTTTTAGGAGGCAACACATT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dCs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dT-Sup

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138	FXN-456 m02	CGCTCCGCCCTCCAGTTT TTAGGAGGCAACACATT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaGs;dGs;lnaAs; dGs;lnaGs;dCs;lnaAs;dAs ;lnaCs;dAs;lnaCs;dAs;lna Ts;dT-Sup
139	FXN-457 m02	TGACCCAAGGGAGACTT TTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dAs;lnaTs;dTs;lnaAs ;dTs;lnaTs;dTs;lnaTs;dGs ;lnaCs;dTs;lnaTs;dTs;lnaT s;dT-Sup
140	FXN-458 m02	TGGCCACTGGCCGCATT TTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dAs;lnaTs;dTs;lnaAs ;dTs;lnaTs;dTs;lnaTs;dGs ;lnaCs;dTs;lnaTs;dTs;lnaT s;dT-Sup
141	FXN-459 m02	CGGCGACCCCTGGTGTT TTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dAs;lnaTs;dTs;lnaAs; dTs;lnaTs;dTs;lnaTs;dGs;l naCs;dTs;lnaTs;dTs;lnaTs ;dT-Sup
142	FXN-460 m02	CGCCCTCCAGCGCTGTT TTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs; lnaTs;dCs;lnaCs;dAs;lnaG s;dCs;lnaGs;dCs;lnaTs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaTs;dTs;lnaAs;d Ts;lnaTs;dTs;lnaTs;dGs;ln aCs;dTs;lnaTs;dTs;lnaTs; dT-Sup
143	FXN-461 m02	CGCTCCGCCCTCCAGTTT TTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaTs;dTs;lnaAs;d Ts;lnaTs;dTs;lnaTs;dGs;ln aCs;dTs;lnaTs;dTs;lnaTs; dT-Sup

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144	FXN-462 m02	TGACCCAAGGGAGACTT TTTCATTTTCCCTCCTGG	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dCs;lnaAs;dTs;lnaTs ;dTs;lnaTs;dCs;lnaCs;dCs ;lnaTs;dCs;lnaCs;dTs;lna Gs;dG-Sup
145	FXN-463 m02	TGGCCACTGGCCGCATT TTTCATTTTCCCTCCTGG	FXN	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dCs;lnaAs;dTs;lnaTs ;dTs;lnaTs;dCs;lnaCs;dCs ;lnaTs;dCs;lnaCs;dTs;lna Gs;dG-Sup
146	FXN-464 m02	CGGCGACCCCTGGTGTT TTTCATTTTCCCTCCTGG	FXN	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dCs;lnaAs;dTs;lnaTs; dTs;lnaTs;dCs;lnaCs;dCs;l naTs;dCs;lnaCs;dTs;lnaG s;dG-Sup
147	FXN-465 m02	CGCCCTCCAGCGCTGTT TTTCATTTTCCCTCCTGG	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs; lnaTs;dCs;lnaCs;dAs;lnaG s;dCs;lnaGs;dCs;lnaTs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dCs;lnaAs;dTs;lnaTs;d Ts;lnaTs;dCs;lnaCs;dCs;ln aTs;dCs;lnaCs;dTs;lnaGs; dG-Sup
148	FXN-466 m02	CGCTCCGCCCTCCAGTTT TTCATTTTCCCTCCTGG	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dCs;lnaAs;dTs;lnaTs;d Ts;lnaTs;dCs;lnaCs;dCs;ln aTs;dCs;lnaCs;dTs;lnaGs; dG-Sup
149	FXN-467 m02	TGACCCAAGGGAGACTT TTTGTAGGCTACCCTTTA	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaTs;dAs;lnaG s;dGs;lnaCs;dTs;lnaAs;dC s;lnaCs;dCs;lnaTs;dTs;lna Ts;dA-Sup

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150	FXN-468 m02	TGGCCACTGGCCGCATT TTTGTAGGCTACCCTTTA	FXN	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaTs;dAs;lnaG s;dGs;lnaCs;dTs;lnaAs;dC s;lnaCs;dCs;lnaTs;dTs;lna Ts;dA-Sup
151	FXN-469 m02	CGGCGACCCCTGGTGTT TTTGTAGGCTACCCTTTA	FXN	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dGs;lnaTs;dAs;lnaGs; dGs;lnaCs;dTs;lnaAs;dCs; lnaCs;dCs;lnaTs;dTs;lnaT s;dA-Sup
152	FXN-470 m02	CGCCCTCCAGCGCTGTT TTTGTAGGCTACCCTTTA	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs; lnaTs;dCs;lnaCs;dAs;lnaG s;dCs;lnaGs;dCs;lnaTs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaTs;dAs;lnaGs;d Gs;lnaCs;dTs;lnaAs;dCs;l naCs;dCs;lnaTs;dTs;lnaTs ;dA-Sup
153	FXN-471 m02	CGCTCCGCCCTCCAGTTT TTGTAGGCTACCCTTTA	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaTs;dAs;lnaGs;d Gs;lnaCs;dTs;lnaAs;dCs;l naCs;dCs;lnaTs;dTs;lnaTs ;dA-Sup
154	FXN-472 m02	TGACCCAAGGGAGACTT TTTGAGGCTTGTTGCTTT	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaAs;dGs;lnaG s;dCs;lnaTs;dTs;lnaGs;dT s;lnaTs;dGs;lnaCs;dTs;ln aTs;dT-Sup
155	FXN-473 m02	TGGCCACTGGCCGCATT TTTGAGGCTTGTTGCTTT	FXN	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dGs;lnaAs;dGs;lnaG s;dCs;lnaTs;dTs;lnaGs;dT s;lnaTs;dGs;lnaCs;dTs;ln aTs;dT-Sup

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156	FXN-474 m02	CGGCGACCCCTGGTGTT TTTGAGGCTTGTTGCTTT	FXN	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dGs;lnaAs;dGs;lnaGs ;dCs;lnaTs;dTs;lnaGs;dTs ;lnaTs;dGs;lnaCs;dTs;lna Ts;dT-Sup
157	FXN-475 m02	CGCCCTCCAGCGCTGTT TTTGAGGCTTGTTGCTTT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs; lnaTs;dCs;lnaCs;dAs;lnaG s;dCs;lnaGs;dCs;lnaTs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaAs;dGs;lnaGs; dCs;lnaTs;dTs;lnaGs;dTs; lnaTs;dGs;lnaCs;dTs;lnaT s;dT-Sup
158	FXN-476 m02	CGCTCCGCCCTCCAGTTT TTGAGGCTTGTTGCTTT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaTs;dCs; lnaCs;dGs;lnaCs;dCs;lnaC s;dTs;lnaCs;dCs;lnaAs;dG s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaAs;dGs;lnaGs; dCs;lnaTs;dTs;lnaGs;dTs; lnaTs;dGs;lnaCs;dTs;lnaT s;dT-Sup
159	FXN-477 m02	TGACCCAAGGGAGACTT TTTCATGTATGATGTTAT	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs; lnaCs;dAs;lnaAs;dGs;lna Gs;dGs;lnaAs;dGs;lnaAs; dCs;lnaTs;dTs;lnaTs;dTs;l naTs;dCs;lnaAs;dTs;lnaG s;dTs;lnaAs;dTs;lnaGs;dA s;lnaTs;dGs;lnaTs;dTs;lna As;dT-Sup
160	FXN-478 m02	TGGCCACTGGCCGCATT TTTCATGTATGATGTTAT	FXN	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaAs;dCs;lnaTs;dGs;lna Gs;dCs;lnaCs;dGs;lnaCs; dAs;lnaTs;dTs;lnaTs;dTs;l naTs;dCs;lnaAs;dTs;lnaG s;dTs;lnaAs;dTs;lnaGs;dA s;lnaTs;dGs;lnaTs;dTs;lna As;dT-Sup
161	FXN-479 m02	CGGCGACCCCTGGTGTT TTTCATGTATGATGTTAT	FXN	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dGs ;lnaAs;dCs;lnaCs;dCs;lna Cs;dTs;lnaGs;dGs;lnaTs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dCs;lnaAs;dTs;lnaGs; dTs;lnaAs;dTs;lnaGs;dAs; lnaTs;dGs;lnaTs;dTs;lnaA s;dT-Sup

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162	FXN-480 m02	CGCCCTCCAGCGCTGTTTTTCATGTATGATGTTAT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dTs;lnaGs;dAs;lnaTs;dGs;lnaTs;dTs;lnaAs;dT-Sup
163	FXN-481 m02	CGCTCCGCCCTCCAGTTTTTCATGTATGATGTTAT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dTs;lnaGs;dAs;lnaTs;dGs;lnaTs;dTs;lnaAs;dT-Sup
164	FXN-482 m02	CGCCCTCCAGTTTTTGGTTTTTAAG	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaAs;dG-Sup
165	FXN-483 m02	CGCCCTCCAGTTTTTGGGGTCTTGG	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaGs;dGs;lnaTs;dCs;lnaTs;dTs;lnaGs;dG-Sup
166	FXN-484 m02	CGCCCTCCAGTTTTTCATAATGAAG	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dAs;lnaAs;dTs;lnaGs;dAs;lnaAs;dG-Sup
167	FXN-485 m02	CGCCCTCCAGTTTTTAGGAGGCAAC	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dAs;lnaAs;dC-Sup
168	FXN-486 m02	CGCCCTCCAGTTTTTATTATTTTGC	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
169	FXN-487 m02	CGCCCTCCAGTTTTTCATTTTCCCT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaCs;dCs;lnaCs;dT-Sup
170	FXN-488 m02	CGCCCTCCAGTTTTTGTAGGCTACC	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaAs;dGs;lnaGs;dCs;lnaTs;dAs;lnaCs;dC-Sup
171	FXN-489 m02	CGCCCTCCAGTTTTTGAGGCTTGTT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dAs;lnaGs;dGs;lnaCs;dTs;lnaTs;dGs;lnaTs;dT-Sup
172	FXN-490 m02	CGCCCTCCAGTTTTTCATGTATGAT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaTs;dGs;lnaAs;dT-Sup
173	FXN-491 m02	TGACCCAAGGGAGACTTTTTTTTTTT	FXN	5' and 3'	human	dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dT-Sup
174	FXN-492 m02	TGGCCACTGGCCGCATTTTTTTTTTT	FXN	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dT-Sup
175	FXN-493 m02	CGGCGACCCCTGGTGTTTTTTTTTTT	FXN	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dT-Sup
176	FXN-494 m02	CGCCCTCCAGCGCTGTTTTTTTTTTT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dT-Sup

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177	FXN-495 m02	CGCTCCGCCCTCCAGTTTTTTTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dT-Sup
178	FXN-496 m02	AAAATAAACAACAAC	FXN	UTR	human	dAs;lnaAs;dAs;lnaAs;dTs;lnaAs;dAs;lnaAs;dCs;lnaAs;dAs;lnaCs;dAs;lnaAs;dC-Sup
179	FXN-497 m02	AGGAATAAAAAAAATA	FXN	UTR	human	dAs;lnaGs;dGs;lnaAs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaAs;dTs;lnaA-Sup
180	FXN-498 m02	TCAAAAGCAGGAATA	FXN	UTR	human	dTs;lnaCs;dAs;lnaAs;dAs;lnaAs;dGs;lnaCs;dAs;lnaGs;dGs;lnaAs;dAs;lnaTs;dA-Sup
181	FXN-499 m02	ACTGTCCTCAAAAGC	FXN	UTR	human	dAs;lnaCs;dTs;lnaGs;dTs;lnaCs;dCs;lnaTs;dCs;lnaAs;dAs;lnaAs;dAs;lnaGs;dC-Sup
182	FXN-500 m02	AGCCCAACTGTCCTC	FXN	UTR	human	dAs;lnaGs;dCs;lnaCs;dCs;lnaAs;dAs;lnaCs;dTs;lnaGs;dTs;lnaCs;dCs;lnaTs;dC-Sup
183	FXN-501 m02	TGACACATAGCCCAA	FXN	UTR	human	dTs;lnaGs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dAs;lnaGs;dCs;lnaCs;dCs;lnaAs;dA-Sup
184	FXN-502 m02	GAGCTGTGACACATA	FXN	UTR	human	dGs;lnaAs;dGs;lnaCs;dTs;lnaGs;dTs;lnaGs;dAs;lnaCs;dAs;lnaCs;dAs;lnaTs;dA-Sup
185	FXN-503 m02	TCTGGGCCTGGGCTG	FXN	UTR/internal	human	dTs;lnaCs;dTs;lnaGs;dGs;lnaGs;dCs;lnaCs;dTs;lnaGs;dGs;lnaGs;dCs;lnaTs;dG-Sup
186	FXN-504 m02	GGTGAGGGTCTGGGC	FXN	UTR/internal	human	dGs;lnaGs;dTs;lnaGs;dAs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaGs;dGs;lnaGs;dC-Sup
187	FXN-505 m02	GGGACCCGGGTGAGG	FXN	UTR/internal	human	dGs;lnaGs;dGs;lnaAs;dCs;lnaCs;dCs;lnaGs;dGs;lnaGs;dTs;lnaGs;dAs;lnaGs;dG-Sup
188	FXN-506 m02	CCGGCCGCGGGACCC	FXN	UTR/internal	human	dCs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dGs;lnaAs;dCs;lnaCs;dC-Sup

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189	FXN-507 m02	CAACTCTGCCGGCCG	FXN	UTR/internal	human	dCs;lnaAs;dAs;lnaCs;dTs;lnaCs;dTs;lnaGs;dCs;lnaCs;dGs;lnaGs;dCs;lnaCs;dG-Sup
190	FXN-508 m02	AGTGGGGCCAACTCT	FXN	UTR/internal	human	dAs;lnaGs;dTs;lnaGs;dGs;lnaGs;dGs;lnaCs;dCs;lnaAs;dAs;lnaCs;dTs;lnaCs;dT-Sup
191	FXN-509 m02	GGCCGCAGAGTGGGG	FXN	UTR/internal	human	dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaGs;dAs;lnaGs;dTs;lnaGs;dGs;lnaGs;dG-Sup
192	FXN-510 m02	GCCACGGCGGCCGCA	FXN	UTR/internal	human	dGs;lnaCs;dCs;lnaAs;dCs;lnaGs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dA-Sup
193	FXN-511 m02	GTGCGCAGGCCACGG	FXN	UTR/internal	human	dGs;lnaTs;dGs;lnaCs;dGs;lnaCs;dAs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaGs;dG-Sup
194	FXN-512 m02	GGGGGACGGGGCAGG	FXN	intron	human	dGs;lnaGs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dG-Sup
195	FXN-513 m02	GGGACGGGGCAGGTT	FXN	intron	human	dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dGs;lnaTs;dT-Sup
196	FXN-514 m02	GACGGGGCAGGTTGA	FXN	intron	human	dGs;lnaAs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dGs;lnaTs;dTs;lnaGs;dA-Sup
197	FXN-515 m02	CGGGGCAGGTTGAGA	FXN	intron	human	dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dGs;lnaTs;dTs;lnaGs;dAs;lnaGs;dA-Sup
198	FXN-516 m02	GGGCAGGTTGAGACT	FXN	intron	human	dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dGs;lnaTs;dTs;lnaGs;dAs;lnaGs;dAs;lnaCs;dT-Sup
199	FXN-517 m02	GCAGGTTGAGACTGG	FXN	intron	human	dGs;lnaCs;dAs;lnaGs;dGs;lnaTs;dTs;lnaGs;dAs;lnaGs;dAs;lnaCs;dTs;lnaGs;dG-Sup
200	FXN-518 m02	AGGTTGAGACTGGGT	FXN	intron	human	dAs;lnaGs;dGs;lnaTs;dTs;lnaGs;dAs;lnaGs;dAs;lnaCs;dTs;lnaGs;dGs;lnaGs;dT-Sup

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201	FXN-519 m02	GGAAAAATTCCAGGA	FXN	Antisense /UTR	human	dGs;lnaGs;dAs;lnaAs;dAs;lnaAs;dAs;lnaTs;dTs;lnaCs;dCs;lnaAs;dGs;lnaGs;dA-Sup
202	FXN-520 m02	AATTCCAGGAGGGAA	FXN	Antisense /UTR	human	dAs;lnaAs;dTs;lnaTs;dCs;lnaCs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dA-Sup
203	FXN-521 m02	GAGGGAAAATGAATT	FXN	Antisense /UTR	human	dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaTs;dT-Sup
204	FXN-522 m02	GAAAATGAATTGTCTTC	FXN	Antisense /UTR	human	dGs;lnaAs;dAs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaTs;dTs;lnaGs;dTs;lnaCs;dTs;lnaTs;dC-Sup
205	FXN-512 m08	GGGGGACGGGGCAGG	FXN	intron	human	lnaGs;lnaGs;lnaGs;dGs;dGs;dAs;dCs;dGs;dGs;dGs;dGs;dCs;lnaAs;lnaGs;lnaG-Sup
206	FXN-513 m08	GGGACGGGGCAGGTT	FXN	intron	human	lnaGs;lnaGs;lnaGs;dAs;dCs;dGs;dGs;dGs;dGs;dCs;dAs;dGs;lnaGs;lnaTs;lnaT-Sup
207	FXN-514 m08	GACGGGGCAGGTTGA	FXN	intron	human	lnaGs;lnaAs;lnaCs;dGs;dGs;dGs;dGs;dCs;dAs;dGs;dGs;dTs;lnaTs;lnaGs;lnaA-Sup
208	FXN-515 m08	CGGGGCAGGTTGAGA	FXN	intron	human	lnaCs;lnaGs;lnaGs;dGs;dGs;dCs;dAs;dGs;dGs;dTs;dTs;dGs;lnaAs;lnaGs;lnaA-Sup
209	FXN-516 m08	GGGCAGGTTGAGACT	FXN	intron	human	lnaGs;lnaGs;lnaGs;dCs;dAs;dGs;dGs;dTs;dTs;dGs;dAs;dGs;lnaAs;lnaCs;lnaT-Sup
210	FXN-517 m08	GCAGGTTGAGACTGG	FXN	intron	human	lnaGs;lnaCs;lnaAs;dGs;dGs;dTs;dTs;dGs;dAs;dGs;dAs;dCs;lnaTs;lnaGs;lnaG-Sup
211	FXN-518 m08	AGGTTGAGACTGGGT	FXN	intron	human	lnaAs;lnaGs;lnaGs;dTs;dTs;dGs;dAs;dGs;dAs;dCs;dTs;dGs;lnaGs;lnaGs;lnaT-Sup
212	FXN-519 m08	GGAAAAATTCCAGGA	FXN	Antisense /UTR	human	lnaGs;lnaGs;lnaAs;dAs;dAs;dAs;dAs;dTs;dTs;dCs;dCs;dAs;lnaGs;lnaGs;lnaA-Sup

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213	FXN-520 m08	AATTCCAGGAGGGAA	FXN	Antisense /UTR	human	lnaAs;lnaAs;lnaTs;dTs;dCs;dCs;dAs;dGs;dGs;dAs;dGs;dGs;lnaGs;lnaAs;lnaA-Sup
214	FXN-521 m08	GAGGGAAAATGAATT	FXN	Antisense /UTR	human	lnaGs;lnaAs;lnaGs;dGs;dGs;dAs;dAs;dAs;dAs;dTs;dGs;dAs;lnaAs;lnaTs;lnaT-Sup
215	FXN-522 m08	GAAAATGAATTGTCTTC	FXN	Antisense /UTR	human	lnaGs;lnaAs;lnaAs;dAs;dAs;dTs;dGs;dAs;dAs;dTs;dTs;dGs;dTs;dCs;lnaTs;lnaTs;lnaC-Sup
216	EPO-37 m02	GGTGGTTTCAGTTCT	EPO	3’	human	dGs;lnaGs;dTs;lnaGs;dGs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaTs;dTs;lnaCs;dT-Sup
217	EPO-38 m02	TTTTTGGTGGTTTCAGTTCT	EPO	3’	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaTs;dGs;lnaGs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dTs;lnaTs;dCs;lnaT-Sup
218	EPO-39 m02	AGCGTGCTATCTGGG	EPO	5’	human	dAs;lnaGs;dCs;lnaGs;dTs;lnaGs;dCs;lnaTs;dAs;lnaTs;dCs;lnaTs;dGs;lnaGs;dG-Sup
219	EPO-40 m02	TGGCCCAGGGACTCT	EPO	5’	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaCs;dAs;lnaGs;dGs;lnaGs;dAs;lnaCs;dTs;lnaCs;dT-Sup
220	EPO-41 m02	TCTGCGGCTCTGGC	EPO	5’	human	dTs;lnaCs;dTs;lnaGs;dCs;lnaGs;dGs;lnaCs;dTs;lnaCs;dTs;lnaGs;dGs;lnaC-Sup
221	EPO-42 m02	CGGTCCGGCTCTGGG	EPO	5’	human	dCs;lnaGs;dGs;lnaTs;dCs;lnaCs;dGs;lnaGs;dCs;lnaTs;dCs;lnaTs;dGs;lnaGs;dG-Sup
222	EPO-43 m02	TCATCCCGGGAAGCT	EPO	5’	human	dTs;lnaCs;dAs;lnaTs;dCs;lnaCs;dCs;lnaGs;dGs;lnaGs;dAs;lnaAs;dGs;lnaCs;dT-Sup
223	EPO-44 m02	CCCCAAGTCCCCGCT	EPO	5’	human	dCs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaTs;dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dT-Sup
224	EPO-45 m02	CCAACCATGCAAGCA	EPO	5’	human	dCs;lnaCs;dAs;lnaAs;dCs;lnaCs;dAs;lnaTs;dGs;lnaCs;dAs;lnaAs;dGs;lnaCs;dA-Sup

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225	EPO-46 m02	TGGCCCAGGGACTCTTC	EPO	5'	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaCs;dAs;lnaGs;dGs;lnaGs;dAs;lnaCs;dTs;lnaCs;dTs;lnaTs;dC-Sup
226	EPO-47 m02	CGGTCCGGCTCTGGGTTC	EPO	5'	human	dCs;lnaGs;dGs;lnaTs;dCs;lnaCs;dGs;lnaGs;dCs;lnaTs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dTs;lnaC-Sup
227	EPO-48 m02	CCAACCATGCAAGCACC	EPO	5'	human	dCs;lnaCs;dAs;lnaAs;dCs;lnaCs;dAs;lnaTs;dGs;lnaCs;dAs;lnaAs;dGs;lnaCs;dAs;lnaCs;dC-Sup
228	EPO-49 m02	TGGCCCAGGGACTCTCACAAAGTGAC	EPO	5'	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaCs;dAs;lnaGs;dGs;lnaGs;dAs;lnaCs;dTs;lnaCs;dTs;lnaCs;dAs;dCs;dAs;dAs;dAs;dGs;dTs;lnaGs;dAs;lnaC-Sup
229	EPO-50 m02	CGGTCCGGCTCTGGGAAGAAACTTTC	EPO	5'	human	dCs;lnaGs;dGs;lnaTs;dCs;lnaCs;dGs;lnaGs;dCs;lnaTs;dCs;lnaTs;dGs;lnaGs;dGs;lnaAs;dAs;dGs;dAs;dAs;dAs;dCs;dTs;lnaTs;dTs;lnaC-Sup
230	EPO-51 m02	CCAACCATGCAAGCACTCAAAGAGTC	EPO	5'	human	dCs;lnaCs;dAs;lnaAs;dCs;lnaCs;dAs;lnaTs;dGs;lnaCs;dAs;lnaAs;dGs;lnaCs;dAs;lnaCs;dTs;dCs;dAs;dAs;dAs;dGs;dAs;lnaGs;dTs;lnaC-Sup
231	EPO-52 m02	TGGCCCAGGGACTCTTTTTGGTGGTTTCAGTTCT	EPO	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs;lnaCs;dAs;lnaGs;dGs;lnaGs;dAs;lnaCs;dTs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaTs;dGs;lnaGs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dTs;lnaTs;dCs;lnaT-Sup
232	EPO-53 m02	CGGTCCGGCTCTGGGTTTTTGGTGGTTTCAGTTCT	EPO	5' and 3'	human	dCs;lnaGs;dGs;lnaTs;dCs;lnaCs;dGs;lnaGs;dCs;lnaTs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dTs;lnaGs;dGs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaTs;dTs;lnaCs;dT-Sup

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233	EPO-54 m02	CCAACCATGCAAGCATT TTTGGTGGTTTCAGTTCT	EPO	5' and 3'	human	dCs;lnaCs;dAs;lnaAs;dCs; lnaCs;dAs;lnaTs;dGs;lnaC s;dAs;lnaAs;dGs;lnaCs;d As;lnaTs;dTs;lnaTs;dTs;ln aTs;dGs;lnaGs;dTs;lnaGs; dGs;lnaTs;dTs;lnaTs;dCs; lnaAs;dGs;lnaTs;dTs;lnaC s;dT-Sup
234	EPO-55 m02	CAGGGACTCTTTTTGGT GGTTTCA	EPO	5' and 3'	human	dCs;lnaAs;dGs;lnaGs;dGs ;lnaAs;dCs;lnaTs;dCs;lna Ts;dTs;lnaTs;dTs;lnaTs;d Gs;lnaGs;dTs;lnaGs;dGs;l naTs;dTs;lnaTs;dCs;lnaA-Sup
235	EPO-56 m02	CGGCTCTGGGTTTTTGG TGGTTTCA	EPO	5' and 3'	human	dCs;lnaGs;dGs;lnaCs;dTs; lnaCs;dTs;lnaGs;dGs;lna Gs;dTs;lnaTs;dTs;lnaTs;d Ts;lnaGs;dGs;lnaTs;dGs;l naGs;dTs;lnaTs;dTs;lnaC s;dA-Sup
236	EPO-57 m02	CATGCAAGCATTTTTGG TGGTTTCA	EPO	5' and 3'	human	dCs;lnaAs;dTs;lnaGs;dCs; lnaAs;dAs;lnaGs;dCs;lna As;dTs;lnaTs;dTs;lnaTs;d Ts;lnaGs;dGs;lnaTs;dGs;l naGs;dTs;lnaTs;dTs;lnaC s;dA-Sup
237	EPO-58 m02	TGGCCCAGGGACTCGGT GGTTTCAGTTCT	EPO	5' and 3'	human	dTs;lnaGs;dGs;lnaCs;dCs; lnaCs;dAs;lnaGs;dGs;lna Gs;dAs;lnaCs;dTs;lnaCs;d Gs;lnaGs;dTs;lnaGs;dGs;l naTs;dTs;lnaTs;dCs;lnaAs ;dGs;lnaTs;dTs;lnaCs;dT-Sup
238	EPO-59 m02	CGGTCCGGCTCTGGTGG TGGTTTCAGTTCT	EPO	5' and 3'	human	dCs;lnaGs;dGs;lnaTs;dCs; lnaCs;dGs;lnaGs;dCs;lna Ts;dCs;lnaTs;dGs;lnaGs;d Ts;lnaGs;dGs;lnaTs;dGs;l naGs;dTs;lnaTs;dTs;lnaC s;dAs;lnaGs;dTs;lnaTs;dC s;lnaT-Sup
239	EPO-60 m02	CCAACCATGCAAGCAGG TGGTTTCAGTTCT	EPO	5' and 3'	human	dCs;lnaCs;dAs;lnaAs;dCs; lnaCs;dAs;lnaTs;dGs;lnaC s;dAs;lnaAs;dGs;lnaCs;d As;lnaGs;dGs;lnaTs;dGs;l naGs;dTs;lnaTs;dTs;lnaC s;dAs;lnaGs;dTs;lnaTs;dC s;lnaT-Sup

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240	KLF4-31 m02	TTTTTAGATAAAATATTA TA	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dAs;lnaTs;dAs;lnaTs;dTs;lnaAs;dTs;lnaA-Sup
241	KLF4-32 m02	TTTTTATTCAGATAAAAT A	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dCs;lnaAs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dAs;lnaTs;dA-Sup
242	KLF4-33 m02	TTTTTGGTTTATTTAAAA CT	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaTs;dTs;lnaTs;dAs;lnaTs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dCs;lnaT-Sup
243	KLF4-34 m02	TTTTTAAATTTATATTAC AT	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaAs;dTs;lnaTs;dTs;lnaAs;dTs;lnaAs;dTs;lnaTs;dAs;lnaCs;dAs;lnaT-Sup
244	KLF4-35 m02	TTTTTCTTAAATTTATAT TA	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dTs;lnaTs;dAs;lnaAs;dAs;lnaTs;dTs;lnaTs;dAs;lnaTs;dAs;lnaTs;dTs;lnaA-Sup
245	KLF4-36 m02	TTTTTCACAAAATGTTCA TT	KLF4	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaCs;dAs;lnaAs;dAs;lnaAs;dTs;lnaGs;dTs;lnaTs;dCs;lnaAs;dTs;lnaT-Sup
246	KLF4-37 m02	CCTCCGCCTTCTCCC	KLF4	5'	human	dCs;lnaCs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dC-Sup
247	KLF4-38 m02	TCTGGTCGGGAAACT	KLF4	5'	human	dTs;lnaCs;dTs;lnaGs;dGs;lnaTs;dCs;lnaGs;dGs;lnaGs;dAs;lnaAs;dAs;lnaCs;dT-Sup
248	KLF4-39 m02	GCTACAGCCTTTTCC	KLF4	5'	human	dGs;lnaCs;dTs;lnaAs;dCs;lnaAs;dGs;lnaCs;dCs;lnaTs;dTs;lnaTs;dTs;lnaCs;dC-Sup
249	KLF4-40 m02	CCTCCGCCTTCTCCCC	KLF4	5'	human	dCs;lnaCs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dCs;lnaC-Sup
250	KLF4-41 m02	TCTGGTCGGGAAACTCC	KLF4	5'	human	dTs;lnaCs;dTs;lnaGs;dGs;lnaTs;dCs;lnaGs;dGs;lnaGs;dAs;lnaAs;dAs;lnaCs;dTs;lnaCs;dC-Sup

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251	KLF4-42 m02	GCTACAGCCTTTTCCC	KLF4	5'	human	dGs;lnaCs;dTs;lnaAs;dCs; lnaAs;dGs;lnaCs;dCs;lnaT s;dTs;lnaTs;dTs;lnaCs;dC s;lnaC-Sup
252	KLF4-43 m02	CCTCCGCCTTCTCCCTCT TTGATC	KLF4	5'	human	dCs;lnaCs;dTs;lnaCs;dCs; lnaGs;dCs;lnaCs;dTs;lnaT s;dCs;lnaTs;dCs;lnaCs;dC s;lnaTs;dCs;dTs;dTs;dTs; dGs;lnaAs;dTs;lnaC-Sup
253	KLF4-44 m02	TCTGGTCGGGAAACTCA ATTATTGTC	KLF4	5'	human	dTs;lnaCs;dTs;lnaGs;dGs; lnaTs;dCs;lnaGs;dGs;lna Gs;dAs;lnaAs;dAs;lnaCs; dTs;lnaCs;dAs;dAs;dTs;d Ts;dAs;dTs;dTs;lnaGs;dT s;lnaC-Sup
254	KLF4-45 m02	GCTACAGCCTTTTCCACT TTGTTC	KLF4	5'	human	dGs;lnaCs;dTs;lnaAs;dCs; lnaAs;dGs;lnaCs;dCs;lnaT s;dTs;lnaTs;dTs;lnaCs;dC s;lnaAs;dCs;dTs;dTs;dTs; dGs;lnaTs;dTs;lnaC-Sup
255	KLF4-46 m02	CCTCCGCCTTCTCCCTTT TTAGATAAAATATTATA	KLF4	5' and 3'	human	dCs;lnaCs;dTs;lnaCs;dCs; lnaGs;dCs;lnaCs;dTs;lnaT s;dCs;lnaTs;dCs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaGs;dAs;lnaTs;d As;lnaAs;dAs;lnaAs;dTs;l naAs;dTs;lnaTs;dAs;lnaTs ;dA-Sup
256	KLF4-47 m02	TCTGGTCGGGAAACTTT TTAGATAAAATATTATA	KLF4	5' and 3'	human	dTs;lnaCs;dTs;lnaGs;dGs; lnaTs;dCs;lnaGs;dGs;lna Gs;dAs;lnaAs;dAs;lnaCs; dTs;lnaTs;dTs;lnaTs;dTs;l naAs;dGs;lnaAs;dTs;lnaA s;dAs;lnaAs;dAs;lnaTs;dA s;lnaTs;dTs;lnaAs;dTs;lna A-Sup
257	KLF4-48 m02	GCTACAGCCTTTTCCTTT TTAGATAAAATATTATA	KLF4	5' and 3'	human	dGs;lnaCs;dTs;lnaAs;dCs; lnaAs;dGs;lnaCs;dCs;lnaT s;dTs;lnaTs;dTs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaGs;dAs;lnaTs;d As;lnaAs;dAs;lnaAs;dTs;l naAs;dTs;lnaTs;dAs;lnaTs ;dA-Sup

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258	KLF4-49 m02	CCTCCGCCTTCTCCCTTT TTGGTTTATTTAAAACT	KLF4	5' and 3'	human	dCs;lnaCs;dTs;lnaCs;dCs; lnaGs;dCs;lnaCs;dTs;lnaT s;dCs;lnaTs;dCs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaGs;dTs;lnaTs;d Ts;lnaAs;dTs;lnaTs;dTs;ln aAs;dAs;lnaAs;dAs;lnaCs; dT-Sup
259	KLF4-50 m02	TCTGGTCGGGAAACTTT TTGGTTTATTTAAAACT	KLF4	5' and 3'	human	dTs;lnaCs;dTs;lnaGs;dGs; lnaTs;dCs;lnaGs;dGs;lna Gs;dAs;lnaAs;dAs;lnaCs; dTs;lnaTs;dTs;lnaTs;dTs;l naGs;dGs;lnaTs;dTs;lnaT s;dAs;lnaTs;dTs;lnaTs;dA s;lnaAs;dAs;lnaAs;dCs;ln aT-Sup
260	KLF4-51 m02	GCTACAGCCTTTTCCTTT TTGGTTTATTTAAAACT	KLF4	5' and 3'	human	dGs;lnaCs;dTs;lnaAs;dCs; lnaAs;dGs;lnaCs;dCs;lnaT s;dTs;lnaTs;dTs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dGs;lnaGs;dTs;lnaTs;d Ts;lnaAs;dTs;lnaTs;dTs;ln aAs;dAs;lnaAs;dAs;lnaCs; dT-Sup
261	KLF4-52 m02	CCTCCGCCTTCTCCCTTT TTAAATTTATATTACAT	KLF4	5' and 3'	human	dCs;lnaCs;dTs;lnaCs;dCs; lnaGs;dCs;lnaCs;dTs;lnaT s;dCs;lnaTs;dCs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaAs;dAs;lnaTs;d Ts;lnaTs;dAs;lnaTs;dAs;l naTs;dTs;lnaAs;dCs;lnaA s;dT
262	KLF4-53 m02	TCTGGTCGGGAAACTTT TTAAATTTATATTACAT	KLF4	5' and 3'	human	dTs;lnaCs;dTs;lnaGs;dGs; lnaTs;dCs;lnaGs;dGs;lna Gs;dAs;lnaAs;dAs;lnaCs; dTs;lnaTs;dTs;lnaTs;dTs;l naAs;dAs;lnaAs;dTs;lnaT s;dTs;lnaAs;dTs;lnaAs;dT s;lnaTs;dAs;lnaCs;dAs;ln aT-Sup
263	KLF4-54 m02	GCTACAGCCTTTTCCTTT TTAAATTTATATTACAT	KLF4	5' and 3'	human	dGs;lnaCs;dTs;lnaAs;dCs; lnaAs;dGs;lnaCs;dCs;lnaT s;dTs;lnaTs;dTs;lnaCs;dC s;lnaTs;dTs;lnaTs;dTs;lna Ts;dAs;lnaAs;dAs;lnaTs;d Ts;lnaTs;dAs;lnaTs;dAs;l naTs;dTs;lnaAs;dCs;lnaA s;dT-Sup

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264	KLF4-55 m02	GCCTTCTCCCTTTTTAGA TAAAATA	KLF4	5' and 3'	human	dGs;lnaCs;dCs;lnaTs;dTs; lnaCs;dTs;lnaCs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaAs;dGs;lnaAs;dTs;lna As;dAs;lnaAs;dAs;lnaTs;d A-Sup
265	KLF4-56 m02	TCGGGAAACTTTTTAGA TAAAATA	KLF4	5' and 3'	human	dTs;lnaCs;dGs;lnaGs;dGs ;lnaAs;dAs;lnaAs;dCs;lna Ts;dTs;lnaTs;dTs;lnaTs;d As;lnaGs;dAs;lnaTs;dAs;l naAs;dAs;lnaAs;dTs;lnaA -Sup
266	KLF4-57 m02	AGCCTTTTCCTTTTTAGA TAAAATA	KLF4	5' and 3'	human	dAs;lnaGs;dCs;lnaCs;dTs; lnaTs;dTs;lnaTs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaAs;dGs;lnaAs;dTs;lna As;dAs;lnaAs;dAs;lnaTs;d A-Sup
267	KLF4-58 m02	GCCTTCTCCCTTTTTGGT TTATTTA	KLF4	5' and 3'	human	dGs;lnaCs;dCs;lnaTs;dTs; lnaCs;dTs;lnaCs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaGs;dGs;lnaTs;dTs;lna Ts;dAs;lnaTs;dTs;lnaTs;d A-Sup
268	KLF4-59 m02	TCGGGAAACTTTTTGGT TTATTTA	KLF4	5' and 3'	human	dTs;lnaCs;dGs;lnaGs;dGs ;lnaAs;dAs;lnaAs;dCs;lna Ts;dTs;lnaTs;dTs;lnaTs;d Gs;lnaGs;dTs;lnaTs;dTs;l naAs;dTs;lnaTs;dTs;lnaA- Sup
269	KLF4-60 m02	AGCCTTTTCCTTTTTGGT TTATTTA	KLF4	5' and 3'	human	dAs;lnaGs;dCs;lnaCs;dTs; lnaTs;dTs;lnaTs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaGs;dGs;lnaTs;dTs;lna Ts;dAs;lnaTs;dTs;lnaTs;d A-Sup
270	KLF4-61 m02	GCCTTCTCCCTTTTTAAA TTTATAT	KLF4	5' and 3'	human	dGs;lnaCs;dCs;lnaTs;dTs; lnaCs;dTs;lnaCs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaAs;dAs;lnaAs;dTs;lna Ts;dTs;lnaAs;dTs;lnaAs;d T-Sup
271	KLF4-62 m02	TCGGGAAACTTTTTAAA TTTATAT	KLF4	5' and 3'	human	dTs;lnaCs;dGs;lnaGs;dGs ;lnaAs;dAs;lnaAs;dCs;lna Ts;dTs;lnaTs;dTs;lnaTs;d As;lnaAs;dAs;lnaTs;dTs;l naTs;dAs;lnaTs;dAs;lnaT- Sup

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272	KLF4-63 m02	AGCCTTTTCCTTTTTAAA TTTATAT	KLF4	5' and 3'	human	dAs;lnaGs;dCs;lnaCs;dTs; lnaTs;dTs;lnaTs;dCs;lnaC s;dTs;lnaTs;dTs;lnaTs;dTs ;lnaAs;dAs;lnaAs;dTs;lna Ts;dTs;lnaAs;dTs;lnaAs;d T-Sup
273	ACTB-01 m02	AGGTGTGCACTTTTA	ACTB	3'	human	dAs;lnaGs;dGs;lnaTs;dGs ;lnaTs;dGs;lnaCs;dAs;lna Cs;dTs;lnaTs;dTs;lnaTs;d A-Sup
274	ACTB-02 m02	TCATTTTTAAGGTGT	ACTB	3'	human	dTs;lnaCs;dAs;lnaTs;dTs;l naTs;dTs;lnaTs;dAs;lnaAs ;dGs;lnaGs;dTs;lnaGs;dT- Sup
275	ACTB-03 m02	TTTTTAGGTGTGCACTTT TA	ACTB	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;l naAs;dGs;lnaGs;dTs;lnaG s;dTs;lnaGs;dCs;lnaAs;dC s;lnaTs;dTs;lnaTs;dTs;lna A-Sup
276	ACTB-04 m02	TTTTTCATTTTTAAGGTG T	ACTB	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;l naCs;dAs;lnaTs;dTs;lnaTs ;dTs;lnaTs;dAs;lnaAs;dGs ;lnaGs;dTs;lnaGs;dT-Sup
277	ACTB-05 m02	CGCGGTCTCGGCGGT	ACTB	5'	human	dCs;lnaGs;dCs;lnaGs;dGs ;lnaTs;dCs;lnaTs;dCs;lna Gs;dGs;lnaCs;dGs;lnaGs; dT-Sup
278	ACTB-06 m02	ATCATCCATGGTGAG	ACTB	5'	human	dAs;lnaTs;dCs;lnaAs;dTs; lnaCs;dCs;lnaAs;dTs;lnaG s;dGs;lnaTs;dGs;lnaAs;d G-Sup
279	ACTB-07 m02	CGCGGTCTCGGCGGTTT TTAGGTGTGCACTTTTA	ACTB	5' and 3'	human	dCs;lnaGs;dCs;lnaGs;dGs ;lnaTs;dCs;lnaTs;dCs;lna Gs;dGs;lnaCs;dGs;lnaGs; dTs;lnaTs;dTs;lnaTs;dTs;l naAs;dGs;lnaGs;dTs;lnaG s;dTs;lnaGs;dCs;lnaAs;dC s;lnaTs;dTs;lnaTs;dTs;lna A-Sup
280	ACTB-08 m02	ATCATCCATGGTGAGTT TTTAGGTGTGCACTTTTA	ACTB	5' and 3'	human	dAs;lnaTs;dCs;lnaAs;dTs; lnaCs;dCs;lnaAs;dTs;lnaG s;dGs;lnaTs;dGs;lnaAs;d Gs;lnaTs;dTs;lnaTs;dTs;ln aTs;dAs;lnaGs;dGs;lnaTs; dGs;lnaTs;dGs;lnaCs;dAs ;lnaCs;dTs;lnaTs;dTs;lnaT s;dA-Sup

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281	ACTB-09 m02	CGCGGTCTCGGCGGTTTTTCATTTTTAAGGTGT	ACTB	5' and 3'	human	dCs;lnaGs;dCs;lnaGs;dGs;lnaTs;dCs;lnaTs;dCs;lnaGs;dGs;lnaCs;dGs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaAs;dGs;lnaGs;dTs;lnaGs;dT-Sup
282	ACTB-10 m02	ATCATCCATGGTGAGTTTTTCATTTTTAAGGTGT	ACTB	5' and 3'	human	dAs;lnaTs;dCs;lnaAs;dTs;lnaCs;dCs;lnaAs;dTs;lnaGs;dGs;lnaTs;dGs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaGs;dGs;lnaTs;dGs;lnaT-Sup
283	ACTB-11 m02	TCTCGGCGGTTTTTAGGTGTGCAC	ACTB	5' and 3'	human	dTs;lnaCs;dTs;lnaCs;dGs;lnaGs;dCs;lnaGs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dGs;lnaTs;dGs;lnaTs;dGs;lnaCs;dAs;lnaC-Sup
284	ACTB-12 m02	CCATGGTGAGTTTTTAGGTGTGCAC	ACTB	5' and 3'	human	dCs;lnaCs;dAs;lnaTs;dGs;lnaGs;dTs;lnaGs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dGs;lnaGs;dTs;lnaGs;dTs;lnaGs;dCs;lnaAs;dC-Sup
285	ACTB-13 m02	TCTCGGCGGTTTTTCATTTTTAA	ACTB	5' and 3'	human	dTs;lnaCs;dTs;lnaCs;dGs;lnaGs;dCs;lnaGs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dA-Sup
286	ACTB-14 m02	CCATGGTGAGTTTTTCATTTTTAA	ACTB	5' and 3'	human	dCs;lnaCs;dAs;lnaTs;dGs;lnaGs;dTs;lnaGs;dAs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaA-Sup
287	ACTB-15 m02	CGCGGTCTCGGCGGTAGGTGTGCACTTTTA	ACTB	5' and 3'	human	dCs;lnaGs;dCs;lnaGs;dGs;lnaTs;dCs;lnaTs;dCs;lnaGs;dGs;lnaCs;dGs;lnaGs;dTs;lnaAs;dGs;lnaGs;dTs;lnaGs;dTs;lnaGs;dCs;lnaAs;dCs;lnaTs;dTs;lnaTs;dTs;lnaA-Sup

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288	ACTB-16 m02	ATCATCCATGGTGAGAG GTGTGCACTTTTA	ACTB	5' and 3'	human	dAs;lnaTs;dCs;lnaAs;dTs; lnaCs;dCs;lnaAs;dTs;lnaG s;dGs;lnaTs;dGs;lnaAs;d Gs;lnaAs;dGs;lnaGs;dTs;l naGs;dTs;lnaGs;dCs;lnaA s;dCs;lnaTs;dTs;lnaTs;dT s;lnaA-Sup
289	ACTB-17 m02	CGCGGTCTCGGCGGTTC ATTTTTAAGGTGT	ACTB	5' and 3'	human	dCs;lnaGs;dCs;lnaGs;dGs ;lnaTs;dCs;lnaTs;dCs;lna Gs;dGs;lnaCs;dGs;lnaGs; dTs;lnaTs;dCs;lnaAs;dTs;l naTs;dTs;lnaTs;dTs;lnaAs ;dAs;lnaGs;dGs;lnaTs;dG s;lnaT-Sup
290	ACTB-18 m02	ATCATCCATGGTGAGTC ATTTTTAAGGTGT	ACTB	5' and 3'	human	dAs;lnaTs;dCs;lnaAs;dTs; lnaCs;dCs;lnaAs;dTs;lnaG s;dGs;lnaTs;dGs;lnaAs;d Gs;lnaTs;dCs;lnaAs;dTs;l naTs;dTs;lnaTs;dTs;lnaAs ;dAs;lnaGs;dGs;lnaTs;dG s;lnaT-Sup
291	UTRN-192 m02	TGGAGCCGAGCGCTG	UTRN	5'	human	dTs;lnaGs;dGs;lnaAs;dGs ;lnaCs;dCs;lnaGs;dAs;lna Gs;dCs;lnaGs;dCs;lnaTs;d G-Sup
292	UTRN-193 m02	GGGCCTGCCCCTTTG	UTRN	5'	human	dGs;lnaGs;dGs;lnaCs;dCs ;lnaTs;dGs;lnaCs;dCs;lna Cs;dCs;lnaTs;dTs;lnaTs;d G-Sup
293	UTRN-194 m02	CCCCAAGTCACCTGA	UTRN	5'	human	dCs;lnaCs;dCs;lnaCs;dAs; lnaAs;dGs;lnaTs;dCs;lna As;dCs;lnaCs;dTs;lnaGs;d A-Sup
294	UTRN-195 m02	GACATCAATACCTAA	UTRN	5'	human	dGs;lnaAs;dCs;lnaAs;dTs; lnaCs;dAs;lnaAs;dTs;lnaA s;dCs;lnaCs;dTs;lnaAs;dA -Sup
295	UTRN-196 m02	AAACTTTACCAAGTC	UTRN	5'	human	dAs;lnaAs;dAs;lnaCs;dTs; lnaTs;dTs;lnaAs;dCs;lnaC s;dAs;lnaAs;dGs;lnaTs;dC -Sup
296	UTRN-197 m02	TGGAGCCGAGCGCTGC C	UTRN	5'	human	dTs;lnaGs;dGs;lnaAs;dGs ;lnaCs;dCs;lnaGs;dAs;lna Gs;dCs;lnaGs;dCs;lnaTs;d Gs;lnaCs;dC-Sup
297	UTRN-198 m02	GGGCCTGCCCCTTTGCC	UTRN	5'	human	dGs;lnaGs;dGs;lnaCs;dCs ;lnaTs;dGs;lnaCs;dCs;lna Cs;dCs;lnaTs;dTs;lnaTs;d Gs;lnaCs;dC-Sup

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298	UTRN-199 m02	CCCCAAGTCACCTGACC	UTRN	5'	human	dCs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaTs;dCs;lnaAs;dCs;lnaCs;dTs;lnaGs;dAs;lnaCs;dC-Sup
299	UTRN-200 m02	GACATCAATACCTAACC	UTRN	5'	human	dGs;lnaAs;dCs;lnaAs;dTs;lnaCs;dAs;lnaAs;dTs;lnaAs;dCs;lnaCs;dTs;lnaAs;dAs;lnaCs;dC-Sup
300	UTRN-201 m02	AAACTTTACCAAGTCCC	UTRN	5'	human	dAs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaAs;dCs;lnaCs;dAs;lnaAs;dGs;lnaTs;dCs;lnaCs;dC-Sup
301	UTRN-202 m1000	TGGAGCCGAGCGCTGGGAAACCAC	UTRN	5'	human	dTs;lnaGs;dGs;lnaAs;dGs;lnaCs;dCs;lnaGs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
302	UTRN-203 m1000	GGGCCTGCCCCTTTGGGAAACCAC	UTRN	5'	human	dGs;lnaGs;dGs;lnaCs;dCs;lnaTs;dGs;lnaCs;dCs;lnaCs;dCs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
303	UTRN-204 m1000	CCCCAAGTCACCTGAGGAAACCAC	UTRN	5'	human	dCs;lnaCs;dCs;lnaCs;dAs;lnaAs;dGs;lnaTs;dCs;lnaAs;dCs;lnaCs;dTs;lnaGs;dAs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
304	UTRN-205 m1000	GACATCAATACCTAAGGAAACCAC	UTRN	5'	human	dGs;lnaAs;dCs;lnaAs;dTs;lnaCs;dAs;lnaAs;dTs;lnaAs;dCs;lnaCs;dTs;lnaAs;dAs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
305	UTRN-206 m1000	AAACTTTACCAAGTCGGAAACCAC	UTRN	5'	human	dAs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaAs;dCs;lnaCs;dAs;lnaAs;dGs;lnaTs;dCs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
306	UTRN-207 m02	ACTGCAATATATTTC	UTRN	3'	human	dAs;lnaCs;dTs;lnaGs;dCs;lnaAs;dAs;lnaTs;dAs;lnaTs;dAs;lnaTs;dTs;lnaTs;dC-Sup
307	UTRN-208 m02	GTGTTAAAATTACTT	UTRN	3'	human	dGs;lnaTs;dGs;lnaTs;dTs;lnaAs;dAs;lnaAs;dAs;lnaTs;dTs;lnaAs;dCs;lnaTs;dT-Sup

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308	UTRN-209 m02	TTTTTACTGCAATATATTTC	UTRN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dTs;lnaAs;dTs;lnaTs;dTs;lnaC-Sup
309	UTRN-210 m02	TTTTTGTGTTAAAATTACTT	UTRN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dTs;lnaTs;dAs;lnaCs;dTs;lnaT-Sup
310	UTRN-211 m02	CCGAGCGCTGTTTTTACTGCAATAT	UTRN	5' and 3'	human	dCs;lnaCs;dGs;lnaAs;dGs;lnaCs;dGs;lnaCs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dT-Sup
311	UTRN-212 m02	TGCCCCTTTGTTTTTACTGCAATAT	UTRN	5' and 3'	human	dTs;lnaGs;dCs;lnaCs;dCs;lnaCs;dTs;lnaTs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dT-Sup
312	UTRN-213 m02	AGTCACCTGATTTTTACTGCAATAT	UTRN	5' and 3'	human	dAs;lnaGs;dTs;lnaCs;dAs;lnaCs;dCs;lnaTs;dGs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dT-Sup
313	UTRN-214 m02	CAATACCTAATTTTTACTGCAATAT	UTRN	5' and 3'	human	dCs;lnaAs;dAs;lnaTs;dAs;lnaCs;dCs;lnaTs;dAs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dT-Sup
314	UTRN-215 m02	TTACCAAGTCTTTTTACTGCAATAT	UTRN	5' and 3'	human	dTs;lnaTs;dAs;lnaCs;dCs;lnaAs;dAs;lnaGs;dTs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaCs;dAs;lnaAs;dTs;lnaAs;dT-Sup
315	UTRN-216 m02	CCGAGCGCTGTTTTTGTGTTAAAAT	UTRN	5' and 3'	human	dCs;lnaCs;dGs;lnaAs;dGs;lnaCs;dGs;lnaCs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
316	UTRN-217 m02	TGCCCCTTTGTTTTTGTGTTAAAAT	UTRN	5' and 3'	human	dTs;lnaGs;dCs;lnaCs;dCs;lnaCs;dTs;lnaTs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dT-Sup
317	UTRN-218 m02	AGTCACCTGATTTTTGTGTTAAAAT	UTRN	5' and 3'	human	dAs;lnaGs;dTs;lnaCs;dAs;lnaCs;dCs;lnaTs;dGs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dT-Sup
318	UTRN-219 m02	CAATACCTAATTTTTGTGTTAAAAT	UTRN	5' and 3'	human	dCs;lnaAs;dAs;lnaTs;dAs;lnaCs;dCs;lnaTs;dAs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dT-Sup
319	UTRN-220 m02	TTACCAAGTCTTTTTGTGTTAAAAT	UTRN	5' and 3'	human	dTs;lnaTs;dAs;lnaCs;dCs;lnaAs;dAs;lnaGs;dTs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dT-Sup
320	HBF-XXX m02	TGTCTGTAGCTCCAG	HBF	5'	human	dTs;lnaGs;dTs;lnaCs;dTs;lnaG;dTs;lnaA;dGs;lnaC;dTs;lnaC;dCs;lnaA;dGs-Sup
321	HBF-XXX m02	TAGCTCCAGTGAGGC	HBF	5'	human	dTs;lnaAs;dGs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dGs;lnaAs;dGs;lnaGs;dC-Sup
322	HBF-XXX m02	TTTCTTCTCCCACCA	HBF	5'	human	dTs;lnaTs;dTs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dCs;lnaAs;dCs;lnaCs;dA-Sup
323	HBF-XXX m02	TGTCTGTAGCTCCAGCC	HBF	5'	human	dTs;lnaGs;dTs;lnaCs;dTs;lnaG;dTs;lnaA;dGs;lnaC;dTs;lnaC;dCs;lnaA;dGs;lnaCs;dC-Sup
324	HBF-XXX m02	TAGCTCCAGTGAGGCCC	HBF	5'	human	dTs;lnaAs;dGs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dGs;lnaAs;dGs;lnaGs;dC;lnaCs;dC-Sup
325	HBF-XXX m02	TTTCTTCTCCCACCACC	HBF	5'	human	dTs;lnaTs;dTs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dCs;lnaAs;dCs;lnaCs;dA;lnaCs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
326	HBF-XXX m03	TGTCTGTAGCTCCAG GGAAACCAC	HBF	5'	human	dTs;lnaGs;dTs;lnaCs;dTs;lnaG;dTs;lnaA;dGs;lnaC;dTs;lnaC;dCs;lnaA;dGs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
327	HBF-XXX m04	TAGCTCCAGTGAGGC GGAAACCAC	HBF	5'	human	dTs;lnaAs;dGs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaTs;dGs;lnaAs;dGs;lnaGs;dC;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
328	HBF-XXX m05	TTTCTTCTCCCACCAG GAAACCAC	HBF	5'	human	dTs;lnaTs;dTs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dCs;lnaAs;dCs;lnaCs;dA;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
329	HBF-XXX m06	TTTTTGTGTGATCTCT TAGC	HBF	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dATs;lnaGs;dTs;lnaGs;dAs;lnaTs;dCs;lnaTs;dCs;lnaTs;dTs;lnaAs;dGs;lnaC-Sup
330	HBF-XXX m07	TTTTTGTGATCTCTTA GCAG	HBF	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dAs;lnaTs;dCs;lnaTs;dCs;lnaTs;dTs;lnaAs;dGs;lnaCs;dAs;lnaG-Sup
331	HBF-XXX m08	TTTTTTGATCTCTTAG CAGA	HBF	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaAs;dTs;lnaCs;dTs;lnaCs;dTs;lnaTs;dAs;lnaGs;dCs;lnaAs;dGs;lnaA-Sup
332	SMN-XXX m02	ATTTCTCTCAATCCT	SMN	5'	human	dAs;lnaTs;dTs;lnaTs;dCs;lnaT;dCs;lnaT;dCs;lnaA;dAs;lnaT;dCs;lnaC;dTs-Sup
333	SMN-XXX m03	GGCGTGTATATTTTT	SMN	5'	human	dGs;lnaGs;dCs;lnaGs;dTs;lnaGs;dTs;lnaAs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dT-Sup
334	SMN-XXX m04	GGTTATCGCCCTCCC	SMN	5'	human	dGs;lnaGs;dTs;lnaTs;dAs;lnaTs;dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
335	SMN-XXX m05	ACGACTTCCGCCGCC	SMN	5′	human	dAs;lnaCs;dGs;lnaAs;dCs;lnaTs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dGs;lnaCs;dC-Sup
336	SMN-XXX m06	ATTTCTCTCAATCCTCC	SMN	5′	human	dAs;lnaTs;dTs;lnaTs;dCs;lnaT;dCs;lnaT;dCs;lnaA;dAs;lnaT;dCs;lnaC;dTs;lnaCs;dC-Sup
337	SMN-XXX m07	GGCGTGTATATTTTTCC	SMN	5′	human	dGs;lnaGs;dCs;lnaGs;dTs;lnaGs;dTs;lnaAs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dT;lnaCs;dC-Sup
338	SMN-XXX m08	GGTTATCGCCCTCCCCC	SMN	5′	human	dGs;lnaGs;dTs;lnaTs;dAs;lnaTs;dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dC;lnaCs;dC-Sup
339	SMN-XXX m09	ACGACTTCCGCCGCCCC	SMN	5′	human	dAs;lnaCs;dGs;lnaAs;dCs;lnaTs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dGs;lnaCs;dC;lnaCs;dC-Sup
340	SMN-XXX m10	ATTTCTCTCAATCCTGGAAACCAC	SMN	5′	human	dAs;lnaTs;dTs;lnaTs;dCs;lnaT;dCs;lnaT;dCs;lnaA;dAs;lnaT;dCs;lnaC;dTs;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
341	SMN-XXX m11	GGCGTGTATATTTTTGGAAACCAC	SMN	5′	human	dGs;lnaGs;dCs;lnaGs;dTs;lnaGs;dTs;lnaAs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dT;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
342	SMN-XXX m12	GGTTATCGCCCTCCCGGAAACCAC	SMN	5′	human	dGs;lnaGs;dTs;lnaTs;dAs;lnaTs;dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dC;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup
343	SMN-XXX m13	ACGACTTCCGCCGCCGGAAACCAC	SMN	5′	human	dAs;lnaCs;dGs;lnaAs;dCs;lnaTs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dGs;lnaCs;dC;lnaGs;dGs;dAs;dAs;dAs;dCs;lnaCs;dAs;lnaC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
344	SMN-XXX m14	TTTTTTAATTTTTTTTTAAA	SMN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaA-Sup
345	SMN-XXX m15	TTTTTATATGCAAAAAAGAA	SMN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaAs;dTs;lnaGs;dCs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaGs;dAs;lnaA-Sup
346	SMN-XXX m16	TTTTTCAAAATATGGGCCAA	SMN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaAs;dAs;lnaAs;dTs;lnaAs;dTs;lnaGs;dGs;lnaGs;dCs;lnaCs;dAs;lnaA-Sup

Example 5. Further oligonucleotides for increasing RNA stability

Table 8 provides exemplary oligonucleotides for targeting the 5' and 3' ends of noncoding RNAs HOTAIR and ANRIL.

5

Table 8: Oligos targeting non-coding RNAs

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region (5' or 3' End)	Organism	Formatted Sequence
347	HOTAIR-1	TTCACCACATGTAAA	HOTAIR	3'	Human	dTs;lnaTs;dCs;lnaAs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaAs;dA-Sup
348	HOTAIR-2	TTTTTTCACCACATGTAAA	HOTAIR	3'	Human	dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaAs;dA-Sup
349	HOTAIR-3	AAATCAGGGCAGAATGT	HOTAIR	5'	Human	dAs;lnaAs;dAs;lnaTs;dCs;lnaAs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaGs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region (5' or 3' End)	Organism	Formatted Sequence
350	HOTAIR-4	AAATCAGGGCAGAATGTCC	HOTAIR	5'	Human	dAs;lnaAs;dAs;lnaTs;dCs;lnaAs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaGs;dTs;lnaCs;dC-Sup
351	HOTAIR-5	AAATCAGGGCAGAATGTCCAAAGGTC	HOTAIR	5'	Human	dAs;lnaAs;dAs;lnaTs;dCs;lnaAs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaGs;dTs;lnaCs;dCs;lnaAs;dAs;lnaAs;dGs;lnaGs;dTs;dC-Sup
352	HOTAIR-6	AAATCAGGGCAGAATGTTTTTTTCACCACATGTAAA	HOTAIR	5' and 3'	Human	dAs;lnaAs;dAs;lnaTs;dCs;lnaAs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaCs;dCs;lnaAs;dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dAs;dA-Sup
353	ANRIL-1	TTATTGTCTGAGCCC	ANRIL	3'	Human	dTs;lnaTs;dAs;lnaTs;dTs;lnaGs;dTs;lnaCs;dTs;lnaGs;dAs;lnaGs;dCs;lnaCs;dC-Sup
354	ANRIL-2	TTTTTATTGTCTGAGCCC	ANRIL	3'	Human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dGs;lnaTs;dCs;lnaTs;dGs;lnaAs;dGs;lnaCs;dCs;dC-Sup
355	ANRIL-3	TCAGGTGACGGATGT	ANRIL	5'	Human	dTs;lnaCs;dAs;lnaGs;dGs;lnaTs;dGs;lnaAs;dCs;lnaGs;dGs;lnaAs;dTs;lnaGs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region (5' or 3' End)	Organism	Formatted Sequence
356	ANRIL-4	TCAGGTGACGGATGTCC	ANRIL	5'	Human	dTs;lnaCs;dAs;lnaGs;dGs;lnaTs;dGs;lnaAs;dCs;lnaGs;dGs;lnaAs;dTs;lnaGs;dTs;lnaCs;dC-Sup
357	ANRIL-5	TCAGGTGACGGATGTCC AAAGGTC	ANRIL	5'	Human	dTs;lnaCs;dAs;lnaGs;dGs;lnaTs;dGs;lnaAs;dCs;lnaGs;dGs;lnaAs;dTs;lnaGs;dTs;lnaCs;dCs;lnaAs;dAs;lnaAs;dGs;lnaGs;dTs;dC-Sup
358	ANRIL-6	TCAGGTGACGGATGTTT TTTATTGTCTGAGCCC	ANRIL	5' and 3'	Human	dTs;lnaCs;dAs;lnaGs;dGs;lnaTs;dGs;lnaAs;dCs;lnaGs;dGs;lnaAs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dAs;lnaTs;dTs;lnaGs;dTs;lnaCs;dTs;lnaGs;dAs;lnaGs;dCs;lnaCs;dC-Sup

Example 6. Other stability oligos

Table 9 provides further exemplary RNA stability oligos for multiple human and mouse genes.

5

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
359	FOXP3-61 m02	TGTGGGGAGCTCGGC	FOXP3	3'	human	dTs;lnaGs;dTs;lnaGs;dGs;lnaGs;dGs;lnaAs;dGs;lnaCs;dTs;lnaCs;dGs;lnaGs;dC-Sup
360	FOXP3-62 m02	GGGGAGCTCGGCTGC	FOXP3	3'	human	dGs;lnaGs;dGs;lnaGs;dAs;lnaGs;dCs;lnaTs;dCs;lnaGs;dGs;lnaCs;dTs;lnaGs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
361	FOXP3-63 m02	TTTTTGTGGGGAGCTCGGC	FOXP3	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dGs;lnaGs;dGs;lnaAs;dGs;lnaCs;dTs;lnaCs;dGs;lnaGs;dC-Sup
362	FOXP3-64 m02	TTTTGGGGAGCTCGGCTGC	FOXP3	3'	human	dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaGs;dAs;lnaGs;dCs;lnaTs;dCs;lnaGs;dGs;lnaCs;dTs;lnaGs;dC-Sup
363	FOXP3-65 m02	TTGTCCAAGGGCAGG	FOXP3	5'	human	dTs;lnaTs;dGs;lnaTs;dCs;lnaCs;dAs;lnaAs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dG-Sup
364	FOXP3-66 m02	TCGATGAGTGTGTGC	FOXP3	5'	human	dTs;lnaCs;dGs;lnaAs;dTs;lnaGs;dAs;lnaGs;dTs;lnaGs;dTs;lnaGs;dTs;lnaGs;dC-Sup
365	FOXP3-67 m02	AGAAGAAAAACCACG	FOXP3	5'	human	dAs;lnaGs;dAs;lnaAs;dGs;lnaAs;dAs;lnaAs;dAs;lnaAs;dCs;lnaCs;dAs;lnaCs;dG-Sup
366	FOXP3-68 m02	AATATGATTTCTTCC	FOXP3	5'	human	dAs;lnaAs;dTs;lnaAs;dTs;lnaGs;dAs;lnaTs;dTs;lnaTs;dCs;lnaTs;dTs;lnaCs;dC-Sup
367	FOXP3-69 m02	GAGATGGGGGACATG	FOXP3	5'	human	dGs;lnaAs;dGs;lnaAs;dTs;lnaGs;dGs;lnaGs;dGs;lnaGs;dAs;lnaCs;dAs;lnaTs;dG-Sup
368	PTEN-101 m02	TTCAGTTTATTCAAG	PTEN	3'	human	dTs;lnaTs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dAs;lnaTs;dTs;lnaCs;dAs;lnaAs;dG-Sup
369	PTEN-102 m02	CTGTCTCCACTTTTT	PTEN	3'	human	dCs;lnaTs;dGs;lnaTs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
370	PTEN-103 m02	TGGAATAAAACGGG	PTEN	3'	human	dTs;lnaGs;dGs;lnaAs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dCs;lnaGs;dGs;lnaG-Sup
371	PTEN-104 m02	ACAATTGAGAAAACA	PTEN	3'	human	dAs;lnaCs;dAs;lnaAs;dTs;lnaTs;dGs;lnaAs;dGs;lnaAs;dAs;lnaAs;dAs;lnaCs;dA-Sup
372	PTEN-105 m02	CAGTTTTAAGTGGAG	PTEN	3'	human	dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaGs;dTs;lnaGs;dGs;lnaAs;dG-Sup
373	PTEN-106 m02	TGACAAGAATGAGAC	PTEN	3'	human	dTs;lnaGs;dAs;lnaCs;dAs;lnaAs;dGs;lnaAs;dAs;lnaTs;dGs;lnaAs;dGs;lnaAs;dC-Sup
374	PTEN-107 m02	CCGGGCGAGGGGAGG	PTEN	5'	human	dCs;lnaCs;dGs;lnaGs;dGs;lnaCs;dGs;lnaAs;dGs;lnaGs;dGs;lnaGs;dAs;lnaGs;dG-Sup
375	PTEN-108 m02	CCGCCGGCCTGCCCG	PTEN	5'	human	dCs;lnaCs;dGs;lnaCs;dCs;lnaGs;dGs;lnaCs;dCs;lnaTs;dGs;lnaCs;dCs;lnaCs;dG-Sup
376	PTEN-109 m02	CGAGCGCGTATCCTG	PTEN	5'	human	dCs;lnaGs;dAs;lnaGs;dCs;lnaGs;dCs;lnaGs;dTs;lnaAs;dTs;lnaCs;dCs;lnaTs;dG-Sup
377	PTEN-110 m02	CTGCTTCTCCTCAGC	PTEN	5'	human	dCs;lnaTs;dGs;lnaCs;dTs;lnaTs;dCs;lnaTs;dCs;lnaCs;dTs;lnaCs;dAs;lnaGs;dC-Sup
378	PTEN-111 m02	TTTTCAGTTTATTCAAG	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dAs;lnaTs;dTs;lnaCs;dAs;lnaAs;dG-Sup
379	PTEN-112 m02	TTTTCTGTCTCCACTTTTT	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dCs;lnaTs;dGs;lnaTs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
380	PTEN-113 m02	TTTTTGGAATAAAACGGG	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaAs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dCs;lnaGs;dGs;lnaG-Sup
381	PTEN-114 m02	TTTTACAATTGAGAAAACA	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dAs;lnaCs;dAs;lnaAs;dTs;lnaTs;dGs;lnaAs;dGs;lnaAs;dAs;lnaAs;dAs;lnaCs;dA-Sup
382	PTEN-115 m02	TTTTCAGTTTTAAGTGGAG	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaGs;dTs;lnaGs;dGs;lnaAs;dG-Sup
383	PTEN-116 m02	TTTTTGACAAGAATGAGAC	PTEN	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dAs;lnaCs;dAs;lnaAs;dGs;lnaAs;dAs;lnaTs;dGs;lnaAs;dGs;lnaAs;dC-Sup
384	NFE2L2-01 m02	AACAGTCATAATAAT	NFE2L2	3'	human	dAs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dAs;lnaAs;dT-Sup
385	NFE2L2-02 m02	TAATTTAACAGTCAT	NFE2L2	3'	human	dTs;lnaAs;dAs;lnaTs;dTs;lnaTs;dAs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaAs;dT-Sup
386	NFE2L2-03 m02	GCACGCTATAAAGCA	NFE2L2	5'	human	dGs;lnaCs;dAs;lnaCs;dGs;lnaCs;dTs;lnaAs;dTs;lnaAs;dAs;lnaAs;dGs;lnaCs;dA-Sup
387	NFE2L2-04 m02	CCCGGGGCTGGGCTT	NFE2L2	5'	human	dCs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaCs;dTs;lnaGs;dGs;lnaGs;dCs;lnaTs;dT-Sup
388	NFE2L2-05 m02	CCCCGCTCCGCCTCC	NFE2L2	5'	human	dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dCs;lnaGs;dCs;lnaCs;dTs;lnaCs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
389	NFE2L2-06 m02	GCGCCTCCCTGATTT	NFE2L2	5'	human	dGs;lnaCs;dGs;lnaCs;dCs;lnaTs;dCs;lnaCs;dCs;lnaTs;dGs;lnaAs;dTs;lnaTs;dT-Sup
390	NFE2L2-07 m02	TCGCCGCGGTGGCTG	NFE2L2	5'	human	dTs;lnaCs;dGs;lnaCs;dCs;lnaGs;dCs;lnaGs;dGs;lnaTs;dGs;lnaGs;dCs;lnaTs;dG-Sup
391	NFE2L2-08 m02	CAGCGAATGGTCGCG	NFE2L2	5'	human	dCs;lnaAs;dGs;lnaCs;dGs;lnaAs;dAs;lnaTs;dGs;lnaGs;dTs;lnaCs;dGs;lnaCs;dG-Sup
392	NFE2L2-09 m02	TTTTTAACAGTCATAATAAT	NFE2L2	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaCs;dAs;lnaGs;dTs;lnaCs;dAs;lnaTs;dAs;lnaAs;dTs;lnaAs;dAs;lnaT-Sup
393	NFE2L2-10 m02	TTTTTAATTTAACAGTCAT	NFE2L2	3'	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dAs;lnaTs;dTs;lnaTs;dAs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaAs;dT-Sup
394	ATP2A2-56 m02	GCGGCGGCTGCTCTA	ATP2A2	5'	human	dGs;lnaCs;dGs;lnaGs;dCs;lnaGs;dGs;lnaCs;dTs;lnaGs;dCs;lnaTs;dCs;lnaTs;dA-Sup
395	ATP2A2-34 m02	TTATCGGCCGCTGCC	ATP2A2	5'	human	dTs;lnaTs;dAs;lnaTs;dCs;lnaGs;dGs;lnaCs;dCs;lnaGs;dCs;lnaTs;dGs;lnaCs;dC-Sup
396	ATP2A2-57 m02	GCGTCGGGGACGGCT	ATP2A2	5'	human	dGs;lnaCs;dGs;lnaTs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dGs;lnaCs;dT-Sup
397	ATP2A2-58 m02	GCGGAGGAAACTGCG	ATP2A2	5'	human	dGs;lnaCs;dGs;lnaGs;dAs;lnaGs;dGs;lnaAs;dAs;lnaAs;dCs;lnaTs;dGs;lnaCs;dG-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
398	ATP2A2-59 m02	GCCGCACGCCCGACA	ATP2A2	5'	human	dGs;lnaCs;dCs;lnaGs;dCs;lnaAs;dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dAs;lnaCs;dA-Sup
399	ATP2A2-60 m02	CCTGACCCACCCTCC	ATP2A2	5'	human	dCs;lnaCs;dTs;lnaGs;dAs;lnaCs;dCs;lnaCs;dAs;lnaCs;dCs;lnaCs;dTs;lnaCs;dC-Sup
400	ATP2A2-61 m02	AGGGCAGGCCGCGGC	ATP2A2	5'	human	dAs;lnaGs;dGs;lnaGs;dCs;lnaAs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dC-Sup
401	ATP2A2-62 m02	CTGAATCACCCCGCG	ATP2A2	5'	human	dCs;lnaTs;dGs;lnaAs;dAs;lnaTs;dCs;lnaAs;dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dG-Sup
402	ATP2A2-63 m02	GGCCCCGAGCTCCGC	ATP2A2	5'	human	dGs;lnaGs;dCs;lnaCs;dCs;lnaCs;dGs;lnaAs;dGs;lnaCs;dTs;lnaCs;dCs;lnaGs;dC-Sup
403	ATP2A2-64 m02	GCGGCTGCTCTAATA	ATP2A2	5'	human	dGs;lnaCs;dGs;lnaGs;dCs;lnaTs;dGs;lnaCs;dTs;lnaCs;dTs;lnaAs;dAs;lnaTs;dA-Sup
404	ATP2A2-65 m02	CGCCGCGGCATGTGG	ATP2A2	5'	human	dCs;lnaGs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaAs;dTs;lnaGs;dTs;lnaGs;dG-Sup
405	ATP2A2-66 m02	CCCTCCTCCTCTTGC	ATP2A2	5'	human	dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;lnaTs;dTs;lnaGs;dC-Sup
406	ATP2A2-67 m02	GGCCGCGGGCTCGTG	ATP2A2	5'	human	dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dGs;lnaCs;dTs;lnaCs;dGs;lnaTs;dG-Sup
407	ATP2A2-68 m02	GTTATTTTTCTCTGT	ATP2A2	3'	human	dGs;lnaTs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dTs;lnaCs;dTs;lnaGs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
408	ATP2A2-69 m02	ATTTAAAATGTTTTA	ATP2A2	3'	human	dAs;lnaTs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dA-Sup
409	ATP2A2-70 m02	TCTCTGTCCATTTAA	ATP2A2	3'	human	dTs;lnaCs;dTs;lnaCs;dTs;lnaGs;dTs;lnaCs;dCs;lnaAs;dTs;lnaTs;dTs;lnaAs;dA-Sup
410	ATP2A2-71 m02	TCATTTGGTCATGTG	ATP2A2	3'	human	dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dGs;lnaGs;dTs;lnaCs;dAs;lnaTs;dGs;lnaTs;dG-Sup
411	ATP2A2-72 m02	TAGTTCTCTGTACAT	ATP2A2	3'	human	dTs;lnaAs;dGs;lnaTs;dTs;lnaCs;dTs;lnaCs;dTs;lnaGs;dTs;lnaAs;dCs;lnaAs;dT-Sup
412	ATP2A2-73 m02	TCTGCTGGCTCAACT	ATP2A2	3'	human	dTs;lnaCs;dTs;lnaGs;dCs;lnaTs;dGs;lnaGs;dCs;lnaTs;dCs;lnaAs;dAs;lnaCs;dT-Sup
413	ATP2A2-74 m02	ATCATAGAATAGATT	ATP2A2	3'	human	dAs;lnaTs;dCs;lnaAs;dTs;lnaAs;dGs;lnaAs;dAs;lnaTs;dAs;lnaGs;dAs;lnaTs;dT-Sup
414	ATP2A2-75 m02	TTATCATAGAATAGA	ATP2A2	3'	human	dTs;lnaTs;dAs;lnaTs;dCs;lnaAs;dTs;lnaAs;dGs;lnaAs;dAs;lnaTs;dAs;lnaGs;dA-Sup
415	ATP2A2-76 m02	AATTGACATTTAGCA	ATP2A2	3'	human	dAs;lnaAs;dTs;lnaTs;dGs;lnaAs;dCs;lnaAs;dTs;lnaTs;dTs;lnaAs;dGs;lnaCs;dA-Sup
416	ATP2A2-77 m02	GACATTTAGCATTTT	ATP2A2	3'	human	dGs;lnaAs;dCs;lnaAs;dTs;lnaTs;dTs;lnaAs;dGs;lnaCs;dAs;lnaTs;dTs;lnaTs;dT-Sup
417	ATP2A2-78 m02	TTAACCATTCAACAC	ATP2A2	3'	human	dTs;lnaTs;dAs;lnaAs;dCs;lnaCs;dAs;lnaTs;dTs;lnaCs;dAs;lnaAs;dCs;lnaAs;dC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
418	mKLF4-01 m02	CTTGGCCGGGGAACT	KLF4	5′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dT-Sup
419	mKLF4-02 m02	GCCGGGGAACTGCCG	KLF4	5′	mouse	dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaGs;dCs;lnaCs;dG-Sup
420	mKLF4-03 m02	CGCCCGGAGCCGCGC	KLF4	5′	mouse	dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dGs;lnaAs;dGs;lnaCs;dCs;lnaGs;dCs;lnaGs;dC-Sup
421	mKLF4-04 m02	CTTGGCCGGGGAACTCC	KLF4	5′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaCs;dC-Sup
422	mKLF4-05 m02	GCCGGGGAACTGCCGC	KLF4	5′	mouse	dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaGs;dCs;lnaCs;dGs;lnaC-Sup
423	mKLF4-06 m02	CGCCCGGAGCCGCGCC	KLF4	5′	mouse	dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dGs;lnaAs;dGs;lnaCs;dCs;lnaGs;dCs;lnaGs;dCs;lnaC-Sup
424	mKLF4-07 m02	CTTGGCCGGGGAACTATAAAATTC	KLF4	5′ and 3′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaAs;dTs;dAs;dAs;dAs;dAs;lnaTs;dTs;lnaC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
425	mKLF4-08 m02	CTTGGCCGGGGAACTTTTTGTCGTTCAGATAAAA	KLF4	5′ and 3′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaCs;dGs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaA-Sup
426	mKLF4-09 m02	CTTGGCCGGGGAACTTTTTCAGATAAAATATT	KLF4	5′ and 3′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dTs;lnaAs;dTs;lnaT-Sup
427	mKLF4-10 m02	CTTGGCCGGGGAACTGTCGTTCAGATAAAA	KLF4	5′ and 3′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaGs;dTs;lnaCs;dGs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaA-Sup
428	mKLF4-11 m02	CTTGGCCGGGGAACTTTCAGATAAAATATT	KLF4	5′ and 3′	mouse	dCs;lnaTs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dTs;lnaAs;dTs;lnaT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
429	mKLF4-12 m02	CCGGGGAACTTTTTGTCGTTCAGA	KLF4	5′ and 3′	mouse	dCs;lnaCs;dGs;lnaGs;dGs;lnaGs;dAs;lnaAs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaTs;dCs;lnaGs;dTs;lnaTs;dCs;lnaAs;dGs;lnaA-Sup
430	mKLF4-13 m02	CGGGGAACTTTTTCAGATAAA	KLF4	5′ and 3′	mouse	dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dA-Sup
431	mKLF4-14 m02	CGGGGAACTGTCGTTCAGA	KLF4	5′ and 3′	mouse	dCs;lnaGs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaGs;dTs;lnaCs;dGs;lnaTs;dTs;lnaCs;dAs;lnaGs;dA-Sup
432	mKLF4-15 m02	CCGGGGAACTTTCAGATAAA	KLF4	5′ and 3′	mouse	dCs;lnaCs;dGs;lnaGs;dGs;lnaGs;dAs;lnaAs;dCs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaAs;dTs;lnaAs;dAs;lnaA-Sup
433	mKLF4-16 m02	GTCGTTCAGATAAAA	KLF4	3′	mouse	dGs;lnaTs;dCs;lnaGs;dTs;lnaTs;dCs;lnaAs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dA-Sup
434	mKLF4-17 m02	TTCAGATAAAATATT	KLF4	3′	mouse	dTs;lnaTs;dCs;lnaAs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dAs;lnaTs;dAs;lnaTs;dT-Sup
435	mKLF4-18 m02	TTTTTGTCGTTCAGATAAAA	KLF4	3′	mouse	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dTs;lnaCs;dGs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaA-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
436	mKLF4-19 m02	TTTTTCAGATAAAATATT	KLF4	3′	mouse	dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dTs;lnaAs;dTs;lnaT-Sup
437	mFXN-01 m02	CTCCGCGGCCGCTCC	FXN	5′	mouse	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dC-Sup
438	mFXN-02 m02	GCCCACATGCTACTC	FXN	5′	mouse	dGs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaCs;dTs;lnaAs;dCs;lnaTs;dC-Sup
439	mFXN-03 m02	TCCGAACGCCCACAT	FXN	5′	mouse	dTs;lnaCs;dCs;lnaGs;dAs;lnaAs;dCs;lnaGs;dCs;lnaCs;dCs;lnaAs;dCs;lnaAs;dT-Sup
440	mFXN-04 m02	CGAGGACTCGGTGGT	FXN	5′	mouse	dCs;lnaGs;dAs;lnaGs;dGs;lnaAs;dCs;lnaTs;dCs;lnaGs;dGs;lnaTs;dGs;lnaGs;dT-Sup
441	mFXN-05 m02	CCAGCTCCGCGGCCG	FXN	5′	mouse	dCs;lnaCs;dAs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dG-Sup
442	mFXN-06 m02	CTCCGCGGCCGCTCCC	FXN	5′	mouse	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dCs;lnaC-Sup
443	mFXN-07 m02	GCCCACATGCTACTCC	FXN	5′	mouse	dGs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaCs;dTs;lnaAs;dCs;lnaTs;dCs;lnaC-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
444	mFXN-08 m02	CTCCGCGGCCGCTCCTCAAAGATC	FXN	5′	mouse	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;dAs;dAs;dAs;dGs;lnaAs;dTs;lnaC-Sup
445	mFXN-09 m02	GCCCACATGCTACTCCCAAAGGTC	FXN	5′	mouse	dGs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaCs;dTs;lnaAs;dCs;lnaTs;dCs;lnaCs;dCs;dAs;dAs;dAs;dGs;lnaGs;dTs;lnaC-Sup
446	mFXN-10 m02	CTCCGCGGCCGCTCCTTTTTGGGAGGGAACACACT	FXN	5′ and 3′	mouse	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaCs;dT-Sup
447	mFXN-11 m02	GCCCACATGCTACTCTTTTTGGGAGGGAACACACT	FXN	5′ and 3′	mouse	dGs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaCs;dTs;lnaAs;dCs;lnaTs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaCs;dT-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
448	mFXN-12 m02	CTCCGCGGCCGCTCCGGGAGGGAACACACT	FXN	5′ and 3′	mouse	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dTs;lnaCs;dCs;lnaGs;dGs;lnaGs;dAs;lnaGs;dGs;lnaGs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dCs;lnaT-Sup
449	mFXN-13 m02	GCCCACATGCTACTCGGGAGGGAACACACT	FXN	5′ and 3′	mouse	dGs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaTs;dGs;lnaCs;dTs;lnaAs;dCs;lnaTs;dCs;lnaGs;dGs;lnaGs;dAs;lnaGs;dGs;lnaGs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dCs;lnaT-Sup
450	mFXN-14 m02	CGGCCGCTCCGGGAGGGAAC	FXN	5′ and 3′	mouse	dCs;lnaGs;dGs;lnaCs;dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaC-Sup
451	mFXN-15 m02	CATGCTACTCGGGAGGGAAC	FXN	5′ and 3′	mouse	dCs;lnaAs;dTs;lnaGs;dCs;lnaTs;dAs;lnaCs;dTs;lnaCs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaC-Sup
452	mFXN-16 m02	GGGAGGGAACACACT	FXN	3′	mouse	dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaCs;dT-Sup
453	mFXN-17 m02	GGGGTCTTCACCTGA	FXN	3′	mouse	dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dTs;lnaTs;dCs;lnaAs;dCs;lnaCs;dTs;lnaGs;dA-Sup

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
454	mFXN-18 m02	GGCTGTTATATCATG	FXN	3'	mouse	dGs;lnaGs;dCs;lnaTs;dGs;lnaTs;dTs;lnaAs;dTs;lnaAs;dTs;lnaCs;dAs;lnaTs;dG-Sup
455	mFXN-19 m02	GGCATTTTAAGATGG	FXN	3'	mouse	dGs;lnaGs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dAs;lnaAs;dGs;lnaAs;dTs;lnaGs;dG-Sup
456	mFXN-20 m02	TTTTTGGGAGGGAACACACT	FXN	3'	mouse	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaGs;dAs;lnaGs;dGs;lnaGs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dCs;lnaT-Sup
457	mFXN-21 m02	TTTTTGGCTGTTATATCATG	FXN	3'	mouse	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaCs;dTs;lnaGs;dTs;lnaTs;dAs;lnaTs;dAs;lnaTs;dCs;lnaAs;dTs;lnaG-Sup

Example 7. PTEN and KLF4 oligos

Methods

Protein measurements: Hepa1-6 and GM04078 cells were plated at 150000 cells per well. The cells were transfected with PTEN or KLF4 oligos using Lipofectamine 2000. 30 nM of each PTEN oligo was used for transfection. If two oligos were combined in an experiment, then 30 nM of each PTEN oligo was used for transfection. 50 nM of each KLF4 oligo was used for transfection. If two oligos were combined in an experiment, then 50 nM of each PTEN oligo was used for transfection. Lysate was harvested from the cells at 1 or 2 days after transfection for PTEN oligos or 3 days after transfection for KLF4 oligos. The antibodies used for detection were Cell Signaling KLF4 4038 and Cell Signaling PTEN 9552.

RNA measurements: Hepa1-6 and GM04078 were plated at 4000 cells per well. The cells were transfected with the oligos using Lipofectamine 2000. 30 nM of each PTEN oligo was used for transfection. If two oligos were combined in an experiment, then 30 nM of each

PTEN oligo was used for transfection. 50 nM of each KLF4 oligo was used for transfection. If two oligos were combined in an experiment, then 50 nM of each PTEN oligo was used for transfection. RNA was extracted from lysate collected 3 days post-transfection. Cells-to-Ct (Life Technologies) procedure was used to analyze RNA levels following manufacturer's protocol. Taqman® probes used were from Life Technologies:

KLF4 Mm00516104_m1

PTEN Hs02621230_s1

Actin Hs01060665_g1

Gapdh Hs02758991_g1

Actinomycin D treatment: Actinomycin D (Life Technologies) was added to cell culture media at 10 microgram/ml concentration and incubated. RNA isolation was done using Trizol (Sigma) following manufacturer's instructions. KLF4 probes were purchased from Life Technologies.

Oligo sequences tested: The oligos tested in FIGs. 44-48 correspond to the same oligo sequences provided in Table 9. For example, PTEN 101 in FIG. 44A is the same as PTEN-101 in Table 9, mKLF4-1 m02 in FIG. 46 is the same as mKLF4-1 m02 in Table 9, etc.

Results

Oligonucleotides specific for PTEN were tested by treating cells with each oligo. Several PTEN oligos were able to upregulate PTEN mRNA levels in the treated cells (FIG. 44A and 44B). PTEN oligos 108 and 113, when combined, were also able to upregulate PTEN protein levels in the treated cells more than either oligo used separately (FIG. 45).

Oligonucleotides specific for KLF4 were tested by treating cells with each oligo. Several KLF4 oligos were able to upregulate KLF4 mRNA levels in the treated cells (FIG. 46). Several KLF4 oligos, used alone or in combination, were also able to upregulate KLF4 protein levels in the treated cells (FIGs. 47 and 48).

In another experiment, cells were treated with actinomycin D and a circularization or other type of stability oligo and the stability of KLF4 was measured. It was found that the RNA stability increase level (~2 hours vs. ~4-8 hours) was comparable between "circularization" and individual 5'/3' end oligos, showing that both types of oligos were effective (FIG. 49).

These results demonstrate that both mRNA and protein levels can be upregulated using oligos that are capable of increasing RNA stability.

Example 8. Increased mRNA stability in a gene with a long mRNA half-life

Methods

RNA measurements: RNA analysis, cDNA synthesis and QRT-PCR was done with Life Technologies Cells-to-Ct kit and StepOne Plus instrument. ACTB oligos were transfected to Hep3B cells at 30nM concentration using RNAimax (Life Technologies). For combinations, each oligo were transfected at 30nM concentration. RNA analysis was done with Cells-to-Ct kit (Life Technologies) using ACTIN (Hs01060665_g1) and GAPDH (Hs02758991_g1, housekeeper control) primers purchased from Life Technologies.

Oligo sequences tested: The oligos tested in FIG. 50 correspond to the same oligo sequences provided in Table 7. For example, ACTB-8 in FIG. 50 is the same as ACTB-8 in Table 7, ACTB-9 in FIG. 50 is the same as ACTB-9 in Table 7, etc.

Results

Actin-beta is a housekeeper gene that has highly stable mRNA. Oligonucleotides specific for Actin-Beta mRNA were tested by treating cells with each oligo or a combination thereof. Several oligos, both 5' and 3' targeting, as well as circularization oligos, were able to upregulate actin-beta mRNA levels (FIG. 50). These data show that stability oligos can improve the stability of even already-highly-stable mRNA.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

Example 9. Further 5' and 3' end targeting oligonucleotides

Table 10 provides further exemplary RNA 5' and 3' end targeting oligos for multiple human and mouse genes.

Table 10. **Oligonucleotides designed to target 5' and 3' ends of RNAs**

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
459	FXN-654 m02	TGTCTCATTTGGAGA	FXN	3'	human	dTs;lnaGs;dTs;lnaCs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dGs;lnaGs;dAs;lnaGs;dA-Sup
460	FXN-655 m02	ATAATGAAGCTGGG	FXN	3'	human	dAs;lnaTs;dAs;lnaAs;dTs;lnaGs;dAs;lnaAs;dGs;lnaCs;dTs;lnaGs;dGs;lnaG-Sup
461	FXN-656 m02	TTTTCCCTCCTGGAA	FXN	3'	human	dTs;lnaTs;dTs;lnaTs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaGs;dGs;lnaAs;dA-Sup
462	FXN-657 m02	TGCATAATGAAGCTG	FXN	3'	human	dTs;lnaGs;dCs;lnaAs;dTs;lnaAs;dAs;lnaTs;dGs;lnaAs;dAs;lnaGs;dCs;lnaTs;dG-Sup
463	FXN-658 m02	AAATCCTTCAAAGAA	FXN	3'	human	dAs;lnaAs;dAs;lnaTs;dCs;lnaCs;dTs;lnaTs;dCs;lnaAs;dAs;lnaAs;dGs;lnaAs;dA-Sup
464	FXN-659 m02	TTGGAAGATTTTTTG	FXN	3'	human	dTs;lnaTs;dGs;lnaGs;dAs;lnaAs;dGs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dG-Sup
465	FXN-660 m02	GCATTCTTGTAGCAG	FXN	3'	human	dGs;lnaCs;dAs;lnaTs;dTs;lnaCs;dTs;lnaTs;dGs;lnaTs;dAs;lnaGs;dCs;lnaAs;dG-Sup
466	FXN-557 m02	ACAACAAAAAACAGA	FXN	3'	human	dAs;lnaCs;dAs;lnaAs;dCs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaCs;dAs;lnaGs;dA-Sup
467	FXN-662 m02	TGAAGCTGGGGTCTT	FXN	3'	human	dTs;lnaGs;dAs;lnaAs;dGs;lnaCs;dTs;lnaGs;dGs;lnaGs;dGs;lnaTs;dCs;lnaTs;dT-Sup

468	FXN-663 m02	CCTGAAAACATTTGT	FXN	3′	human	dCs;lnaCs;dTs;lnaGs;dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dTs;lnaTs;dTs;lnaGs;dT-Sup
469	FXN-664 m02	TTCATTTTCCCTCCT	FXN	3′	human	dTs;lnaTs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dT-Sup
470	FXN-665 m02	TTATTATTATTATAT	FXN	3′	human	dTs;lnaTs;dAs;lnaTs;dTs;lnaAs;dTs;lnaTs;dAs;lnaTs;dTs;lnaAs;dTs;lnaAs;dT-Sup
471	FXN-666 m02	TAACTTTGCATGAAT	FXN	3′	human	dTs;lnaAs;dAs;lnaCs;dTs;lnaTs;dTs;lnaGs;dCs;lnaAs;dTs;lnaGs;dAs;lnaAs;dT-Sup
472	FXN-667 m02	ATACAAACATGTATG	FXN	3′	human	dAs;lnaTs;dAs;lnaCs;dAs;lnaAs;dAs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaTs;dG-Sup
473	FXN-668 m02	ATTGTAAACCTATAA	FXN	3′	human	dAs;lnaTs;dTs;lnaGs;dTs;lnaAs;dAs;lnaAs;dCs;lnaCs;dTs;lnaAs;dTs;lnaAs;dA-Sup
474	FXN-669 m02	TGGAGTTGGGGTTAT	FXN	3′	human	dTs;lnaGs;dGs;lnaAs;dGs;lnaTs;dTs;lnaGs;dGs;lnaGs;dGs;lnaTs;dTs;lnaAs;dT-Sup
475	FXN-670 m02	GTTGGGGTTATTTAG	FXN	3′	human	dGs;lnaTs;dTs;lnaGs;dGs;lnaGs;dGs;lnaTs;dTs;lnaAs;dTs;lnaTs;dTs;lnaAs;dG-Sup
476	FXN-671 m02	CTCCGCCCTCCAG	FXN	5′	human	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dG-Sup
477	FXN-672 m02	CCGCCCTCCAG	FXN	5′	human	dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dG-Sup
478	FXN-673 m02	GCCCTCCAG	FXN	5′	human	dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dG-Sup

479	FXN-674 m02	CCCGCTCCGCCCTCC	FXN	5′	human	dCs;lnaCs;dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dC-Sup
480	FXN-675 m02	CGCTCCGCCCTCC	FXN	5′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dC-Sup
481	FXN-676 m02	CTCCGCCCTCC	FXN	5′	human	dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dC-Sup
482	FXN-677 m02	CCGCCCTCC	FXN	5′	human	dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dC-Sup
483	FXN-678 m02	GCCACTGGCCGCA	FXN	5′	human	dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dA-Sup
484	FXN-679 m02	CACTGGCCGCA	FXN	5′	human	dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dA-Sup
485	FXN-680 m02	GCGACCCCTGGTG	FXN	5′	human	dGs;lnaCs;dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dG-Sup
486	FXN-681 m02	GACCCCTGGTG	FXN	5′	human	dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dG-Sup
487	FXN-682 m02	CTGGCCGCAGGCA	FXN	5′	human	dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dGs;lnaCs;dAs;lnaGs;dGs;lnaCs;dA-Sup
488	FXN-683 m02	GGCCACTGGCCGC	FXN	5′	human	dGs;lnaGs;dCs;lnaCs;dAs;lnaCs;dTs;lnaGs;dGs;lnaCs;dCs;lnaGs;dC-Sup
489	FXN-684 m02	CTGGTGGCCACTG	FXN	5′	human	dCs;lnaTs;dGs;lnaGs;dTs;lnaGs;dGs;lnaCs;dCs;lnaAs;dCs;lnaTs;dG-Sup
490	FXN-685 m02	GACCCCTGGTGGC	FXN	5′	human	dGs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dGs;lnaGs;dC-Sup
491	FXN-686 m02	GCGGCGACCCCTG	FXN	5′	human	dGs;lnaCs;dGs;lnaGs;dCs;lnaGs;dAs;lnaCs;dCs;lnaCs;dCs;lnaTs;dG-Sup

492	FXN-687 m02	GTGCTGCGGCGAC	FXN	5′	human	dGs;lnaTs;dGs;lnaCs;dTs;lnaGs;dCs;lnaGs;dGs;lnaCs;dGs;lnaAs;dC-Sup
493	FXN-688 m02	GCTGGGTGCTGCG	FXN	5′	human	dGs;lnaCs;dTs;lnaGs;dGs;lnaGs;dTs;lnaGs;dCs;lnaTs;dGs;lnaCs;dG-Sup
494	FXN-689 m02	CCAGCGCTGGGTG	FXN	5′	human	dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dG-Sup
495	FXN-690 m02	GCCCTCCAGCGCT	FXN	5′	human	dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;lnaCs;dGs;lnaCs;dT-Sup
496	FXN-691 m02	CGCCCGCTCCGCC	FXN	5′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dC-Sup
497	FXN-460 m1000	CGCCCTCCAGCGCTGTTTTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;dT;dT;dT;dT;dT;dAs;lnaTs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dGs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
498	FXN-461 m1000	CGCTCCGCCCTCCAGTTTTTATTATTTTGCTTTTT	FXN	5′ and 3′	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dGs;dT;dT;dT;dT;dT;dAs;lnaTs;dTs;lnaAs;dTs;lnaTs;dTs;lnaTs;dGs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
499	FXN-523 m01	CAAGTCCAGTTTGGTTT	FXN	3′	human	lnaCs;omeAs;lnaAs;omeGs;lnaTs;omeCs;lnaCs;omeAs;lnaGs;omeUs;lnaTs;omeUs;lnaGs;omeGs;lnaTs;omeUs;lnaT-Sup
500	FXN-524 m01	GAATAGGCCAAGGAAGA	FXN	3′	human	lnaGs;omeAs;lnaAs;omeUs;lnaAs;omeGs;lnaGs;omeCs;lnaCs;omeAs;lnaAs;omeGs;lnaGs;omeAs;lnaAs;omeGs;lnaA-Sup

501	FXN-525 m01	ATCAAGCATCTTTTCCG	FXN	3′	human	lnaAs;omeUs;lnaCs;omeAs;lnaAs;omeGs;lnaCs;omeAs;lnaTs;omeCs;lnaTs;omeUs;lnaTs;omeUs;lnaCs;omeCs;lnaG-Sup
502	FXN-526 m01	TTAAAACGGGGCTGGGC	FXN	3′	human	lnaTs;omeUs;lnaAs;omeAs;lnaAs;omeAs;lnaCs;omeGs;lnaGs;deaGs;lnaGs;omeCs;lnaTs;omeGs;lnaGs;omeGs;lnaC-Sup
503	FXN-527 m01	GATAGCTTTTAATGTCC	FXN	3′	human	lnaGs;omeAs;lnaTs;omeAs;lnaGs;omeCs;lnaTs;omeUs;lnaTs;omeUs;lnaAs;omeAs;lnaTs;omeGs;lnaTs;omeCs;lnaC-Sup
504	FXN-528 m01	AGCTGGGGTCTTGGCCT	FXN	3′	human	lnaAs;omeGs;lnaCs;omeUs;lnaGs;deaGs;lnaGs;omeGs;lnaTs;omeCs;lnaTs;omeUs;lnaGs;omeGs;lnaCs;omeCs;lnaT-Sup
505	FXN-529 m01	CCTCAGCTGCATAATGA	FXN	3′	human	lnaCs;omeCs;lnaTs;omeCs;lnaAs;omeGs;lnaCs;omeUs;lnaGs;omeCs;lnaAs;omeUs;lnaAs;omeAs;lnaTs;omeGs;lnaA-Sup
506	FXN-530 m01	CAACAACAAAAAACAGA	FXN	3′	human	lnaCs;omeAs;lnaAs;omeCs;lnaAs;omeAs;lnaCs;omeAs;lnaAs;omeAs;lnaAs;omeAs;lnaAs;omeCs;lnaAs;omeGs;lnaA-Sup
507	FXN-531 m01	AAAAAAATAAACAACAA	FXN	3′	human	lnaAs;omeAs;lnaAs;omeAs;lnaAs;omeAs;lnaAs;omeUs;lnaAs;omeAs;lnaAs;omeCs;lnaAs;omeAs;lnaCs;omeAs;lnaA-Sup

508	FXN-532 m01	CCTCAAAAGCAGGAATA	FXN	3′	human	lnaCs;omeCs;lnaTs;omeCs;lnaAs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaAs;omeGs;lnaGs;omeAs;lnaAs;omeUs;lnaA-Sup
509	FXN-533 m01	ACACATAGCCCAACTGT	FXN	3′	human	lnaAs;omeCs;lnaAs;omeCs;lnaAs;omeUs;lnaAs;omeGs;lnaCs;omeCs;lnaCs;omeAs;lnaAs;omeCs;lnaTs;omeGs;lnaT-Sup
510	FXN-534 m01	CTTTCTACAGAGCTGTG	FXN	3′	human	lnaCs;omeUs;lnaTs;omeUs;lnaCs;omeUs;lnaAs;omeCs;lnaAs;omeGs;lnaAs;omeGs;lnaCs;omeUs;lnaGs;omeUs;lnaG-Sup
511	FXN-535 m01	GTAGGAGGCAACACATT	FXN	3′	human	lnaGs;omeUs;lnaAs;omeGs;lnaGs;omeAs;lnaGs;omeGs;lnaCs;omeAs;lnaAs;omeCs;lnaAs;omeCs;lnaAs;omeUs;lnaT-Sup
512	FXN-536 m01	CAGAACTTGGGGGCAAG	FXN	3′	human	lnaCs;omeAs;lnaGs;omeAs;lnaAs;omeCs;lnaTs;omeUs;lnaGs;deaGs;lnaGs;deaGs;lnaGs;omeCs;lnaAs;omeAs;lnaG-Sup
513	FXN-537 m01	CCATAGAAATTAAAAAT	FXN	3′	human	lnaCs;omeCs;lnaAs;omeUs;lnaAs;omeGs;lnaAs;omeAs;lnaAs;omeUs;lnaTs;omeAs;lnaAs;omeAs;lnaAs;omeAs;lnaT-Sup
514	FXN-538 m01	ACAATCCAAAAAATCTT	FXN	3′	human	lnaAs;omeCs;lnaAs;omeAs;lnaTs;omeCs;lnaCs;omeAs;lnaAs;omeAs;lnaAs;omeAs;lnaAs;omeUs;lnaCs;omeUs;lnaT-Sup

515	FXN-539 m01	GTGAGGGAGGAAATCC G	FXN	3′	human	lnaGs;omeUs;lnaGs ;omeAs;lnaGs;ome Gs;lnaGs;omeAs;ln aGs;omeGs;lnaAs;o meAs;lnaAs;omeUs ;lnaCs;omeCs;lnaG-Sup
516	FXN-540 m01	AAGATAAGGGGTATCAT	FXN	3′	human	lnaAs;omeAs;lnaGs ;omeAs;lnaTs;ome As;lnaAs;omeGs;ln aGs;omeGs;lnaGs; omeUs;lnaAs;ome Us;lnaCs;omeAs;ln aT-Sup
517	FXN-541 m01	GGCATAAGACATTATAA	FXN	3′	human	lnaGs;omeGs;lnaCs ;omeAs;lnaTs;ome As;lnaAs;omeGs;ln aAs;omeCs;lnaAs;o meUs;lnaTs;omeAs ;lnaTs;omeAs;lnaA-Sup
518	FXN-542 m01	TGTTATATTCAGGTATA	FXN	3′	human	lnaTs;omeGs;lnaTs; omeUs;lnaAs;ome Us;lnaAs;omeUs;ln aTs;omeCs;lnaAs;o meGs;lnaGs;omeU s;lnaAs;omeUs;lna A-Sup
519	FXN-543 m01	TTTGCTTTTTTAAAGGT	FXN	3′	human	lnaTs;omeUs;lnaTs; omeGs;lnaCs;ome Us;lnaTs;omeUs;ln aTs;omeUs;lnaTs;o meAs;lnaAs;omeAs ;lnaGs;omeGs;lnaT-Sup
520	FXN-544 m01	TTTTTCCTTCTTATTAT	FXN	3′	human	lnaTs;omeUs;lnaTs; omeUs;lnaTs;omeC s;lnaCs;omeUs;lna Ts;omeCs;lnaTs;om eUs;lnaAs;omeUs;l naTs;omeAs;lnaT-Sup
521	FXN-545 m01	CATTTTCCCTCCTGGAA	FXN	3′	human	lnaCs;omeAs;lnaTs; omeUs;lnaTs;ome Us;lnaCs;omeCs;ln aCs;omeUs;lnaCs;o meCs;lnaTs;omeGs ;lnaGs;omeAs;lnaA-Sup

522	FXN-546 m01	GAAGAGTGAAGACAAT T	FXN	3′	human	lnaGs;omeAs;lnaAs ;omeGs;lnaAs;ome Gs;lnaTs;omeGs;ln aAs;omeAs;lnaGs;o meAs;lnaCs;omeAs ;lnaAs;omeUs;lnaT-Sup
523	FXN-547 m01	TAAATCCTTCAAAGAAT	FXN	3′	human	lnaTs;omeAs;lnaAs; omeAs;lnaTs;omeC s;lnaCs;omeUs;lna Ts;omeCs;lnaAs;o meAs;lnaAs;omeGs ;lnaAs;omeAs;lnaT-Sup
524	FXN-548 m01	TCATGTACTTCTTGCAG	FXN	3′	human	lnaTs;omeCs;lnaAs; omeUs;lnaGs;ome Us;lnaAs;omeCs;ln aTs;omeUs;lnaCs;o meUs;lnaTs;omeGs ;lnaCs;omeAs;lnaG-Sup
525	FXN-549 m01	GGTTGACCAGCTGCTCT	FXN	3′	human	lnaGs;omeGs;lnaTs ;omeUs;lnaGs;ome As;lnaCs;omeCs;lna As;omeGs;lnaCs;o meUs;lnaGs;omeCs ;lnaTs;omeCs;lnaT-Sup
526	FXN-550 m01	AGATAGAACAGTGAGC A	FXN	3′	human	lnaAs;omeGs;lnaAs ;omeUs;lnaAs;ome Gs;lnaAs;omeAs;ln aCs;omeAs;lnaGs;o meUs;lnaGs;omeAs ;lnaGs;omeCs;lnaA-Sup
527	FXN-551 m01	TAATGTGTCTCATTTGG	FXN	3′	human	lnaTs;omeAs;lnaAs; omeUs;lnaGs;ome Us;lnaGs;omeUs;ln aCs;omeUs;lnaCs;o meAs;lnaTs;omeUs ;lnaTs;omeGs;lnaG-Sup
528	FXN-552 m01	ATTTGTAGGCTACCCTT	FXN	3′	human	lnaAs;omeUs;lnaTs ;omeUs;lnaGs;ome Us;lnaAs;omeGs;ln aGs;omeCs;lnaTs;o meAs;lnaCs;omeCs ;lnaCs;omeUs;lnaT-Sup

529	FXN-553 m01	GAAAGAAGCCTGAAAAC	FXN	3′	human	lnaGs;omeAs;lnaAs;omeAs;lnaGs;omeAs;lnaAs;omeGs;lnaCs;omeCs;lnaTs;omeGs;lnaAs;omeAs;lnaAs;omeAs;lnaC-Sup
530	FXN-554 m01	AGAAGTGCTTACACTTT	FXN	3′	human	lnaAs;omeGs;lnaAs;omeAs;lnaGs;omeUs;lnaGs;omeCs;lnaTs;omeUs;lnaAs;omeCs;lnaAs;omeCs;lnaTs;omeUs;lnaT-Sup
531	FXN-555 m01	TCAATGCTAAAGAGCTC	FXN	3′	human	lnaTs;omeCs;lnaAs;omeAs;lnaTs;omeGs;lnaCs;omeUs;lnaAs;omeAs;lnaAs;omeGs;lnaAs;omeGs;lnaCs;omeUs;lnaC-Sup
532	Apoa1_mus-01 m12	AGTCTGGGTGTCC	Apoa1	5′	mouse	lnaAs;dGs;lnaTs;dCs;lnaTs;dGs;lnaGs;dGs;lnaTs;dGs;lnaTs;dCs;lnaC-Sup
533	Apoa1_mus-02 m12	CCGACAGTCTGGG	Apoa1	5′	mouse	lnaCs;dCs;lnaGs;dAs;lnaCs;dAs;lnaGs;dTs;lnaCs;dTs;lnaGs;dGs;lnaG-Sup
534	Apoa1_mus-03 m12	CTCCGACAGTCTG	Apoa1	5′	mouse	lnaCs;dTs;lnaCs;dCs;lnaGs;dAs;lnaCs;dAs;lnaGs;dTs;lnaCs;dTs;lnaG-Sup
535	Apoa1_mus-04 m12	GACAGTCTGGGTG	Apoa1	5′	mouse	lnaGs;dAs;lnaCs;dAs;lnaGs;dTs;lnaCs;dTs;lnaGs;dGs;lnaGs;dTs;lnaG-Sup
536	Apoa1_mus-05 m12	CAGTCTGGGTG	Apoa1	5′	mouse	lnaCs;dAs;lnaGs;dTs;lnaCs;dTs;lnaGs;dGs;lnaGs;dTs;lnaG-Sup
537	Apoa1_mus-06 m12	CTCAGCCTGGCCCTG	Apoa1	5′	mouse	lnaCs;dTs;lnaCs;dAs;lnaGs;dCs;lnaCs;dTs;lnaGs;dGs;lnaCs;dCs;lnaCs;dTs;lnaG-Sup

538	Apoa1_mus-07m12	AGTTCAAGGATCAGC	Apoa1	5′	mouse	lnaAs;dGs;lnaTs;dTs;lnaCs;dAs;lnaAs;dGs;lnaGs;dAs;lnaTs;dCs;lnaAs;dGs;lnaC-Sup
539	Apoa1_mus-08m12	GCTCTCCGACAGTCT	Apoa1	5′	mouse	lnaGs;dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaT-Sup
540	Apoa1_mus-09m12	TCTCCGACAGTCT	Apoa1	5′	mouse	lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaT-Sup
541	Apoa1_mus-10m12	TCCGACAGTCT	Apoa1	5′	mouse	lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaAs;dGs;lnaTs;dCs;lnaT-Sup
542	Apoa1_mus-11m12	CGGAGCTCTCCGACA	Apoa1	5′	mouse	lnaCs;dGs;lnaGs;dAs;lnaGs;dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaA-Sup
543	Apoa1_mus-12m12	GAGCTCTCCGACA	Apoa1	5′	mouse	lnaGs;dAs;lnaGs;dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaA-Sup
544	Apoa1_mus-13m12	GCTCTCCGACA	Apoa1	5′	mouse	lnaGs;dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dCs;lnaA-Sup
545	Apoa1_mus-14m12	CTATTCCATTTTGGA	Apoa1	3′	mouse	lnaCs;dTs;lnaAs;dTs;lnaTs;dCs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaA-Sup
546	Apoa1_mus-15m12	CTATTCCATTTTG	Apoa1	3′	mouse	lnaCs;dTs;lnaAs;dTs;lnaTs;dCs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaG-Sup
547	Apoa1_mus-16m12	ATTCCATTTTGGAAA	Apoa1	3′	mouse	lnaAs;dTs;lnaTs;dCs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaAs;dAs;lnaA-Sup

548	Apoa1_mus-17m12	CCATTTTGGAAAGGT	Apoa1	3’	mouse	lnaCs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dAs;lnaAs;dAs;lnaGs;dGs;lnaT-Sup
549	Apoa1_mus-18m12	CCATTTTGGAAAG	Apoa1	3’	mouse	lnaCs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dGs;lnaGs;dAs;lnaAs;dAs;lnaG-Sup
550	Apoa1_mus-19m12	CATTTTGGAAAGGTT	Apoa1	3’	mouse	lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaAs;dAs;lnaAs;dGs;lnaGs;dTs;lnaT-Sup
551	Apoa1_mus-20m12	CATTTTGGAAAGG	Apoa1	3’	mouse	lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaGs;dGs;lnaAs;dAs;lnaAs;dGs;lnaG-Sup
552	Apoa1_mus-21m12	GGAAAGGTTTATTGT	Apoa1	3’	mouse	lnaGs;dGs;lnaAs;dAs;lnaAs;dGs;lnaGs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dGs;lnaT-Sup
553	Apoa1_mus-22m22	TCCGACAGTCTCCATTTTGGAA	Apoa1	5’ and 3’	mouse	lnaTs;dCs;dCs;lnaGs;dAs;dCs;lnaAs;dGs;dTs;lnaCs;dTs;dCs;lnaCs;dAs;dTs;lnaTs;dTs;dTs;lnaGs;dGs;dAs;lnaA-Sup
554	Apoa1_mus-23m22	GCTCTCCGACACCATTTTGGAA	Apoa1	5’ and 3’	mouse	lnaGs;dCs;dTs;lnaCs;dTs;dCs;lnaCs;dGs;dAs;lnaCs;dAs;dCs;lnaCs;dAs;dTs;lnaTs;dTs;dTs;lnaGs;dGs;dAs;lnaA-Sup
555	Apoa1_mus-24m22	TCCGACAGTCTCATTTTGGAAA	Apoa1	5’ and 3’	mouse	lnaTs;dCs;dCs;lnaGs;dAs;dCs;lnaAs;dGs;dTs;lnaCs;dTs;dCs;lnaAs;dTs;dTs;lnaTs;dTs;dGs;lnaGs;dAs;dAs;lnaA-Sup

556	Apoa1_mus-25m22	GCTCTCCGACACATTTTGGAAA	Apoa1	5′ and 3′	mouse	lnaGs;dCs;dTs;lnaCs;dTs;dCs;lnaCs;dGs;dAs;lnaCs;dAs;dCs;lnaAs;dTs;dTs;lnaTs;dTs;dGs;lnaGs;dAs;dAs;lnaA-Sup
557	FXN-761m01	CCTCAAAAGCAGGAA	FXN	3′	human	lnaCs;omeCs;lnaTs;omeCs;lnaAs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaAs;omeGs;lnaGs;omeAs;lnaA-Sup
558	FXN-762m01	CCTCAAAAGCAGG	FXN	3′	human	lnaCs;omeCs;lnaTs;omeCs;lnaAs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaAs;omeGs;lnaG-Sup
559	FXN-763m01	CCTCAAAAGCA	FXN	3′	human	lnaCs;omeCs;lnaTs;omeCs;lnaAs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaA-Sup
560	FXN-764m01	TCAAAAGCAGGAA	FXN	3′	human	lnaTs;omeCs;lnaAs;omeAs;lnaAs;omeAs;lnaGs;omeCs;lnaAs;omeGs;lnaGs;omeAs;lnaA-Sup
561	FXN-765m01	CAAAAGCAGGA	FXN	3′	human	lnaCs;omeAs;lnaAs;omeAs;lnaAs;omeGs;lnaCs;omeAs;lnaGs;omeGs;lnaA-Sup
562	FXN-766m01	CCGCCCTCCAGCCTCAAAAGCAGGAAT	FXN	5′ and 3′	human	lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaCs;omeAs;lnaGs;omeCs;lnaCs;omeTs;lnaCs;omeAs;lnaAs;omeAs;lnaAs;omeGs;lnaCs;omeAs;lnaGs;omeGs;lnaAs;omeAs;lnaT-Sup

563	FXN-767 m01	CCGCCCTCCAGCCTCA AAAGCAGGA	FXN	5' and 3'	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaGs;omeCs;lna Cs;omeTs;lnaCs;o meAs;lnaAs;ome As;lnaAs;omeGs;l naCs;omeAs;lnaG s;omeGs;lnaA-Sup
564	FXN-768 m01	CCGCCCTCCAGCCTCA AAAGCAG	FXN	5' and 3'	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaGs;omeCs;lna Cs;omeTs;lnaCs;o meAs;lnaAs;ome As;lnaAs;omeGs;l naCs;omeAs;lnaG -Sup
565	FXN-769 m01	CCGCCCTCCAGCCTCA AAAGC	FXN	5' and 3'	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaGs;omeCs;lna Cs;omeTs;lnaCs;o meAs;lnaAs;ome As;lnaAs;omeGs;l naC-Sup
566	FXN-770 m01	GCCCTCCAGCCTCAAA AGCAGGAAT	FXN	5' and 3'	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeCs;l naCs;omeTs;lnaC s;omeAs;lnaAs;o meAs;lnaAs;ome Gs;lnaCs;omeAs;l naGs;omeGs;lna As;omeAs;lnaT-Sup

567	FXN-771 m01	GCCCTCCAGCCTCAAA AGCAGGA	FXN	5' and 3'	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeCs;l naCs;omeTs;lnaC s;omeAs;lnaAs;o meAs;lnaAs;ome Gs;lnaCs;omeAs;l naGs;omeGs;lna A-Sup
568	FXN-772 m01	GCCCTCCAGCCTCAAA AGCAG	FXN	5' and 3'	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeCs;l naCs;omeTs;lnaC s;omeAs;lnaAs;o meAs;lnaAs;ome Gs;lnaCs;omeAs;l naG-Sup
569	FXN-773 m01	GCCCTCCAGCCTCAAA AGC	FXN	5' and 3'	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeCs;l naCs;omeTs;lnaC s;omeAs;lnaAs;o meAs;lnaAs;ome Gs;lnaC-Sup
570	FXN-774 m01	CCCTCCAGCCTCAAAA G	FXN	5' and 3'	human	lnaCs;omeCs;lna Cs;omeTs;lnaCs;o meCs;lnaAs;ome Gs;lnaCs;omeCs;l naTs;omeCs;lnaA s;omeAs;lnaAs;o meAs;lnaG-Sup
571	FXN-776 m01	CCTCCAGCCTCAAAA	FXN	5' and 3'	human	lnaCs;omeCs;lnaT s;omeCs;lnaCs;o meAs;lnaGs;ome Cs;lnaCs;omeTs;l naCs;omeAs;lnaA s;omeAs;lnaA-Sup

572	FXN-777 m01	GCCCTCCAGTCAAAA GCAGGA	FXN	5’ and 3’	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeTs;l naCs;omeAs;lnaA s;omeAs;lnaAs;o meGs;lnaCs;ome As;lnaGs;omeGs;l naA-Sup
573	FXN-778 m01	GCCCTCCAGCAAAAG CAGG	FXN	5’ and 3’	human	lnaGs;omeCs;lna Cs;omeCs;lnaTs;o meCs;lnaCs;ome As;lnaGs;omeCs;l naAs;omeAs;lnaA s;omeAs;lnaGs;o meCs;lnaAs;ome Gs;lnaG-Sup
574	FXN-779 m01	CCGCCCTCCAGTCAAA AGCAGGA	FXN	5’ and 3’	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaGs;omeTs;lna Cs;omeAs;lnaAs; omeAs;lnaAs;om eGs;lnaCs;omeAs ;lnaGs;omeGs;lna A-Sup
575	FXN-780 m01	CCGCCCTCCAGCAAA AGCAGG	FXN	5’ and 3’	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaGs;omeCs;lna As;omeAs;lnaAs; omeAs;lnaGs;om eCs;lnaAs;omeGs ;lnaG-Sup
576	FXN-671 m01	CTCCGCCCTCCAG	FXN	5’	human	lnaCs;omeTs;lnaC s;omeCs;lnaGs;o meCs;lnaCs;ome Cs;lnaTs;omeCs;l naCs;omeAs;lnaG -Sup
577	FXN-672 m01	CCGCCCTCCAG	FXN	5’	human	lnaCs;omeCs;lna Gs;omeCs;lnaCs; omeCs;lnaTs;om eCs;lnaCs;omeAs; lnaG-Sup

578	FXN-673 m01	GCCCTCCAG	FXN	5′	human	lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaCs;omeAs;lnaG-Sup
579	FXN-674 m01	CCCGCTCCGCCCTCC	FXN	5′	human	lnaCs;omeCs;lnaCs;omeGs;lnaCs;omeTs;lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaC-Sup
580	FXN-675 m01	CGCTCCGCCCTCC	FXN	5′	human	lnaCs;omeGs;lnaCs;omeTs;lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaC-Sup
581	FXN-676 m01	CTCCGCCCTCC	FXN	5′	human	lnaCs;omeTs;lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaC-Sup
582	FXN-677 m01	CCGCCCTCC	FXN	5′	human	lnaCs;omeCs;lnaGs;omeCs;lnaCs;omeCs;lnaTs;omeCs;lnaC-Sup
SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Targeting Region	Organism	Formatted Sequence
583	CD247-90 m02	GCCTTTGAGAAAGCA	CD247	5′	human	dGs;lnaCs;dCs;lnaTs;dTs;lnaTs;dGs;lnaAs;dGs;lnaAs;dAs;lnaAs;dGs;lnaCs;dA-Sup
584	CD247-91 m02	GACTGTGGGGCCTTT	CD247	5′	human	dGs;lnaAs;dCs;lnaTs;dGs;lnaTs;dGs;lnaGs;dGs;lnaGs;dCs;lnaCs;dTs;lnaTs;dT-Sup
585	CD247-92 m02	AGGAAGTGGAGGACT	CD247	5′	human	dAs;lnaGs;dGs;lnaAs;dAs;lnaGs;dTs;lnaGs;dGs;lnaAs;dGs;lnaGs;dAs;lnaCs;dT-Sup

586	CD247-93 m02	TGCATTTTCACTGAA	CD247	3′	human	dTs;lnaGs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dCs;lnaTs;dGs;lnaAs;dA-Sup
587	CD247-94 m02	CATTTTCACTGAAGC	CD247	3′	human	dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dCs;lnaTs;dGs;lnaAs;dAs;lnaGs;dC-Sup
588	CD247-95 m02	ACTGAAGCATTTATT	CD247	3′	human	dAs;lnaCs;dTs;lnaGs;dAs;lnaAs;dGs;lnaCs;dAs;lnaTs;dTs;lnaTs;dAs;lnaTs;dT-Sup
589	CFTR-84 m02	CACACAAATGTATGG	CFTR	3′	human	dCs;lnaAs;dCs;lnaAs;dCs;lnaAs;dAs;lnaAs;dTs;lnaGs;dTs;lnaAs;dTs;lnaGs;dG-Sup
590	CFTR-85 m02	GGATTTTATTGACAA	CFTR	3′	human	dGs;lnaGs;dAs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaTs;dGs;lnaAs;dCs;lnaAs;dA-Sup
591	CFTR-86 m02	AAAACAACAAAGTTT	CFTR	3′	human	dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dAs;lnaCs;dAs;lnaAs;dAs;lnaGs;dTs;lnaTs;dT-Sup
592	CFTR-87 m02	AGTGCCATAAAAAGT	CFTR	3′	human	dAs;lnaGs;dTs;lnaGs;dCs;lnaCs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dAs;lnaGs;dT-Sup
593	CFTR-88 m02	TCAAATATAAAAATT	CFTR	3′	human	dTs;lnaCs;dAs;lnaAs;dAs;lnaTs;dAs;lnaTs;dAs;lnaAs;dAs;lnaAs;dAs;lnaTs;dT-Sup
594	CFTR-89 m02	TTCCCCCCACCCACC	CFTR	3′	human	dTs;lnaTs;dCs;lnaCs;dCs;lnaCs;dCs;lnaCs;dAs;lnaCs;dCs;lnaCs;dAs;lnaCs;dC-Sup

595	CFTR-90 m02	CATTTGCTTCCAATT	CFTR	5′	human	dCs;lnaAs;dTs;lnaTs;dTs;lnaGs;dCs;lnaTs;dTs;lnaCs;dCs;lnaAs;dAs;lnaTs;dT-Sup
596	CFTR-91 m02	GCTCAACCCTTTTTC	CFTR	5′	human	dGs;lnaCs;dTs;lnaCs;dAs;lnaAs;dCs;lnaCs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dC-Sup
597	CFTR-92 m02	AGACCTACTACTCTG	CFTR	5′	human	dAs;lnaGs;dAs;lnaCs;dCs;lnaTs;dAs;lnaCs;dTs;lnaAs;dCs;lnaTs;dCs;lnaTs;dG-Sup
598	FMR1-58 m02	CCCTCCACCGGAAGT	FMR1	5′	human	dCs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dCs;lnaGs;dGs;lnaAs;dAs;lnaGs;dT-Sup
599	FMR1-59 m02	GCCCGCGCTCGCCGT	FMR1	5′	human	dGs;lnaCs;dCs;lnaCs;dGs;lnaCs;dGs;lnaCs;dTs;lnaCs;dGs;lnaCs;dCs;lnaGs;dT-Sup
600	FMR1-60 m02	ACGCCCCCTGGCAGC	FMR1	5′	human	dAs;lnaCs;dGs;lnaCs;dCs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaCs;dAs;lnaGs;dC-Sup
601	FMR1-61 m02	GCTCAGCCCCTCGGC	FMR1	5′	human	dGs;lnaCs;dTs;lnaCs;dAs;lnaGs;dCs;lnaCs;dCs;lnaCs;dTs;lnaCs;dGs;lnaGs;dC-Sup
602	FMR1-62 m02	AGCAGAGGAAGATCA	FMR1	3′	human	dAs;lnaGs;dCs;lnaAs;dGs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaAs;dTs;lnaCs;dA-Sup
603	FMR1-63 m02	CAGAGGAAGATCAAA	FMR1	3′	human	dCs;lnaAs;dGs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaAs;dTs;lnaCs;dAs;lnaAs;dA-Sup

604	FMR1-64 m02	CAGATTTTTGAAACT	FMR1	3′	human	dCs;lnaAs;dGs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dAs;lnaAs;dAs;lnaCs;dT-Sup
605	FMR1-65 m02	CAGACTAATTTTTTG	FMR1	3′	human	dCs;lnaAs;dGs;lnaAs;dCs;lnaTs;dAs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dG-Sup
606	FMR1-66 m02	TTTTTGCTTTTTCAT	FMR1	3′	human	dTs;lnaTs;dTs;lnaTs;dTs;lnaGs;dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dT-Sup
607	FMR1-67 m02	AATTTTTTGCTTTTT	FMR1	3′	human	dAs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dGs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
608	FMR1-68 m02	ATGTTTGGCAATACT	FMR1	3′	human	dAs;lnaTs;dGs;lnaTs;dTs;lnaTs;dGs;lnaGs;dCs;lnaAs;dAs;lnaTs;dAs;lnaCs;dT-Sup
609	FMR1-69 m02	TTGGCAATACTTTTT	FMR1	3′	human	dTs;lnaTs;dGs;lnaGs;dCs;lnaAs;dAs;lnaTs;dAs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
610	LAMA1-105 m02	GCTGCCCTGGCCCCG	LAMA 1	5′	human	dGs;lnaCs;dTs;lnaGs;dCs;lnaCs;dCs;lnaTs;dGs;lnaGs;dCs;lnaCs;dCs;lnaCs;dG-Sup
611	LAMA1-106 m02	CGGACACACCCCTCG	LAMA 1	5′	human	dCs;lnaGs;dGs;lnaAs;dCs;lnaAs;dCs;lnaAs;dCs;lnaCs;dCs;lnaCs;dTs;lnaCs;dG-Sup
612	LAMA1-107 m02	ACGGGACGCGAGTCC	LAMA 1	5′	human	dAs;lnaCs;dGs;lnaGs;dGs;lnaAs;dCs;lnaGs;dCs;lnaGs;dAs;lnaGs;dTs;lnaCs;dC-Sup

613	LAMA1-108 m02	GTCTGGGGAGAAAGC	LAMA 1	5′	human	dGs;lnaTs;dCs;lnaTs;dGs;lnaGs;dGs;lnaGs;dAs;lnaGs;dAs;lnaAs;dAs;lnaGs;dC-Sup
614	LAMA1-109 m02	CCACTCGGTGGGTCT	LAMA 1	5′	human	dCs;lnaCs;dAs;lnaCs;dTs;lnaCs;dGs;lnaGs;dTs;lnaGs;dGs;lnaGs;dTs;lnaCs;dT-Sup
615	LAMA1-110 m02	TGATCTGTTATCATC	LAMA 1	5′	human	dTs;lnaGs;dAs;lnaTs;dCs;lnaTs;dGs;lnaTs;dTs;lnaAs;dTs;lnaCs;dAs;lnaTs;dC-Sup
616	LAMA1-111 m02	CTGTTATCATCTGTA	LAMA 1	3′	human	dCs;lnaTs;dGs;lnaTs;dTs;lnaAs;dTs;lnaCs;dAs;lnaTs;dCs;lnaTs;dGs;lnaTs;dA-Sup
617	LAMA1-112 m02	GTGTATAAAGATTTT	LAMA 1	3′	human	dGs;lnaTs;dGs;lnaTs;dAs;lnaTs;dAs;lnaAs;dAs;lnaGs;dAs;lnaTs;dTs;lnaTs;dT-Sup
618	LAMA1-113 m02	CAATTTACATTTTAG	LAMA 1	3′	human	dCs;lnaAs;dAs;lnaTs;dTs;lnaTs;dAs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaAs;dG-Sup
619	LAMA1-114 m02	TACATTTTAGACCAT	LAMA 1	3′	human	dTs;lnaAs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dAs;lnaGs;dAs;lnaCs;dCs;lnaAs;dT-Sup
620	MBNL1-73 m02	TGCTATAAGATGTAA	MBNL 1	5′	human	dTs;lnaGs;dCs;lnaTs;dAs;lnaTs;dAs;lnaAs;dGs;lnaAs;dTs;lnaGs;dTs;lnaAs;dA-Sup
621	MBNL1-74 m02	AAGGAAGCCGGCAAG	MBNL 1	5′	human	dAs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaCs;dCs;lnaGs;dGs;lnaCs;dAs;lnaAs;dG-Sup

622	MBNL1-75 m02	CGCCACAACTCATTC	MBNL1	5′	human	dCs;lnaGs;dCs;lnaCs;dAs;lnaCs;dAs;lnaAs;dCs;lnaTs;dCs;lnaAs;dTs;lnaTs;dC-Sup
623	MBNL1-76 m02	ATGGGAGCATTGTGG	MBNL1	5′	human	dAs;lnaTs;dGs;lnaGs;dGs;lnaAs;dGs;lnaCs;dAs;lnaTs;dTs;lnaGs;dTs;lnaGs;dG-Sup
624	MBNL1-77 m02	CGCCCGCCCAGCCCC	MBNL1	5′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dCs;lnaCs;dCs;lnaAs;dGs;lnaCs;dCs;lnaCs;dC-Sup
625	MBNL1-78 m02	CCCCTCCCCCGCCCG	MBNL1	5′	human	dCs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dG-Sup
626	MBNL1-79 m02	CTTCCGCTGCTGCTG	MBNL1	5′	human	dCs;lnaTs;dTs;lnaCs;dCs;lnaGs;dCs;lnaTs;dGs;lnaCs;dTs;lnaGs;dCs;lnaTs;dG-Sup
627	MBNL1-80 m02	CTTCTTAGTACCAAC	MBNL1	5′	human	dCs;lnaTs;dTs;lnaCs;dTs;lnaTs;dAs;lnaGs;dTs;lnaAs;dCs;lnaCs;dAs;lnaAs;dC-Sup
628	MBNL1-81 m02	TTTAGAGCAAAATCG	MBNL1	5′	human	dTs;lnaTs;dTs;lnaAs;dGs;lnaAs;dGs;lnaCs;dAs;lnaAs;dAs;lnaAs;dTs;lnaCs;dG-Sup
629	MBNL1-82 m02	GGTAGTTAAATGTTT	MBNL1	5′	human	dGs;lnaGs;dTs;lnaAs;dGs;lnaTs;dTs;lnaAs;dAs;lnaAs;dTs;lnaGs;dTs;lnaTs;dT-Sup
630	MBNL1-83 m02	TACTTAAGAAAGAGA	MBNL1	3′	human	dTs;lnaAs;dCs;lnaTs;dTs;lnaAs;dAs;lnaGs;dAs;lnaAs;dAs;lnaGs;dAs;lnaGs;dA-Sup

631	MBNL1-84 m02	TATACTTAAGAAAGA	MBNL1	3′	human	dTs;lnaAs;dTs;lnaAs;dCs;lnaTs;dTs;lnaAs;dAs;lnaGs;dAs;lnaAs;dAs;lnaGs;dA-Sup
632	MECP2-61 m02	CGCCGCCGACGCCGG	MECP2	5′	human	dCs;lnaGs;dCs;lnaCs;dGs;lnaCs;dCs;lnaGs;dAs;lnaCs;dGs;lnaCs;dCs;lnaGs;dG-Sup
633	MECP2-62 m02	CTCTCTCCGAGAGGA	MECP2	5′	human	dCs;lnaTs;dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dGs;lnaAs;dGs;lnaGs;dA-Sup
634	MECP2-63 m02	CGCCCCGCCCTCTTG	MECP2	5′	human	dCs;lnaGs;dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dTs;lnaTs;dG-Sup
635	MECP2-64 m02	CCGCGCGCTGCTGCA	MECP2	5′	human	dCs;lnaCs;dGs;lnaCs;dGs;lnaCs;dGs;lnaCs;dTs;lnaGs;dCs;lnaTs;dGs;lnaCs;dA-Sup
636	MECP2-65 m02	CACTTTCACAGAGAG	MECP2	3′	human	dCs;lnaAs;dCs;lnaTs;dTs;lnaTs;dCs;lnaAs;dCs;lnaAs;dGs;lnaAs;dGs;lnaAs;dG-Sup
637	MECP2-66 m02	CTTTCACATGTATTAA	MECP2	3′	human	dCs;lnaTs;dTs;lnaTs;dCs;lnaAs;dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dTs;lnaTs;dAs;dA-Sup
638	MECP2-67 m02	ATGTATTAAAAAACT	MECP2	3′	human	dAs;lnaTs;dGs;lnaTs;dAs;lnaTs;dTs;lnaAs;dAs;lnaAs;dAs;lnaAs;dAs;lnaCs;dT-Sup
639	MECP2-68 m02	GACATTTTTATGTAA	MECP2	3′	human	dGs;lnaAs;dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaGs;dTs;lnaAs;dA-Sup

640	MECP2-69 m02	CATTTTTATGTAAAT	MECP2	3′	human	dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dTs;lnaGs;dTs;lnaAs;dAs;lnaAs;dT-Sup
641	MECP2-70 m02	AAATTTATAAGGCAA	MECP2	3′	human	dAs;lnaAs;dAs;lnaTs;dTs;lnaTs;dAs;lnaTs;dAs;lnaAs;dGs;lnaGs;dCs;lnaAs;dA-Sup
642	MECP2-71 m02	AGGCAAACTCTTTAT	MECP2	3′	human	dAs;lnaGs;dGs;lnaCs;dAs;lnaAs;dAs;lnaCs;dTs;lnaCs;dTs;lnaTs;dTs;lnaAs;dT-Sup
643	MECP2-72 m02	GTCTCTGGAACAATT	MECP2	3′	human	dGs;lnaTs;dCs;lnaTs;dCs;lnaTs;dGs;lnaGs;dAs;lnaAs;dCs;lnaAs;dAs;lnaTs;dT-Sup
644	MECP2-73 m02	CAGTTCAAACACAGA	MECP2	3′	human	dCs;lnaAs;dGs;lnaTs;dTs;lnaCs;dAs;lnaAs;dAs;lnaCs;dAs;lnaCs;dAs;lnaGs;dA-Sup
645	MECP2-74 m02	CAAACACAGAAGAGA	MECP2	3′	human	dCs;lnaAs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dGs;lnaAs;dAs;lnaGs;dAs;lnaGs;dA-Sup
646	MECP2-75 m02	AACACAGAAGAGATT	MECP2	3′	human	dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dGs;lnaAs;dAs;lnaGs;dAs;lnaGs;dAs;lnaTs;dT-Sup
647	MECP2-76 m02	GGGGGAGAAGAAAGG	MECP2	3′	human	dGs;lnaGs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dAs;lnaGs;dAs;lnaAs;dAs;lnaGs;dG-Sup
648	MECP2-77 m02	TCGTTTTTTTTCTT	MECP2	3′	human	dTs;lnaCs;dGs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dCs;lnaTs;dT-Sup

649	MECP2-78 m02	CTTTTTTTTCTTTTT	MECP2	3′	human	dCs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaTs;dTs;lnaCs;dTs;lnaTs;dTs;lnaTs;dT-Sup
650	MECP2-79 m02	CCTATGCTATGGTTA	MECP2	3′	human	dCs;lnaCs;dTs;lnaAs;dTs;lnaGs;dCs;lnaTs;dAs;lnaTs;dGs;lnaGs;dTs;lnaTs;dA-Sup
651	MECP2-80 m02	AGTTTACTGAAAGAA	MECP2	3′	human	dAs;lnaGs;dTs;lnaTs;dTs;lnaAs;dCs;lnaTs;dGs;lnaAs;dAs;lnaAs;dGs;lnaAs;dA-Sup
652	MECP2-81 m02	ACTGAAAGAAAAAAA	MECP2	3′	human	dAs;lnaCs;dTs;lnaGs;dAs;lnaAs;dAs;lnaGs;dAs;lnaAs;dAs;lnaAs;dAs;lnaAs;dA-Sup
653	MERTK-66 m02	CCTTATTCATATTTT	MERTK	3′	human	dCs;lnaCs;dTs;lnaTs;dAs;lnaTs;dTs;lnaCs;dAs;lnaTs;dAs;lnaTs;dTs;lnaTs;dT-Sup
654	MERTK-67 m02	CTTCCTTATTCATAT	MERTK	3′	human	dCs;lnaTs;dTs;lnaCs;dCs;lnaTs;dTs;lnaAs;dTs;lnaTs;dCs;lnaAs;dTs;lnaAs;dT-Sup
655	MERTK-68 m02	CAATCCTTCAATATT	MERTK	3′	human	dCs;lnaAs;dAs;lnaTs;dCs;lnaCs;dTs;lnaTs;dCs;lnaAs;dAs;lnaTs;dAs;lnaTs;dT-Sup
656	MERTK-69 m02	GGCATTTCATTTTAC	MERTK	3′	human	dGs;lnaGs;dCs;lnaAs;dTs;lnaTs;dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dTs;lnaAs;dC-Sup
657	MERTK-70 m02	CATTTTACAAATATT	MERTK	3′	human	dCs;lnaAs;dTs;lnaTs;dTs;lnaTs;dAs;lnaCs;dAs;lnaAs;dAs;lnaTs;dAs;lnaTs;dT-Sup

658	MERTK-71 m02	GAAATGAAATAAGTA	MERTK	3′	human	dGs;lnaAs;dAs;lnaAs;dTs;lnaGs;dAs;lnaAs;dAs;lnaTs;dAs;lnaAs;dGs;lnaTs;dA-Sup
659	MERTK-72 m02	AGATATGCAAGATAA	MERTK	3′	human	dAs;lnaGs;dAs;lnaTs;dAs;lnaTs;dGs;lnaCs;dAs;lnaAs;dGs;lnaAs;dTs;lnaAs;dA-Sup
660	MERTK-73 m02	GCGGGCCCAGCAGGT	MERTK	5′	human	dGs;lnaCs;dGs;lnaGs;dGs;lnaCs;dCs;lnaCs;dAs;lnaGs;dCs;lnaAs;dGs;lnaGs;dT-Sup
661	MERTK-74 m02	CAGTGAGTGCCGAGT	MERTK	5′	human	dCs;lnaAs;dGs;lnaTs;dGs;lnaAs;dGs;lnaTs;dGs;lnaCs;dCs;lnaGs;dAs;lnaGs;dT-Sup
662	MERTK-75 m02	GCCCGGGCAGTGAGT	MERTK	5′	human	dGs;lnaCs;dCs;lnaCs;dGs;lnaGs;dGs;lnaCs;dAs;lnaGs;dTs;lnaGs;dAs;lnaGs;dT-Sup
663	MERTK-76 m02	TGTCCGGGCGGCCCG	MERTK	5′	human	dTs;lnaGs;dTs;lnaCs;dCs;lnaGs;dGs;lnaGs;dCs;lnaGs;dGs;lnaCs;dCs;lnaCs;dG-Sup
664	SSPN-47 m02	CGCGCGTGTGCGAGT	SSPN	5′	human	dCs;lnaGs;dCs;lnaGs;dCs;lnaGs;dTs;lnaGs;dTs;lnaGs;dCs;lnaGs;dAs;lnaGs;dT-Sup
665	SSPN-48 m02	CTTCAGACAGGCTGC	SSPN	5′	human	dCs;lnaTs;dTs;lnaCs;dAs;lnaGs;dAs;lnaCs;dAs;lnaGs;dGs;lnaCs;dTs;lnaGs;dC-Sup
666	SSPN-49 m02	ACCTCTGCACTTCAG	SSPN	5′	human	dAs;lnaCs;dCs;lnaTs;dCs;lnaTs;dGs;lnaCs;dAs;lnaCs;dTs;lnaTs;dCs;lnaAs;dG-Sup

667	SSPN-50 m02	CGGCGCGGGTCCCTT	SSPN	5′	human	dCs;lnaGs;dGs;lnaCs;dGs;lnaCs;dGs;lnaGs;dGs;lnaTs;dCs;lnaCs;dCs;lnaTs;dT-Sup
668	SSPN-51 m02	TGGTATTCGAATTAT	SSPN	5′	human	dTs;lnaGs;dGs;lnaTs;dAs;lnaTs;dTs;lnaCs;dGs;lnaAs;dAs;lnaTs;dTs;lnaAs;dT-Sup
669	SSPN-52 m02	CGGCCTGCCCTGGTA	SSPN	5′	human	dCs;lnaGs;dGs;lnaCs;dCs;lnaTs;dGs;lnaCs;dCs;lnaCs;dTs;lnaGs;dGs;lnaTs;dA-Sup
670	SSPN-53 m02	TCAGAGATTATGAAA	SSPN	3′	human	dTs;lnaCs;dAs;lnaGs;dAs;lnaGs;dAs;lnaTs;dTs;lnaAs;dTs;lnaGs;dAs;lnaAs;dA-Sup
671	SSPN-54 m02	TGTTTTCAGAGATTA	SSPN	3′	human	dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dCs;lnaAs;dGs;lnaAs;dGs;lnaAs;dTs;lnaTs;dA-Sup
672	SSPN-55 m02	CATGTAGAAATGCTT	SSPN	3′	human	dCs;lnaAs;dTs;lnaGs;dTs;lnaAs;dGs;lnaAs;dAs;lnaAs;dTs;lnaGs;dCs;lnaTs;dT-Sup
673	SSPN-56 m02	AAACATGTAGAAATG	SSPN	3′	human	dAs;lnaAs;dAs;lnaCs;dAs;lnaTs;dGs;lnaTs;dAs;lnaGs;dAs;lnaAs;dAs;lnaTs;dG-Sup
674	SSPN-57 m02	TTGATACCATTTATG	SSPN	3′	human	dTs;lnaTs;dGs;lnaAs;dTs;lnaAs;dCs;lnaCs;dAs;lnaTs;dTs;lnaTs;dAs;lnaTs;dG-Sup
675	SSPN-58 m02	GAACTCAATTATTAT	SSPN	3′	human	dGs;lnaAs;dAs;lnaCs;dTs;lnaCs;dAs;lnaAs;dTs;lnaTs;dAs;lnaTs;dTs;lnaAs;dT-Sup

676	UTRN-972 m02	AAAACGACTCCACAA	UTRN	5′	human	dAs;lnaAs;dAs;lnaAs;dCs;lnaGs;dAs;lnaCs;dTs;lnaCs;dCs;lnaAs;dCs;lnaAs;dA-Sup
677	UTRN-312 m02	CTCCGAGGAAAAACG	UTRN	5′	human	dCs;lnaTs;dCs;lnaCs;dGs;lnaAs;dGs;lnaGs;dAs;lnaAs;dAs;lnaAs;dAs;lnaCs;dG-Sup
678	UTRN-313 m02	GCTCCGAGGAAAAAC	UTRN	5′	human	dGs;lnaCs;dTs;lnaCs;dCs;lnaGs;dAs;lnaGs;dGs;lnaAs;dAs;lnaAs;dAs;lnaAs;dC-Sup
679	UTRN-975 m02	CTCGGCGGGAGAAAG	UTRN	5′	human	dCs;lnaTs;dCs;lnaGs;dGs;lnaCs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dAs;lnaAs;dG-Sup
680	UTRN-976 m02	GAACCGAAATTTT	UTRN	5′	human	dGs;lnaAs;dAs;lnaCs;dCs;lnaGs;dAs;lnaAs;dAs;lnaTs;dTs;lnaTs;dT-Sup
681	UTRN-977 m02	GAGAAGGGTGCAGAT	UTRN	5′	human	dGs;lnaAs;dGs;lnaAs;dAs;lnaGs;dGs;lnaGs;dTs;lnaGs;dCs;lnaAs;dGs;lnaAs;dT-Sup
682	UTRN-978 m02	CTCTCCAGATGAGAA	UTRN	5′	human	dCs;lnaTs;dCs;lnaTs;dCs;lnaCs;dAs;lnaGs;dAs;lnaTs;dGs;lnaAs;dGs;lnaAs;dA-Sup
683	UTRN-979 m02	CAGGGGTCCGCTCTC	UTRN	5′	human	dCs;lnaAs;dGs;lnaGs;dGs;lnaGs;dTs;lnaCs;dCs;lnaGs;dCs;lnaTs;dCs;lnaTs;dC-Sup
684	UTRN-980 m02	TCCGGGCAGCCAGGG	UTRN	5′	human	dTs;lnaCs;dCs;lnaGs;dGs;lnaGs;dCs;lnaAs;dGs;lnaCs;dCs;lnaAs;dGs;lnaGs;dG-Sup

685	UTRN-981 m02	GGGGCTCGCCTCCGG	UTRN	5′	human	dGs;lnaGs;dGs;lnaGs;dCs;lnaTs;dCs;lnaGs;dCs;lnaCs;dTs;lnaCs;dCs;lnaGs;dG-Sup
686	UTRN-982 m02	CCCCCGGGAAGGGGC	UTRN	5′	human	dCs;lnaCs;dCs;lnaCs;dCs;lnaGs;dGs;lnaGs;dAs;lnaAs;dGs;lnaGs;dGs;lnaGs;dC-Sup
687	UTRN-983 m02	CCCACCCCCCGGGAA	UTRN	5′	human	dCs;lnaCs;dCs;lnaAs;dCs;lnaCs;dCs;lnaCs;dCs;lnaCs;dGs;lnaGs;dGs;lnaAs;dA-Sup
688	UTRN-984 m02	GCGTTGCCGCCCCCAC	UTRN	5′	human	dGs;lnaCs;dGs;lnaTs;dTs;lnaGs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dCs;lnaCs;dAs;dC-Sup
689	UTRN-985 m02	GCTGGGTCGCGCGTT	UTRN	5′	human	dGs;lnaCs;dTs;lnaGs;dGs;lnaGs;dTs;lnaCs;dGs;lnaCs;dGs;lnaCs;dGs;lnaTs;dT-Sup
690	UTRN-986 m02	GCGCAGGACCGCTGG	UTRN	5′	human	dGs;lnaCs;dGs;lnaCs;dAs;lnaGs;dGs;lnaAs;dCs;lnaCs;dGs;lnaCs;dTs;lnaGs;dG-Sup
691	UTRN-987 m02	AGGAGGGAGGGTGGG	UTRN	5′	human	dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaTs;dGs;lnaGs;dG-Sup
692	UTRN-988 m02	CGCTGGAGGCGGAGG	UTRN	5′	human	dCs;lnaGs;dCs;lnaTs;dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dGs;lnaGs;dAs;lnaGs;dG-Sup
693	UTRN-192 m02	TGGAGCCGAGCGCTG	UTRN	5′	human	dTs;lnaGs;dGs;lnaAs;dGs;lnaCs;dCs;lnaGs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dG-Sup

694	UTRN-303 m02	CTGCCCCTTTGTTGG	UTRN	5′	human	dCs;lnaTs;dGs;lnaCs;dCs;lnaCs;dCs;lnaTs;dTs;lnaTs;dGs;lnaTs;dTs;lnaGs;dG-Sup
695	UTRN-991 m02	CTCCCCGCTGCGGGC	UTRN	5′	human	dCs;lnaTs;dCs;lnaCs;dCs;lnaCs;dGs;lnaCs;dTs;lnaGs;dCs;lnaGs;dGs;lnaGs;dC-Sup
696	UTRN-992 m02	CGGCTCCTCCTCCTC	UTRN	5′	human	dCs;lnaGs;dGs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaCs;dCs;lnaTs;dC-Sup
697	UTRN-993 m02	GGCTCGCTCCTTCGG	UTRN	5′	human	dGs;lnaGs;dCs;lnaTs;dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dTs;lnaTs;dCs;lnaGs;dG-Sup
698	UTRN-994 m02	TTTGTGCGCGAGAGA	UTRN	5′	human	dTs;lnaTs;dTs;lnaGs;dTs;lnaGs;dCs;lnaGs;dCs;lnaGs;dAs;lnaGs;dAs;lnaGs;dA-Sup
699	UTRN-995 m02	ACGACTCCACAACTT	UTRN	5′	human	dAs;lnaCs;dGs;lnaAs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dAs;lnaAs;dCs;lnaTs;dT-Sup
700	UTRN-997 m02	GCCCGCTTCCCTGCT	UTRN	5′	human	dGs;lnaCs;dCs;lnaCs;dGs;lnaCs;dTs;lnaTs;dCs;lnaCs;dCs;lnaTs;dGs;lnaCs;dT-Sup
701	UTRN-662 m02	CGGCCGGCTGCTGCT	UTRN	5′	human	dCs;lnaGs;dGs;lnaCs;dCs;lnaGs;dGs;lnaCs;dTs;lnaGs;dCs;lnaTs;dGs;lnaCs;dT-Sup
702	UTRN-999 m02	GCGGGAGAAAGCCCG	UTRN	5′	human	dGs;lnaCs;dGs;lnaGs;dGs;lnaAs;dGs;lnaAs;dAs;lnaAs;dGs;lnaCs;dCs;lnaCs;dG-Sup

703	UTRN-1000 m02	CCTCCTCGCCCCTCG	UTRN	5′	human	dCs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;lnaGs;dCs;lnaCs;dCs;lnaCs;dTs;lnaCs;dG-Sup
704	UTRN-1001 m02	AGAGGCTCCTCCTCG	UTRN	5′	human	dAs;lnaGs;dAs;lnaGs;dGs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaCs;dG-Sup
705	UTRN-1002 m02	TCGGCTTCTGGAGCC	UTRN	5′	human	dTs;lnaCs;dGs;lnaGs;dCs;lnaTs;dTs;lnaCs;dTs;lnaGs;dGs;lnaAs;dGs;lnaCs;dC-Sup
706	UTRN-1003 m02	CCGTGATTCCCCAAT	UTRN	5′	human	dCs;lnaCs;dGs;lnaTs;dGs;lnaAs;dTs;lnaTs;dCs;lnaCs;dCs;lnaCs;dAs;lnaAs;dT-Sup
707	UTRN-1004 m02	AGGGGGGCGCCGCTC	UTRN	5′	human	dAs;lnaGs;dGs;lnaGs;dGs;lnaGs;dGs;lnaCs;dGs;lnaCs;dCs;lnaGs;dCs;lnaTs;dC-Sup
708	UTRN-323 m02	AAATGACCCAAAAGA	UTRN	5′	human	dAs;lnaAs;dAs;lnaTs;dGs;lnaAs;dCs;lnaCs;dCs;lnaAs;dAs;lnaAs;dAs;lnaGs;dA-Sup
709	UTRN-328 m02	GTTTTCCGTTTGCAG	UTRN	5′	human	dGs;lnaTs;dTs;lnaTs;dTs;lnaCs;dCs;lnaGs;dTs;lnaTs;dTs;lnaGs;dCs;lnaAs;dG-Sup
710	UTRN-334 m02	CCAAACGCTACAGAG	UTRN	5′	human	dCs;lnaCs;dAs;lnaAs;dAs;lnaCs;dGs;lnaCs;dTs;lnaAs;dCs;lnaAs;dGs;lnaAs;dG-Sup
711	UTRN-1008 m02	CAGGCACCAACTTTG	UTRN	5′	human	dCs;lnaAs;dGs;lnaGs;dCs;lnaAs;dCs;lnaCs;dAs;lnaAs;dCs;lnaTs;dTs;lnaTs;dG-Sup

712	UTRN-1009 m02	CCTGGAAGGGGCGCG	UTRN	5′	human	dCs;lnaCs;dTs;lnaGs;dGs;lnaAs;dAs;lnaGs;dGs;lnaGs;dGs;lnaCs;dGs;lnaCs;dG-Sup
713	UTRN-345 m02	CAGTCAAAGCGCAAA	UTRN	5′	human	dCs;lnaAs;dGs;lnaTs;dCs;lnaAs;dAs;lnaAs;dGs;lnaCs;dGs;lnaCs;dAs;lnaAs;dA-Sup
714	UTRN-1011 m02	CCAAAAACAAAACAG	UTRN	5′	human	dCs;lnaCs;dAs;lnaAs;dAs;lnaAs;dAs;lnaCs;dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dG-Sup
715	UTRN-674 m02	TTCCGCCAAAAACAA	UTRN	5′	human	dTs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaAs;dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dA-Sup
716	UTRN-1013 m02	GGAGGAGGGAGGGTG	UTRN	5′	human	dGs;lnaGs;dAs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaAs;dGs;lnaGs;dGs;lnaTs;dG-Sup
717	UTRN-1014 m02	CGAGCGCTGGAGGCG	UTRN	5′	human	dCs;lnaGs;dAs;lnaGs;dCs;lnaGs;dCs;lnaTs;dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dG-Sup
718	UTRN-1015 m02	CCTGCCCCTTTGTTG	UTRN	5′	human	dCs;lnaCs;dTs;lnaGs;dCs;lnaCs;dCs;lnaCs;dTs;lnaTs;dTs;lnaGs;dTs;lnaTs;dG-Sup
719	UTRN-1016 m02	GGCGGCTCCTCCTCC	UTRN	5′	human	dGs;lnaGs;dCs;lnaGs;dGs;lnaCs;dTs;lnaCs;dCs;lnaTs;dCs;lnaCs;dTs;lnaCs;dC-Sup

Example 10. Further data for FXN oligos

Using FXN-374 and FXN-375 as 5' oligos, all 3' oligos available in Table 3 were screened for RNA upregulation of human FXN in GM03816 cells via transfection at 20nM, 50nM and 100nM concentrations (FIG. 51). Concentrations were total oligo concentrations

(e.g. 20nM means 10nM for each oligo). In general, cell treated with the oligo combinations that included the 375 oligo had upregulation of human FXN compared to untreated cells. The 375 and 390 combination gave a dose responsive upregulation of human FXN at the highest levels (FIG. 51).

Various FXN oligos from Table 3, Table 6, Table 7 and Table 10 were transfected to the GM03816 cell lines (FXN-375/ FXN-398 combo at 10 or 30 nM, FXN-429 at 10 or 30 nM, 511 at 10nM, FXN-456 at 10 nM, FXN-485 at 10nM or 30 nM, FXN-458 at 10 nM, FXN-461 m02 at 10 or 30 nM). Abcam ab48281 antibody was used to measure premature and mature FXN protein levels. Oligos 456, 458, 485 and 461 are pseudo-circularization oligos. Oligo 461 is a pseudo-circularization oligo that contains the sequences of the 375 (5') and 390 (3') oligo. Actin was used as the loading control (Cell signaling, 8457). Levels of premature and mature FXN, in general, were upregulated in all oligo-treated cells (FIG. 52). Premature and mature FXN were dramatically upregulated in a dose responsive manner by FXN-458 and FXN-461 (FIG. 52).

A further study with FXN-461 m02 oligo was performed. FXN-461 m02 dose response was measured with transfection to GM03816 cell line at the indicated concentrations. Abcam ab48281 antibody was used to measure premature and mature FXN protein levels. Actin was used as the loading control (Cell signaling, 8457). FXN protein levels were also upregulated strongly in the follow-up study (FIG. 53).

Next, further 3'-targeting FXN oligos (shown in Table 10) were designed to examine potential alternative 3' locations based on public polyA-seq data. The FXN-375 oligo was used as the 5' oligo and was combined with the further 3'-targeting FXN oligos. Transfection into GM03816 cells was done at a 30nM concentration. FXN mRNA upregulation was observed in several of the oligo combinations and was highest with 3' oligos FXN-527 and FXN-532 (FIG. 54).

A subset of the further 3'-targeting FXN oligos were screened with an alternate 5' oligo (FXN-675) instead of the 375 oligo to examine reproducibility of 3' oligo mediated upregulation of FXN mRNA. While differences are observed, similar 3' oligos were identified as lead compounds with both 5' oligos, e.g., FXN-654, FXN-663, FXN-666, FXN-668 and FXN-670 (FIG. 55).

Expression changes of candidate FXN downstream genes, PPARGC1 and NFE2L2, were evaluated in the 3' oligo study. The largest changes were observed with the PPARGC1 gene (FIG. 56).

Next, further 5'-targeting FXN oligos were designed to examine potential alternative 5' locations, and to examine oligos with shorter lengths. Transfection into GM03816 cells was done at a30nM concentration. The FXN-390 oligo was used as the 3' oligo. FXN mRNA upregulation was highest with 5' oligo FXN-673 (FIG. 57). Oligos 671-673 were 13mer, 11mer and 9mer versions of FXN-375 (15mer), respectively.

Subsequently, several 5' (FXN-374, FXN-375), 3' (FXN-390) and pseudo-circularization (483, 484, 487) FXN oligos were tested gymnotically in FRDA mouse model (Sarsero) fibroblasts for 4, 7 and 10 days in vitro. FXN mRNA levels were highest with the FXN-374+390 and FXN-375+390 combinations (FIG. 58A-C).

Next, various 3' and 5' FXN oligos (FXN-527, FXN-528, FXN-532, FXN-533, FXN-553, FXN-674, and FXN-675) were examined by transfection in GM03816 cells for dose-response patterns of FXN mRNA levels (FIG. 59A and B). Oligos FXN-527, FXN-532, FXN-674, and FXN-675 showed a dose-dependent increase of FXN mRNA.

Subsequently, various 5' FXN oligos were combined with a lead 3' oligo, FXN-532. Dose response patterns of FXN mRNA were measured with transfection in GM03816 cells. All tested oligos showed a dose-dependent increase of FXN mRNA. Measurements were done at day5. FXN-674 is a 15mer that overlaps with FXN-375 by 11 nucleotides. FXN-675, FXN-676 and FXN-677 are 13mer, 11mer and 9-mer versions of FXN-674, respectively. FXN-671, FXN-672 and FXN-673 are 13mer, 11mer and 9-mer versions of FXN-375, respectively (FIG. 60A and B).

Next, 5' oligos (FXN-375, FXN-671, FXN-672, FXN-673, FXN-674, FXN-675, FXN-676, and FXN-677) were tested alone or in combination with 3' oligo FXN-532 for upregulation of FXN protein. The oligos were transfected either alone or in combinations to GM03816 cells at 30nM and 10nM concentrations. Measurements were taken at day 5. A Western blot was done with the Abcam (ab110328) antibody to detect premature and mature FXN protein. In general, FXN protein levels were upregulated in all cells treated with oligos,

either alone or in combination (FIG. 61). The highest protein upregulation was observed with the FXN-672+532 combination (FIG. 61).

Several lead 5' (FXN-374, FXN-375), 3' (FXN-390), pseudo-circularization oligos (FXN-460: FXN-374+390; FXN-461: FXN-375+390) and multi-targeting oligos (FXN-460 MTO and FXN-461 MTO) are tested gymnotically in normal human cardiomyocytes for human FXN mRNA upregulation. Multitargeting Oligos (MTO) comprise 5' and 3' targeting oligos linked by a cleavable linker (e.g., oligo-dT linker (e.g., dTdTdTdTdT)). Oligos are incubated at multiple concentrations for 8 days, changing media and oligos at day4.

Example 11. Data for UTRN oligos

Pseudo-circularization oligos for Utrophin (UTRN-211-220) as shown in Table 7 were screened gymnotically in differentiated human patient Duchenne muscular dystrophy (DMD) myotubes. Westerns were done with the Mancho 5 antibody. UTRN protein western signal was normalized relative to beta-actin levels and untreated sample. Oligo UTRN-217 was shown to upregulate the level of UTRN protein compared to negative control oligo 293LM and compared to cells only (FIG. 62 and 63).

Next, UTRN 5' and 3' oligos were screened individually and gymnotically in differentiated human patient DMD myotubes. Samples were separated into pellet and supernatant through centrigfugation for Western analysis. Samples were lysed in SDS solution, kept on ice and then spun down to separate pellet and supernatant fractions. Westerns were done with the Mancho 5 antibody. UTRN protein western signal was normalized relative to beta-actin levels and untreated sample. Positive upregulation of UTRN protein was observed in the pellet of cells treated with UTRN-202, 208, 209, 210 and 217 oligos (FIG. 64A-C).

Example 12. Data for APOA1 oligos

Mouse APOA1 5' (APOA1_mus-1-13) and 3' (APOA1_mus -21) oligo combinations were screened in duplicate in primary mouse hepatocytes gymnotically at 20uM and 5uM concentrations. APOA1 mRNA was measured and normalized relative to the water control

well. Several of the tested oligos caused an upregulation of APOA1 compared to water (FIG. 65).

Next, mouse APOA1 5' and 3' oligo combinations were screened in primary mouse hepatocytes gymnotically to measure APOA1 protein levels. Measurements were taken at day 2. Abcam ab20453 was used as APOA1 antibody. Tubulin (ab125267) was used as loading control. Oligos APOA1_mus -3+17, APOA1_mus -6+17 and APOA1_mus -7+20 show dose-dependent APOA1 protein upregulation in both cell media and cell lysates (FIG. 66).

Subsequently, two mouse APOA1 5' and 3' oligo combinations (APOA1_mus-3 + APOA1_mus-17 or APOA1_mus-7 + APOA1_mus-20) were tesed *in vivo* in mice. The oligo combinations were injected subcutaneously at days 1, 2 and 3 at 50mg/kg for each oligo in the combinations tested. The vehicle (PBS) treatment was used as control. In a first study (FIG. 70A), collection was done at day 5, 2 days after the last dose. In a second study (FIG. 70B), collection was done at day 7, 4 days after the last dose. RNA measurements in liver in both studies (FIGs. 70A and B) suggest APOA1 mRNA upregulation of up to 80% with the 7+20 and 3+20 APOAA1 oligo combinations. The 5 genes in close proximity to APOA1 (APOC3, APOA4,APOA5,APOB, Sik3) were not significantly affected by oligo treatment.

Levels of APOA1 protein were also measured in the two *in vivo* studies. FIG. 70C shows APOA1 protein data from the first study for oligo combination 3+17. APOA1 protein upregulation was seen in blood plasma in all 4 treated animals. FIG. 70D shows APOA1 protein data from the second study for oligo combination 7+20. Pre-bleeding data from all 10 animals showed relatively equal levels of plasma APOA1 across animals before the start of treatments (top panel, FIG. 70D). Samples 5 and 10 showed upregulation of mouse APOA1 protein in plasma after treatment with oligo combination 7+20.

The lack of RNA changes (FIG. 70A) for oligo combination 3+17 in the presence of protein upregulation (FIG. 70C), as well as the upregulation of APOA1 in 2 out of 5 animals with oligo combination 7+20 treatment (FIG. 70D) may be due to the oligo treatment regimen and the collection points chosen.

Example 13. Additional non-coding RNA-targeting oligos

Table 11 provides further exemplary non-coding RNA 5' and 3' end targeting oligos.

Table 11. Oligonucleotides designed to target 5' and 3' ends of non-coding RNAs

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
720	DINO-1 m02	TAGACACTTCCAGAA	DINO	3'	human	dTs;lnaAs;dGs;lnaAs;dCs;lnaAs;dCs;lnaTs;dTs;lnaCs;dCs;lnaAs;dGs;lnaAs;dA-Sup
721	DINO-2 m02	TTCCAGAATTGTCCT	DINO	3'	human	dTs;lnaTs;dCs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaTs;dGs;lnaTs;dCs;lnaCs;dT-Sup
722	DINO-3 m02	CAGAATTGTCCTTTA	DINO	3'	human	dCs;lnaAs;dGs;lnaAs;dAs;lnaTs;dTs;lnaGs;dTs;lnaCs;dCs;lnaTs;dTs;lnaTs;dA-Sup
723	DINO-4 m02	CTGCTGGAACTCGGC	DINO	5'	human	dCs;lnaTs;dGs;lnaCs;dTs;lnaGs;dGs;lnaAs;dAs;lnaCs;dTs;lnaCs;dGs;lnaGs;dC-Sup
724	DINO-5 m02	GGCCAGGCTCAGCTG	DINO	5'	human	dGs;lnaGs;dCs;lnaCs;dAs;lnaGs;dGs;lnaCs;dTs;lnaCs;dAs;lnaGs;dCs;lnaTs;dG-Sup
725	DINO-6 m02	GCAGCCAGGAGCCTG	DINO	5'	human	dGs;lnaCs;dAs;lnaGs;dCs;lnaCs;dAs;lnaGs;dGs;lnaAs;dGs;lnaCs;dCs;lnaTs;dG-Sup
726	DINO-7 m02	ACTCGGCCAGGCTCA	DINO	5'	human	dAs;lnaCs;dTs;lnaCs;dGs;lnaGs;dCs;lnaCs;dAs;lnaGs;dGs;lnaCs;dTs;lnaCs;dA-Sup
727	DINO-8 m02	GCTGGCCTGCTGGAA	DINO	5'	human	dGs;lnaCs;dTs;lnaGs;dGs;lnaCs;dCs;lnaTs;dGs;lnaCs;dTs;lnaGs;dGs;lnaAs;dA-Sup
728	HOTTIP-1 m02	TTTAAATTGTATCGG	HOTTIP	3'	human	dTs;lnaTs;dTs;lnaAs;dAs;lnaAs;dTs;lnaTs;dGs;lnaTs;dAs;lnaTs;dCs;lnaGs;dG-Sup
729	HOTTIP-2 m02	ATTGTATCGGGCAAA	HOTTIP	3'	human	dAs;lnaTs;dTs;lnaGs;dTs;lnaAs;dTs;lnaCs;dGs;lnaGs;dGs;lnaCs;dAs;lnaAs;dA-Sup

730	HOTTIP-3 m02	GATTAAAACAAAAGA	HOTTIP	3′	human	dGs;lnaAs;dTs;lnaTs;dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dAs;lnaAs;dAs;lnaGs;dA-Sup
731	HOTTIP-4 m02	AAAACAAAAGAAACC	HOTTIP	3′	human	dAs;lnaAs;dAs;lnaAs;dCs;lnaAs;dAs;lnaAs;dAs;lnaGs;dAs;lnaAs;dAs;lnaCs;dC-Sup
732	HOTTIP-5 m02	GGGATAAAGGAAGGG	HOTTIP	5′	human	dGs;lnaGs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaGs;dG-Sup
733	HOTTIP-6 m02	CACTGGGATAAAGGA	HOTTIP	5′	human	dCs;lnaAs;dCs;lnaTs;dGs;lnaGs;dGs;lnaAs;dTs;lnaAs;dAs;lnaAs;dGs;lnaGs;dA-Sup
734	HOTTIP-7 m02	GAGCCGCCCGCTTTG	HOTTIP	5′	human	dGs;lnaAs;dGs;lnaCs;dCs;lnaGs;dCs;lnaCs;dCs;lnaGs;dCs;lnaTs;dTs;lnaTs;dG-Sup
735	HOTTIP-8 m02	TCTGGGCCCCACTG	HOTTIP	5′	human	dTs;lnaCs;dTs;lnaGs;dGs;lnaGs;dCs;lnaCs;dCs;lnaCs;dAs;lnaCs;dTs;lnaG-Sup
736	NEST-1 m02	CAAAAGGTCTTAGCT	NEST	3′	human	dCs;lnaAs;dAs;lnaAs;dAs;lnaGs;dGs;lnaTs;dCs;lnaTs;dTs;lnaAs;dGs;lnaCs;dT-Sup
737	NEST-2 m02	TAGCTATTATTACTG	NEST	3′	human	dTs;lnaAs;dGs;lnaCs;dTs;lnaAs;dTs;lnaTs;dAs;lnaTs;dTs;lnaAs;dCs;lnaTs;dG-Sup
738	NEST-3 m02	ACTGTTGTTGTTTTA	NEST	3′	human	dAs;lnaCs;dTs;lnaGs;dTs;lnaTs;dGs;lnaTs;dTs;lnaGs;dTs;lnaTs;dTs;lnaTs;dA-Sup
739	NEST-4 m02	ACCTTAGAGGTTGTA	NEST	3′	human	dAs;lnaCs;dCs;lnaTs;dTs;lnaAs;dGs;lnaAs;dGs;lnaGs;dTs;lnaTs;dGs;lnaTs;dA-Sup

740	NEST-5 m02	TACCTGAAATTGCAG	NEST	5’	human	dTs;lnaAs;dCs;lnaCs;dTs;lnaGs;dAs;lnaAs;dAs;lnaTs;dTs;lnaGs;dCs;lnaAs;dG-Sup
741	NEST-6 m02	GTCAGAAAAGCTACC	NEST	5’	human	dGs;lnaTs;dCs;lnaAs;dGs;lnaAs;dAs;lnaAs;dAs;lnaGs;dCs;lnaTs;dAs;lnaCs;dC-Sup
742	NEST-7 m02	CACGCTTGGTGTGCA	NEST	5’	human	dCs;lnaAs;dCs;lnaGs;dCs;lnaTs;dTs;lnaGs;dGs;lnaTs;dGs;lnaTs;dGs;lnaCs;dA-Sup
743	NEST-8 m02	CTGTGAATGTGTGAA	NEST	5’	human	dCs;lnaTs;dGs;lnaTs;dGs;lnaAs;dAs;lnaTs;dGs;lnaTs;dGs;lnaTs;dGs;lnaAs;dA-Sup
744	NEST-9 m02	AACAGGAAGCACCTG	NEST	5’	human	dAs;lnaAs;dCs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaCs;dAs;lnaCs;dCs;lnaTs;dG-Sup

Example 14. Data from a Friedreich’s ataxia (FRDA) mouse model

Indicated 5’ (FXN-375,380,385), 3’ (FXN-398) and multi-targeting oligos (FXN-434: 375+398, FXN-436:385+398) were injected subcutaneously to the Sarsero FRDA mouse model. Vehicle (PBS) was injected as control. The sequences of FXN-434 and 436 are shown below in Table 12.

Table 12. Sequences for FXN-434 and FXN-436

SEQ ID NO	Oligo Name	Base Sequence	Gene Name	Target Region	Organism	Formatted Sequence
745	FXN-434 m02	CGCTCCGCCCTCCAGTTTTTTTTTAGGAGGCAACACATT	FXN	5’ and 3’	human	dCs;lnaGs;dCs;lnaTs;dCs;lnaCs;dGs;lnaCs;dCs;lnaCs;dTs;lnaCs;dCs;lnaAs;dG;dT;dT;dT;dT;dTs;lnaTs;dTs;lnaTs;dTs;lnaAs;dGs;lnaGs;dAs;lnaGs;dGs;lnaCs;dAs;lnaAs;dCs;lnaAs;dCs;lnaAs;dTs;lnaT-Sup

746	FXN-436 m02	CGCTCCGCCCTCCAGCC TTTTTTTTTAGGAGGCA ACACATT	FXN	5' and 3'	human	dCs;lnaGs;dCs;lnaT s;dCs;lnaCs;dGs;lna Cs;dCs;lnaCs;dTs;ln aCs;dCs;lnaAs;dGs;l naCs;dC;dT;dT;dT;d T;dTs;lnaTs;dTs;lna Ts;dTs;lnaAs;dGs;ln aGs;dAs;lnaGs;dGs; lnaCs;dAs;lnaAs;dC s;lnaAs;dCs;lnaAs;d Ts;lnaT-Sup

For short arm (SA) studies, oligos and control were injected at 25mg/kg at day0 and day4. Tissues were collected at day7. For long arm (LA) studies, injections were done at the same dose at day0, day4, day7 and collections were done at day14. The human FXN and mouse FXN in the hearts and lviers of this model were measured with QPCR and normalized to the PBS group. Each treatment group had 5 mice (n=5).

It was found that human FXN-targeting oligos upregulated mouse frataxin mRNA in heart in the short-arm study (FIG. 67). A slight but statistically insignificant upregulation trend was also present for human FXN in the long-arm study in liver and heart (FIG. 67). Two of the oligos, FXN-375 and 389, overlapped with the mouse FXN transcript, with some mismatches (FIG. 68). The major mouse FXN 3' site was at chr19: 24261501. The major mouse FXN 5' site is at chr19: 24280595. EST as well as RefSeq annotations suggested the potential binding of these oligos to mouse transcript. These data indicate that oligos containing mismatches to the FXN RNA transcript can still result in upregulation of FXN, showing that mismatches can be tolerated.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will

recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Use of ordinal terms such as "first," "second," "third," etc., in the claims to modify a claim element does not by itself connote any priority, precedence, or order of one claim element over another or the temporal order in which acts of a method are performed, but are used merely as labels to distinguish one claim element having a certain name from another element having a same name (but for use of the ordinal term) to distinguish the claim elements.

CLAIMS

What is claimed is:

1. A method of increasing gene expression in a cell, the method comprising:

delivering to a cell an oligonucleotide comprising the general formula 5'-X_1-X_2-3', wherein X_1 comprises 5 to 20 nucleotides that have a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript encoded by the gene, wherein the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide at the transcription start site of the RNA transcript; and X_2 comprises 1 to 20 nucleotides.

2. The method of claim 1, wherein the RNA transcript has a 7-methylguanosine cap at its 5'-end.

3. The method of claim 1, wherein the RNA transcript has a 7-methylguanosine cap, and wherein the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide of the RNA transcript that is immediately internal to the 7-methylguanosine cap.

4. The method of claim 1, wherein at least the first nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine.

5. The method of claim 2, wherein the second nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine.

6. The method of claim 1, wherein X_2 comprises the formula 5'-Y_1-Y_2-Y_3-3', wherein X_2 forms a stem-loop structure having a loop region comprising the nucleotides of Y_2 and a stem region comprising at least two contiguous nucleotides of Y_1 hybridized with at least two contiguous nucleotides of Y_3.

7. The method of claim 6, wherein Y_1, Y_2 and Y_3 independently comprise 1 to 10 nucleotides.

8. The method of claim 6 or 7, wherein Y_3 comprises, at a position immediately following the 3'-end of the stem region, a pyrimidine complementary with guanine.

9. The method of any one of claims 2 to 8, wherein the pyrimidine complementary with guanine is cytosine.

10. The method of claim 1, wherein X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides of the RNA transcript that do not overlap the region of the RNA transcript that is complementary with the region of complementarity of X_1.

11. The method of claim 10, wherein the region of complementarity of X_2 is within 100 nucleotides of a polyadenylation junction of the RNA transcript.

12. The method of claim 11, wherein the region of complementarity of X_2 is complementary with the RNA transcript immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript.

13. The method of claim 11 or 12, wherein X_2 further comprises at least 2 consecutive pyrimidine nucleotides complementary with adenine nucleotides of the poly(A) tail of the RNA transcript.

14. The method of any one of claims 1 to 13, wherein the RNA transcript is an mRNA, non-coding RNA, long non-coding RNA, miRNA, or snoRNA or any other suitable RNA.

15. The method of any one of claims 1 to 14, wherein the RNA transcript is an mRNA transcript, and wherein X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides in the 3'-UTR of the transcript.

16. The method of any one of claims 1 to 15, wherein the RNA transcript is an mRNA and the delivery results in an increase in the level of a protein encoded by the mRNA.

17. The method of any one of claims 16, the increase in the level of the protein encoded by the mRNA is at least a 50 % increase compared with an appropriate control cell to which the oligonucleotide was not delivered.

18. The method of any one of claims 1 to 15, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN, HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3.

19. The method of claim 1, wherein X_1 comprises the sequence 5'-CGCCCTCCAG-3'.

20. The method of claim 19, wherein X_2 comprises the sequence CC.

21. The method of any preceding claim 20, wherein X_2 comprises the sequence 5'-CCAAAGGTC-3'.

22. The method of claim 1, wherein the oligonucleotide comprises the sequence 5'-CGCCCTCCAGCCAAAGGTC-3'.

23. The method of any one of claims 1 to 22, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE, BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2, MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST.

24. A method of increasing gene expression in a cell, the method comprising delivering to a cell an oligonucleotide of 10 to 50 nucleotides in length having a first region complementary with at least 5 consecutive nucleotides of the 5'-UTR of an mRNA transcript encoded by the gene, and a second region complementary with at least 5 consecutive nucleotides of the 3'-UTR, poly(A) tail, or overlapping the polyadenylation junction of the mRNA transcript.

25. The method of claim 24, wherein the first of the at least 5 consecutive nucleotides of the 5'-UTR is within 10 nucleotides of the 5'-methylguanosine cap of the mRNA transcript.

26. The method of claim 24 or 25, wherein the second region is complementary with at least 5 consecutive nucleotides overlapping the polyadenylation junction.

27. The method of any one of claims 24 to 26, further comprising 2-20 nucleotides that link the 5' end of the first region with the 3' end of the second region.

28. The method of any one of claims 24 to 26, further comprising 2-20 nucleotides that link the 3' end of the first region with the 5' end of the second region.

29. The method of any one of claims 24 to 28, wherein the oligonucleotide is 10 to 50 nucleotide in length.

30. The method of any one of claims 24 to 28, wherein the oligonucleotide is 9 to 20 nucleotide in length.

31. A method of increasing gene expression in a cell, the method comprising delivering to a cell an oligonucleotide comprising the general formula 5'-X_1-X_2-3', wherein X_1 comprises 2 to 20 pyrimidine nucleotides that form base pairs with adenine; and X_2 comprises a region of complementarity that is complementary with at least 3 contiguous nucleotides of a poly-adenylated RNA transcript encoded by the gene, wherein the nucleotide at the 5'-end of the region of complementary of X_2 is complementary with the nucleotide of the RNA transcript that is immediately internal to the poly-adenylation junction of the RNA transcript.

32. The method of claim 31, wherein X_1 comprises 2 to 20 thymidines or uridines.

33. The method of any one of claims 1 to 32, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

34. The method of any one of claims 1 to 33, wherein the oligonucleotide comprises at least one modified nucleotide.

35. The method of any one of claims 1 to 34, wherein at least one nucleotide comprises a 2' O-methyl.

36. The method of any one of claims 1 to 35, wherein the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, at least one 2'-fluoro-deoxyribonucleotides or at least one bridged nucleotide.

37. The method of claim 36, wherein the bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide.

38. The method of any one of claims 1 to 37, wherein each nucleotide of the oligonucleotide is a LNA nucleotide.

39. The oligonucleotide of any one of claims 1 to 38, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides, 2'-O-methyl nucleotides, or bridged nucleotides.

40. The method of any one of claims 1 to 39, wherein the oligonucleotide is mixmer.

41. The method of any one of claims 1 to 40, wherein the oligonucleotide is morpholino.

42. The method of any one of claims 1 to 41, wherein the cell is *in vitro*.

43. The method of any one of claims 1 to 41, wherein the cell is *in vivo*.

44. A method of increasing gene expression in a cell, the method comprising delivering to a cell, expressing an RNA transcript of the gene, an oligonucleotide of 8 to 50 nucleotides in length, the oligonucleotide comprising a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript, wherein the nucleotide at the 3'-end of the region of complementary is complementary with a nucleotide within 10 nucleotides of the transcription start site of the RNA transcript, wherein the oligonucleotide comprises nucleotides linked by at least one modified internucleoside linkage or at least one bridged nucleotide.

45. A method of increasing gene expression in a cell, the method comprising delivering to a cell, expressing an RNA transcript of the gene, an oligonucleotide comprising two regions of complementarity each of which is complementary with at least 5 contiguous nucleotides of an RNA transcript, wherein the nucleotide at the 3'-end of the first region of complementary is complementary with a nucleotide within 100 nucleotides of the transcription start site of the RNA transcript and wherein the second region of complementarity is complementary with a region of the RNA transcript that ends within 300 nucleotides of the 3'-end of the RNA transcript.

46. A method of increasing stability of an RNA transcript in a cell, the method comprising delivering to the cell a first stabilizing oligonucleotide that targets a 5' region of the RNA transcript and a second stabilizing oligonucleotide that targets the 3' region of the RNA transcript.

47. The method of claim 46, wherein the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide.

48. The method of claim 46 or 47, wherein the first stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 10 nucleotides of the first transcribed nucleotide at the 5' end of the RNA transcript.

49. The method of any one of claims 46 to 48, wherein the RNA transcript comprises a 5'-methylguanosine cap, and wherein the first stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 10 nucleotides of the nucleotide immediately internal to the 5'-methylguanosine cap.

50. The method any one of claims 46 to 49, wherein the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 250 nucleotides of the 3' end of the RNA transcript.

51. The method any one of claims 46 to 50, wherein the RNA transcript comprises a 3'-poly(A) tail, and wherein the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the RNA transcript at a position within 100 nucleotides of the polyadenylation junction of the RNA transcript.

52. The method any one of claims 46 to 51, wherein the region of complementarity of the second stabilizing oligonucleotide is immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript.

53. A method of increasing stability of an RNA transcript in a cell, the method comprising delivering to the cell expressing the RNA transcript an oligonucleotide of any one of claims 64-104 that targets the RNA transcript, thereby increasing stability of the RNA transcript.

54. The method of any one of claims 46 to 53, wherein the cell is *in vitro*.

55. The method of any one of claims 46 to 53, wherein the cell is *in vivo*.

56. A method of treating a condition or disease associated with decreased levels of an RNA transcript in a subject, the method comprising administering an oligonucleotide of any one of claims 64-104 to the subject.

57. The method of any one of claims 46 to 56, wherein the RNA transcript is an mRNA, non-coding RNA, long non-coding RNA, miRNA, snoRNA, tRNAs, snRNAs, extracellular RNAs or any other suitable RNA.

58. The method of any one of claims 46 to 56, wherein the RNA transcript is a mRNA.

59. The method of any one of claims 46 to 56, wherein the RNA transcript is a long non-coding RNA.

60. The method of any one of claims 46 to 58, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN, HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3.

61. The method of any one of claims 46 to 58, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE, BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2, MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST.

62. An oligonucleotide of 8 to 50 nucleotides in length, the oligonucleotide comprising a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript, wherein the nucleotide at the 3'-end of the region of complementary is complementary with a nucleotide within 10 nucleotides of the transcription start site of the RNA transcript, wherein the oligonucleotide comprises nucleotides linked by at least one modified internucleoside linkage or at least one bridged nucleotide.

63. An oligonucleotide comprising two regions of complementarity each of which is complementary with at least 5 contiguous nucleotides of an RNA transcript, wherein the nucleotide at the 3'-end of the first region of complementary is complementary with a nucleotide within 100 nucleotides of the transcription start site of the RNA transcript and

wherein the second region of complementarity is complementary with a region of the RNA transcript that ends within 300 nucleotides of the 3'-end of the RNA transcript.

64. An oligonucleotide comprising the general formula 5'-X_1-X_2-3', wherein

X_1 comprises 5 to 20 nucleotides that have a region of complementarity that is complementary with at least 5 contiguous nucleotides of an RNA transcript , wherein the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide at the transcription start site of the RNA transcript; and X_2 comprises 1 to 20 nucleotides.

65. The oligonucleotide of any one of claims 62 to 64, wherein the RNA transcript has a 7-methylguanosine cap at its 5'-end.

66. The oligonucleotide of claim 64, wherein the RNA transcript has a 7-methylguanosine cap, and wherein the nucleotide at the 3'-end of the region of complementary of X_1 is complementary with the nucleotide of the RNA transcript that is immediately internal to the 7-methylguanosine cap.

67. The oligonucleotide of claim 64, wherein at least the first nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine.

68. The oligonucleotide of claim 67, wherein the second nucleotide at the 5'-end of X_2 is a pyrimidine complementary with guanine.

69. The oligonucleotide of claim 64, wherein X_2 comprises the formula 5'-Y_1-Y_2-Y_3-3', wherein X_2 forms a stem-loop structure having a loop region comprising the nucleotides of Y_2 and a stem region comprising at least two contiguous nucleotides of Y_1 hybridized with at least two contiguous nucleotides of Y_3.

70. The oligonucleotide of claim 69, wherein Y_1, Y_2 and Y_3 independently comprise 1 to 10 nucleotides.

71. The oligonucleotide of claim 69 or 70, wherein Y_3 comprises, at a position immediately following the 3'-end of the stem region, a pyrimidine complementary with guanine.

72. The oligonucleotide of any one of claims 67 to 71, wherein the pyrimidine complementary with guanine is cytosine.

73. The oligonucleotide of claim 64, wherein X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides of the RNA transcript that do not overlap the region of the RNA transcript that is complementary with the region of complementarity of X_1.

74. The oligonucleotide of claim 73, wherein the region of complementarity of X_2 is within 100 nucleotides of a polyadenylation junction of the RNA transcript.

75. The oligonucleotide of claim 74, wherein the region of complementarity of X_2 is complementary with the RNA transcript immediately adjacent to or overlapping the polyadenylation junction of the RNA transcript.

76. The oligonucleotide of claim 74 or 75, wherein X_2 further comprises at least 2 consecutive pyrimidine nucleotides complementary with adenine nucleotides of the poly(A) tail of the RNA transcript.

77. The oligonucleotide of any one of claims 62 to 76, wherein the RNA transcript is an mRNA, non-coding RNA, long non-coding RNA, miRNA, or snoRNA or any other suitable RNA.

78. The oligonucleotide of any one of claims 64 to 77, wherein the RNA transcript is an mRNA transcript, and wherein X_2 comprises a region of complementarity that is complementary with at least 5 contiguous nucleotides in the 3'-UTR of the transcript.

79. The oligonucleotide of any one of claims 62 to 78, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA1, APOA1, ATP2A2, BDNF, FXN, HBA2, HBB, HBD, HBE1, HBG1, HBG2, SMN, UTRN, PTEN, MECP2, and FOXP3.

80. The oligonucleotide of claim 64, wherein X_1 comprises the sequence 5'-CGCCCTCCAG-3'.

81. The oligonucleotide of claim 79, wherein X_2 comprises the sequence CC.

82. The oligonucleotide of any preceding claim 79, wherein X_2 comprises the sequence 5'-CCAAAGGTC-3'.

83. The oligonucleotide of claim 64, wherein the oligonucleotide comprises the sequence 5'-CGCCCTCCAGCCAAAGGTC-3'.

84. The oligonucleotides of any one of claims 62 to 78, wherein the RNA transcript is an mRNA expressed from a gene selected from the group consisting of: ABCA4, ABCB11, ABCB4, ABCG5, ABCG8, ADIPOQ, ALB, APOE, BCL2L11, BRCA1, CD274, CEP290, CFTR, EPO, F7, F8, FLI1, FMR1, FNDC5, GCH1, GCK, GLP1R, GRN, HAMP, HPRT1, IDO1, IGF1, IL10, IL6, KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4, KLF1, KLF4, LDLR, MSX2, MYBPC3, NANOG, NF1, NKX2-1, NKX2-1-AS1, PAH, PTGS2, RB1, RPS14, RPS19, SCARB1, SERPINF1, SIRT1, SIRT6, SMAD7, ST7, STAT3, TSIX, and XIST.

85. An oligonucleotide of 10 to 50 nucleotides in length having a first region complementary with at least 5 consecutive nucleotides of the 5'-UTR of an mRNA transcript, and a second region complementary with at least 5 consecutive nucleotides of the 3'-UTR, poly(A) tail, or overlapping the polyadenylation junction of the mRNA transcript.

86. The oligonucleotide of claim 85, wherein the first of the at least 5 consecutive nucleotides of the 5'-UTR is within 10 nucleotides of the 5'-methylguanosine cap of the mRNA transcript.

87. The oligonucleotide of claim 85 or 86, wherein the second region is complementary with at least 5 consecutive nucleotides overlapping the polyadenylation junction.

88. The oligonucleotide of any one of claims 85 to 87, further comprising 2-20 nucleotides that link the 5' end of the first region with the 3' end of the second region.

89. The oligonucleotide of any one of claims 85 to 87, further comprising 2-20 nucleotides that link the 3' end of the first region with the 5' end of the second region.

90. The oligonucleotide of any one of claims 85 to 87, wherein the oligonucleotide is 10 to 50 nucleotide in length.

91. The oligonucleotide of any one of claims 85 to 87, wherein the oligonucleotide is 9 to 20 nucleotide in length.

92. An oligonucleotide comprising the general formula 5'-X_1-X_2-3', wherein

X_1 comprises 2 to 20 pyrimidine nucleotides that form base pairs with adenine; and X_2 comprises a region of complementarity that is complementary with at least 3 contiguous

nucleotides of a poly-adenylated RNA transcript, wherein the nucleotide at the 5'-end of the region of complementary of X_2 is complementary with the nucleotide of the RNA transcript that is immediately internal to the poly-adenylation junction of the RNA transcript.

93. The oligonucleotide of claim 80, wherein X_1 comprises 2 to 20 thymidines or uridines.

94. The oligonucleotide of any one of claims 62 to 93, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

95. The oligonucleotide of any one of claims 62 to 93, wherein the oligonucleotide comprises at least one modified nucleotide.

96. The oligonucleotide of any one of claims 62 to 95, wherein at least one nucleotide comprises a 2' O-methyl.

97. The oligonucleotide of any one of claims 62 to 93, wherein the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, at least one 2'-fluoro-deoxyribonucleotides or at least one bridged nucleotide.

98. The oligonucleotide of claim 97, wherein the bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide.

99. The oligonucleotide of any one of claims 64 to 98, wherein each nucleotide of the oligonucleotide is a LNA nucleotide.

100. The oligonucleotide of any one of claims 64 to 99, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides, 2'-O-methyl nucleotides, or bridged nucleotides.

101. The oligonucleotide of any one of claims 64 to 94, wherein the oligonucleotide is mixmer.

102. The oligonucleotide of any one of claims 64 to 94, wherein the oligonucleotide is morpholino.

103. An oligonucleotide comprising a nucleotide sequence as set forth in Table 3, 7, 8, or 9.

104. An oligonucleotide comprising a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in Table 3, 7, 8, or 9.

105. A composition comprising a first oligonucleotide having 5 to 25 nucleotides linked through internucleoside linkages, and a second oligonucleotide having 5 to 25 nucleotides linked through internucleoside linkages, wherein the first oligonucleotide is complementary with at least 5 consecutive nucleotides within 100 nucleotides of the 5'-end of an RNA transcript and wherein the second oligonucleotide is complementary with at least 5 consecutive nucleotides within 100 nucleotides of the 3'-end of an RNA transcript.

106. The composition of claim 105, wherein the first oligonucleotide and second oligonucleotide are joined by a linker that is not an oligonucleotide having a sequence complementary with the RNA transcript.

107. The composition of claim 106, wherein the linker is an oligonucleotide.

108. The composition of claim 106, wherein the linker is a polypeptide.

109. A composition comprising a plurality of oligonucleotides, wherein each of at least 75% of the oligonucleotides is an oligonucleotide selected from any one of claims 64 to 104.

110. The composition of claim 109, wherein the oligonucleotides are complexed with a monovalent cation.

111. The composition of claim 109 or 110, wherein the oligonucleotides are in a lyophilized form.

112. The composition of claim 109 or 110, wherein the oligonucleotides are in an aqueous solution.

113. A composition comprising an oligonucleotide of any one of claims 64 to 104 and a carrier.

114. A composition comprising an oligonucleotide of any one of claims 64 to 104 in a buffered solution.

115. A composition of comprising an oligonucleotide of any one of claims 64 to 104 conjugated to the carrier.

116. The composition of claim 115, wherein the carrier is a peptide.

117. The composition of claim 115, wherein the carrier is a steroid.

118. A pharmaceutical composition comprising an oligonucleotide of any one of claims 64 to 104 and a pharmaceutically acceptable carrier.

119. A kit comprising a container housing the composition of any one of claims 109 to 118.

120. A method for increasing expression of a protein in a cell, the method comprising delivering to a cell a circularized synthetic RNA that encodes the protein, wherein synthesis of the protein in the cell is increased following delivery of the circularized synthetic RNA to the cell.

121. The method of claim 120, wherein the circularized synthetic RNA comprises one or more modified nucleotides.

122. A method of stabilizing a synthetic RNA, the method comprising contacting a synthetic RNA with a first stabilizing oligonucleotide that targets a 5' region of the synthetic RNA and a second stabilizing oligonucleotide that targets the 3' region of the synthetic RNA under conditions in which the first stabilizing oligonucleotide and second stabilizing oligonucleotide hybridize with target sequences on the synthetic RNA, wherein the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide such that the synthetic RNA when hybridized with the first and second stabilizing oligonucleotides is capable of forming a circularized product.

123. The method of claim 122, wherein the synthetic RNA is contacted with the first and second stabilizing oligonucleotides outside of a cell.

124. A method of delivering a synthetic RNA to a cell, the method comprising:

contacting a synthetic RNA with a first stabilizing oligonucleotide that targets a 5' region of the synthetic RNA and a second stabilizing oligonucleotide that targets the 3' region of the synthetic RNA under conditions in which the first stabilizing oligonucleotide and second stabilizing oligonucleotide hybridize with target sequences on the synthetic RNA, wherein the first stabilizing oligonucleotide is covalently linked with the second stabilizing

oligonucleotide such that the synthetic RNA when hybridized with the first and second stabilizing oligonucleotide is capable of forming a circularized product; and

delivering to the cell the circularized product.

125. The method of any one of claim 122 to 124, wherein the first stabilizing oligonucleotide and second stabilizing oligonucleotide are covalently linked through an internucleoside linkage.

126. The method of claim 124 or 125, wherein the first stabilizing oligonucleotide and second stabilizing oligonucleotide are covalently linked through an oligonucleotide.

127. The composition of claim 126, wherein the first stabilizing oligonucleotide and second stabilizing oligonucleotide are covalently linked through any appropriate linker disclosed herein.

128. The method of any one of claims 122 to 127, wherein the first stabilizing oligonucleotide comprises a region of complementarity that is complementary with the synthetic RNA at a position within 10 nucleotides of the first nucleotide at the 5' end of the synthetic RNA.

129. The method of any one of claims 122 to 128, wherein the synthetic RNA comprises a 5'-methylguanosine cap, and wherein the first stabilizing oligonucleotide comprises a region of complementarity that is complementary with the synthetic RNA at a position within 10 nucleotides of the nucleotide immediately internal to the 5'-methylguanosine cap.

130. The method any one of claims 122 to 129, wherein the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the synthetic RNA at a position within 250 nucleotides of the 3' end of the synthetic RNA.

131. The method any one of claims 122 to 130, wherein the synthetic RNA comprises a 3'-poly(A) tail, and wherein the second stabilizing oligonucleotide comprises a region of complementarity that is complementary with the synthetic RNA at a position within 100 nucleotides of the polyadenylation junction of the synthetic RNA.

132. The method any one of claims 122 to 131, wherein the region of complementarity of the second stabilizing oligonucleotide is immediately adjacent to or overlapping the polyadenylation junction of the synthetic RNA.

133. The method of any one of claims 120 to 132, wherein the synthetic RNA comprises one or more modified nucleotides.

134. The method of claim 133, wherein the one or more modified nucleotides are selected from the group consisting of: 2'-amino-2'-deoxynucleotide, 2'-azido-2'-deoxynucleotide, 2'-fluoro-2'-deoxynucleotide, 2'-O-methyl-nucleotide, 2' sugar super modifier, 2'-modified thermostability enhancer, 2'-fluoro-2'-deoxyadenosine-5'-triphosphate, 2'-fluoro-2'-deoxycytidine-5'-triphosphate, 2'-fluoro-2'-deoxyguanosine-5'-triphosphate, 2'-fluoro-2'-deoxyuridine-5'-triphosphate, 2'-O-methyladenosine-5'-triphosphate, 2'-O-methylcytidine-5'-triphosphate, 2'-O-methylguanosine-5'-triphosphate, 2'-O-methyluridine-5'-triphosphate, pseudouridine-5'-triphosphate, 2'-O-methylinosine-5'-triphosphate, 2'-amino-2'-deoxycytidine-5'-triphosphate, 2'-amino-2'-deoxyuridine-5'-triphosphate, 2'-azido-2'-deoxycytidine-5'-triphosphate, 2'-azido-2'-deoxyuridine-5'-triphosphate, 2'-O-methylpseudouridine-5'-triphosphate, 2'-O-methyl-5-methyluridine-5'-triphosphate, 2'-azido-2'-deoxyadenosine-5'-triphosphate, 2'-amino-2'-deoxyadenosine-5'-triphosphate, 2'-fluoro-thymidine-5'-triphosphate, 2'-azido-2'-deoxyguanosine-5'-triphosphate, 2'-amino-2'-deoxyguanosine-5'-triphosphate, and N4-methylcytidine-5'-triphosphate.

135. A circularized synthetic RNA comprising one or more modified nucleotides.

136. The circularized synthetic RNA of claim 135, comprising:

a first stabilizing oligonucleotide hybridized with a 5' region of a synthetic RNA and

a second stabilizing oligonucleotide hybridized with a 3' region of the synthetic, wherein the first stabilizing oligonucleotide is covalently linked with the second stabilizing oligonucleotide and form a circularized product with the synthetic RNA.

137. A pharmaceutical composition comprising a circularized synthetic RNA of claim 135 or 136 and a pharmaceutically acceptable carrier or excipient.

138. A composition comprising a circularized synthetic RNA of claim 135 or 136 and one of more of a nanoparticle, poly(lactic-co-glycolic acid) (PLGA) microsphere,

lipidoid, lipoplexe, liposome, polymer, carbohydrate (including simple sugars), cationic lipid, a fibrin gel, a fibrin hydrogel, a fibrin glue, a fibrin sealant, fibrinogen, thrombin, and rapidly eliminated lipid nanoparticles (reLNPs).

139. The circularized synthetic RNA of claim 135, wherein the circularized synthetic RNA is conjugated with a carbohydrate, such as GalNac, or other targeting moiety.

140. The circularized synthetic RNA of claim 135, wherein the first or second stabilizing oligonucleotide is conjugated with a carbohydrate, such as GalNac, or other targeting moiety.