**(12) STANDARD PATENT** (11) Application No. **AU 2010317599 B2**
**(19) AUSTRALIAN PATENT OFFICE**

(54) Title
**Antisense molecules and methods for treating pathologies**

(51) International Patent Classification(s)
***C12N 15/113*** (2010.01) ***A61K 48/00*** (2006.01)
***A61K 31/7088*** (2006.01) ***A61P 21/00*** (2006.01)
***A61K 31/712*** (2006.01)

(21) Application No: **2010317599** (22) Date of Filing: **2010.11.12**

(87) WIPO No: **WO11/057350**

(30) Priority Data

| (31) Number | (32) Date | (33) Country |
|---|---|---|
| **2009905549** | **2009.11.12** | **AU** |

(43) Publication Date: **2011.05.19**
(44) Accepted Journal Date: **2016.02.11**

(71) Applicant(s)
**The University of Western Australia**

(72) Inventor(s)
**Wilton, Stephen;Fletcher, Sue;Adams, Abbie;Meloni, Penny**

(74) Agent / Attorney
**Davies Collison Cave, 1 Nicholson ST, Melbourne, VIC, 3000**

(56) Related Art
**WO 2006/000057 A1**
**WO 2009/101399 A1**
**WO 2010/048586 A1**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2011 (19.05.2011)

PCT

(10) International Publication Number
WO 2011/057350 A1

(51) International Patent Classification:
*C12N 15/113* (2010.01) *A61K 31/7088* (2006.01)
*A61K 31/712* (2006.01) *A61K 48/00* (2006.01)
*A61P 21/00* (2006.01)

(21) International Application Number:
PCT/AU2010/001520

(22) International Filing Date:
12 November 2010 (12.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2009905549 12 November 2009 (12.11.2009) AU

(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF WESTERN AUSTRALIA** [AU/AU]; Stirling Highway, Nedlands, Western Australia 6907 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WILTON, Stephen** [AU/AU]; 18 Spey Road, Applecross, Western Australia 6153 (AU). **FLETCHER, Sue** [AU/AU]; 14 Roberts Street, Bayswater, Western Australia 6053 (AU). **ADAMS, Abbie** [AU/AU]; 10 Crayden Road, Kalamunda, Western Australia 6076 (AU). **MELONI, Penny** [AU/AU]; 10 Purslowe Street, Mount Hawthorne, Western Australia 6016 (AU).

(74) Agent: **WRAYS**; Ground Floor, 56 Ord Street, West Perth, Western Australia 6005 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published**:

— *with international search report (Art. 21(3))*

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

WO 2011/057350 A1

(54) Title: ANTISENSE MOLECULES AND METHODS FOR TREATING PATHOLOGIES

(57) Abstract: An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 59.

**Antisense Molecules and Methods for Treating Pathologies**

**Field of the Invention**

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

**Background Art**

The following discussion of the background art is intended to facilitate an understanding of the present invention only. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

Significant effort is currently being expended into researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II.

To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that

mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations.

Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) Proc Natl Acad Sci USA 93,12840-12844; Wilton SD, et al., (1999) Neuromusc Disorders 9,330-338; van Deutekom JC et al., (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multi-particle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat TG, et al., (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease- causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu QL, et al., (2003) Nature Medicine 9,1009-1014; Aartsma-Rus A et al., (2004) Am J Hum Genet 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of -80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1 ) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin pre-mRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo et al., (1991) J Clin Invest. 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19

inhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), J. Clin. Invest. 95:515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al. (1997) Nucleosides & Nucleotides, 16,1665-1668 described *in vitro* constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-0- methoxyethyl phosphodiesters are described (Dunckley et al. (1998) Human Mol. Genetics, 5:1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success.

Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) J Gen Med 5: 518-527).

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley et al, (1998) did not show any time course of induced

exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) Neuromuscular Disorders 9,330- 338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton et al., (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al. (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann CJ et al., (2002) J Gen Med 4,644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

The preceding discussion of the background to the invention is intended only to facilitate an understanding of the present invention. It should be appreciated that the discussion is not an acknowledgment or admission that any of the material referred to was part of the common general knowledge as at the priority date of the application.

**Summary of the Invention**

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points. The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see Figure 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 5, 12, 17, 21, 22, 24, 43-47, 49, 50, 54-64, 66, 67, 70 and 72 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

The invention provides an antisense oligonucleotide selected from the group consisting of:

(i) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(ii) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA,

2010317599 06 Jan 2016

wherein the target region is annealing site H45A (-03+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(iii) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(iv) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(v) an antisense oligonucleotide of 22 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(vi) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(vii) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+16), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the

antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(viii) an antisense oligonucleotide of 32 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-14+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(ix) an antisense oligonucleotide of 27 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-08+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(x) an antisense oligonucleotide of 32 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-07+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xi) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xii) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xiii) an antisense oligonucleotide of 39 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+30), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xiv) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xv) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+28), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xvi) an antisense oligonucleotide of 25 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping; and

(xvii) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+28), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

or a pharmaceutically acceptable salt thereof.

The invention also provides an antisense oligonucleotide selected from the group consisting of:

(i) an antisense oligonucleotide of 34 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 11), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(ii) an antisense oligonucleotide of 28 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 55), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(iii) an antisense oligonucleotide of 31 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 61), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(iv) an antisense oligonucleotide of 31 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 62), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base,

(v) an antisense oligonucleotide of 22 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 63), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(vi) an antisense oligonucleotide of 28 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 64), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(vii) an antisense oligonucleotide of 28 bases comprising the base sequence UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 66),

wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(viii) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 227), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(ix) an antisense oligonucleotide of 27 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA (SEQ ID NO: 230), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(x) an antisense oligonucleotide of 34 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 237), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xi) an antisense oligonucleotide of 31 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 239), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xii) an antisense oligonucleotide of 39 bases comprising the base sequence UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU (SEQ ID NO: 240), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xiii) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 241), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xiv) an antisense oligonucleotide of 28 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 242), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xv) an antisense oligonucleotide of 34 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 243), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xvi) an antisense oligonucleotide of 25 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 244), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base; and

(xvii) an antisense oligonucleotide of 31 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 245), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

or a pharmaceutically acceptable salt thereof.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce more efficient exon skipping in exons 3, 4, 8, 10, 26, 36, 48, 60, 66 and 68. A combination or "cocktail" of antisense oligonucleotides are directed at exons to induce efficient exon skipping.

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

**Brief Description of the Drawings**

Figure 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process.

Figure 2. Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

Figure 3. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 3 which induce strong and consistent exon skipping at a transfection concentration of 10 nanomolar in cultured normal human muscle cells.

Figure 4. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 4 which induce strong and consistent exon skipping at a transfection concentration of 25 nanomolar in cultured normal human muscle cells.

Figure 5 Gel electrophoresis showing strong and efficient human exon 5 skipping using an antisense molecules [H5A(+35+65)] directed at an exon 5 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 25 nanomolar in cultured human muscle cells.

Figure 6. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 8 which induce strong and consistent exon skipping of both exon 8 and exon8/9 at a transfection concentration of 10 nanomolar in cultured normal human muscle cells.

Figure 7. Gel electrophoresis showing various cocktails and single antisense molecules wich induce skipping of exon 10 and surrounding exons. A combination of [H10A(-05+16)] and [H10A(+98+119)] or [H10A(-05+16)] and [H10A(+130+149)] induces skipping of exon 10 and exons 9-12, whilst [H10A(-05+16)] alone induces skipping of exons 9-14.

Figure 8. Gel electrophoresis showing exon 14 skipping using antisense molecule H14A(+31+61) directed at exon 14.

Figure 9. Gel electrophoresis showing exon 17 skipping using antisense molecule H17A(+10+35) directed at exon 17.

Figure 10. Gel electrophoresis showing two cocktails of antisense molecules directed at exon 26. The double cocktail of [H26A(-07+19)] and [H26A(+24+50)] induces good skipping of exon 26, and the addition of a further antisense molecule to the cocktail does not affect the efficiency of skipping.

Figure 11. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 36 which induce strong and consistent exon skipping at a transfection concentration of 25 nanomolar in cultured normal human muscle cells.

Figure 12. Gel electrophoresis showing strong and consistent exon 43 skipping to 25 nanomolar in cultured normal human muscle cells using antisense molecule H43A(+92+117).

Figure 13. Gel electrophoresis showing dose dependant exon 55 skipping using antisense molecule H44A(+65+90).

Figure 14. Gel electrophoresis showing strong and consistent exon 45 skipping using antisense molecule H45A(-09+25).

Figure 15. Gel electrophoresis showing strong and consistent exon 46 skipping using antisense molecule H46A(+81+109).

Figure 16. Gel electrophoresis showing strong and consistent exon 47 skipping using antisense molecule H47A(+01+29).

Figure 17. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 47 which induce strong and consistent exon skipping.

Figure 18. Gel electrophoresis showing strong and consistent exon 49 skipping using antisense molecule H49A(+45+70).

Figure 19. Gel electrophoresis showing strong and consistent exon 50 skipping using antisense molecule H50A(+48+74).

Figure 20. Gel electrophoresis showing strong and consistent exon 51 skipping using antisense molecule H51A(+66+95).

Figure 21. Gel electrophoresis showing strong and consistent exon 54 skipping using antisense molecule H54A(+67+97).

Figure 22. Gel electrophoresis showing antisense molecule H55A(-10+20) induced dose dependant exon 55 skipping.

Figure 23. Gel electrophoresis showing strong and consistent exon 56 skipping using antisense molecule H56A(+92+121).

Figure 24. Gel electrophoresis showing antisense molecule H57A(-10+20) induced dose dependant exon 57 skipping.

Figure 25. Gel electrophoresis showing exon 59 and exon 58/59 skipping using antisense molecule H59A(+96+120) directed at exon 59.

Figure 26. Gel electrophoresis showing two different cocktails which induce exon skipping of exon 60.

Figure 27. Gel electrophoresis showing exon 63 skipping using antisense molecule H63A(+20+49).

Figure 28. Gel electrophoresis showing exon 64 skipping using antisense molecule H64A(+34+62).

Figure 29. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 66 which induce dose dependant exon skipping.

Figure 30. Gel electrophoresis showing exon 67 skipping using antisense molecule H67A(+17+47).

Figure 31. Gel electrophoresis showing a "cocktail" of antisense molecules directed at exon 68 which induce dose dependant exon skipping.

Figure 32. Gel electrophoresis showing a "cocktail" of antisense molecules which induce strong and consistent exon skipping of exons 69/70 at a transfection concentration of 25 nanomolar.

Figure 33. Gel electrophoresis showing various "cocktails" of antisense molecules which induce various levels of skipping in exon 50.

Figure 34. Gel electrophoresis showing a cocktail of three antisense molecules which induce efficient skipping of exons 50/51.

Figure 35. Graph of densitometry results showing various efficiencies of exon skipping. The antisense molecules tested were Exon 3 [H3A(+30+60) & H3A(+61+85)]; Exon 4 [H4D(+14-11) & H4A(+11+40)]; Exon 14 [H14A(+32+61)]; Exon 17 [H17A(+10+35)]; Exon 26 [H26A(-07+19), H26A(+24+50) & H26A(+68+92)]; Exon 36 [H36A(-16+09) & H36A(+22+51)].

Figure 36. Graph of densitometry results showing various efficiencies of exon skipping. The antisense molecules tested were Exon 46 [H46A(+81+109)]; Exon 47 [H47A(+01+29)]; Exon 48 [H48A(+01+28) & H48A(+40+67)]; Exon 49 [H49A(+45+70)].

Figure 37. Gel electrophoresis showing exon 11 skipping using antisense molecule H11A(+50+79).

Figure 38. Gel electrophoresis showing exon 12 skipping using antisense molecule H12A(+30+57).

Figure 39. Gel electrophoresis showing exon 44 skipping using antisense molecule H44A(+59+85).

Figure 40. Gel electrophoresis showing exon 45 skipping using antisense molecule H45A(-03+25).

Figure 41. Gel electrophoresis showing exon 51 skipping using antisense molecule H51A(+71+100).

Figure 42. Gel electrophoresis showing exon 52 skipping using antisense molecule H52A(+09+38).

Figure 43. Gel electrophoresis showing exon 53 skipping using antisense molecule H53A(+33+65).

Figure 44. Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+93+122).

Figure 45. Gel electrophoresis showing exon 73 skipping using antisense molecule H73A(+02+26).

Figure 46. Sequences of antisense molecules.

**Detailed Description**

**BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS**

Table 1A: Single antisense molecules

| SEQ ID | Exon | Sequence |
|---|---|---|
| | **Exon 5** | |
| 1 | H5A(+35+65) | AAA CCA AGA GUC AGU UUA UGA UUU CCA UCU A |
| | **Exon 11** | |
| 52 | H11A(+50+79) | CUG UUC CAA UCA GCU UAC UUC CCA AUU GUA |
| | **Exon 12** | |
| 2 | H12A(+52+75) | UCU UCU GUU UUU GUU AGC CAG UCA |
| 53 | H12A(+30+57) | CAG UCA UUC AAC UCU UUC AGU UUC UGA U |
| | **Exon 17** | |
| 3 | H17A(-07+23) | GUG GUG GUG ACA GCC UGU GAA AUC UGU GAG |
| 4 | H17A(+61+86) | UGU UCC CUU GUG GUC ACC GUA GUU AC |
| | **Exon 21** | |
| 5 | H21A(+86+114) | CAC AAA GUC UGC AUC CAG GAA CAU GGG UC |
| 6 | H21A(+90+119) | AAG GCC ACA AAG UCU GCA UCC AGG AAC AUG |
| | **Exon 22** | |
| 7 | H22A(+125+146) | CUG CAA UUC CCC GAG UCU CUG C |
| | **Exon 24** | |
| 8 | H24A(+51+73) | CAA GGG CAG GCC AUU CCU CCU UC |
| | **Exon 43** | |
| 9 | H43A(+92 +117) | GAG AGC UUC CUG UAG CUU CAC CCU UU |
| | **Exon 44** | |
| 10 | H44A(+65+90) | UGU UCA GCU UCU GUU AGC CAC UGA |
| 54 | H44A(+59+85) | CUG UUC AGC UUC UGU UAG CCA CUG AUU |
| | **Exon 45** | |
| 11 | H45A (-09+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U |
| 55 | H45A(-03+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU G |
| 61 | H45A(-06+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A |
| 62 | H45A(-12+19) | CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C |
| | **Exon 46** | |
| 12 | H46A(+81+109) | UCC AGG UUC AAG UGG GAU ACU AGC AAU GU |
| 56 | H46A(+93+122) | GUU GCU GCU CUU UUC CAG GUU CAA GUG GGA |
| | **Exon 47** | |
| 13 | H47A(+01+29) | UGG CGC AGG GGC AAC UCU UCC ACC AGU AA |
| | **Exon 49** | |
| 14 | H49A(+45+70) | ACA AAU GCU GCC CUU UAG ACA AAA UC |
| | **Exon 50** | |

| | | |
|---|---|---|
| 15 | H50A(+48+74) | GGC UGC UUU GCC CUC AGC UCU UGA AGU |
| | **Exon 51** | |
| 57 | H51A(+71+100) | GGU ACC UCC AAC AUC AAG GAA GAU GGC AUU |
| | **Exon 52** | |
| 58 | H52A(+09+38) | UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC UGC |
| | **Exon 53** | |
| 59 | H53A(+33+65) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU |
| | **Exon 54** | |
| 16 | H54A(+67+97) | UGG UCU CAU CUG CAG AAU AAU CCC GGA GAA G |
| | **Exon 55** | |
| 17 | H55A(-10 +20) | CAG CCU CUC GCU CAC UCA CCC UGC AAA GGA |
| | **Exon 56** | |
| 18 | H56A(+92+121) | CCA AAC GUC UUU GUA ACA GGA CUG CAU |
| 19 | H56A(+112+141) | CCA CUU GAA GUU CAU GUU AUC CAA ACG UCU |
| | **Exon 57** | |
| 20 | H57A(-10+20) | AAC UGG CUU CCA AAU GGG ACC UGA AAA AGA |
| | **Exon 58** | |
| 21 | H58A(+34+64) | UUC GUA CAG UCU CAA GAG UAC UCA UGA UUA C |
| 22 | H58D(+17-07) | CAA UUA CCU CUG GGC UCC UGG UAG |
| | **Exon 59** | |
| 23 | H59A(+96 +120) | CUA UUU UUC UCU GCC AGU CAG CGG A |
| | **Exon 60** | |
| 24 | H60A(+33+62) | CGA GCA AGG UCA UUG ACG UGG CUC ACG UUC |
| | **Exon 61** | |
| 25 | H61A(+10+40) | GGG CUU CAU GCA GCU GCC UGA CUC GGU CCU C |
| | **Exon 62** | |
| 26 | H62A(23+52) | UAG GGC ACU UUG UUU GGC GAG AUG GCU CUC |
| | **Exon 63** | |
| 27 | H63A(+20+49) | GAG CUC UGU CAU UUU GGG AUG GUC CCA GCA |
| | **Exon 64** | |
| 28 | H64A(+34+62) | CUG CAG UCU UCG GAG UUU CAU GGC AGU CC |
| | **Exon 66** | |
| 29 | H66A(-8+19) | GAU CCU CCC UGU UCG UCC CCU AUU AUG |
| | **Exon 67** | |
| 30 | H67A(+17+47) | GCG CUG GUC ACA AAA UCC UGU UGA ACU UGC |
| | **Exon 73** | |
| 60 | H73A(+02+26) | CAU UGC UGU UUU CCA UUU CUG GUA G |

Table 1B: Cocktails of antisense molecules

| SEQ ID | Exon | Sequence |
|---|---|---|
| | **Exon 3 cocktails** | |
| 31 | H3A(+30+60) | UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G |
| 32 | H3A(+61+85) | G CCC UGU CAG GCC UUC GAG GAG GUC |
| | **Exon 4 cocktails** | |
| 33 | H4A(+11+40) | UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU |
| 34 | H4D(+14-11) | GUA CUA CUU ACA UUA UUG UUC UGC A |
| | **Exon 8 cocktails** | |
| 35 | H8A(-06+24) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA |
| 36 | H8A(+134+158) | AUG UAA CUG AAA AUG UUC UUC UUU A |
| | **Exon 10 cocktails** | |
| 37 | H10A(-05+16) | CAG GAG CUU CCA AAU GCU GCA |
| 38 | H10A(+98+119) | UCC UCA GCA GAA AGA AGC CAC G |
| | **Exon 26 cocktails** | |
| 39 | H26A(-07+19) | CCU CCU UUC UGG CAU AGA CCU UCC AC |
| 40 | H26A(+24+50) | CUU ACA GUU UUC UCC AAA CCU CCC UUC |

| | | |
|---|---|---|
| 41 | H26A(+68+92) | UGU GUC AUC CAU UCG UGC AUC UCU G |
| | **Exon 36 cocktails** | |
| 42 | H36A(-16+09) | CUG GUA UUC CUU AAU UGU ACA GAG A |
| 43 | H36A(+22+51) | UGU GAU GUG GUC CAC AUU CUG GUC AAA AGU |
| | **Exon 48 cocktails** | |
| 44 | H48A(+01+28) | CUU GUU UCU CAG GUA AAG CUC UGG AAA C |
| 45 | H48A(+40+67) | CAA GCU GCC CAA GGU CUU UUA UUU GAG C |
| | **Exon 60 cocktails** | |
| 46 | H60A(+87+116) | UCC AGA GUG CUG AGG UUA UAC GGU GAG AGC |
| 47 | H60A(+37+66) | CUG GCG AGC AAG GUC CUU GAC GUG GCU CAC |
| | **Exon 66 cocktails** | |
| 48 | H66A(-02+28) | CAG GAC ACG GAU CCU CCC UGU UCG UCC CCU |
| 49 | H66D(+13-17) | UAA UAU ACA CGA CUU ACA UCU GUA CUU GUC |
| | **Exon 68 cocktails** | |
| 50 | H68A(+48+72) | CAC CAU GGA CUG GGG UUC CAG UCU C |
| 51 | H68D(+23-03) | UAC CUG AAU CCA AUG AUU GGA CAC UC |

## GENERAL

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme PatentIn Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and

amino acid sequences referred to in the specification are defined by the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc.).

An antisense molecule nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann *et al.*, (2002) J Gen Med 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H # A/D (x : y).

The first letter designates the species (e.g. H: human, M: murine, C: canine)

"#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65$^{th}$ and 85$^{th}$ nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source *albeit* not necessarily directly from that source.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

**DESCRIPTION OF THE PREFERRED EMBODIMENT**

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited, causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in Figure 2.

In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. However, in some proteins it is possible to shorten the protein by deleting one or more exons from within the protein, without disrupting the reading frame and without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

A preferred aim of a therapy based on antisense molecules is to get maximum exon skipping by providing the lowest possible concentration of the antisense molecule. Generally, an antisense molecule may cause strong, robust exon skipping; weak, sporadic exon skipping or no exon skipping at all. It is preferable to develop antisense molecules (alone or in combination) which can deliver strong, robust consistent exon skipping at a low therapeutic dose.

**Antisense Molecules**

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A.

There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides. However, in the present invention it has been generally found that longer antisense molecules are often more effective at inducing exon skipping than shorter molecules. Thus preferably, the antisense molecules of the present invention are between 24 and 30 nucleic acids in length, preferably about 28 nucleotides in length. For example, it has previously been found that an antisense oligonucleotide of 20 bases (H16A(-07+13)) was ineffective at inducing exon skipping of exon 16, but an oligonucleotide of 31 bases (H16A(-06+25)), which completely encompassed the shorter oligonucleotide, was effective at inducing skipping (Harding et al (2007) Mol Ther 15:157-166).

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice

site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the *mdx* mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather, the splicing of these two exons is generally linked. This is not an isolated instance, as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping or induce poor skipping, while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 4) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

It is also not possible to predict which cocktails of antisense molecules will induce exon skipping. For example, the combination of two antisense molecules which, on their own, are very good at inducing skipping of a given exon may not cause skipping of an exon when combined in a cocktail. For example, each of H50A(+02+30) and H50A(+66+95) on their own induce good skipping of exon 50 and 51. Hoowever, in combination as a cocktail, they only induced poor skipping of the two exons. Likewise, the combination of H50A(+02+30) and H51A(+66+90) or H50A(+02+30) and H51A(+61+90) did not cause efficient skipping of exons 50 and 51, even though the individual antisense molecules were effective. Yet the introduction of a third antisense molecule ([H51D(+16-07)] which by itself did not cause skipping), created a three element cocktail ([H50A(+02+30)], H51A(+66+90) and [H51D(+16-07)]) that was able to cause skipping of exons 50 and 51 down to 1 nM.

Alternatively, the combination of two or three antisense molecules which are ineffective or only moderately effective on their own may cause excellent skipping when combined. For example, individually H26A(-07+19) [SEQ ID NO: 39], H26A(+24+50) [SEQ ID NO: 40] and H26A(+68+92) [SEQ ID NO: 41] cause inefficient skipping of exon 26, and also induce multiple exon skipping (26-29 or 27-30). However, when the three exons are combined as a cocktail, highly efficient skipping of exon 26 occurs.

From the above examples and discussion, it is clear that there is no way to accurately predict whether a combination will work or not.

Antisense molecules may cause skipping of exons in a 'dose dependant' or 'non-dose dependant' manner. By dose dependant, it is meant that a larger amount of the antisense molecule induces better skipping of the exon, whereas non-dose dependant antisense molecules are able to induce skipping even at very low doses. For example, from Figure 15 it can be seen that H46A(+81+109) [SEQ ID NO: 12] gives equally good skipping of exon 46 regardless of the amount of antisense molecule present (from 600nM to 25nM). In contrast, H57A(-10+20) [SEQ ID NO: 20] (Figure 24) induces strong skipping of exon 57 at 100nM, but reduced skipping at 50nM and an even greater reduction in skipping at 25nM.

It is preferable to select antisense molecules that induce skipping in a dose independant manner, as these molecules may be administered at very low concentrations and still give a therapeutic effect. However, it is also acceptable to select as preferred molecules those antisense molecules that induce skipping in a dose dependant manner, particularly if those molecules induce good or excellent skipping at low concentrations. Preferably, the antisense molecules of the present invention are able to induce good or excellent exon skipping at concentrations of less than 500nM, preferably less than 200nM and more preferably as low as 100nM, 50 nM or even 25 nM. Most preferably, the oligonucleotide molecules of the present invention are able to induce skipping at levels of greater that 30% at a concentration of 100 nM.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or micro-deletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene (with 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases), there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the

different disease-causing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., 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.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be

a reading frame shift that would lead to the generation of a truncated or a non-functional protein.

It will be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon. Consequently, there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention, wherein each is directed to a different region responsible for inducing splicing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. However, it will be appreciated that any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length. Surprisingly, it has been found that longer antisense molecules are often more effective at inducing exon skipping. Thus, most preferably the antisense molecule is between 24 and 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant

transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame.

Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone. This produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred, as the presence of unmethylated RNA oligonucleotides in an intracellularly environment or in contact with crude extracts that contain RNase H will lead to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that are capable of by-passing or not inducing such degradation may be used in the present method. The nuclease resistance may be achieved by modifying the antisense molecules of the invention so that it comprises partially unsaturated aliphatic hydrocarbon chain and one or more polar or charged groups including carboxylic acid groups, ester groups, and alcohol groups.

An example of antisense molecules which, when duplexed with RNA, are not cleaved by cellular RNase H are 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo- counterparts. Alternatively, the nuclease resistant antisense molecules of the invention may have at least one of the last 3'-terminus nucleotides fluoridated. Still alternatively, the nuclease resistant antisense molecules of the invention have phosphorothioate bonds linking between at least two of the last 3-terminus nucleotide bases, preferably having phosphorothioate bonds linking between the last four 3'-terminal nucleotide bases.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl moiety (e.g., $C_1$-$C_4$, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside 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, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain 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 O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-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-oxycholesterol moiety.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

**Methods of Manufacturing Antisense Molecules**

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, *et al.*, (1981) *Tetrahedron Letters*, 22:1859-1862.

The antisense molecules of the invention are synthesised *in vitro* and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the *in vivo* synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds,

as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

**Therapeutic Agents**

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, PA, (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (*e.g.*, Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol, benzyl alcohol) and bulking substances (*e.g.*, lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds

such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the present proteins and derivatives. *See, e.g., Martin, Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

*Antisense molecule based therapy*

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann CJ *et al.*, (2001) ["*Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse*". Proc., Natl. Acad. Science, 98(1) 42-47] and in Gebski *et al.*, (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in US patent US 6,806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles *in vitro* and *in vivo*. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with *in vitro*, *in vivo* and *ex vivo* delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0 .PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., Biotechniques, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for

parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. 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 and to mucous membranes including rectal delivery),

pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

**Kits of the Invention**

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

The contents of the kit can be lyophilized and the kit can additionally contain a suitable solvent for reconstitution of the lyophilized components. Individual components of the kit would be packaged in separate containers and, associated with such containers, can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

When the components of the kit are provided in one or more liquid solutions, the liquid solution can be an aqueous solution, for example a sterile aqueous solution.

For in vivo use, the expression construct may be formulated into a pharmaceutically acceptable syringeable composition. In this case the container means may itself be an inhalant, syringe, pipette, eye dropper, or other such like apparatus, from which the formulation may be applied to an affected area of the animal, such as the lungs, injected into an animal, or even applied to and mixed with the other components of the kit.

The components of the kit may also be provided in dried or lyophilized forms. When reagents or components are provided as a dried form, reconstitution generally is by the addition of a suitable solvent. It is envisioned that the solvent also may be provided in another container means. Irrespective of the number or type of containers, the kits of the invention also may comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measured spoon, eye dropper or any such medically approved delivery vehicle.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

**Examples**

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of

the art, included, for example: Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989); Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL Press, Ltd., Oxford, U.K. (1985); and Ausubel, F., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., Struhl, K. *Current Protocols in Molecular Biology*. Greene Publishing Associates/Wiley Intersciences, New York (2002).

Determining Induced Exon Skipping in Human Muscle Cells

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 2OMe antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an *in vitro* assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the cells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less. Most preferably, the oligonucleotide molecules of the present invention are able to induce skipping at levels of greater that 30% at a concentration of 100 nM.

Densitometry Methods

Densitometry analysis of the results of the exon skipping procedures was carried out, in order to determine which antisense molecules achieved the desired efficiency. Amplification products were fractionated on 2% agarose gels, stained with ethidium bromide and the images captured by a Chemi-Smart 3000 gel documentation system (Vilber Lourmat, Marne La Vallee).The bands were then analyzed using gel documentation system (Bio-Profil, Bio-1D version 11.9, Vilber Lourmat, Marne La Vallee), according to the manufacturer's instructions.

Densitometry was carried out on the following antisense molecules:

**Figure 35**

| | |
|---|---|
| Exon 3 | H3A(+30+60) & H3A(+61+85) |
| Exon 4 | H4D(+14-11) & H4A(+11+40) |
| Exon 14 | H14A(+32+61) |
| Exon 17 | H17A(+10+35) |
| Exon 26 | H26A(-07+19), H26A(+24+50) & H26A(+68+92) |
| Exon 36 | H36A(-16+09) & H36A(+22+51) |

**Figure 36**

| | |
|---|---|
| Exon 46 | H46A(+81+109) |
| Exon 47 | H47A(+01+29) |
| Exon 48 | H48A(+01+28) & H48A(+40+67) |
| Exon 49 | H49A(+45+70) |

Antisense Oligonucleotides Directed at Exon 17

Antisense oligonucleotides directed at exon 17 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

From Table 2 below, it can be seen that the effect of antisense molecules directed at the same site (the exon 17 acceptor splice site) can be very different, even though the binding location of the two antisense molecules are overlapping. H17A(-07+23) [SEQ ID NO:3], which anneals to the last 7 bases of intron 16 and the first 23 bases of exon 17, induces exon 17 skipping when delivered into the cell at a concentration of 25nM. In contrast, the antisense molecule H17A(-12+18), which anneals to the last 12 bases of intron 16 and the first 18 bases of exon 17, and thus overlaps the location of binding of H17A(-07+23), was not able to induce exon skipping at all. Furthermore, H17A(-07+16), which anneals to the

last 7 bases of intron 16 and the first 16 bases of exon 17 caused skipping of both exon 17 and 18 at 200nM. Antisense molecule H17A(+61+86) [SEQ ID NO:4], which binds in an intra-exonic splicing enhancer motif of exon 17, is also able to induce good skipping. It can be seen that the ability of antisense molecules to induce exon skipping cannot be predicted simply from their binding location and must be determined through rigourous testing.

Table 2: Antisense molecule sequences tested to determine if they induce exon 17 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 459 | H17A(-12 +18) | GGU GAC AGC CUG UGA AAU CUG UGA GAA GUA | No Skipping |
| 3 | H17A(-07+23) | GUG GUG GUG ACA GCC UGU GAA AUC UGU GAG | Skipping at 25nM |
| 460 | H17A(-07+16) | UGA CAG CCU GUG AAA UCU GUG AG | Skipping ex 17 +18 at 200nM |
| 461 | H17A(+10 +35) | AGU GAU GGC UGA GUG GUG GUG ACA GC | Skipping at 50nM |
| 462 | H17A(+31+50) | ACA GUU GUC UGU GUU AGU GA | inconsistent skipping |
| 4 | H17A(+61 +86) | UGU UCC CUU GUG GUC ACC GUA GUU AC | Skipping at 50nM |
| 463 | H17A(+144+163) | CAG AAU CCA CAG UAA UCU GC | skipping at 300nM |

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one molecule is able to induce targeted exon skipping at 20-25 nM while a less efficient antisense molecule might only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the

human dystrophin gene, many induced transcripts are missing both exons 8 and 9.

Antisense Oligonucleotides Directed at Exon 2

Antisense oligonucleotides directed at exon 2 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 3: Antisense molecule sequences tested to determine if they induce exon 2 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 75 | H2A(-14+10) | UCU CUU UCA UCU AAA AUG CAA AAU | No Skipping |
| 76 | H2A(-1+23) | CUU UUG AAC AUC UUC UCU UUC AUC | No Skipping |
| 77 | H2A(+7+38) | UUU UGU GAA UGU UUU CUU UUG AAC AUC UUC UC | No Skipping |
| 78 | H2A(+16+39) | AUU UUG UGA AUG UUU UCU UUU GAA | No Skipping |
| 79 | H2A(+30+60) | UAG AAA AUU GUG CAU UUA CCC AUU UUG UGA A | No Skipping |
| 80 | H2D(+19-11) | ACC AUU CUU ACC UUA GAA AAU UGU GCA UUU | No Skipping |
| 81 | H2D(+03-21) | AAA GUA ACA AAC CAU UCU UAC CUU | No Skipping |

Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Each used alone, antisense molecules H3A(+30+60) [SEQ ID NO: 31] and H3A(+61+85) [SEQ ID NO: 32] induce exon 3 skipping. However, in combination, the two molecules are even more effective at inducing skipping (Figure 3), and are also able to induce skipping of exons 4 and 5 at 300nM and 600nM, a result not seen or predicted by the results of the use of each antisense molecule alone. Additional products above the induced transcript missing exon 3 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 4: Antisense molecule sequences tested to determine if they induce exon 3 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 82 | H3A(+14+38) | AGG UCA CUG AAG AGG UUC UCA AUA U | Moderate skipping to 10nM |
| 83 | H3A(+20+40) | GUA GGU CAC UGA AGA GGU UCU | Strong skipping to 50nM |
| 84 | H3A(+25+60) | AGG AGG CGU CUC CCA UCC UGU AGG UCA CUG AAG AG | weak skipping |
| 85 | H3A(+45+65) | AGG UCU AGG AGG CGC CUC CCA | No skipping |
| 86 | H3A(+48+73) | CUU CGA GGA GGU CUA GGA GGC GCC UC | No Skipping |
| 32 | H3A(+61+85) | GCC CUG UCA GGC CUU CGA GGA GGU C | Skipping to 300nM |
| 87 | H3D(+17-08) | uca cau acA GUU UUU GCC CUG UCA G | No skipping |
| 88 | H3D(+19-02) | UAC AGU UUU UGC CCU GUC AGG | No skipping |
| 89 | H3D(+14-10) | AAG UCA CAU ACA GUU UUU GCC CUG | No skipping |
| 90 | H3D(+12-07) | UCA CAU ACA GUU UUU GCC C | No skipping |
| | | | |
| | **Cocktails for exon 3** | | |
| 31 & 32 | H3A(+30+60)<br>H3A(+61+85) | UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G<br>G CCC UGU CAG GCC UUC GAG GAG GUC | Excellent skipping to 100nM, skipping to 10nM.<br>Also taking out 4&5 to 300nM |
| 32 & 464 | H3A(+61+85)<br>H3A(+30+54) | G CCC UGU CAG GCC UUC GAG GAG GUC<br>GCG CCU CCC AUC CUG UAG GUC ACU G | Very strong skipping to 50nM |
| 32 & 84 | H3A(+61+85)<br>H3A(+25+60) | G CCC UGU CAG GCC UUC GAG GAG GUC<br>AGG AGG CGU CUC CCA UCC UGU AGG UCA CUG AAG AG | Very strong skipping to 50nM |

Antisense Oligonucleotides Directed at Exon 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. Figure 4 shows skipping of exon 4 using a cocktail of H4A(+11+40) [SEQ ID NO: 33] and H4D(+14-11) [SEQ ID NO: 34].

Table 5: Antisense molecule sequences tested to determine if they induce exon 4 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 91 | H4A(-08+17) | GAU CCU UUU UCU UUU GGC UGA GAA C | Weak skipping down to 10nM |
| 92 | H4A(+36+60) | CCG CAG UGC CUU GUU GAC AUU GUU C | Good skipping to 10nM |
| 93 | H4D(+14-11) | GUA CUA CUU ACA UUA UUG UUC UGC A | Very poor skipping to 10nM |
| | | | |
| | **Exon 4 Cocktails** | | |
| 33 & 34 | H4A(+11+40)<br>H4D(+14-11) | UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU<br>GUA CUA CUU ACA UUA UUG UUC UGC A | Excellent skipping( 100% to 100nM) and good skipping down to 5nM |

Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. H5D(+26-05) would be regarded as a non-preferred antisense molecule as it failed to induce even low level skipping of exon 5. However, H5A(+35+65) [SEQ ID NO: 1], which presumably targets an exonic splicing enhancer was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in Figure 5 and is regarded as the preferred compound for induced exon 5 skipping.

Table 6: Antisense molecule sequences tested to determine if they induce exon 5 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 1 | H5A(+35+65) | AAA CCA AGA GUC AGU UUA UGA UUU CCA UCU A | Great skipping to 10nM |
| 94 | H5D(+26-05) | CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A | No skipping |

Antisense Oligonucleotides Directed at Exon 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 7: Antisense molecule sequences tested to determine if they induce exon 6 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 95 | H6A(-09+17) | UUC AUU ACA UUU UUG ACC UAC AUG UG | faint to 600nM |
| 96 | H6A(+32+57) | CUU UUC ACU GUU GGU UUG UUG CAA UC | skipping at 25nM |
| 97 | KH9 6A(+66+94) | AAU UAC GAG UUG AUU GUC GGA CCC AGC UC | skipping at 25nM |
| 98 | H6A(+69+96) | AUA AUU ACG AGU UGA UUG UCG GAC CCA G | skipping to 100 nM |
| 99 | H6A(+98+123) | GGU GAA GUU GAU UAC AUU AAC CUG UG | No skipping |
| 100 | H6D(+18-06) | UCU UAC CUA UGA CUA UGG AUG AGA | No skipping |
| 101 | H6D(+07-15) | CAG UAA UCU UCU UAC CUA UGA C | No skipping |
| 102 | H6D(+07-16) | UCA GUA AUC UUC UUA CCU AUG AC | No skipping |
| 103 | H6D(+04-20) | UGU CUC AGU AAU CUU CUU ACC UAU | No skipping |

Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 8: Antisense molecule sequences tested to determine if they induce exon 7 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 104 | H7A(-07+15) | UCA AAU AGG UCU GGC CUA AAA C | no skipping |
| 105 | H7A(-03+18) | CCA GUC AAA UAG GUC UGG CCU A | no skipping |
| 106 | H7A(+41+63) | UGU UCC AGU CGU UGU GUG GCU GA | skipping 50nM |
| 73 | H7A(+41+67) | UGC AUG UUC CAG UCG UUG UGU GGC UGA | skipping 25nM |
| 107 | H7A(+47+74) | UGU UGA AUG CAU GUU CCA GUC GUU GUG U | skippking 25nM but weak |
| 72 | H7A(+49+71) | UGA AUG CAU GUU CCA GUC GUU GU | good skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 6.

Table 9: Antisense molecule sequences tested to determine if they induce exon 8 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 108 | H8A(-10+20) | UGG AUA GGU GGU AUC AAC AUC UGU AAG CAC | Very weak skipping of 8+9 to 10nM |
| 109 | H8A(-07+15) | AGG UGG UAU CAA CAU CUG UAA G | Very,very weak skipping of 8+9 to 10nM |
| 35 | H8A(-06+24) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA | Weak skipping of 8+9 to 10nM |
| 110 | H8A(-04+18) | GAU AGG UGG UAU CAA CAU CUG U | works strongly to 40nM |
| 71 | H8A(+42+66) | AAA CUU GGA AGA GUG AUG UGA UGU A | good skipping of 8+9 to 10nM |
| 70 | H8A(+57+83) | GCU CAC UUG UUG AGG CAA AAC UUG GAA | good skipping of 8+9 at high conc,down to 10nM |
| 111 | H8A(+96+120) | GCC UUG GCA ACA UUU CCA CUU CCU G | Weak skipping of 8+9 to 300nM |
| 36 | H8A(+134+158) | AUG UAA CUG AAA AUG UUC UUC UUU A | Weak skipping of 8+9 to 100nM |
| 112 | H8D(+13-12) | UAC ACA CUU UAC CUG UUG AGA AUA G | Weak skipping of 8+9 to 50nM |
| | | | |
| | **Exon 8 Cocktails** | | |
| 35 & 36 | H8A(-06+24) H8A(+134+158) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA AUG UAA CUG AAA AUG UUC UUC UUU A | Good skipping to 10nM (8+9) but also 8 on its own |
| 35 & 112 | H8A(-06+24) H8D(+13-12) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA UAC ACA CUU UAC CUG UUG AGA AUA G | Good skipping to 10nM (8+9) but also 8 on its own |
| 35 & 70 | H8A(-06+24) H8A(+57+83) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA GCU CAC UUG UUG AGG CAA AAC UUG GAA | Good skipping to 10nM (8+9) but also 8 on its own |
| 35 & 111 | H8A(-06+24) H8A(+96+120) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA GCC UUG GCA ACA UUU CCA CUU CCU G | Good skipping to 10nM (8+9) but also 8 on its own |

Antisense Oligonucleotides Directed at Exon 9

Antisense oligonucleotides directed at exon 9 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 10: Antisense molecule sequences tested to determine if they induce exon 9 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 113 | H9A(+154+184) | AGC AGC CUG UGU GUA GGC AUA GCU CUU GAA U | working strongly to 100nM |
| 114 | H9D(+26-04) | AGA CCU GUG AAG GAA AUG GGC UCC GUG UAG | working strongly to 200nM |

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 7 for examples of a single antisense oligonucleotide molecule and cocktails which induce skippig of exon 10 and surrounding exons. Single antisense oligonuceotide molecule H10A(-05+16) [SEQ ID NO: 37] was able to induce skipping of exons 9-14, whilst the combination with H10A(+98+119) [SEQ ID NO: 38] was able to induce skipping of exon 10 alone and exons 9-12 (and some skipping of exons 10-12). The combination of H10A(-05+16) and H10A(+130+149) was able to induce skipping of exon 10 and exons 9-12.

Table 11: Antisense molecule sequences tested to determine if they induce exon 10 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 115 | H10A(-09+16) | CAG GAG CUU CCA AAU GCU GCA CAA U | no skipping |
| 116 | H10A(+08+27) | UGA CUU GUC UUC AGG AGC UU | no skipping |
| 117 | H10A (+21 +42) | CAA UGA ACU GCC AAA UGA CUU G | Skipping at 100nM |
| 118 | H10A(+27+51) | ACU CUC CAU CAA UGA ACU GCC AAA U | No Skipping |
| 119 | H10A(+55+79) | CUG UUU GAU AAC GGU CCA GGU UUA C | No Skipping |
| 120 | H10A(+80+103) | GCC ACG AUA AUA CUU CUU CUA AAG | No Skipping |
| 121 | H10D(+16-09) | UUA GUU UAC CUC AUG AGU AUG AAA C | No Skipping |
| | | | |
| | **Cocktails Exon 10** | | |
| 37 & 38 | H10A(-05+16) H10A(+98+119) | CAG GAG CUU CCA AAU GCU GCA UCC UCA GCA GAA AGA AGC CAC G | Strong skipping at 200nM |
| 37 & 122 | H10A(-05+16) H10A(+130+149) | CAG GAG CUU CCA AAU GCU GCA UUA GAA AUC UCU CCU UGU GC | Skipping at 200nM |

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 37.

Table 12: Antisense molecule sequences tested to determine if they induce exon 11 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 123 | H11A(-07+13) | CCA UCA UGU ACC CCU GAC AA | Skipping at 300nM |
| 124 | H11A+(+134+157) | CCC UGA GGC AUU CCC AUC UUG AAU | Skipping at 100nM |
| 125 | H11A(+20+45) | AUU ACC AAC CCG GCC CUG AUG GGC UG | skipping to 25 nM |
| 126 | H11A(+46+75) | UCC AAU CAG CUU ACU UCC CAA UUG UAG AAU | Strong skipping to 25 nM hint at 2.5 nM |
| 127 | H11A(+50+75) | UCC AAU CAG CUU ACU UCC CAA UUG UA | Strong skipping to 10 nM faint at 2.5 nM |
| 52 | H11A(+50+79) | CUG UUC CAA UCA GCU UAC UUC CCA AUU GUA | Strong skipping to 5 nM faint at 2.5 nM |
| 128 | H11A(+80+105) | AGU UUC UUC AUC UUC UGA UAA UUU UC | Faint skipping to 25 nM |
| 129 | H11A(+106+135) | AUU UAG GAG AUU CAU CUG CUC UUG UAC UUC | Strong skipping to 25 nM (20%) |
| 130 | H11A(+110+135) | AUU UAG GAG AUU CAU CUG CUC UUG UA | Strong skipping to 25 nM (20%) |
| 131 | H11A(+110+139) | UUG AAU UUA GGA GAU UCA UCU GCU CUU GUA | Strong skipping to 25 nM (20%) |

Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 38.

Table 13: Antisense molecule sequences tested to determine if they induce exon 12 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 132 | H12D(+06-16) | CAU AAG AUA CAC CUA CCU UAU G | No Skipping |
| 2 | H12A(+52+75) | UCU UCU GUU UUU GUU AGC CAG UCA | Strong skipping |
| 53 | H12A(+30+57) | CAG UCA UUC AAC UCU UUC AGU UUC UGA U | Strong skipping to 10 nM faint at 2.5 nM |
| 133 | H12A(+60+87) | UUC CUU GUU CUU UCU UCU GUU UUU GUU A | Strong skipping to 25 nM faint at 5 nM |
| 134 | H12A(+90+117) | AGA UCA GGU CCA AGA GGC UCU UCC UCC A | Strong skipping to 25 nM (30%) |
| 135 | H12A(+120+147) | UGU UGU UGU ACU UGG CGU UUU AGG UCU U | Strong skipping to 25 nM (30%) |

Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 14: Antisense molecule sequences tested to determine if they induce exon 13 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 136 | H13A(-12+12) | UUC UUG AAG CAC CUG AAA GAU AAA | No Skipping |

Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 8.

Table 15: Antisense molecule sequences tested to determine if they induce exon 14 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 137 | H14A(+45 +73) | GAA GGA UGU CUU GUA AAA GAA CCC AGC GG | Skipping at 25nM |

Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 16: Antisense molecule sequences tested to determine if they induce exon 16 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 138 | H16A(-07+19) | CUA GAU CCG CUU UUA AAA CCU GUU AA | No skipping |
| 139 | H16A(+09+31) | GCU UUU UCU UUU CUA GAU CCG CU | No skipping |
| 140 | H16D(+18-07) | CAC UAA CCU GUG CUG UAC UCU UUU C | No skipping |

Antisense Oligonucleotides Directed at Exon 17

Antisense oligonucleotides directed at exon 17 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 64: Antisense molecule sequences tested to determine if they induce exon 17 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 141 | H17A(+48+78) | UGU GGU CAC CGU AGU UAC UGU UUC CAU UCA A | No skipping |
| 142 | H17A(+55+85) | GUU CCC UUG UGG UCA CCG UAG UUA CUG UUU C | Skipping to 100 nM |

Antisense Oligonucleotides Directed at Exon 18

Antisense oligonucleotides directed at exon 18 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 9.

Table 17: Antisense molecule sequences tested to determine if they induce exon 18 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 143 | H18A(-09+11) | CAA CAU CCU UCC UAA GAC UG | No skipping |
| 144 | H18A(+24+43) | GCG AGU AAU CCA GCU GUG AA | Inconsistent skipping of both exon 17 + 18 |
| 145 | H18A(+41 +70) | UUC AGG ACU CUG CAA CAG AGC UUC UGA GCG | Skipping exons 17+18 300nM |
| 146 | H18A(+83+108) | UUG UCU GUG AAG UUG CCU UCC UUC CG | Skipping exons 17+18 300nM |
| 147 | H18D(+04-16) | UUA AUG CAU AAC CUA CAU UG | No skipping |

Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18: Antisense molecule sequences tested to determine if they induce exon 19 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 148 | H19A(+19+48) | GGC AUC UUG CAG UUU UCU GAA CUU CUC AGC | skipping to 25 nM |
| 149 | H19A(+27+54) | UCU GCU GGC AUC UUG CAG UUU UCU GAA C | skipping to 25 nM |
| 150 | H19D(+3-17) | UCA ACU CGU GUA AUU ACC GU | skipping |

Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 19: Antisense molecule sequences tested to determine if they induce exon 20 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 151 | H20A(+23+47) | GUU CAG UUG UUC UGA GGC UUG UUU G | faint shadow at 600 nM |
| 152 | H20A(+140+164) | AGU AGU UGU CAU CUG CUC CAA UUG U | no skipping |

Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. H23(+69+98)-SNP contains a single nucleotide polymorphism (SNP) that has been previously documented.

Table 65: Antisense molecule sequences tested to determine if they induce exon 23 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 153 | H23(+69+98)-SNP | CGG CUA AUU UCA GAG GGC GCU UUC UU**U** GAC | skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 20: Antisense molecule sequences tested to determine if they induce exon 24 skipping.

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 8 | H24A(+51+73) | CAA GGG CAG GCC AUU CCU CCU UC | Strong skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. Oligonucleotide H25A(+95+119)-DupA is a patient specific antisense molecule.

Table 21: Antisense molecule sequences tested to determine if they induce exon 25 skipping.

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 154 | H25A(+10+33) | UGG GCU GAA UUG UCU GAA UAU CAC | strong at 25nM but did not reduce the full length product |
| 155 | H25D(+06-14) | GAG AUU GUC UAU ACC UGU UG | very strong at 25nM |
| 156 | H25A(+10+38) | AGA CUG GGC UGA AUU GUC UGA AUA UCA CU | Strong skipping at 5 nM faint 2.5 nM |
| 157 | H25A(+95+119)-DupA* | UUG AGU UCU GUU CUC AAG UCU CGA AG | Strong skipping at 25 nM faint 5 nM (patient specific) |
| 158 | H25D(+13-14) | GAG AUU GUC UAU ACC UGU UGG CAC AUG | Strong skipping at 10 nM |

Antisense Oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 10.

Table 22: Antisense molecule sequences tested to determine if they induce exon 26 skipping.

| SEQ | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 159 | H26A(-16+09) | GGC AUA GAC CUU CCA CAA AAC AAA C | Faint skipping 600 nM &300 nM |
| 160 | H26A(-7+23) | AAG GCC UCC UUU CUG GCA UAG ACC UUC CAC | Faint at 600, 300nM , multiple exons 26-29 or 27-30 |
| 161 | H26A(-03+27) | CUU CAA GGC CUC CUU UCU GGC AUA GAC CUU | Faint at 600, 300nM , multiple exons 26-29 or 27-30 |
| 162 | H26A(+5+35) | AAC CUC CCU UCA AGG CCU CCU UUC UGG CAU | No skipping |
| 40 | H26A(+24+50) | CUU ACA GUU UUC UCC AAA CCU CCC UUC | Faint at 600, 300nM , multiple exons 26-29 or 27-30 |
| 163 | H26D(+06-19) | UUU CUU UUU UUU UUU UUA CCU UCA U | Faint at 600 , multiple exons 26-29 or 27-30 |
| 164 | H26D(+21-04) | UUA CCU UCA UCU CUU CAA CUG CUU U | multiple exons 26-29 or 27-30 |
| 165 | H26D(+10-10) | UUU UUU UUA CCU UCA UCU CU | Not skipping 26 other bands |
| | | | |
| | **Exon 26 cocktails** | | |
| 39, 40 & 41 | H26A(-07+19) H26A(+24+50) H26A(+68+92) | CCU CCU UUC UGG CAU AGA CCU UCC AC CUU ACA GUU UUC UCC AAA CCU CCC UUC UGU GUC AUC CAU UCG UGC AUC UCU G | strong skipping down to 25nM |

Antisense Oligonucleotides Directed at Exon 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 23: Antisense molecule sequences tested to determine if they induce exon 31 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 166 | H31D(+12-18) | UUC UGA AAU UUC AUA UAC CUG UGC AAC AUC | skipping to 100nM |
| 167 | H31D(+08-22) | UAG UUU CUG AAA UAA CAU AUA CCU GUG CAA | skipping to 100nM |
| 168 | H31D(+06-24) | CUU AGU UUC UGA AAU AAC AUA UAC CUG UGC | skipping to 100nM |
| 169 | H31D(+02-22) | UAG UUU CUG AAA UAA CAU AUA CCU | skipping to 100nM |
| 170 | H31D(+01-25) | CCU UAG UUU CUG AAA UAA CAU AUA CC | strong skipping at 300nM |

Antisense Oligonucleotides Directed at Exon 32

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 24: Antisense molecule sequences tested to determine if they induce exon 32 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 171 | H32A(+49+78) | ACU UUC UUG UAG ACG CUG CUC AAA AUU GGC | skipping to 100nM |

Antisense Oligonucleotides Directed at Exon 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 25: Antisense molecule sequences tested to determine if they induce exon 34 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 172 | H34A(+36+59) | UUU CGC AUC UUA CGG GAC AAU UUC | skipping to 200 nM |
| 173 | H34A(+41+70) | CAU UCA UUU CCU UUC GCA UCU UAC GGG ACA | skipping to 200 nM |
| 174 | H34A(+43+72) | GAC AUU CAU UUC CUU UCG CAU CUU ACG GGA | skipping to 100 nM |
| 175 | H34A(+51+83) | UCU GUC AAG ACA UUC AUU UCC UUU CGC AUC | skipping to 200 nM |

| | | | |
|---|---|---|---|
| 176 | H34A(+91+120) | UGA UCU CUU UGU CAA UUC CAU AUC UGU AGC | skipping to 100 nM |
| 177 | H34A(+92+121) | CUG AUC UCU UUG UCA AUU CCA UAU CUG U**G**G | skipping to 100 nM |
| 178 | H34A(+95+120) | UGA UCU CUU UGU CAA UUC CAU AUC UG | Faint to 25nM |
| 179 | H34A(+95+124) | CUG CUG AUC UCU UUG UCA AUU CCA UAU CUG | skipping to 100 nM |

Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 26: Antisense molecule sequences tested to determine if they induce exon 35 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 180 | H35A(+14+43) | UCU UCA GGU GCA CCU UCU GUU UCU CAA UCU | skipping to 100 nM |
| 181 | H35A(+24+53) | UCU GUG AUA CUC UUC AGG UGC ACC UUC UGU | skipping to 100 nM |

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 11.

Table 27: Antisense molecule sequences tested to determine if they induce exon 36 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 42 | H36A(-16+09) | CUG GUA UUC CUU AAU UGU ACA GAG A | no skipping |
| 182 | H36A(-01+19) | CCA UGU GUU UCU GGU AUU CC | very faint skipping 300 nM |
| 183 | H36A(+10+39) | CAC AUU CUG GUC AAA AGU UUC CAU GUG UUU | Skipping to 25nM |
| 43 | H36A(+22+51) | UGU GAU GUG GUC CAC AUU CUG GUC AAA AGU | Skipping at 100nM |
| 184 | H36A(+27+51) | UGU GAU GUG GUC CAC AUU CUG GUC A | Skipping at 100nM |
| 185 | H36A(+27+56) | CAC UUU GUG AUG UGG UCC ACA UUC UGG UCA | Skipping at 300nM |
| 186 | H36A(+32+61) | UGA UCC ACU UUG UGA UGU GGU CCA CAU UCU | Skipping to 25nM |
| 187 | H36A(+59+78) | AAG UGU GUC AGC CUG AAU GA | very weak skipping |
| 188 | H36A(+65+94) | UCU CUG AUU CAU CCA AAA GUG UGU CAG CCU | 100% skipping at 600nM, skipoping to 25nM |
| 189 | H36A(+80+109) | GCU GGG GUU UCU UUU UCU CUG AUU CAU CCA | 100% skipping at 600nM, skipoping to 25nM |
| 190 | H36D(+15-10) | UAU UUG CUA CCU UAA GCA CGU CUU C | very weak skipping |
| | | | |
| | | | |
| | **Exon 36 cocktails** | | |
| 42 & 43 | H36A(-16+09)<br>H36A(+22+51) | CUG GUA UUC CUU AAU UGU ACA GAG A<br>UGU GAU GUG GUC CAC AUU CUG GUC AAA AGU | good skipping down to 25nM |

Antisense Oligonucleotides Directed at Exon 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 28: Antisense molecule sequences tested to determine if they induce exon 38 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 191 | H38A(-21-01) | CUA AAA AAA AAG AUA GUG CUA | skipping to 25 nM |
| 192 | H38A(-12+14) | AAA GGA AUG GAG GCC UAA AAA AAA AG | skipping to 25 nM |
| 193 | H38D(+14-11) | AAC CAA UUU ACC AUA UCU UUA UUG A | skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29: Antisense molecule sequences tested to determine if they induce exon 39 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 194 | H39A(-07+23) | ACA GUA CC**A** UCA UUG UCU UCA UUC UGA UC | skipping to 600 nM |
| 195 | H39A(-07+23) | ACA GUA CC**C** UCA UUG UCU UCA UUC UGA UC | skipping to 600 nM |
| 196 | H39A(+58+87) | CUC UCG CUU UCU CUC AUC UGU GAU UCU UUG | skipping to 100 nM |
| 197 | H39A(+60+89) | UCC UCU CGC UUU CUC UCA UCU GUG AUU CUU | skipping to 100 nM |
| 198 | H39A(+102+126) | UAU GUU UUG UCU GUA ACA GCU GCU G | skipping to 600 nM |

Antisense Oligonucleotides Directed at Exon 41

Antisense oligonucleotides directed at exon 41 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 30: Antisense molecule sequences tested to determine if they induce exon 41 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 199 | H41A(-15+5) | AUU UCC UAU UGA GCA AAA CC | Skipping down to 200nM |

| | | | |
|---|---|---|---|
| 200 | H41A(+66+90) | CAU UGC GGC CCC AUC CUC AGA CAA G | Skipping down to 100nM |
| 201 | H41A(+92+120) | GCU GAG CUG GAU CUG AGU UGG CUC CAC UG | Skipping down to 10nM |
| 202 | H41A(+143+171) | GUU GAG UCU UCG AAA CUG AGC AAA UUU GC | No visible skipping |
| 203 | H41D(+5-15) | CCA GUA ACA ACU CAC AAU UU | Skipping down to 200nM |

Antisense Oligonucleotides Directed at Exon 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 31: Antisense molecule sequences tested to determine if they induce exon 20 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 42** | | |
| 204 | H42D(+18-02) | ACC UUC AGA GAC UCC UCU UGC | strong skipping |

Antisense Oligonucleotides Directed at Exon 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 12.

Table 32: Antisense molecule sequences tested to determine if they induce exon 20 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 43** | | |
| 205 | H43A(+83+110) | UCC UGU AGC UUC ACC CUU UCC ACA GGC G | No skipping |
| 9 | H43A(+92 +117) | GAG AGC UUC CUG UAG CUU CAC CCU UU | Skipping at 10nM |
| 206 | H43A(+101 +130) | AAU CA GCU GGG AGA GAG CUU CCU GUA GCU | No skipping |
| 207 | H43D(+08-12) | UGU GUU ACC UAC CCU UGU CG | Skipping down to 200nM |
| 208 | H43A(-09+18) | UAG ACU AUC UUU UAU AUU CUG UAA UAU | Faint skipping to 25 nM |
| 209 | H43A(+89+117) | GAG AGC UUC CUG UAG CUU CAC CCU UUC CA | Strong skipping at 25 nM faint 2.5 nM |
| 210 | H43A(+81+111) | UUC CUG UAG CUU CAC CCU UUC CAC AGG CGU U | Strong skipping at 50 nM faint 2.5 nM |
| 211 | H43A(+92+114) | AGC UUC CUG UAG CUU CAC CCU UU | Faint skipping to 2.5 nM |
| 74 | H43A(+92+120) | GGA GAG AGC UUC CUG UAG CUU CAC CCU UU | Strong skipping at 10 nM faint 5 nM |
| 212 | H43A(+95+117) | GAG AGC UUC CUG UAG CUU CAC CC | Strong skipping at 25 nM faint 10 nM |

Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 13 and Figure 39.

Table 33: Antisense molecule sequences tested to determine if they induce exon 44 skipping

| SEQ | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 44** | | |
| 213 | H44A(-13+13) | UCU GUC AAA UCG CCU GCA GGU AAA AG | |
| 214 | H44A(-06+24) | UUC UCA ACA GAU CUG UCA AAU CGC CUG CAG | No skipping |
| 215 | H44A(+44+68) | GCC ACU GAU UAA AUA UCU UUA UAU C | Skipping at 100nM |
| 216 | H44A(+46+75) | UCU GUU AGC CAC UGA UUA AAU AUC UUU AUA | Skipping at 50nM |
| 217 | H44A(+61+84) | UGU UCA GCU UCU GUU AGC CAC UGA | Skipping at 100nM |
| 218 | H44A(+61+91) | GAG AAA CUG UUC AGC UUC UGU UAG CCA CUG A | Skipping at 25nM |
| 10 | H44A(+65+90) | UGU UCA GCU UCU GUU AGC CAC UGA | Skipping at 10nM |
| 219 | H44A(+68+98) | UCU UUC UGA GAA ACU GUU CAG CUU CUG UUA G | weak at 50 nM |
| 220 | H44A(-09+17) | CAG AUC UGU CAA AUC GCC UGC AGG UA | Faint skipping to 10nM |
| 68 | H44A(-06+20) | CAA CAG AUC UGU CAA AUC GCC UGC AG | Faint skipping to 2.5 nM |
| 221 | H44A(+56+88) | AAA CUG UUC AGC UUC UGU UAG CCA CUG AUU AAA | Strong skipping at 5 nM faint 2.5 nM |
| 54 | H44A(+59+85) | CUG UUC AGC UUC UGU UAG CCA CUG AUU | Strong skipping at 5 nM |
| 222 | H44A(+59+89) | GAA ACU GUU CAG CUU CUG UUA GCC ACU GAU U | Faint skipping to 10 nM |
| 223 | H44A(+61+88) | AAA CUG UUC AGC UUC UGU UAG CCA CUG A | Faint skipping to 25 nM |
| 224 | H44A(+65+92) | UGA GAA ACU GUU CAG CUU CUG UUA GCC A | Faint skipping to 25 nM |
| 225 | H44A(+64+95) | UUC UGA GAA ACU GUU CAG CUU CUG UUA GCCA C | Faint skipping to 25 nM |
| 226 | H44A(+70+95) | UUC UGA GAA ACU GUU CAG CUU CUG UU | Faint skipping to 50 nM |

Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 14 and Figure 40.

Table 34: Antisense molecule sequences tested to determine if they induce exon 45 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 45** | | |
| 227 | H45A(-14+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG | Generates multiple bands |
| 228 | H45A(-10 +20) | CCA AUG CCA UCC UGG AGU UCC UGU AAG AUA | Skipping at 10nM |
| 229 | H45A(-09+30) | UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU | No Skipping |
| 11 | H45A (-09+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U | Skipping at 10nM (100% skipping at 25nM) |
| 230 | H45A(-08 +19) | CAA UGC CAU CCU GGA GUU CCU GUA AGA | Skipping at 50nM |

| | | | |
|---|---|---|---|
| 231 | HM45A(-07+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG | Skipping at 25nM |
| 232 | H45A(+09 +34) | CAG UUU GCC GCU GCC CAA UGC CAU CC | No Skipping |
| 233 | H45A(+41 +64) | CUU CCC CAG UUG CAU UCA AUG UUC | No Skipping |
| 234 | H45A(+76 +98) | CUG GCA UCU GUU UUU GAG GAU UG | No Skipping |
| 235 | H45D(+02-18) | UUA GAU CUG UCG CCC UAC CU | No Skipping |
| 236 | H45A(-14+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC CAA | |
| 237 | H45A(-12+22) | GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C | Strong skipping at 5 nM faint 2.5 nM |
| 238 | H45A(-12+13) | CAU CCU GGA GUU CCU GUA AGA UAC C | No skipping |
| 66 | H45A(-12+16) | UGC CAU CCU GGA GUU CCU GUA AGA UAC C | Strong skipping at 25 nM faint 5 nM |
| 65 | H45A(-09+16) | UGC CAU CCU GGA GUU CCU GUA AGA U | skipping to 10 nM |
| 64 | H45A(-09+19) | CAA UGC CAU CCU GGA GUU CCU GUA AGA U | Strong skipping at 25 nM faint 2.5 nM |
| 239 | H45A(-09+22) | GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U | Strong skipping at 10 nM faint 5 nM |
| 240 | H45A(-09+30) | UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU | Strong skipping at 5 nM faint 2.5 nM |
| 241 | HM45A(-07+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG | Strong skipping at 2.5 nM |
| 242 | H45A(-06+22) | GCC CAA UGC CAU CCU GGA GUU CCU GUA A | Strong skipping at 5 nM faint 2.5 nM |
| 243 | H45A(-06+28) | GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A | Strong skipping at 2.5 nM |
| 63 | H45A(-03+19) | CAA UGC CAU CCU GGA GUU CCU G | Strong skipping at 5 nM faint 2.5 nM |
| 244 | H45A(-03+22) | GCC CAA UGC CAU CCU GGA GUU CCU G | Strong skipping at 10 nM faint 2.5 nM |
| 55 | H45A(-03+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU G | Strong skipping at 2.5 nM |
| 245 | H45A(-03+28) | GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU G | Strong skipping at 10 nM faint 2.5 nM |
| 246 | H45D(+10-19) | AUU AGA UCU GUC GCC CUA CCU CUU UUU UC | No skipping |
| 247 | H45D(+16-11) | UGU CGC CCU ACC UCU UUU UUC UGU CUG | No skipping |
| 61 | H45A(-06+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A | strong skipping at 2.5 nM |
| 62 | H45A(-12+19) | CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C | strong skipping at 25 nM |

Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 15 and Figure 44.

Table 35: Antisense molecule sequences tested to determine if they induce exon 46 skipping

| SEQ | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 46** | | |
| 248 | H46A(-05+19) | AUU CUU UUG UUC UUC UAG CCU GGA | No skipping |
| 249 | H46A(+16+42) | UCU CUU UGA AAU UCU GAC AAG AUA UUC | skipping to 25 nM, other bands |
| 250 | H46A(+27+44) | UUA AAU CUC UUU GAA AUU CU | No skipping |
| 251 | H46A(+35+60) | AAA ACA AAU UCA UUU AAA UCU CUU UG | very faint skipping to 50 nM |
| 252 | H46A(+56+77) | CUG CUU CCU CCA ACC AUA AAA C | No skipping |
| 253 | H46A(+63+87) | GCA AUG UUA UCU GCU UCC UCC AAC C | No skipping |
| 12 | H46A(+81+109) | UCC AGG UUC AAG UGG GAU ACU AGC AAU GU | strong skipping at 25nM |

| | | | |
|---|---|---|---|
| 254 | H46A(+83+103) | UUC AAG UGG GAU ACU AGC AAU | skipping at 25nM |
| 255 | H46A(+90+109) | UCC AGG UUC AAG UGG GAU AC | no skipping |
| 256 | H46A(+91+118) | CUG CUC UUU UCC AGG UUC AAG UGG GAU A | strong skipping at 25nM |
| 257 | H46A(+95+122) | GUU GCU GCU CUU UUC CAG GUU CAA GUG G | strong skipping at 25nM |
| 258 | H46A(+101+128) | CUU UUA GUU GCU GCU CUU UUC CAG GUU C | strong skipping at 25nM |
| 259 | H46A(+113+136) | AAG CUU UUC UUU UAG UUG CUG CUC | skipping at 100nM |
| 260 | H46A(+115+134) | GCU UUU CUU UUA GUU GCU GC | skipping at 100nM |
| 261 | H46A(+116+145) | GAC UUG CUC AAG CUU UUC UUU UAG UUG CUG | strong skipping at 25nM |
| 262 | H46D(+02-18) | UUC AGA AAA UAA AAU UAC CU | no skipping |
| 56 | H46A(+93+122) | GUU GCU GCU CUU UUC CAG GUU CAA GUG GGA | 100% skipping at 25 nM strong at 5 nM |
| 263 | H46A(+95+124) | UAG UUG CUG CUC UUU UCC AGG UUC AAG UGG | 100% skipping at 25 nM |

Antisense Oligonucleotide Cocktails Directed at Exons 44 to 46

Antisense oligonucleotide cocktails directed at exons 44 to 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 36: Antisense molecule sequence cocktails that induce exon 44 to 45 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Cocktails for skipping 44 + 45** | | |
| 10 & 228 | H44A(+65 +90)<br>H45A(-10 +20) | AGA AAC UGU UCA GCU UCU GUU AGC CA<br>CCA AUG CCA UCC UGG AGU UCC UGU AAG AUA | Skipping at 25nM |
| | | | |
| | **Cocktails for skipping exons 45 and 46** | | |
| 228 & 256 | H45A(-10 +20)<br>H46A(+91 +118) | CCA AUG CCA UCC UGG AGU UCC UGU AAG AUA<br>CUG CUC UUU UCC AGG UUC AGG UGG GAU A | Skipping at 25nM |
| 228 & 264 | H45A(-10 +20)<br>H46A(+107 +137) | CCA AUG CCA UCC UGG AGU UCC UGU AAG AUA<br>CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C | Skipping at 25nM |
| | | | |
| | **Cocktail for skipping exon 44 / 45 / 46** | | |
| | | | |
| 228, 10 & 256 | H45A(-10 +20)<br>H44A(+65 +90)<br>H46A(+91 +118) | CCA AUG CCA UCC UGG AGU UCC UGU AAG AUA<br>AGA AAC UGU UCA GCU UCU GUU AGC CA<br>CUG CUC UUU UCC AGG UUC AGG UGG GAU A | Skipping at 25nM |

Antisense Oligonucleotides Directed at Exon 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 16.

Table 37: Antisense molecule sequences tested to determine if they induce exon 47 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 47** | | |
| 265 | H47A(-07+19) | GCA ACU CUU CCA CCA GUA ACU GAA AC | Skipping at 100nM |
| 13 | H47A(+01+29) | UGG CGC AGG GGC AAC UCU UCC ACC AGU AA | strong skipping at 25nM |
| 266 | H47A(+44+70) | GCA CGG GUC CUC CAG UUU CAU UUA AUU | Skipping at 600nM |
| 267 | H47A(+68+92) | GGG CUU AUG GGA GCA CUU ACA AGC A | No skipping |
| 268 | H47A(+73+103) | CUU GCU CUU CUG GGC UUA UGG GAG CAC UUA C | No skipping |
| 269 | H47A(+76+103) | CUU GCU CUU CUG GGC UUA UGG GAG CAC U | Faint skipping at 200nM, full length product not reduced |
| 270 | H47D(+17-10) | AAU GUC UAA CCU UUA UCC ACU GGA GAU | No skipping |

Antisense Oligonucleotides Directed at Exon 48

Antisense oligonucleotides directed at exon 48 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 17.

Table 38: Antisense molecule sequences tested to determine if they induce exon 48 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 48** | | |
| 271 | H48A(-09+21) | CUC AGG UAA AGC UCU GGA AAC CUG AAA GGA | No skipping |
| 272 | H48A(-08+19) | CAG GUA AAG CUC UGG AAA CCU GAA AGG | No skipping |
| 273 | H48A(-07+23) | UUC UCA GGU AAA GCU CUG GAA ACC UGA AAG | Skipping at 600, 300nM |
| 274 | H48A(-05+25) | GUU UCU CAG GUA AAG CUC UGG AAA CCU GAA | No skipping |
| 44 | H48A(+01+28) | CUU GUU UCU CAG GUA AAG CUC UGG AAA C | faint to 50 nM |
| 275 | H48A(+07+33) | UUC UCC UUG UUU CUC AGG UAA AGC UCU | faint to 50 nM |
| 45 | H48A(+40+67) | CAA GCU GCC CAA GGU CUU UUA UUU GAG C | No skipping (sporadic) |
| 276 | H48A(+75+100) | UUA ACU GCU CUU CAA GGU CUU CAA GC | faint to 1000 nM |
| 277 | H48A(+96+122) | GAU AAC CAC AGC AGC AGA UGA UUU AAC | No skipping |
| 278 | H48D(+17-10) | AGU UCC CUA CCU GAA CGU CAA AUG GUC | No skipping |
| 279 | H48D(+16-09) | GUU CCC UAC CUG AAC GUC AAA UGG U | No skipping |
| | | | |
| | **Cocktail 48** | | |
| 44 & 45 | H48A(+01+28) H48A(+40+67) | CUU GUU UCU CAG GUA AAG CUC UGG AAA C CAA GCU GCC CAA GGU CUU UUA UUU GAG C | Strong skipping at 25 nM |

Antisense Oligonucleotides Directed at Exon 49

Antisense oligonucleotides directed at exon 49 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 18.

Table 39: Antisense molecule sequences tested to determine if they induce exon 49 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 49** | | |
| 280 | H49A(-07+19) | GAA CUG CUA UUU CAG UUU CCU GGG GA | Skipping to 100nM |
| 281 | H49A(+22+47) | AUC UCU UCC ACA UCC GGU UGU UUA GC | Skipping to 25nM |
| 14 | H49A(+45+70) | ACA AAU GCU GCC CUU UAG ACA AAA UC | Skipping to 25nM |
| 282 | H49D(+18-08) | UUC AUU ACC UUC ACU GGC UGA GUG GC | Skipping to 100nM |

Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figures 19 and 33.

Table 40: Antisense molecule sequences tested to determine if they induce exon 50 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 50** | | |
| 283 | H50A(-07+20) | CUC AGA UCU UCU AAC UUC CUC UUU AAC | Faint skipping 25 nM |
| 284 | H50A(-02+27) | CUC AGA GCU CAG AUC UUC UAA CUU CCU CU | faint skipping 100 nM |
| 285 | H50A(+10+36) | CGC CUU CCA CUC AGA GCU CAG AUC UUC | skipping faintly to 25 |
| 286 | H50A(+35+61) | UCA GCU CUU GAA GUA AAC GGU UUA CCG | strong skipping to 25 nM |
| 287 | H50A(+42+68) | UUU GCC CUC AGC UCU UGA AGU AAA CGG | reasonable skipping to 25 nM |
| 15 | H50A(+48+74) | GGC UGC UUU GCC CUC AGC UCU UGA AGU | strong skipping at 25 nM |
| 288 | H50A(+63+88) | CAG GAG CUA GGU CAG GCU GCU UUG CC | strong skipping to 25 nM |
| 289 | H50A(+81+105) | UCC AAU AGU GGU CAG UCC AGG AGC U | |
| 290 | H50D(-01-27) | AAA GAG AAU GGG AUC CAG UAU ACU UAC | faint skipping 100 nM |
| 291 | H50D(-15-41) | AAA UAG CUA GAG CCA AAG AGA AUG GGA | No skipping |
| 292 | H50A(+42+74) | GGC UGC UUU GCC CUC AGC UCU UGA AGU AAA CGG | Strong skipping to 10 nM faint at 5 nM |
| 293 | H50A(+46+75) | AGG CUG CUU UGC CCU CAG CUC UUG AAG UAA | Strong skipping to 25 nM faint at 10 nM |
| 294 | H50A(+48+78) | GUC AGG CUG CUU UGC CCU CAG CUC UUG AAG U | Strong skipping to 10 nM faint at 2.5 nM |
| 295 | H50A(+51+80) | AGG UCA GGC UGC UUU GCC CUC AGC UCU UGA | Strong skipping to 25 nM faint at 2.5 nM |
| 296 | Hint49(-72-46) | AAG AUA AUU CAU GAA CAU CUU AAU CCA | No skipping |

Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 20 and Figure 41.

Table 41: Antisense molecule sequences tested to determine if they induce exon 51 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 51** | | |
| 297 | H51A(-29-10) | UUU GGG UUU UUG CAA AAA GG | No skipping |
| 298 | H51A(-22-01) | CUA AAA UAU UUU GGG UUU UUG C | No skipping |
| 299 | H51A(-14+10) | UGA GUA GGA GCU AAA AUA UUU UGG | No skipping |
| 300 | H51(+26+52) | GUU UCC UUA GUA ACC ACA GGU UGU GUC | very faint skipping to 25 nM |
| 301 | H51A(+40+67) | AGU UUG GAG AUG GCA GUU UCC UUA GUA A | skipping to 25nM also skips 50 or 52 a well |
| 302 | H51A(+66+77) | UGG CAU UUC UAG | No skipping |
| 303 | H51A(+66+80) | AGA UGG CAU UUC UAG | No skipping |
| 304 | H51A(+66+83) | GGA AGA UGG CAU UUC UAG | No skipping |
| 305 | H51A(+78+95) | CUC CAA CAU CAA GGA AGA | No skipping |
| 306 | H51A(+81+95) | CUC CAA CAU CAA GGA | No skipping |
| 307 | H51A(+84+95) | CUC CAA CAU CAA | No skipping |
| 308 | H51A(+90+116) | GAA AUC UGC CAG AGC AGG UAC CUC CAA | No skipping |
| 309 | H51A(+53+79) | GAU GGC AUU UCU AGU UUG GAG AUG GCA | Strong skipping to 25 nM |
| 310 | H51A(+57+85) | AAG GAA GAU GGC AUU UCU AGU UUG GAG AU | Strong skipping to 25 nM faint at 2.5 nM |
| 69 | H51A(+71+100) | GGU ACC UCC AAC AUC AAG GAA GAU GGC AUU | Strong skipping to 5 nM |
| 311 | H51A(+76+104) | AGC AGG UAC CUC CAA CAU CAA GGA AGA UG | Strong skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 42.

Table 42: Antisense molecule sequences tested to determine if they induce exon 52 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 52** | | |
| 312 | H52A(-12+13) | CCU GCA UUG UUG CCU GUA AGA ACA A | No skipping |
| 313 | H52A(-10+10) | GCA UUG UUG CCU GUA AGA AC | No skipping |
| 314 | H52A(+07+33) | GGG ACG CCU CUG UUC CAA AUC CUG CAU | skippping 50 nM |
| 315 | H52A(+17+46) | GUU CUU CCA ACU GGG GAC GCC UCU GUU CCA | skippping 25 nM |
| 316 | H52A(+17+37) | ACU GGG GAC GCC UCU GUU CCA | skippping 25 nM |
| 317 | H52A(+67+94) | CCU CUU GAU UGC UGG UCU UGU UUU UCA A | vey very faint skipping to 25 nM |
| 318 | Hint51(-40-14) | UA**C** CCC UUA GUA UCA GGG UUC UUC AGC | No skipping (SNP C or T) |
| 58 | H52A(+09+38) | AAC UGG GGA CGC CUC UGU UCC AAA UCC UGC | Strong skipping to 2.5 nM |
| 319 | H52A(+09+41) | UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC UGC | Strong skipping to 5nM faint at 5 nM |
| 320 | H52A(+15+44) | UCU UCC AAC UGG GGA CGC CUC UGU UCC AAA | Strong skipping to 10nM faint at 5 nM |

Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 43.

Table 43: Antisense molecule sequences tested to determine if they induce exon 53 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 53** | | |
| 321 | H53A(-49-26) | AUA GUA GUA AAU GCU AGU CUG GAG | No skipping |
| 322 | H53A(-38-13) | GAA AAA UAA AUA UAU AGU AGU AAA UG | No skipping |
| 323 | H53A(-32-06) | AUA AAA GGA AAA AUA AAU AUA UAG UAG | No skipping |
| 324 | H53A(-15+15) | UCU GAA UUC UUU CAA CUA GAA UAA AAG GAA | No skipping |
| 325 | H53A(+39+65) | CAA CUG UUG CCU CCG GUU CUG AAG GUG | skippping 50 nM |
| 326 | H53A(+39+67) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UG | skippping 100 nM |
| 327 | H39A(+39+69)SNP | CGU UCA ACU GUU GCC UCC GGU UCU GAA GGU G | skipping to 25 nM |
| 328 | H53A(+40+70) | UCA UUC AAC UGU UGC CUC CGG UUC UGA AGG U | skippping 50 nM |
| 329 | H53A(+41+69) | CAU UCA ACU GUU GCC UCC GGU UCU GAA GG | skippping 50 nM |
| 330 | H53A(+43+69) | CAU UCA ACU GUU GCC UCC GGU UCU GAA | skippping 50 nM |
| 331 | H53A(+69+98) | CAG CCA UUG UGU UGA AUC CUU UAA CAU UUC | Skipping at 50 nM |
| 332 | Hint52(-47-23) | UAU AUA GUA GUA AAU GCU AGU CUG G | No skipping |
| 67 | H53A(+27+56) | CCU CCG GUU CUG AAG GUG UUC UUG UAC UUC | strong skipping to 25 nM faint at 5 nM |
| 333 | H53A(+27+59) | UUG CCU CCG GUU CUG AAG GUG UUC UUG UAC UUC | strong skipping to 10 nM faint at 5 nM |
| 334 | H53A(+30+59) | UUG CCU CCG GUU CUG AAG GUG UUC UUG UAC | |
| 335 | H53A(+30+64) | AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU UGU AC | strong skipping to 25 nM faint at 10 nM |
| 336 | H53A(+30+69) | CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU GUU CUU GUA C | strong skipping to 25 nM faint at 5 nM |
| 337 | H53A(+33+63) | ACU GUU GCC UCC GGU UCU GAA GGU GUU CUU G | strong skipping to 25 nM faint at 5 nM |
| 338 | H53A(+33+67) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU UG | strong skipping to 50 nM faint at 5 nM |
| 59 | H53A(+33+65) | CAA CUG UUG CCU CCG GUU CUG AAG GUG UUC UUG | strong skipping to 25 nM faint at 2.5 nM |
| 339 | H53A(+35+67) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU | strong skipping to 25 nM |
| 340 | H53A(+37+67) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU U | strong skipping to 25 nM |
| 341 | H53A(+36+70) | UCA UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU UC | reasonable sipping to 5 nM |
| 342 | H53A(+39+71) | UUC AUU CAA CUG UUG CCU CCG GUU CUG AAG GUG | strong skipping to 25 nM |
| 343 | H53A(+42+71) | UUC AUU CAA CUG UUG CCU CCG GUU CUG AAG | strong skipping to 100 nM faint at 5 nM |

Antisense Oligonucleotides Directed at Exon 54

Antisense oligonucleotides directed at exon 54 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 21.

Table 44: Antisense molecule sequences tested to determine if they induce exon 54 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 54** | | |
| 344 | H54A(+13+34) | UUG UCU GCC ACU GGC GGA GGU C | Skipping at 300nM brings out 55+54 |
| 345 | H54A(+60+90) | AUC UGC AGA AUA AUC CCG GAG AAG UUU CAG | Skipping at 25nM |
| 346 | H54A (+67+89) | UCU GCA GAA UAA UCC CGG AGA AG | Weak skipping to 40nM - both 54+55 |
| 16 | H54A(+67+97) | UGG UCU CAU CUG CAG AAU AAU CCC GGA GAA G | Skipping at 10nM |
| 347 | H54A(+77+106) | GGA CUU UUC UGG UAU CAU CUG CAG AAU AAU | Skipping 50 nM |
| | | | |
| | **Cocktail for Exons 54+55** | | |
| 16 & 348 | H54A(+67+97)<br>H55A(-10+14) | UGG UCU CAU CUG CAG AAU AAU CCC GGA GAA G<br>CUC GCU CAC UCA CCC UGC AAA GGA | Specific for 54&55<br>Skipping at 10nM<br>No additional bands |

Antisense Oligonucleotides Directed at Exon 55

Antisense oligonucleotides directed at exon 55 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 22.

Table 45: Antisense molecule sequences tested to determine if they induce exon 55 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 55** | | |
| 348 | H55A(-10+14) | CUC GCU CAC UCA CCC UGC AAA GGA | No Skipping |
| 17 | H55A(-10 +20) | CAG CCU CUC GCU CAC UCA CCC UGC AAA GGA | Skipping at 10nM |
| 349 | H55A(+39 +61) | CAG GGG GAA CUG UUG CAG UAA UC | No Skipping |
| 350 | H55A(+41+71) | UCU UUU ACU CCC UUG GAG UCU UCU AGG AGC C | No Skipping |
| 351 | H55A(+73+93) | UCU GUA AGC CAG GCA AGA AAC | No Skipping |
| 352 | H55A(+107+137) | CCU UAC GGG UAG CAU CCU GAU GGA CAU UGG C | No Skipping |
| 353 | H55A(+112 +136) | CUU ACG GGU AGC AUC CUG UAG GAC A | very weak skipping at 100 nM |
| 354 | H55A(+132 +161) | CCU UGG AGU CUU CUA GGA GCC UUU CCU UAC | Skipping at 200nM |
| 355 | H55A(+141 +160) | CUU GGA GUC UUC UAG GAG CC | Skipping at 100nM |
| 356 | H55A(+143 +171) | CUC UUU UAC UCC CUU GGA GUC UUC UAG GAG | No skipping |
| 357 | H55D(+11 -09) | CCU GAC UUA CUU GCC AUU GU | No skipping |

Antisense Oligonucleotides Directed at Exon 56

Antisense oligonucleotides directed at exon 56 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 23.

Table 46: Antisense molecule sequences tested to determine if they induce exon 56 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 56** | | |
| 358 | H56A(-06+23) | GCU UCA AUU UCA CCU UGG AGG UCC UAC AG | Skipping at 25nM |
| 359 | H56A(-06+15) | UUC ACC UUG GAG GUC CUA CAG | No Skipping |
| 360 | H56A(+23 +44) | GUU GUG AUA AAC AUC UGU GUG A | No skipping |
| 361 | H56A(+56 +81) | CCA GGG AUC UCA GGA UUU UUU GGC UG | No skipping |
| 362 | H56A(+67+91) | CGG AAC CUU CCA GGG AUC UCA GGA U | Skipping at 200nM |
| 18 | H56A(+92+121) | CCA AAC GUC UUU GUA ACA GGA CUG CAU | skipping at 25 nM |
| 363 | H56A(+102+126) | GUU AUC CAA ACG UCU UUG UAA CAG G | skipping at 100 nM |
| 364 | H56A(+102+131) | UUC AUG UUA UCC AAA CGU CUU UGU AAC AGG | skipping at 25 nM |
| 19 | H56A(+112+141) | CCA CUU GAA GUU CAU GUU AUC CAA ACG UCU | skipping at 25 nM |
| 365 | H56A(+117+146) | UCA CUC CAC UUG AAG UUC AUG UUA UCC AAA | skipping weakly at 25 nM |
| 366 | H56A(+121+143) | CUC CAC UUG AAG UUC AUG UUA UC | No Skipping |
| 367 | H56D(+11-10) | CUU UUC CUA CCA AAU GUU GAG | Skipping at 600nM |

Antisense Oligonucleotides Directed at Exon 57

Antisense oligonucleotides directed at exon 57 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 24.

Table 47: Antisense molecule sequences tested to determine if they induce exon 57 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 57** | | |
| 368 | H57A(-15+18) | CUG GCU UCC AAA UGG GAC CUG AAA AAG AAC AGC | No Skipping |
| 369 | H57A (-12 +18) | CUG GCU UCC AAA UGG GAC CUG AAA AAG AAC | Skipping at 50nM |
| 20 | H57A(-10+20) | AAC UGG CUU CCA AAU GGG ACC UGA AAA AGA | Skipping at 300nM |
| 370 | H57A(-06 +24) | UCA GAA CUG GCU UCC AAA UGG GAC CUG AAA | Skipping at 300nM |
| 371 | H57A(+21+44) | GGU GCA GAC GCU UCC ACU GGU CAG | No Skipping |
| 372 | H57A(+47 +77) | GCU GUA GCC ACA CCA GAA GUU CCU GCA GAG A | No Skipping |
| 373 | H57A(+79+103) | CUG CCG GCU UAA UUC AUC AUC UUU C | No Skipping |
| 374 | H57A(+105+131) | CUG CUG GAA AGU CGC CUC CAA UAG GUG | No Skipping |

Antisense Oligonucleotides Directed at Exon 59

Antisense oligonucleotides directed at exon 59 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 25.

Table 48: Antisense molecule sequences tested to determine if they induce exon 59 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 59** | | |
| 375 | H59A (-06 +16) | UCC UCA GGA GGC AGC UCU AAA U | No skipping |
| 376 | H59A(+31 +61) | UCC UC GCC UGC UUU CGU AGA AGC CGA GUG A | No skipping |
| 377 | H59A(+66+91) | AGG UUC AAU UUU UCC CAC UCA GUA UU | No Skipping |
| 23 | H59A(+96 +120) | CUA UUU UUC UCU GCC AGU CAG CGG A | Skipping at 100nM |
| 378 | H59A(+96+125) | CUC AUC UAU UUU UCU CUG CCA GUC AGC GGA | No skipping |
| 379 | H59A(+101 +132) | CA GGG UCU CAU CUA UUU UUC UCU GCC AGU CA | No skipping |
| 380 | H59A(+141 +165) | CAU CCG UGG CCU CUU GAA GUU CCU G | Skipping exon 58& 59 at 200nM |
| 381 | H59A(+151 +175) | AGG UCC AGC UCA UCC GUG GCC UCU U | Skipping at 300nM |
| 382 | H59A(+161 +185) | GCG CAG CUU GAG GUC CAG CUC AUC C | weak skipping at 200 nM |
| 383 | H59A(+161+190) | GCU UGG CGC AGC UUG AGG UCC AGC UCA UCC | Skipping at 100nM |
| 384 | H59A(+171+197) | CAC CUC AGC UUG GCG CAG CUU GAG GUC | No skipping |
| 385 | H59A(+181+205) | CCC UUG AUC ACC UCA GCU UGG CGC A | No Skipping |
| 386 | H59A(+200+220) | ACG GGC UGC CAG GAU CCC UUG | No Skipping |
| 387 | H59A(+221+245) | GAG AGA GUC AAU GAG GAG AUC GCC C | No Skipping |
| 388 | H59A(+92+125) | CUC AUC UAU UUU UCU CUG CCA GUC AGC GGA GUG C | |

Antisense Oligonucleotides Directed at Exon 60

Antisense oligonucleotides directed at exon 60 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 26.

Table 49: Antisense molecule sequences tested to determine if they induce exon 60 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 60** | | |
| 389 | H60A(-10+20) | GCA AUU UCU CCU CGA AGU GCC UGU GUG CAA | no skipping |
| 390 | H60A(-8+19) | CAA UUU CUC CUC GAA GUG CCU GUG UGC | no skipping |
| 391 | H60A(+29+58) | CAA GGU CAU UGA CGU GGC UCA CGU UCU CUU | skipping to 50 nM |
| 24 | H60A(+33+62) | CGA GCA AGG UCA UUG ACG UGG CUC ACG UUC | strong skipping to 50 nM |
| 47 | H60A(+37+66) | CUG GCG AGC AAG GUC CUU GAC GUG GCU CAC | good skipping at 100nM |
| 392 | H60A(+37+66) | CUG GCG AGC AAG GUC AUU GAC GUG GCU CAC | SNP |
| 393 | H60A(+39+66) | CUG GCG AGC AAG GUC CUU GAC GUG GCU C | good skipping at 100nM |
| 394 | H60A(+43+73) | UGG UAA GCU GGC GAG CAA GGU CCU UGA CGU G | weak skipping at 100nM |

| | | | |
|---|---|---|---|
| 395 | H60A(+51+75) | AGU GGU AAG CUG GCG UGC AAG GUC A | weak skipping at 100nM |
| 396 | H60A(+72+102) | UUA UAC GGU GAG AGC UGA AUG CCC AAA GUG | no skipping |
| 397 | H60A(+75+105) | GAG GUU AUA CGG UGA GAG CUG AAU GCC CAA A | no skipping |
| 398 | H60A(+80+109) | UGC UGA GGU UAU ACG GUG AGA GCU GAA | good skipping at 100nM |
| 46 | H60A(+87+116) | UCC AGA GUG CUG AGG UUA UAC GGU GAG AGC | weak skipping at 100nM |
| 399 | H60D(+25-5) | CUU UCC UGC AGA AGC UUC CAU CUG GUG UUC | weak skipping at 600nM |
| | | | |
| | **Exon 60 cocktails** | | |
| 390<br>392 | H60A(-8+19)<br>H60A(+37+66) | CAA UUU CUC CUC GAA GUG CCU GUG UGC<br>CUG GCG AGC AAG GUC CUU GAC GUG GCU CAC | weak skipping at 10nM |
| 46 &<br>47 | H60A(+87+116)<br>H60A(+37+66) | UCC AGA GUG CUG AGG UUA UAC GGU GAG AGC<br>CUG GCG AGC AAG GUC CUU GAC GUG GCU CAC | skipping at 10nM |
| 389<br>394 | H60A(-10+20)<br>H60A(+43+73) | GCA AUU UCU CCU CGA AGU GCC UGU GUG CAA<br>UGG UAA GCU GGC GAG CAA GGU CCU UGA CGU G | skipping at 10nM |
| 393<br>389 | H60A(+39+66)<br>H60A(-10+20) | CUG GCG AGC AAG GUC CUU GAC GUG GCU C<br>GCA AUU UCU CCU CGA AGU GCC UGU GUG CAA | skipping at 10nM |

Antisense Oligonucleotides Directed at Exon 61

Antisense oligonucleotides directed at exon 61 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 50: Antisense molecule sequences tested to determine if they induce exon 61 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 61** | | |
| 400 | H61A(-7+19) | CUC GGU CCU CGA CGG CCA CCU GGG AG | no skipping |
| 401 | H61A(+05+34) | CAU GCA GCU GCC UGA CUC GGU CCU CGC CGG | skipping to 50 nM |
| 25 | H61A(+10+40) | GGG CUU CAU GCA GCU GCC UGA CUC GGU CCU C | Skipping at 100nM |
| 402 | H61A(+16+40) | GGG CUU CAU GCA GCU GCC UGA CUC G | no skipping |
| 403 | H61A(+16+45) | CCU GUG GGC UUC AUG CAG CUG CCU GAC UCG | skipping to 50 nM |
| 404 | H61A(+42+67) | GCU GAG AUG CUG GAC CAA AGU CCC UG | no skipping |
| 405 | H61D(+10-16) | GCU GAA AAU GAC UUA CUG GAA AGA AA | no skipping |

Antisense Oligonucleotides Directed at Exon 62

Antisense oligonucleotides directed at exon 62 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 51: Antisense molecule sequences tested to determine if they induce exon 62 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 62** | | |

| | | | |
|---|---|---|---|
| 406 | H62A(-15+15) | GAC CCU GGA CAG ACG CUG AAA AGA AGG GAG | No skipping |
| 407 | H62A(-10+20) | CCA GGG ACC CUG GAC AGA CGC UGA AAA GAA | No skipping |
| 408 | H62A(-05+15) | GAC CCU GGA CAG ACG CUG AA | Faint to 25nM |
| 409 | H62A(-3+25) | CUC UCC CAG GGA CCC UGG ACA GAC GCU G | No skipping |
| 410 | H62A(+01+30) | UGG CUC UCU CCC AGG GAC CCU GGA CAG ACG | almost 100% skipping to 300 nM |
| 411 | H62A(+8+34) | GAG AUG GCU CUC UCC CAG GGA CCC UGG | Skipping at 300nM |
| 412 | H62A(+13+43) | UUG UUU GGU GAG AUG GCU CUC UCC CAG GGA C | Faint to 25nM |
| 26 | H62A(23+52) | UAG GGC ACU UUG UUU GGC GAG AUG GCU CUC | Skipping at 100nM |
| 413 | H62D(+17-03) | UAC UUG AUA UAG UAG GGC AC | Faint to 100nM |
| 414 | H62D(+25-5) | CUU ACU UGA UAU AGU AGG GCA CUU UGU UUG | No skipping |

Antisense Oligonucleotides Directed at Exon 63

Antisense oligonucleotides directed at exon 63 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 27.

Table 52: Antisense molecule sequences tested to determine if they induce exon 63 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 63** | | |
| 415 | H63A(-14+11) | GAG UCU CGU GGC UAA AAC ACA AAA C | No visible skipping |
| 416 | H63A(+11+35) | UGG GAU GGU CCC AGC AAG UUG UUU G | Possible skipping at 600nM |
| 27 | H63A(+20+49) | GAG CUC UGU CAU UUU GGG AUG GUC CCA GCA | Skipping to 100 nM |
| 417 | H63A(+33+57) | GAC UGG UAG AGC UCU GUC AUU UUG G | No visible skipping |
| 418 | H63A(+40+62) | CUA AAG ACU GGU AGA GCU CUG UC | No Skipping |
| 419 | H63D(+8-17) | CAU GGC CAU GUC CUU ACC UAA AGA C | No visible skipping |

Antisense Oligonucleotides Directed at Exon 64

Antisense oligonucleotides directed at exon 64 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 28.

Table 53: Antisense molecule sequences tested to determine if they induce exon 64 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 64** | | |
| 420 | H64A(-3+27) | CUG AGA AUC UGA CAU UAU UCA GGU CAG CUG | No skipping |
| 28 | H64A(+34+62) | CUG CAG UCU UCG GAG UUU CAU GGC AGU CC | Skipping at 50 nM |
| 421 | H64A(+43+72) | AAA GGG CCU UCU GCA GUC UUC GGA GUU UCA | Skipping at 50 nM |
| 422 | H64A(+47+74) | GCA AAG GGC CUU CUG CAG UCU UCG GAG | Skipping at 200nM |
| 423 | H64D(+15-10) | CAA UAC UUA CAG CAA AGG GCC UUC U | No skipping |

Antisense Oligonucleotides Directed at Exon 65

Antisense oligonucleotides directed at exon 65 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 54: Antisense molecule sequences tested to determine if they induce exon 65 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 65** | | |
| 424 | H65A(+123+148) | UUG ACC AAA UUG UUG UGC UCU UGC UC | No skipping |

Antisense Oligonucleotides Directed at Exon 66

Antisense oligonucleotides directed at exon 66 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 29.

Table 55: Antisense molecule sequences tested to determine if they induce exon 66 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 66** | | |
| 29 | H66A(-8+19) | GAU CCU CCC UGU UCG UCC CCU AUU AUG | Skipping at 100nM |
| 48 | H66A(-02+28) | CAG GAC ACG GAU CCU CCC UGU UCG UCC CCU | No skipping |
| 49 | H66D(+13-17) | UAA UAU ACA CGA CUU ACA UCU GUA CUU GUC | No skipping |
| | | | |
| | **Exon 66 cocktails** | | |
| 48 & 49 | H66A(-02+28)<br>H66D(+13-17) | CAG GAC ACG GAU CCU CCC UGU UCG UCC CCU<br>UAA UAU ACA CGA CUU ACA UCU GUA CUU GUC | skipping at 25nM |

Antisense Oligonucleotides Directed at Exon 67

Antisense oligonucleotides directed at exon 67 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 30.

Table 56: Antisense molecule sequences tested to determine if they induce exon 67 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 67** | | |
| 30 | H67A(+17+47) | GCG CUG GUC ACA AAA UCC UGU UGA ACU UGC | strong skipping at 25 nM |
| 425 | H67A(+120+147) | AGC UCC GGA CAC UUG GCU CAA UGU UAC U | No skipping |
| 426 | H67A(+125+149) | GCA GCU CCG GAC ACU UGG CUC AAU G | Skipping at 600nM |
| 427 | H67D(+22-08) | UAA CUU ACA AAU UGG AAG CAG CUC CGG ACA | No skipping |

Antisense Oligonucleotides Directed at Exon 68

Antisense oligonucleotides directed at exon 68 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 31.

Table 57: Antisense molecule sequences tested to determine if they induce exon 68 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 68** | | |
| 428 | H68A(-4+21) | GAU CUC UGG CUU AUU AUU AGC CUG C | Skipping at 100nM |
| 429 | H68A(+22+48) | CAU CCA GUC UAG GAA GAG GGC CGC UUC | Skipping at 200nM |
| 50 | H68A(+48+72) | CAC CAU GGA CUG GGG UUC CAG UCU C | Skipping at 200nM |
| 430 | H68A(+74+103) | CAG CAG CCA CUC UGU GCA GGA CGG GCA GCC | No skipping |
| 51 | H68D(+23-03) | UAC CUG AAU CCA AUG AUU GGA CAC UC | No skipping |
| | | | |
| | **Exon 68 cocktails** | | |
| 50 & 51 | H68A(+48+72)<br>H68D(+23-03) | CAC CAU GGA CUG GGG UUC CAG UCU C<br>UAC CUG AAU CCA AUG AUU GGA CAC UC | skipping at 10 nM |

Antisense Oligonucleotides Directed at Exon 69

Antisense oligonucleotides directed at exon 69 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. See Figure 32 which shows a cocktail of H69A(+32+60) and H70A(-06+18) to remove both exons 69 and 70.

Table 58: Antisense molecule sequences tested to determine if they induce exon 69 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 69** | | |
| 431 | H69A(-12+19) | GUG CUU UAG ACU CCU GUA CCU GAU AAA GAG C | No skipping |
| 432 | H69A(+09 +39) | UGG CAG AUG UCA UAA UUA AAG UGC UUU AGAC | Skipping 68-71 at 200nM |
| 433 | H69A(+29 +57) | CCA GAA AAA AAG CAG CUU UGG CAG AUG UC | Skipping 68-71 at 200nM also 68+69 & 69+70 |
| 434 | H69A(+51+74) | GGC CUU UUG CAA CUC GAC CAG AAA | Skipping 68-71 |

| | | | |
|---|---|---|---|
| 435 | H69A(+51 +80) | UUU UAU GGC CUU UUG CAA CUC GAC CAG AAA | ~90% Skipping of 68-71 at 200nM |
| 436 | H69D(+08-16) | CUG GCG UCA AAC UUA CCG GAG UGC | no skipping |

Antisense Oligonucleotides Directed at Exon 70

Antisense oligonucleotides directed at exon 70 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 59: Antisense molecule sequences tested to determine if they induce exon 70 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 70** | | |
| 437 | H70A(-09+15) | UUC UCC UGA UGU AGU CUA AAA GGG | no skipping |
| 438 | H70A(-07 +23) | CGA ACA UCU UCU CCU GAU GUA GUC UAA AAG | No skipping |
| 439 | H70A(+16 +40) | GUA CCU UGG CAA AGU CUC GAA CAU C | No skipping |
| 440 | H70A(+25 +48) | GUU UUU UAG UAC CUU GGC AAA GUC | No Skipping |
| 441 | H70A(+32+60) | GGU UCG AAA UUU GUU UUU UAG UAC CUU GG | No skipping |
| 442 | H70A(+64 +93) | GCC CAU UCG GGG AUG CUU CGC AAA AUA CCU | No skipping |

Antisense Oligonucleotides Directed at Exon 71

Antisense oligonucleotides directed at exon 71 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 60: Antisense molecule sequences tested to determine if they induce exon 71 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 71** | | |
| 443 | H71A(-08+16) | GAU CAG AGU AAC GGG ACU GCA AAA | |
| 444 | H71A(+07+30) | ACU GGC CAG AAG UUG AUC AGA GUA | weak skipping at 100nM |
| 445 | H71A(+16+39) | GCA GAA UCU ACU GGC CAG AAG UUG | skipping at 100nM |
| 446 | H71D(+19-05) | CUC ACG CAG AAU CUA CUG GCC AGA | |

Antisense Oligonucleotides Directed at Exon 72

Antisense oligonucleotides directed at exon 72 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 61: Antisense molecule sequences tested to determine if they induce exon 72 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 72** | | |
| 447 | H72A(-8+22) | AAG CUG AGG GGA CGA GGC AGG CCU AUA AGG | faint skipping at 600 nM |
| 448 | H72A(+02+28) | GUG UGA AAG CUG AGG GGA CGA GGC AGG | no skipping |
| 449 | H72D(+14-10) | AGU CUC AUA CCU GCU AGC AUA AUG | no skipping |

Antisense Oligonucleotides Directed at Exon 73

Antisense oligonucleotides directed at exon 73 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 62: Antisense molecule sequences tested to determine if they induce exon 73 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 73** | | |
| 450 | H73A(+24+49) | AUG CUA UCA UUU AGA UAA GAU CCA U | weak skipping |
| 451 | H73A(-16+10) | UUC UGC UAG CCU GAU AAA AAA CGU AA | Faint to 25 nM |
| 60 | H73A(+02+26) | CAU UGC UGU UUU CCA UUU CUG GUA G | Strong to 25 nM |
| 452 | H73D(+23-02) | ACA UGC UCU CAU UAG GAG AGA UGC U | Skipping to 25 nM |
| 453 | HM73A(+19+44) | UAU CAU UUA GAU AAG AUC CAU UGC UG | Faint skipping to 25 nM |

Antisense Oligonucleotides Directed at Exon 74

Antisense oligonucleotides directed at exon 74 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 66: Antisense molecule sequences tested to determine if they induce exon 74 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| 454 | HM74A(+20+46) | GUU CAA ACU UUG GCA GUA AUG CUG GAU | skipping 25 nM |
| 455 | HM74A(+50+77) | GAC UAC GAG GCU GGC UCA GGG GGG AGU C | 100 % skipping at 25 nM |
| 456 | HM74A(+96+122) | GCU CCC CUC UUU CCU CAC UCU CUA AGG | skipping 25 nM |

Antisense Oligonucleotides Directed at Exon 76

Antisense oligonucleotides directed at exon 76 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 63: Antisense molecule sequences tested to determine if they induce exon 76 skipping

| SEQ ID | Antisense Oligonucleotide name | Sequence | Ability to induce skipping |
|---|---|---|---|
| | **Exon 76** | | |
| 457 | H76A(-02+25) | CAU UCA CUU UGG CCU CUG CCU GGG GCU | no detectable skipping |
| 458 | H76A(+80+106) | GAC UGC CAA CCA CUC GGA GCA GCA UAG | no detectable skipping |

Modifications of the above-described modes of carrying out the various embodiments of this invention will be apparent to those skilled in the art based on the above teachings related to the disclosed invention. The above embodiments of the invention are merely exemplary and should not be construed to be in any way limiting.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication

(or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2010317599 06 Jan 2016

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An antisense oligonucleotide selected from the group consisting of:

(i) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(ii) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(iii) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(iv) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(v) an antisense oligonucleotide of 22 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(vi) an antisense oligonucleotide of 28 bases in length 100%

complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(vii) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+16), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(viii) an antisense oligonucleotide of 32 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-14+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(ix) an antisense oligonucleotide of 27 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-08+19), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(x) an antisense oligonucleotide of 32 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-07+25), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xi) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-12+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the

antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xii) an antisense oligonucleotide of 31 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xiii) an antisense oligonucleotide of 39 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-09+30), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xiv) an antisense oligonucleotide of 28 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xv) an antisense oligonucleotide of 34 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-06+28), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

(xvi) an antisense oligonucleotide of 25 bases in length 100% complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+22), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping; and

(xvii) an antisense oligonucleotide of 31 bases in length 100%

complementary to a target region of exon 45 of the human dystrophin pre-mRNA, wherein the target region is annealing site H45A (-03+28), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide specifically hybridizes to the annealing site inducing exon 45 skipping;

or a pharmaceutically acceptable salt thereof.

2. An antisense oligonucleotide selected from the group consisting of:

(i) an antisense oligonucleotide of 34 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 11), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(ii) an antisense oligonucleotide of 28 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 55), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(iii) an antisense oligonucleotide of 31 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 61), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(iv) an antisense oligonucleotide of 31 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 62), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base,

(v) an antisense oligonucleotide of 22 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 63), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(vi) an antisense oligonucleotide of 28 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 64),

wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(vii) an antisense oligonucleotide of 28 bases comprising the base sequence UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 66), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(viii) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 227), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(ix) an antisense oligonucleotide of 27 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA (SEQ ID NO: 230), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(x) an antisense oligonucleotide of 34 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 237), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xi) an antisense oligonucleotide of 31 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 239), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xii) an antisense oligonucleotide of 39 bases comprising the base sequence UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU (SEQ ID NO: 240), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xiii) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 241), wherein the antisense oligonucleotide is a morpholino antisense

oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xiv) an antisense oligonucleotide of 28 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 242), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xv) an antisense oligonucleotide of 34 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 243), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

(xvi) an antisense oligonucleotide of 25 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 244), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base; and

(xvii) an antisense oligonucleotide of 31 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 245), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base;

or a pharmaceutically acceptable salt thereof.

3. The antisense oligonucleotide of claim 2, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

4. The antisense oligonucleotide of claim 2 wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

5. An antisense oligonucleotide of 34 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 11), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide

and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

6. The antisense oligonucleotide of claim 5, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

7. The antisense oligonucleotide of claim 5, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

8. An antisense oligonucleotide of 28 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 55), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

9. The antisense oligonucleotide of claim 8, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

10. The antisense oligonucleotide of claim 8, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

11. An antisense oligonucleotide of 31 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 61), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

12. The antisense oligonucleotide of claim 11, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that

enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

13. The antisense oligonucleotide of claim 11, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

14. An antisense oligonucleotide of 31 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 62), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

15. The antisense oligonucleotide of claim 14, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

16. The antisense oligonucleotide of claim 14, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

17. An antisense oligonucleotide of 22 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 63), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

18. The antisense oligonucleotide of claim 17, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

19. The antisense oligonucleotide of claim 17, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

20. An antisense oligonucleotide of 28 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 64), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

21. The antisense oligonucleotide of claim 20, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

22. The antisense oligonucleotide of claim 20, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

23. An antisense oligonucleotide of 28 bases comprising the base sequence UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 66), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

24. The antisense oligonucleotide of claim 23, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

25. The antisense oligonucleotide of claim 23, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

26. An antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 227), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a

2010317599 06 Jan 2016

pharmaceutically acceptable salt thereof.

27. The antisense oligonucleotide of claim 26, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

28. The antisense oligonucleotide of claim 26, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

29. An antisense oligonucleotide of 27 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA (SEQ ID NO: 230), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

30. The antisense oligonucleotide of claim 29, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

31. The antisense oligonucleotide of claim 29, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

32. An antisense oligonucleotide of 34 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 237), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

33. The antisense oligonucleotide of claim 32, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense

oligonucleotide.

34. The antisense oligonucleotide of claim 32, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

35. An antisense oligonucleotide of 31 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 239), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

36. The antisense oligonucleotide of claim 35, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

37. The antisense oligonucleotide of claim 35, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

38. An antisense oligonucleotide of 39 bases comprising the base sequence UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU (SEQ ID NO: 240), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

39. The antisense oligonucleotide of claim 38, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

40. The antisense oligonucleotide of claim 38, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

41. An antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 241), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

42. The antisense oligonucleotide of claim 41, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

43. The antisense oligonucleotide of claim 41, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

44. An antisense oligonucleotide of 28 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 242), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

45. The antisense oligonucleotide of claim 44, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

46. The antisense oligonucleotide of claim 44, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

47. An antisense oligonucleotide of 34 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 243), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

2010317599 06 Jan 2016

48. The antisense oligonucleotide of claim 47, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

49. The antisense oligonucleotide of claim 47, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

50. An antisense oligonucleotide of 25 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 244), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

51. The antisense oligonucleotide of claim 50, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

52. The antisense oligonucleotide of claim 50, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

53. An antisense oligonucleotide of 31 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 245), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide and is uniformly modified to comprise a 5-substituted pyrimidine base, or a pharmaceutically acceptable salt thereof.

54. The antisense oligonucleotide of claim 53, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

55. The antisense oligonucleotide of claim 53, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

56. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 34 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 11), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

57. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 28 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 55), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

58. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 31 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 61), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

59. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 31 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU

GUA AGA UAC C (SEQ ID NO: 62), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 22 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 63), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

61. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 28 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 64), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

62. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 28 bases comprising the base sequence UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 66), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

2010317599 06 Jan 2016

63. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 227), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 27 bases comprising the base sequence CAA UGC CAU CCU GGA GUU CCU GUA AGA (SEQ ID NO: 230), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 34 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C (SEQ ID NO: 237), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 31 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U (SEQ ID NO: 239), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the

2010317599 06 Jan 2016

antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 39 bases comprising the base sequence UUG CCG CUG CCC AAU GCC AUC CUG GAG UUC CUG UAA GAU (SEQ ID NO: 240), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 32 bases comprising the base sequence GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AG (SEQ ID NO: 241), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

69. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 28 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU GUA A (SEQ ID NO: 242), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

70. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 34 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU

2010317599 06 Jan 2016

GGA GUU CCU GUA A (SEQ ID NO: 243), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

71. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 25 bases comprising the base sequence GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 244), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

72. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 31 bases comprising the base sequence GCC GCU GCC CAA UGC CAU CCU GGA GUU CCU G (SEQ ID NO: 245), wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, wherein the antisense oligonucleotide is uniformly modified to comprise a 5-substituted pyrimidine base, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

73. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is chemically linked to one or more moieties or conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

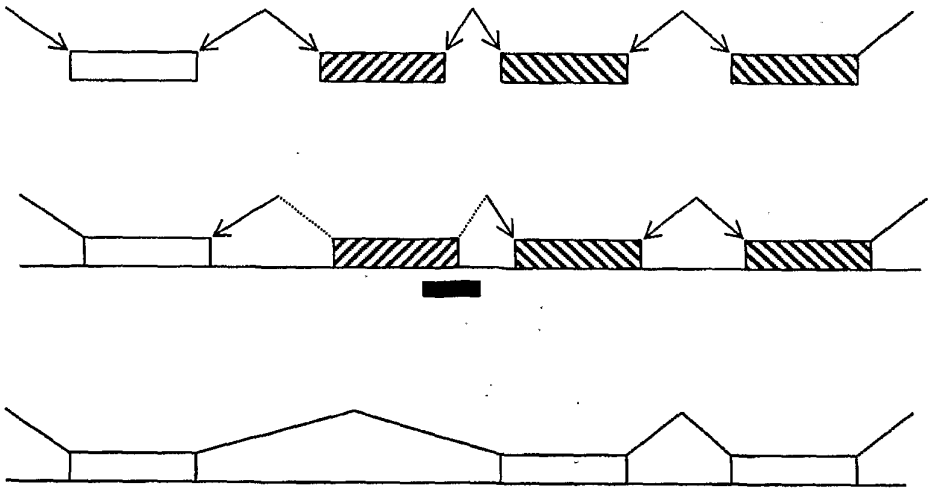
74. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

**Figure 1**

bp Acceptor ESE Donor

ucaugcacugagugaccucuuucucgcagGCGCUAGCUGGAGCA////CCGUGCAGACUGACGgucucau

## Figure 2



## Figure 3

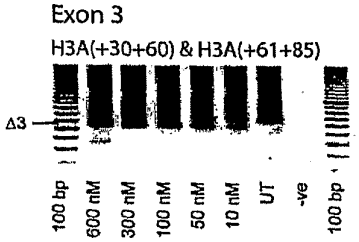


**Figure 4**

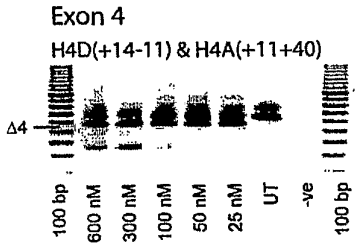



**Figure 5**

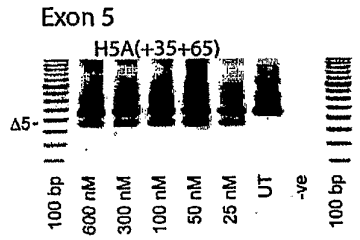
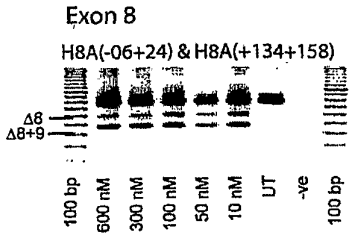
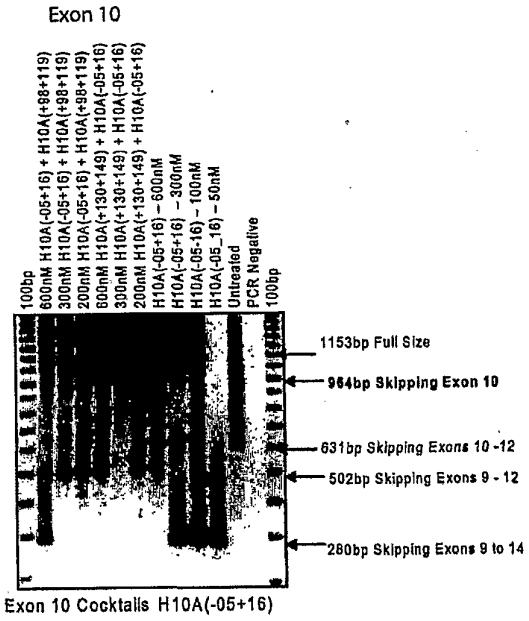



**Figure 6**



## Figure 7




## Figure 8

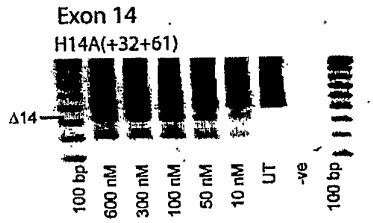


**Figure 9**

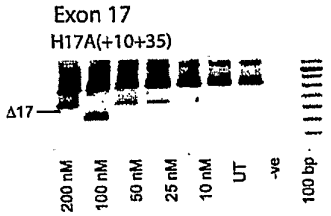



**Figure 10**

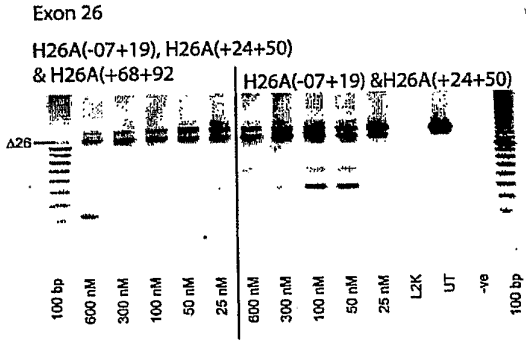



**Figure 11**

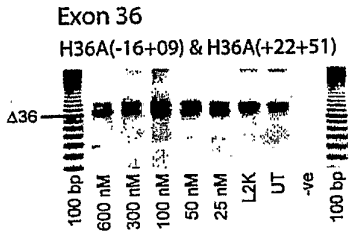


Figure 12

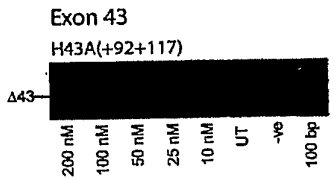



Figure 13

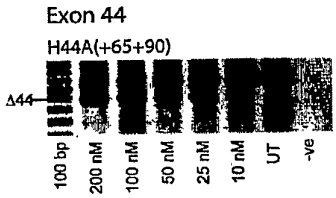



Figure 14

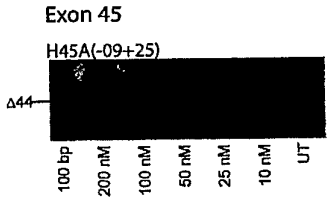


**Figure 15**

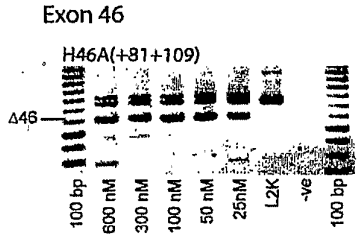



**Figure 16**

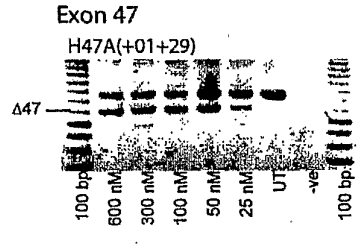



**Figure 17**

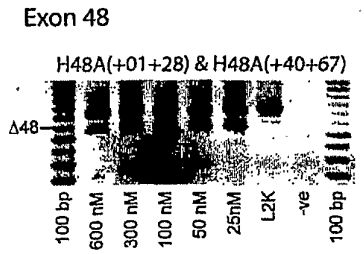


**Figure 18**


**Figure 19**

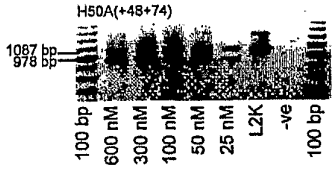



**Figure 20**

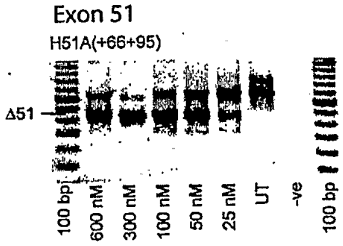


Figure 21

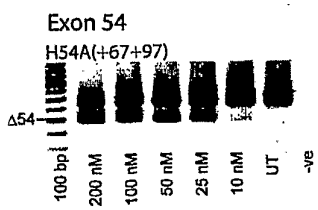



Figure 22

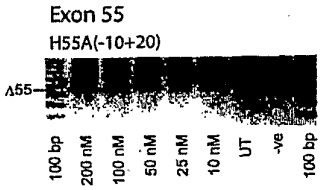



Figure 23

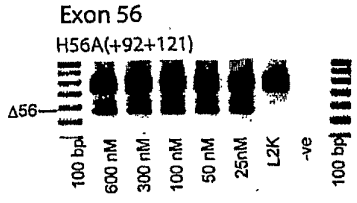


**Figure 24**

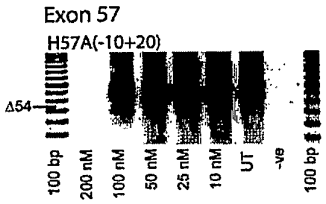



**Figure 25**

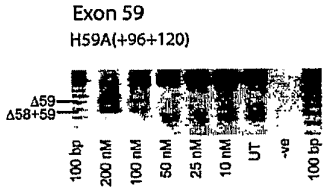



**Figure 26**

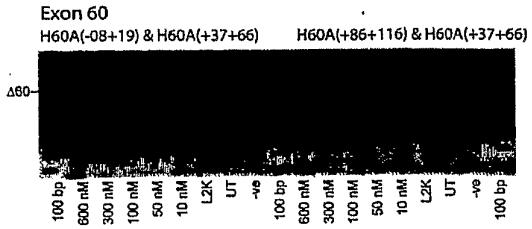


**Figure 27**

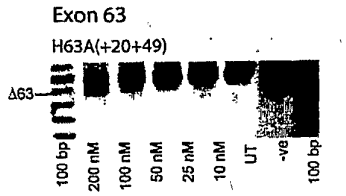



**Figure 28**

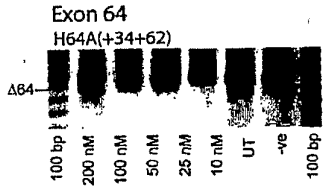



**Figure 29**

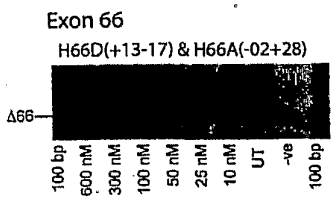


**Figure 30**

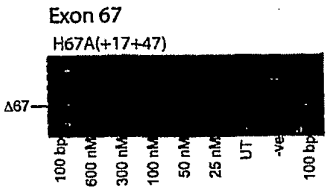



**Figure 31**

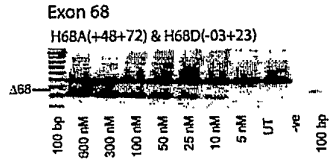
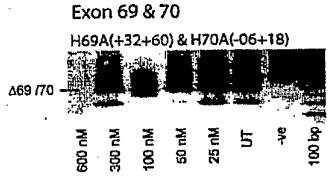
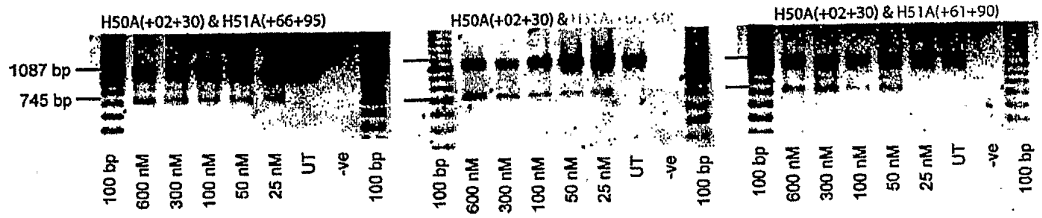



**Figure 32**



## Figure 33




## Figure 34

## Best 50/51 cocktail

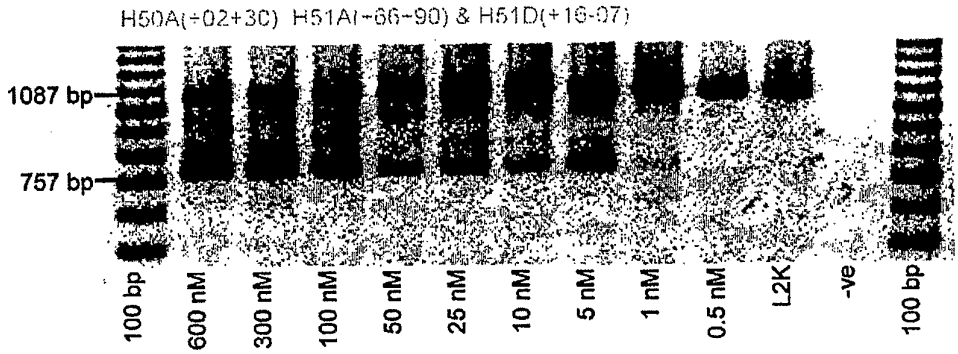


**Figure 35**

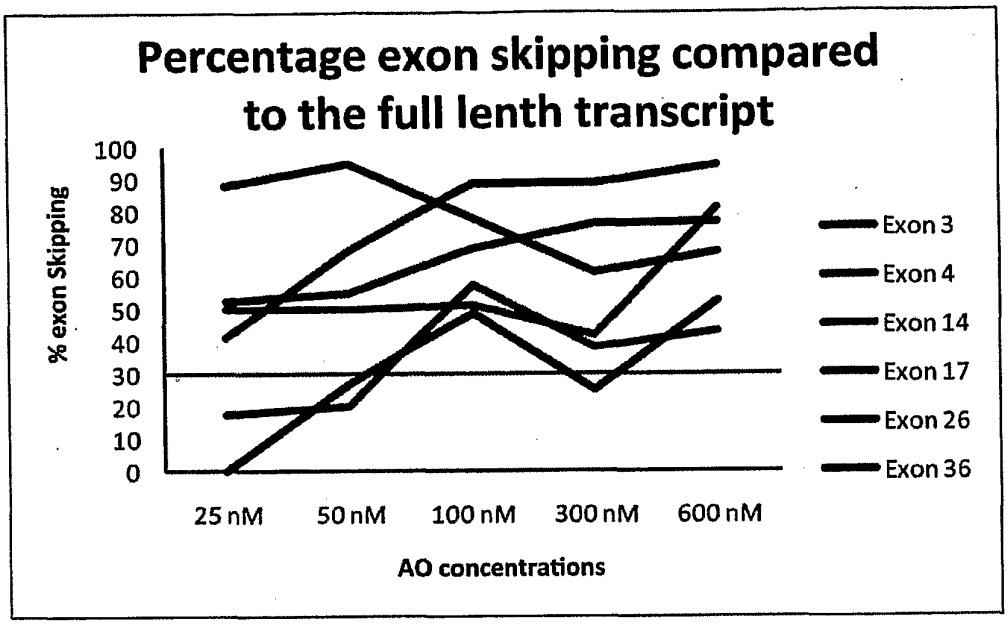
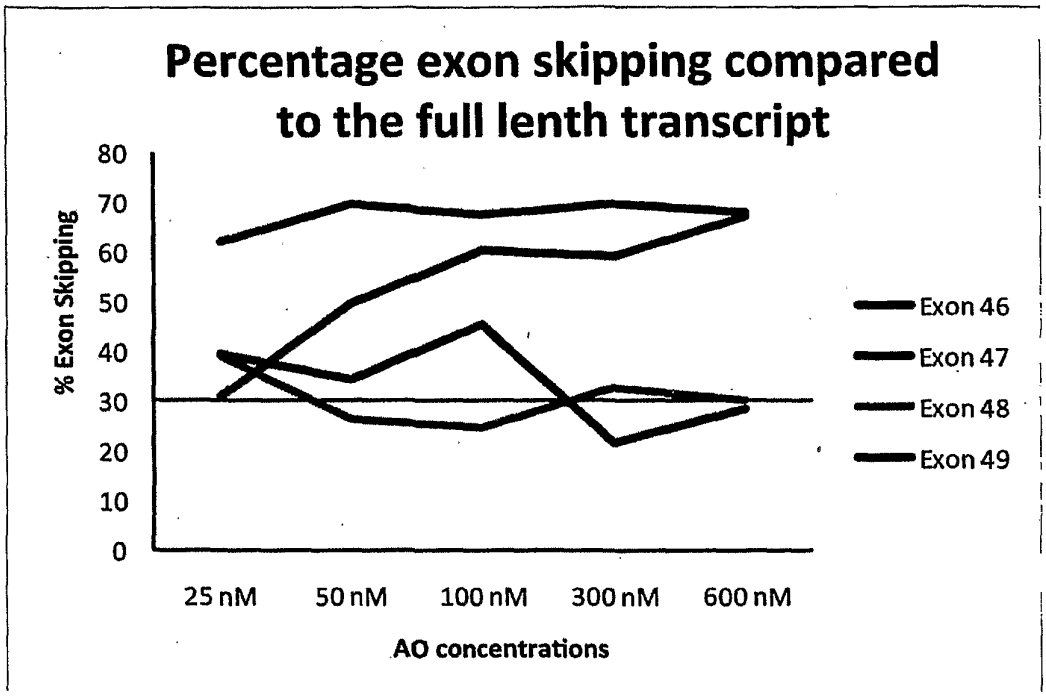

Percentage exon skipping compared to the full lenth transcript
% exon Skipping
100
90
80
70
60
50
40
30
20
10
0
25 nM
50 nM
100 nM
300 nM
600 nM
AO concentrations
Exon 3
Exon 4
Exon 14
Exon 17
Exon 26
Exon 36

**Figure 36**


Percentage exon skipping compared to the full lenth transcript
% Exon Skipping
80
70
60
50
40
30
20
10
0
25 nM
50 nM
100 nM
300 nM
600 nM
AO concentrations
Exon 46
Exon 47
Exon 48
Exon 49

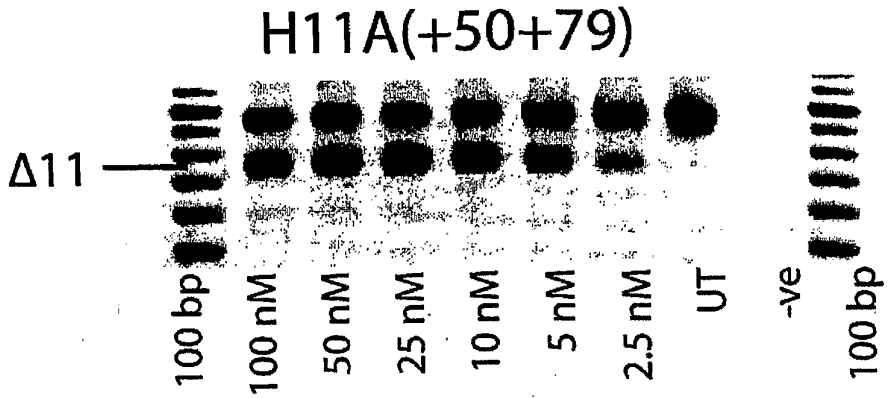



**Figure 37**

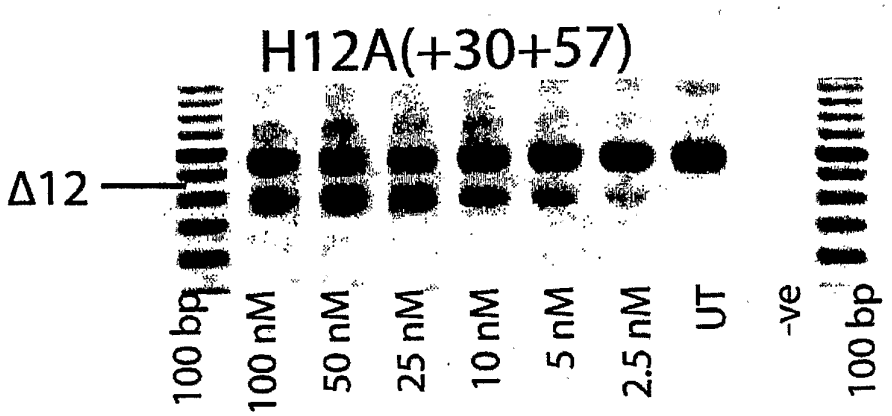



**Figure 38**

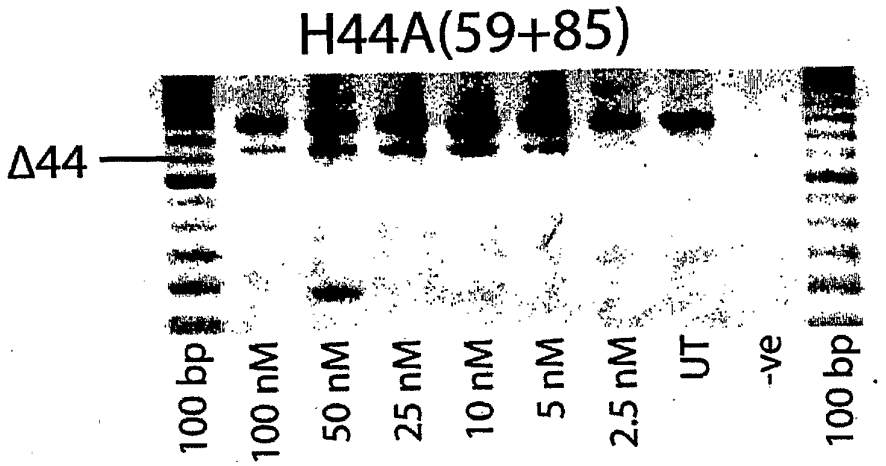



**Figure 39**

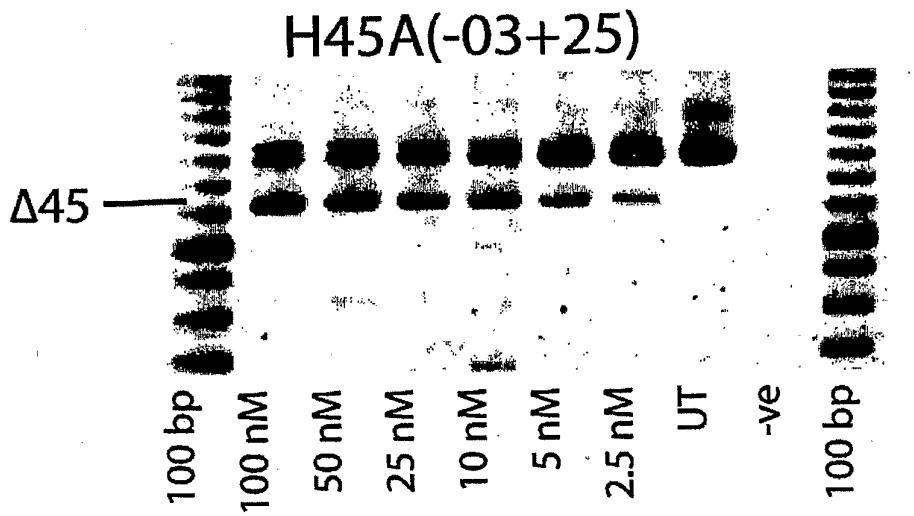



**Figure 40**

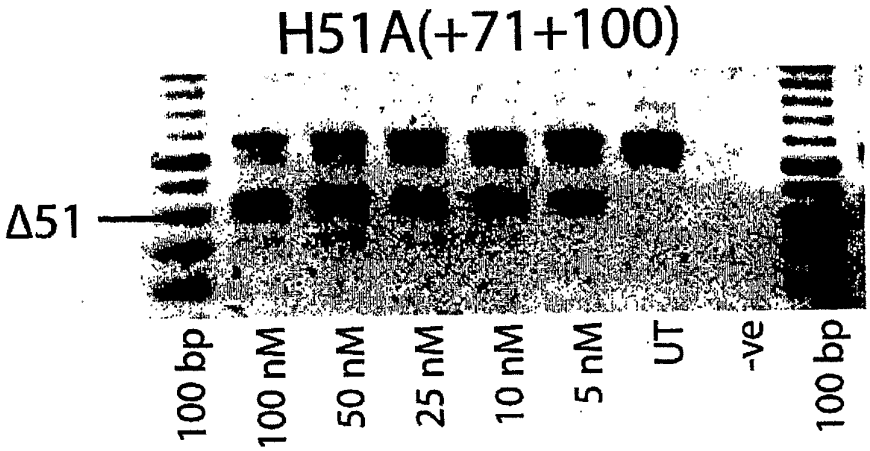



**Figure 41**

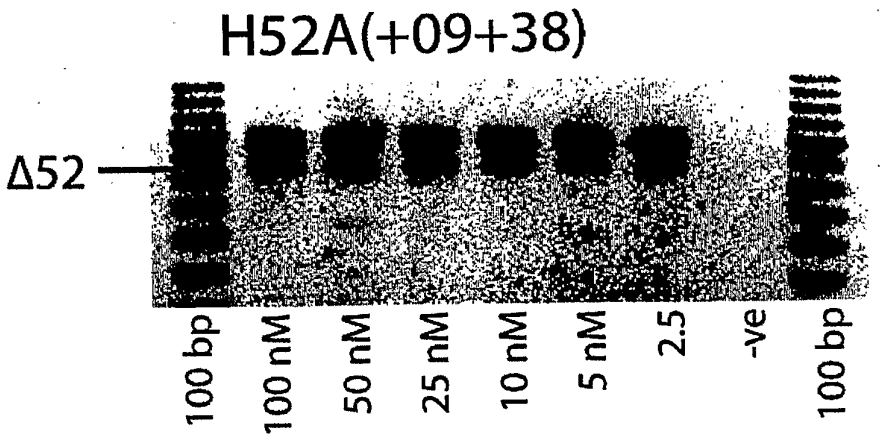



**Figure 42**

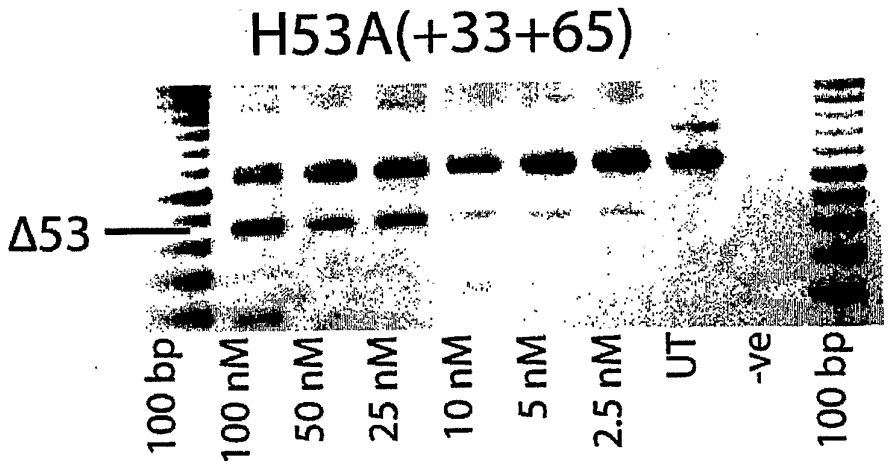



**Figure 43**

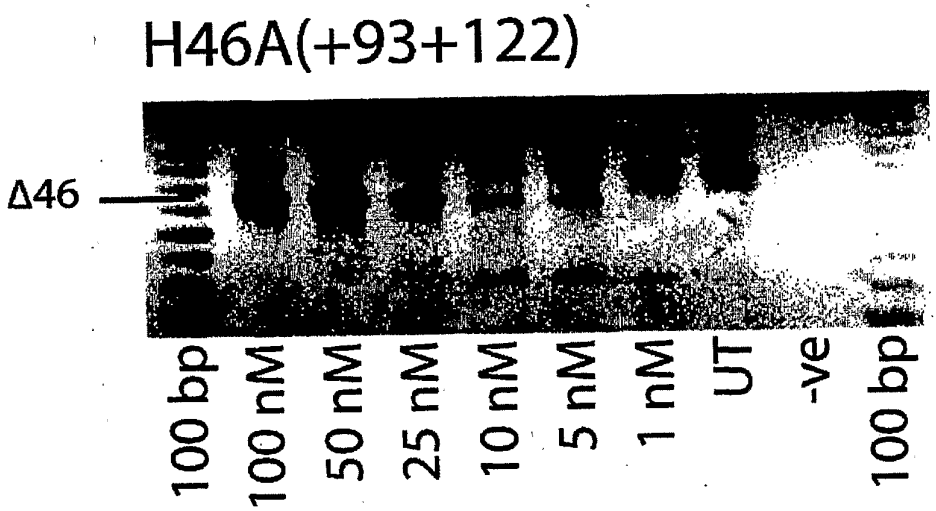



**Figure 44**

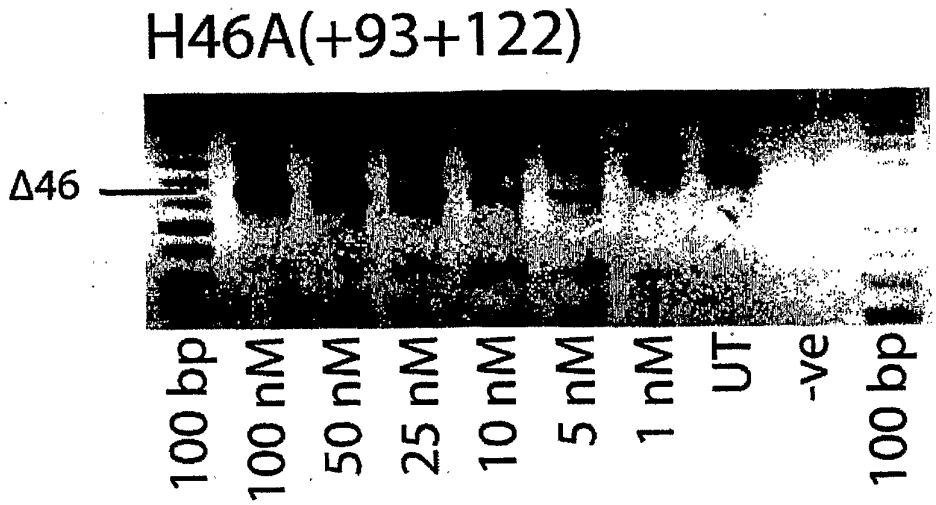



**Figure 45**

# Figure 46A

| SEQ ID | Exon | Sequence |
|---|---|---|
| 1 | H5A(+35+65) | AAA CCA AGA GUC AGU UUA UGA UUU CCA UCU A |
| 2 | H12A(+52+75) | UCU UCU GUU UUU GUU AGC CAG UCA |
| 3 | H17A(-07+23) | GUG GUG GUG ACA GCC UGU GAA AUC UGU GAG |
| 4 | H17A(+61+86) | UGU UCC CUU GUG GUC ACC GUA GUU AC |
| 5 | H21A(+86+114) | CAC AAA GUC UGC AUC CAG GAA CAU GGG UC |
| 6 | H21A(+90+119) | AAG GCC ACA AAG UCU GCA UCC AGG AAC AUG |
| 7 | H22A(+125+146) | CUG CAA UUC CCC GAG UCU CUG C |
| 8 | H24A(+51+73) | CAA GGG CAG GCC AUU CCU CCU UC |
| 9 | H43A(+92 +117) | GAG AGC UUC CUG UAG CUU CAC CCU UU |
| 10 | H44A(+65+90) | UGU UCA GCU UCU GUU AGC CAC UGA |
| 11 | H45A (-09+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA AGA U |
| 12 | H46A(+81+109) | UCC AGG UUC AAG UGG GAU ACU AGC AAU GU |
| 13 | H47A(+01+29) | UGG CGC AGG GGC AAC UCU UCC ACC AGU AA |
| 14 | H49A(+45+70) | ACA AAU GCU GCC CUU UAG ACA AAA UC |
| 15 | H50A(+48+74) | GGC UGC UUU GCC CUC AGC UCU UGA AGU |
| 16 | H54A(+67+97) | UGG UCU CAU CUG CAG AAU AAU CCC GGA GAA G |
| 17 | H55A(-10 +20) | CAG CCU CUC GCU CAC UCA CCC UGC AAA GGA |
| 18 | H56A(+92+121) | CCA AAC GUC UUU GUA ACA GGA CUG CAU |
| 19 | H56A(+112+141) | CCA CUU GAA GUU CAU GUU AUC CAA ACG UCU |
| 20 | H57A(-10+20) | AAC UGG CUU CCA AAU GGG ACC UGA AAA AGA |
| 21 | H58A(+34+64) | UUC GUA CAG UCU CAA GAG UAC UCA UGA UUA C |
| 22 | H58D(+17-07) | CAA UUA CCU CUG GGC UCC UGG UAG |
| 23 | H59A(+96 +120) | CUA UUU UUC UCU GCC AGU CAG CGG A |
| 24 | H60A(+33+62) | CGA GCA AGG UCA UUG ACG UGG CUC ACG UUC |
| 25 | H61A(+10+40) | GGG CUU CAU GCA GCU GCC UGA CUC GGU CCU C |
| 26 | H62A(23+52) | UAG GGC ACU UUG UUU GGC GAG AUG GCU CUC |
| 27 | H63A(+20+49) | GAG CUC UGU CAU UUU GGG AUG GUC CCA GCA |
| 28 | H64A(+34+62) | CUG CAG UCU UCG GAG UUU CAU GGC AGU CC |
| 29 | H66A(-8+19) | GAU CCU CCC UGU UCG UCC CCU AUU AUG |
| 30 | H67A(+17+47) | GCG CUG GUC ACA AAA UCC UGU UGA ACU UGC |
| 31 | H3A(+30+60) | UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G |
| 32 | H3A(+61+85) | G CCC UGU CAG GCC UUC GAG GAG GUC |
| 33 | H4A(+11+40) | UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU |
| 34 | H4D(+14-11) | GUA CUA CUU ACA UUA UUG UUC UGC A |
| 35 | H8A(-06+24) | UAU CUG GAU AGG UGG UAU CAA CAU CUG UAA |

## Figure 46B

| SEQ ID | Exon | Sequence |
|---|---|---|
| 36 | H8A(+134+158) | AUG UAA CUG AAA AUG UUC UUC UUU A |
| 37 | H10A(-05+16) | CAG GAG CUU CCA AAU GCU GCA |
| 38 | H10A(+98+119) | UCC UCA GCA GAA AGA AGC CAC G |
| 39 | H26A(-07+19) | CCU CCU UUC UGG CAU AGA CCU UCC AC |
| 40 | H26A(+24+50) | CUU ACA GUU UUC UCC AAA CCU CCC UUC |
| 41 | H26A(+68+92) | UGU GUC AUC CAU UCG UGC AUC UCU G |
| 42 | H36A(-16+09) | CUG GUA UUC CUU AAU UGU ACA GAG A |
| 43 | H36A(+22+51) | UGU GAU GUG GUC CAC AUU CUG GUC AAA AGU |
| 44 | H48A(+01+28) | CUU GUU UCU CAG GUA AAG CUC UGG AAA C |
| 45 | H48A(+40+67) | CAA GCU GCC CAA GGU CUU UUA UUU GAG C |
| 46 | H60A(+87+116) | UCC AGA GUG CUG AGG UUA UAC GGU GAG AGC |
| 47 | H60A(+37+66) | CUG GCG AGC AAG GUC CUU GAC GUG GCU CAC |
| 48 | H66A(-02+28) | CAG GAC ACG GAU CCU CCC UGU UCG UCC CCU |
| 49 | H66D(+13-17) | UAA UAU ACA CGA CUU ACA UCU GUA CUU GUC |
| 50 | H68A(+48+72) | CAC CAU GGA CUG GGG UUC CAG UCU C |
| 51 | H68D(+23-03) | UAC CUG AAU CCA AUG AUU GGA CAC UC |
| 52 | H11A(+50+79) | CUG UUC CAA UCA GCU UAC UUC CCA AUU GUA |
| 53 | H12A(+30+57) | CAG UCA UUC AAC UCU UUC AGU UUC UGA U |
| 54 | H44A(+59+85) | CUG UUC AGC UUC UGU UAG CCA CUG AUU |
| 55 | H45A(-03+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU G |
| 56 | H46A(+93+122) | GUU GCU GCU CUU UUC CAG GUU CAA GUG GGA |
| 57 | H51A(+71+100) | CGU ACC UCC AAC AUC AAG GAA GAU GGC AUU |
| 58 | H52A(+09+38) | UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC UGC |
| 59 | H53A(+33+65) | UUC AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU |
| 60 | H73A(+02+26) | CAU UGC UGU UUU CCA UUU CUG GUA G |
| 61 | H45A(-06+25) | GCU GCC CAA UGC CAU CCU GGA GUU CCU GUA A |
| 62 | H45A(-12+19) | CAA UGC CAU CCU GGA GUU CCU GUA AGA UAC C |

2010317599 06 Jan 2016



SEQUENCE LISTING

<110> THE UNIVERSITY OF WESTERN AUSTRALIA
WILTON, Stephen
FLETCHER, Sue
ADAMS, Abbie
MELONI, Penny

<120> ANTISENSE MOLECULES AND METHODS FOR TREATING PATHOLOGIES

<130> AVN-015USCN

<140> US
<141> Herewith

<150> US 13/509,331
<151> 2012-07-09

<150> PCT/AU2010/001520
<151> 2010-11-12

<150> AU 2009905549
<151> 2009-11-12

<160> 464

<170> PatentIn version 3.5

<210> 1
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H5A(+35+65)

<400> 1
aaaccaagag ucaguuuaug auuuccaucu a 31

<210> 2
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H12A(+52+75)

<400> 2
ucuucuguuu uuguuagcca guca 24

2010317599 06 Jan 2016



<210> 3
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H17A(-07+23)

<400> 3
gugugugguga cagccuguga aaucugugag 30

<210> 4
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H17A(+61+86)

<400> 4
uguucccuug uggucaccgu aguuac 26

<210> 5
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H21A(+86+114)

<400> 5
cacaaagucu gcauccagga acauggguc 29

<210> 6
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H21A(+90+119)

<400> 6
aaggccacaa agucugcauc caggaacaug 30

2010317599 06 Jan 2016



<210> 7
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H22A(+125+146)

<400> 7
cugcaauucc ccgagucucu gc 22

<210> 8
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H24A(+51 +73)

<400> 8
caagggcagg ccauuccucc uuc 23

<210> 9
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H43A(+92 +117)

<400> 9
gagagcuucc uguagcuuca cccuuu 26

<210> 10
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H44A(+65+90)

2010317599 06 Jan 2016



<400> 10
uguucagcuu cuguuagcca cuga 24

<210> 11
<211> 34
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(34)
<223> Exon: H45A (-09+25)

<400> 11
gcugcccaau gccauccugg aguuccugua agau 34

<210> 12
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H46A(+81+109)

<400> 12
uccagguuca agugggauac uagcaaugu 29

<210> 13
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H47A(+01+29)

<400> 13
uggcgcaggg gcaacucuuc caccaguaa 29

<210> 14
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)

2010317599 06 Jan 2016



<223> Exon: H49A(+45+ 70)

<400> 14
acaaaugcug cccuuuagac aaaauc 26

<210> 15
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50A(+48+74)

<400> 15
ggcugcuuug cccucagcuc uugaagu 27

<210> 16
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H54A(+67+97)

<400> 16
uggucucauc ugcagaauaa ucccggagaa g 31

<210> 17
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H55A(-10 +20)

<400> 17
cagccucucg cucacucacc cugcaaagga 30

<210> 18
<211> 27
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(27)
<223> Exon: H56A(+92+121)

<400> 18
ccaaacgucu uuguaacagg acugcau 27

<210> 19
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H56A(+112+141)

<400> 19
ccacuugaag uucauguuau ccaaacgucu 30

<210> 20
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H57A(-10+20)

<400> 20
aacuggcuuc caaaugggac cugaaaaaga 30

<210> 21
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H58A(+34+64)

<400> 21
uucguacagu cucaagagua cucaugauua c 31

<210> 22
<211> 24
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H58D(+17-07)

<400> 22
caauuaccuc ugggcuccug guag 24

<210> 23
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+96 +120)

<400> 23
cuauuuuucu cugccaguca gcgga 25

<210> 24
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+33+62)

<400> 24
cgagcaaggu cauugacgug gcucacguuc 30

<210> 25
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H61A(+10+40)

<400> 25
gggcuucaug cagcugccug acucgguccu c 31

<210> 26
<211> 30
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H62A(23+52)

<400> 26
uagggcacuu uguuuggcga gauggcucuc 30

<210> 27
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H63A(+20+49)

<400> 27
gagcucuguc auuuugggau ggucccagca 30

<210> 28
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H64A(+34+62)

<400> 28
cugcagucuu cggaguuuca uggcagucc 29

<210> 29
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H66A(-8+19)

<400> 29
gauccucccu guucgucccc uauuaug 27

<210> 30

<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H67A(+17+47)

<400> 30
gcgcugguca caaaauccug uugaacuugc 30

<210> 31
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H3A(+30+60)

<400> 31
uaggaggcgc cucccauccu guaggucacu g 31

<210> 32
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H3A(+61 +85)

<400> 32
gcccugucag gccuucgagg agguc 25

<210> 33
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H4A(+11+40)

<400> 33
uguucagggc augaacucuu guggauccuu 30

2010317599 06 Jan 2016



<210> 34
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H4D(+14-11 )

<400> 34
guacuacuua cauuauuguu cugca 25

<210> 35
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H8A(-06+24)

<400> 35
uaucuggaua ggugguauca acaucuguaa 30

<210> 36
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H8A{+134+158)

<400> 36
auguaacuga aaauguucuu cuuua 25

<210> 37
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H10A{-05+16)

<400> 37

caggagcuuc gaaauggugg a 21

<210> 38
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H10A(+98+119)

<400> 38
uccucagcag aaagaagcca cg 22

<210> 39
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H26A(-07+19)

<400> 39
ccuccuuucu ggcauagacc uuccac 26

<210> 40
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H26A{+24+50)

<400> 40
cuuacaguuu ucuccaaacc ucccuuc 27

<210> 41
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H26A{ +68+92)

2010317599 06 Jan 2016



<400> 41
ugugucaugc auucgugcau gucug 25

<210> 42
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H36A( -16+09)

<400> 42
cugguauucc uuaauuguac agaga 25

<210> 43
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H36A(+22+51)

<400> 43
ugugaugugg uccacauucu ggucaaaagu 30

<210> 44
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H48A(+01 +28)

<400> 44
cuuguuucuc agguaaagcu cuggaaac 28

<210> 45
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (1)..(28)
<223> Exon: H48A(+40+67)

<400> 45
caagcugccg aaggucuuuu auuugagc 28

<210> 46
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+87+116)

<400> 46
uccagagugc ugagguuaua cggugagagc 30

<210> 47
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+37+66)

<400> 47
cuggcgagca agguccuuga cguggcucac 30

<210> 48
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H66A(-02+28)

<400> 48
caggacacgg auccucccug uuggucccu 30

<210> 49
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H66D(+13-17)

<400> 49
uaauauacac gacuuacauc uguacuuguc 30

<210> 50
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H68A(+48+ 72)

<400> 50
cagcauggac ugggguucca gucuc 25

<210> 51
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H68D(+23-03)

<400> 51
uaccugaauc caaugauugg acacuc 26

<210> 52
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H11A(+50+79)

<400> 52
cuguuccaau cagcuuacuu cccaauugua 30

<210> 53
<211> 28
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H12A(+30+57)

<400> 53
cagucauuca agucuuucag uuugugau 28

<210> 54
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H44A(+59+85)

<400> 54
cuguucagcu ucuguuagcc acugauu 27

<210> 55
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H45A(-03+25)

<400> 55
gcugcccaau gccauccugg aguuccug 28

<210> 56
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H46A(+93+122)

<400> 56
guugcugcuc uuuuccaggu ucaaguggga 30

<210> 57
<211> 30

2010317599 06 Jan 2016

<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H51A(+71 +100)

<400> 57
gguaccucca acaucaagga agauggcauu 30

<210> 58
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H52A(+09+38)

<400> 58
uccaacuggg gacgccucug uuccaaaucc ugc 33

<210> 59
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H53A(+33+65)

<400> 59
uucaacuguu gccuccgguu cugaaggugu ucu 33

<210> 60
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H73A(+02+26)

<400> 60
cauugcuguu uuccauuucu gguag 25

2010317599 06 Jan 2016

<210> 61
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H45A(-06+25)

<400> 61
gcugcccaau gccauccugg aguuccugua a 31

<210> 62
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H45A(-12+19)

<400> 62
caaugccauc cuggaguucc uguaagauac c 31

<210> 63
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H45A(-3+19)

<400> 63
caaugccauc cuggaguucc ug 22

<210> 64
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H45A(-9+19)

<400> 64
caaugccauc cuggaguucc uguaagau 28

2010317599 06 Jan 2016

<210> 65
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H45A(-9+16)

<400> 65
ugccauccug gaguuccugu aagau 25

<210> 66
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H45A(-7+21)

<400> 66
ugccauccug gaguuccugu aagauacc 28

<210> 67
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H53A(+27+56)

<400> 67
ccuccgguuc ugaagguguu cuuguacuuc 30

<210> 68
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H44A(-6+20)

2010317599 06 Jan 2016



<400> 68
caacagaucu gucaaaucgc cugcag 26

<210> 69
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H51A(+71+100)

<400> 69
gguaccucca acaucaagga agauggcauu 30

<210> 70
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H8A(+57+83)

<400> 70
gcucacuugu ugaggcaaaa cuuggaa 27

<210> 71
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H8A(+42+66)

<400> 71
aaacuuggaa gagugaugug augua 25

<210> 72
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)

<223> Exon: H7A(+49+71)

<400> 72
ugaaugcaug uuccagucgu ugu 23

<210> 73
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H7A(+41+67)

<400> 73
ugcauguucc agucguugug uggcuga 27

<210> 74
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H43A(+92+120)

<400> 74
ggagagagcu uccuguagcu ucacccuuu 29

<210> 75
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H2A(-14+10)

<400> 75
ucucuuucau cuaaaaugca aaau 24

<210> 76
<211> 24
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(24)
<223> Exon: H2A(-1+23)

<400> 76
cuuuugaaca ucuucucuuu cauc 24

<210> 77
<211> 32
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(32)
<223> Exon: H2A(+7+38)

<400> 77
uuuugugaau guuuucuuuu gaacaucuuc uc 32

<210> 78
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H2A(+16+39)

<400> 78
auuuugugaa uguuuucuuu ugaa 24

<210> 79
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H2A(+30+60)

<400> 79
uagaaaauug ugcauuuacc cauuuuguga a 31

<210> 80
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H2D(+19-11)

<400> 80
accauucuua ccuuagaaaa uugugcauuu 30

<210> 81
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H2D(+03-21)

<400> 81
aaaguaacaa accauucuua ccuu 24

<210> 82
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H3A(+14+38)

<400> 82
aggucacuga agagguucuc aauau 25

<210> 83
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H3A(+20+40)

<400> 83
guaggucacu gaagagguuc u 21

<210> 84
<211> 35
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(35)
<223> Exon: H3A(+25+60)

<400> 84
aggaggcguc ucccauccug uaggucacug aagag 35

<210> 85
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H3A(+45+65)

<400> 85
aggucuagga ggcgccuccc a 21

<210> 86
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H3A(+48+73)

<400> 86
cuucgaggag gucuaggagg cgccuc 26

<210> 87
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H30D(+17-08)

<400> 87
ucacauacag uuuuugcccu gucag 25

<210> 88

2010317599 06 Jan 2016



<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H3D(+19-02)

<400> 88
uacaguuuuu gcccugucag g 21

<210> 89
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H3D(+14-10)

<400> 89
aagucacaua caguuuuugc ccug 24

<210> 90
<211> 19
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(19)
<223> Exon: H3D(+12-07)

<400> 90
ucacauacag uuuuugccc 19

<210> 91
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H4A(-08+17)

<400> 91
gauccuuuuu cuuuuggcug agaac 25

2010317599 06 Jan 2016



<210> 92
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H4A(+36+60)

<400> 92
ccgcagugcc uuguugacau uguuc 25

<210> 93
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H4D(+14-11)

<400> 93
guacuacuua cauuauuguu cugca 25

<210> 94
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H5D(+26-05)

<400> 94
cuuaccugcc aguggaggau uauauuccaa a 31

<210> 95
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H6A{-09+17)

<400> 95

2010317599 06 Jan 2016

uucauuacau uuuugaccua caugug 26

<210> 96
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H6A(+32+57)

<400> 96
cuuuucacug uugguuuguu gcaauc 26

<210> 97
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: KH9 6A(+66+94)

<400> 97
aauuacgagu ugauugucgg acccagcuc 29

<210> 98
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H6A(+69+96)

<400> 98
auaauuacga guugauuguc ggacccag 28

<210> 99
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H6A(+98+123)

2010317599 06 Jan 2016

<400> 99
ggugaaguug auuacauuaa ccugug 26

<210> 100
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H6D(+18-06)

<400> 100
ucuuaccuau gacuauggau gaga 24

<210> 101
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H6D(+07-15)

<400> 101
caguaaucuu cuuaccuaug ac 22

<210> 102
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H6D(+07-16)

<400> 102
ucaguaaucu ucuuaccuau gac 23

<210> 103
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016

<222> (1)..(24)
<223> Exon: H6D(+04-20)

<400> 103
ugucucagua aucuucuuac cuau 24

<210> 104
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H7A(-07+15)

<400> 104
ucaaauaggu cuggccuaaa ac 22

<210> 105
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H7A(-03+18)

<400> 105
ccagucaaau aggucuggcc ua 22

<210> 106
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H7A(+41+63)

<400> 106
uguuccaguc guugugguggc uga 23

<210> 107
<211> 28
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H7A(+47+74)

<400> 107
uguugaaugc auguuccagu cguugugu 28

<210> 108
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H8A(-10+20)

<400> 108
uggauaggug guaucaacau cuguaagcac 30

<210> 109
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H8A(-07+15)

<400> 109
aggugguauc aacaucugua ag 22

<210> 110
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H8A(-04+18)

<400> 110
gauagguggu aucaacaucu gu 22

<210> 111
<211> 25
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H8A(+96+120)

<400> 111
gccuuggcaa cauuuccacu uccug 25

<210> 112
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H8D(+13-12)

<400> 112
uacacacuuu accuguugag aauag 25

<210> 113
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H9A(+154+184)

<400> 113
agcagccugu guguaggcau agcucuugaa u 31

<210> 114
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H9D(+26-04)

<400> 114
agaccuguga aggaaauggg cuccguguag 30

<210> 115
<211> 25

2010317599 06 Jan 2016

<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H10A(-09+16)

<400> 115
caggagcuuc caaaugcugc acaau 25

<210> 116
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H10A(+08+27)

<400> 116
ugacuugucu ucaggagcuu 20

<210> 117
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H10A (+21 +42)

<400> 117
caaugaacug ccaaaugacu ug 22

<210> 118
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H10A(+27+51)

<400> 118
acucuccauc aaugaacugc caaau 25

2010317599 06 Jan 2016

<210> 119
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H10A(+55+79)

<400> 119
cuguuugaua acgguccagg uuuac 25

<210> 120
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H10A(+80+103)

<400> 120
gccacgauaa uacuucuucu aaag 24

<210> 121
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H10D(+16-09)

<400> 121
uuaguuuacc ucaugaguau gaaac 25

<210> 122
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H10A(+130+149)

<400> 122
uuagaaaucu cuccuugugc 20

2010317599 06 Jan 2016



<210> 123
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H11A(-07+13)

<400> 123
ccaucaugua ccccugacaa 20

<210> 124
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H11A+(+134+157)

<400> 124
cccugaggca uucccaucuu gaau 24

<210> 125
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H11A(+20+45)

<400> 125
auuaccaacc cggcccugau gggcug 26

<210> 126
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H11A(+46+75)

2010317599 06 Jan 2016



<400> 126
uccaaucagc uuacuuccca auuguagaau 30

<210> 127
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H11A(+50+75)

<400> 127
uccaaucagc uuacuuccca auugua 26

<210> 128
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H11A(+80+105)

<400> 128
aguuucuuca ucuucugaua auuuuc 26

<210> 129
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H11A(+106+135)

<400> 129
auuuaggaga uucaucugcu cuuguacuuc 30

<210> 130
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)

<223> Exon: H11A(+110+135)

<400> 130
auuuaggaga uucaucugcu cuugua 26

<210> 131
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H11A(+110+139)

<400> 131
uugaauuuag gagauucauc ugcucuugua 30

<210> 132
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H12D(+06-16)

<400> 132
cauaagauac accuaccuua ug 22

<210> 133
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H12A(+60+87)

<400> 133
uuccuuguuc uuucuucugu uuuuguua 28

<210> 134
<211> 28
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(28)
<223> Exon: H12A(+90+117)

<400> 134
agaucagguc caagaggcuc uuccucca 28

<210> 135
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H12A(+120+147)

<400> 135
uguuguugua cuuggcguuu uaggucuu 28

<210> 136
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H13A(-12+12)

<400> 136
uucuugaagc accugaaaga uaaa 24

<210> 137
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H14A(+45 +73)

<400> 137
gaaggauguc uuguaaaaga acccagcgg 29

<210> 138
<211> 26
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H16A(-07+19)

<400> 138
cuagauccgc uuuuaaaacc uguuaa 26

<210> 139
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H16A(+09+31)

<400> 139
gcuuuuucuu uucuagaucc gcu 23

<210> 140
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H16D(+18-07)

<400> 140
cacuaaccug ugcuguacuc uuuuc 25

<210> 141
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H17A(+48+78)

<400> 141
uguggucacc guaguuacug uuuccauuca a 31

<210> 142
<211> 31
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H17A(+55+85)

<400> 142
guucccuugu ggucaccgua guuacuguuu c 31

<210> 143
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H18A(-09+11)

<400> 143
caacauccuu ccuaagacug 20

<210> 144
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H18A(+24+43)

<400> 144
gcgaguaauc cagcugugaa 20

<210> 145
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H18A(+41 +70)

<400> 145
uucaggacuc ugcaacagag cuucugagcg 30

<210> 146

2010317599 06 Jan 2016

<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H18A(+83+108)

<400> 146
uugucuguga aguugccuuc cuuccg 26

<210> 147
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H18D(+04-16)

<400> 147
uuaaugcaua accuacauug 20

<210> 148
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H19A(+19+48)

<400> 148
ggcaucuugc aguuuucuga acuucucagc 30

<210> 149
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H19A(+27+54)

<400> 149
ucugcuggca ucuugcaguu uucugaac 28

2010317599 06 Jan 2016

<210> 150
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H19D(+3-17)

<400> 150
ucaacucgug uaauuaccgu 20

<210> 151
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H20A(+23+47)

<400> 151
guucaguugu ucugaggcuu guuug 25

<210> 152
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H20A(+140+164)

<400> 152
aguaguuguc aucugcucca auugu 25

<210> 153
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H23(+69+98)-SNP

<400> 153

cggcuaauuu cagagggcgc uuucuuugac 30

<210> 154
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H25A(+10+33)

<400> 154
ugggcugaau ugucugaaua ucac 24

<210> 155
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H25D(+06-14)

<400> 155
gagauugucu auaccuguug 20

<210> 156
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H25A(+10+38)

<400> 156
agacugggcu gaauugucug aauaucacu 29

<210> 157
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H25A(+95+119)-DupA

2010317599 06 Jan 2016

<400> 157
uugaguucug uucucaaguc ucgaag 26

<210> 158
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H25D(+13-14)

<400> 158
gagauugucu auaccuguug gcacaug 27

<210> 159
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H26A(-16+09)

<400> 159
ggcauagacc uuccacaaaa caaac 25

<210> 160
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H26A(-7+23)

<400> 160
aaggccuccu uucuggcaua gaccuuccac 30

<210> 161
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(30)
<223> Exon: H26A(-03+27)

<400> 161
cuucaaggcc uccuuucugg cauagaccuu 30

<210> 162
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H26A(+5+35)

<400> 162
aaccucccuu caaggccucc uuucuggcau 30

<210> 163
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H26D(+06-19)

<400> 163
uuucuuuuuu uuuuuuuacc uucau 25

<210> 164
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H26D(+21-04)

<400> 164
uuaccuucau cucuucaacu gcuuu 25

<210> 165
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H26D(+10-10)

<400> 165
uuuuuuuuac cuucaucucu 20

<210> 166
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H31D(+12-18)

<400> 166
uucugaaauu ucauauaccu gugcaacauc 30

<210> 167
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H31D(+08-22)

<400> 167
uaguuucuga aauaacauau accugugcaa 30

<210> 168
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H31D(+06-24)

<400> 168
cuuaguuucu gaaauaacau auaccugugc 30

<210> 169
<211> 24
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H31D(+02-22)

<400> 169
uaguuucuga aauaacauau accu 24

<210> 170
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H31D(+01-25)

<400> 170
ccuuaguuuc ugaaauaaca uauacc 26

<210> 171
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H32A(+49+78)

<400> 171
acuuucuugu agacgcugcu caaaauuggc 30

<210> 172
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H34A(+36+59)

<400> 172
uuucgcaucu uacgggacaa uuuc 24

<210> 173
<211> 30

2010317599 06 Jan 2016



<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+41+70)

<400> 173
cauucauuuc cuuucgcauc uuacgggaca 30

<210> 174
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+43+72)

<400> 174
gacauucauu uccuuucgca ucuuacggga 30

<210> 175
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+51+83)

<400> 175
ucugucaaga cauucauuuc cuuucgcauc 30

<210> 176
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+91+120)

<400> 176
ugaucucuuu gucaauucca uaucuguagc 30

2010317599 06 Jan 2016



<210> 177
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+92+121)

<400> 177
cugaucucuu ugucaauucc auaucugugg 30

<210> 178
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H34A(+95+120)

<400> 178
ugaucucuuu gucaauucca uaucug 26

<210> 179
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H34A(+95+124)

<400> 179
cugcugaucu cuuugucaau uccauaucug 30

<210> 180
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H35A(+14+43)

<400> 180
ucuucaggug caccuucugu uucucaaucu 30

2010317599 06 Jan 2016



<210> 181
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H35A(+24+53)

<400> 181
ucugugauac ucuucaggug caccuucugu 30

<210> 182
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H36A(-01+19)

<400> 182
ccauguguuu cugguauucc 20

<210> 183
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H36A(+10+39)

<400> 183
cacauucugg ucaaaaguuu ccauguguuu 30

<210> 184
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H36A(+27+51)

2010317599 06 Jan 2016



<400> 184
ugugaugugg uccacauucu gguca 25

<210> 185
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H36A(+27+56)

<400> 185
cacuuuguga ugugguccac auucugguca 30

<210> 186
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H36A(+32+61)

<400> 186
ugauccacuu ugugaugugg uccacauucu 30

<210> 187
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H36A(+59+78)

<400> 187
aaguguguca gccugaauga 20

<210> 188
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)

2010317599 06 Jan 2016



<223> Exon: H36A(+65+94)

<400> 188
ucucugauuc auccaaaagu gugucagccu 30

<210> 189
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H36A(+80+109)

<400> 189
gcugggguuu cuuuuucucu gauucaucca 30

<210> 190
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H36D(+15-10)

<400> 190
uauuugcuac cuuaagcacg ucuuc 25

<210> 191
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H38A(-21-01)

<400> 191
cuaaaaaaaa agauagugcu a 21

<210> 192
<211> 26
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(26)
<223> Exon: H38A(-12+14)

<400> 192
aaaggaaugg aggccuaaaa aaaaag 26

<210> 193
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H38D(+14-11)

<400> 193
aaccaauuua ccauaucuuu auuga 25

<210> 194
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H39A(-07+23)

<400> 194
acaguaccau cauugucuuc auucugauc 29

<210> 195
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H39A(-07+23)

<400> 195
acaguacccu cauugucuuc auucugauc 29

<210> 196
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H39A(+58+87)

<400> 196
cucucgcuuu cucucaucug ugauucuuug 30

<210> 197
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H39A(+60+89)

<400> 197
uccucucgcu uucucucauc ugugauucuu 30

<210> 198
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H39A(+102+126)

<400> 198
uauguuuugu cuguaacagc ugcug 25

<210> 199
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H41A(-15+5)

<400> 199
auuuccuauu gagcaaaacc 20

<210> 200
<211> 25
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H41A(+66+90)

<400> 200
cauugcggcc ccauccucag acaag 25

<210> 201
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H41A(+92+120)

<400> 201
gcugagcugg aucugaguug gcuccacug 29

<210> 202
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H41A(+143+171)

<400> 202
guugagucuu cgaaacugag caaauuugc 29

<210> 203
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H41D(+5-15)

<400> 203
ccaguaacaa cucacaauuu 20

<210> 204

2010317599 06 Jan 2016



<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H42D(+18-02)

<400> 204
accuucagag acuccucuug c 21

<210> 205
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H43A(+83+110)

<400> 205
uccuguagcu ucacccuuuc cacaggcg 28

<210> 206
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H43A(+101 +130)

<400> 206
aaucagcugg gagagagcuu ccuguagcu 29

<210> 207
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H43D(+08-12)

<400> 207
uguguuaccu acccuugucg 20

2010317599 06 Jan 2016



<210> 208
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H43A(-09+18)

<400> 208
uagacuaucu uuuauauucu guaauau 27

<210> 209
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H43A(+89+117)

<400> 209
gagagcuucc uguagcuuca cccuuucca 29

<210> 210
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H43A(+81+111)

<400> 210
uuccuguagc uucacccuuu ccacaggcgu u 31

<210> 211
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H43A(+92+114)

<400> 211

agcuuccugu agcuucaccc uuu 23

<210> 212
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H43A(+95+117)

<400> 212
gagagcuucc uguagcuuca ccc 23

<210> 213
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H44A(-13+13)

<400> 213
ucugucaaau cgccugcagg uaaaag 26

<210> 214
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H44A(-06+24)

<400> 214
uucucaacag aucugucaaa ucgccugcag 30

<210> 215
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H44A(+44+68)

2010317599 06 Jan 2016



<400> 215
gccacugauu aaauaucuuu auauc 25

<210> 216
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H44A(+46+75)

<400> 216
ucuguuagcc acugauuaaa uaucuuuaua 30

<210> 217
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H44A(+61+84)

<400> 217
uguucagcuu cuguuagcca cuga 24

<210> 218
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H44A(+61+91)

<400> 218
gagaaacugu ucagcuucug uuagccacug a 31

<210> 219
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(31)
<223> Exon: H44A(+68+98)

<400> 219
ucuuucugag aaacuguuca gcuucuguua g 31

<210> 220
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H44A(-09+17)

<400> 220
cagaucuguc aaaucgccug caggua 26

<210> 221
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H44A(+56+88)

<400> 221
aaacuguuca gcuucuguua gccacugauu aaa 33

<210> 222
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H44A(+59+89)

<400> 222
gaaacuguuc agcuucuguu agccacugau u 31

<210> 223
<211> 28
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H44A(+61+88)

<400> 223
aaacuguuca gcuucuguua gccacuga 28

<210> 224
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H44A(+65+92)

<400> 224
ugagaaacug uucagcuucu guuagcca 28

<210> 225
<211> 32
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(32)
<223> Exon: H44A(+64+95)

<400> 225
uucugagaaa cuguucagcu ucuguuagcc ac 32

<210> 226
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H44A(+70+95)

<400> 226
uucugagaaa cuguucagcu ucuguu 26

<210> 227
<211> 32
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(32)
<223> Exon: H45A(-14+25)

<400> 227
gcugcccaau gccauccugg aguuccugua ag 32

<210> 228
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H45A(-10 +20)

<400> 228
ccaaugccau ccuggaguuc cuguaagaua 30

<210> 229
<211> 39
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(39)
<223> Exon: H45A(-09+30)

<400> 229
uugccgcugc ccaaugccau ccuggaguuc cuguaagau 39

<210> 230
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H45A(-08 +19)

<400> 230
caaugccauc cuggaguucc uguaaga 27

<210> 231
<211> 32

<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(32)
<223> Exon: HM45A(-07+25)

<400> 231
gcugcccaau gccauccugg aguuccugua ag 32

<210> 232
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H45A(+09 +34)

<400> 232
caguuugccg cugcccaaug ccaucc 26

<210> 233
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H45A(+41 +64)

<400> 233
cuucccagu ugcauucaau guuc 24

<210> 234
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H45A(+76 +98)

<400> 234
cuggcaucug uuuuugagga uug 23

2010317599 06 Jan 2016



<210> 235
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H45D(+02-18)

<400> 235
uuagaucugu cgcccuaccu 20

<210> 236
<211> 39
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(39)
<223> Exon: H45A(-14+25)

<400> 236
gcugcccaau gccauccugg aguuccugua agauaccaa 39

<210> 237
<211> 34
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(34)
<223> Exon: H45A(-12+22)

<400> 237
gcccaaugcc auccuggagu uccuguaaga uacc 34

<210> 238
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H45A(-12+13)

<400> 238
cauccuggag uuccuguaag auacc 25

2010317599 06 Jan 2016



<210> 239
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H45A(-09+22)

<400> 239
gcccaaugcc auccuggagu uccuguaaga u 31

<210> 240
<211> 39
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(39)
<223> Exon: H45A(-09+30)

<400> 240
uugccgcugc ccaaugccau ccuggaguuc cuguaagau 39

<210> 241
<211> 32
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(32)
<223> Exon: HM45A(-07+25)

<400> 241
gcugcccaau gccauccugg aguuccugua ag 32

<210> 242
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H45A(-06+22)

2010317599 06 Jan 2016



<400> 242
gcccaaugcc auccuggagu uccuguaa 28

<210> 243
<211> 34
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(34)
<223> Exon: H45A(-06+28)

<400> 243
gccgcugccc aaugccaucc uggaguuccu guaa 34

<210> 244
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H45A(-03+22)

<400> 244
gcccaaugcc auccuggagu uccug 25

<210> 245
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H45A(-03+28)

<400> 245
gccgcugccc aaugccaucc uggaguuccu g 31

<210> 246
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)

2010317599 06 Jan 2016



<223> Exon: H45D(+10-19)

<400> 246
auuagaucug ucgcccuacc ucuuuuuuc 29

<210> 247
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H45D(+16-11)

<400> 247
ugucgcccua ccucuuuuuu cugucug 27

<210> 248
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H46A(-05+19)

<400> 248
auucuuuugu ucuucuagcc ugga 24

<210> 249
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H46A(+16+42)

<400> 249
ucucuuugaa auucugacaa gauauuc 27

<210> 250
<211> 20
<212> RNA
<213> Homo sapiens

<220>

06 Jan 2016

2010317599

<221> misc_feature
<222> (1)..(20)
<223> Exon: H46A(+27+44)

<400> 250
uuaaaucucu uugaaauucu 20

<210> 251
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H46A(+35+60)

<400> 251
aaaacaaauu cauuuaaauc ucuuug 26

<210> 252
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H46A(+56+77)

<400> 252
cugcuuccuc caaccauaaa ac 22

<210> 253
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H46A(+63+87)

<400> 253
gcaauguuau cugcuuccuc caacc 25

<210> 254
<211> 21
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H46A(+83+103)

<400> 254
uucaaguggg auacuagcaa u 21

<210> 255
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H46A(+90+109)

<400> 255
uccagguuca agugggauac 20

<210> 256
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H46A(+91+118)

<400> 256
cugcucuuuu ccagguucaa gugggaua 28

<210> 257
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H46A(+95+122)

<400> 257
guugcugcuc uuuuccaggu ucaagugg 28

<210> 258
<211> 28
<212> RNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H46A(+101+128)

<400> 258
cuuuuaguug cugcucuuuu ccagguuc 28

<210> 259
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H46A(+113+136)

<400> 259
aagcuuuucu uuuaguugcu gcuc 24

<210> 260
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H46A(+115+134)

<400> 260
gcuuuucuuu uaguugcugc 20

<210> 261
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H46A(+116+145)

<400> 261
gacuugcuca agcuuuucuu uuaguugcug 30

<210> 262

2010317599 06 Jan 2016



<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H46D(+02-18)

<400> 262
uucagaaaau aaaauuaccu 20

<210> 263
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H46A(+95+124)

<400> 263
uaguugcugc ucuuuuccag guucaagugg 30

<210> 264
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H46A(+107 +137)

<400> 264
caagcuuuuc uuuuaguugc ugcucuuuuc c 31

<210> 265
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H47A(-07+19)

<400> 265
gcaacucuuc caccaguaac ugaaac 26

2010317599 06 Jan 2016



<210> 266
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H47A(+44+70)

<400> 266
gcacgggucc uccaguuuca uuuaauu 27

<210> 267
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H47A(+68+92)

<400> 267
gggcuuaugg gagcacuuac aagca 25

<210> 268
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H47A(+73+103)

<400> 268
cuugcucuuc ugggcuuaug ggagcacuua c 31

<210> 269
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H47A(+76+103)

<400> 269

2010317599 06 Jan 2016



cuugcucuuc ugggcuuaug ggagcacu 28

<210> 270
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H47D(+17-10)

<400> 270
aaugucuaac cuuuauccac uggagau 27

<210> 271
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H48A(-09+21)

<400> 271
cucagguaaa gcucuggaaa ccugaaagga 30

<210> 272
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H48A(-08+19)

<400> 272
cagguaaagc ucuggaaacc ugaaagg 27

<210> 273
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H48A(-07+23)

2010317599 06 Jan 2016



<400> 273
uucucaggua aagcucugga aaccugaaag 30

<210> 274
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H48A(-05+25)

<400> 274
guuucucagg uaaagcucug gaaaccugaa 30

<210> 275
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H48A(+07+33)

<400> 275
uucuccuugu uucucaggua aagcucu 27

<210> 276
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H48A(+75+100)

<400> 276
uuaacugcuc uucaaggucu ucaagc 26

<210> 277
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(27)
<223> Exon: H48A(+96+122)

<400> 277
gauaaccaca gcagcagaug auuuaac 27

<210> 278
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H48D(+17-10)

<400> 278
aguucccuac cugaacguca aaugguc 27

<210> 279
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H48D(+16-09)

<400> 279
guucccuacc ugaacgucaa auggu 25

<210> 280
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H49A(-07+19)

<400> 280
gaacugcuau uucaguuucc ugggga 26

<210> 281
<211> 26
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H49A(+22+47)

<400> 281
aucucuucca cauccgguug uuuagc 26

<210> 282
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H49D(+18-08)

<400> 282
uucauuaccu ucacuggcug aguggc 26

<210> 283
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50A(-07+20)

<400> 283
cucagaucuu cuaacuuccu cuuuaac 27

<210> 284
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H50A(-02+27)

<400> 284
cucagagcuc agaucuucua acuuccucu 29

<210> 285
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50A(+10+36)

<400> 285
cgccuuccac ucagagcuca gaucuuc 27

<210> 286
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50A(+35+61)

<400> 286
ucagcucuug aaguaaacgg uuuaccg 27

<210> 287
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50A(+42+68)

<400> 287
uuugcccuca gcucuugaag uaaacgg 27

<210> 288
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H50A(+63+88)

<400> 288
caggagcuag gucaggcugc uuugcc 26

<210> 289
<211> 25

2010317599 06 Jan 2016



<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H50A(+81+105)

<400> 289
uccaauagug gucaguccag gagcu 25

<210> 290
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50D(-01-27)

<400> 290
aaagagaaug ggauccagua uacuuac 27

<210> 291
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H50D(-15-41)

<400> 291
aaauagcuag agccaaagag aauggga 27

<210> 292
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H50A(+42+74)

<400> 292
ggcugcuuug cccucagcuc uugaaguaaa cgg 33

2010317599 06 Jan 2016



<210> 293
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H50A(+46+75)

<400> 293
aggcugcuuu gcccucagcu cuugaaguaa 30

<210> 294
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H50A(+48+78)

<400> 294
gucaggcugc uuugcccuca gcucuugaag u 31

<210> 295
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H50A(+51+80)

<400> 295
aggucaggcu gcuuugcccu cagcucuuga 30

<210> 296
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: Hint49(-72-46)

<400> 296
aagauaauuc augaacaucu uaaucca 27

<210> 297
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H51A(-29-10)

<400> 297
uuuggguuuu ugcaaaaagg 20

<210> 298
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H51A(-22-01)

<400> 298
cuaaaauauu uuggguuuuu gc 22

<210> 299
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H51A(-14+10)

<400> 299
ugaguaggag cuaaaauauu uugg 24

<210> 300
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H51(+26+52)

2010317599 06 Jan 2016



<400> 300
guuuccuuag uaaccacagg uuguguc 27

<210> 301
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H51A(+40+67)

<400> 301
aguuuggaga uggcaguuuc cuuaguaa 28

<210> 302
<211> 12
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(12)
<223> Exon: H51A(+66+77)

<400> 302
uggcauuucu ag 12

<210> 303
<211> 15
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(15)
<223> Exon: H51A(+66+80)

<400> 303
agauggcauu ucuag 15

<210> 304
<211> 18
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(18)

2010317599 06 Jan 2016

<223> Exon: H51A(+66+83)

<400> 304
ggaagauggc auuucuag 18

<210> 305
<211> 18
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(18)
<223> Exon: H51A(+78+95)

<400> 305
cuccaacauc aaggaaga 18

<210> 306
<211> 15
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(15)
<223> Exon: H51A(+81+95)

<400> 306
cuccaacauc aagga 15

<210> 307
<211> 12
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(12)
<223> Exon: H51A(+84+95)

<400> 307
cuccaacauc aa 12

<210> 308
<211> 27
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(27)
<223> Exon: H51A(+90+116)

<400> 308
gaaaucugcc agagcaggua ccuccaa 27

<210> 309
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H51A(+53+79)

<400> 309
gauggcauuu cuaguuugga gauggca 27

<210> 310
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H51A(+57+85)

<400> 310
aaggaagaug gcauuucuag uuuggagau 29

<210> 311
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H51A(+76+104)

<400> 311
agcagguacc uccaacauca aggaagaug 29

<210> 312
<211> 25
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H52A(-12+13)

<400> 312
ccugcauugu ugccuguaag aacaa 25

<210> 313
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H52A(-10+10)

<400> 313
gcauuguugc cuguaagaac 20

<210> 314
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H52A(+07+33)

<400> 314
gggacgccuc uguuccaaau ccugcau 27

<210> 315
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H52A(+17+46)

<400> 315
guucuuccaa cuggggacgc cucuguucca 30

<210> 316
<211> 21
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H52A(+17+37)

<400> 316
acuggggacg ccucuguucc a 21

<210> 317
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H52A(+67+94)

<400> 317
ccucuugauu gcuggucuug uuuuucaa 28

<210> 318
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: Hint51(-40-14)

<400> 318
uaccccuuag uaucaggguu cuucagc 27

<210> 319
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H52A(+09+41)

<400> 319
uccaacuggg gacgccucug uuccaaaucc ugc 33

<210> 320

2010317599 06 Jan 2016

<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H52A(+15+44)

<400> 320
ucuuccaacu ggggacgccu cuguuccaaa 30

<210> 321
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H53A(-49-26)

<400> 321
auaguaguaa augcuagucu ggag 24

<210> 322
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H53A(-38-13)

<400> 322
gaaaaauaaa uauauaguag uaaaug 26

<210> 323
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H53A(-32-06)

<400> 323
auaaaaggaa aaauaaauau auaguag 27

2010317599 06 Jan 2016



<210> 324
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H53A(-15+15)

<400> 324
ucugaauucu uucaacuaga auaaaaggaa 30

<210> 325
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H53A(+39+65)

<400> 325
caacuguugc cuccgguucu gaaggug 27

<210> 326
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H53A(+39+67)

<400> 326
uucaacuguu gccuccgguu cugaaggug 29

<210> 327
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H39A(+39+69)SNP

<400> 327

2010317599 06 Jan 2016

cguucaacug uugccuccgg uucugaaggu g 31

<210> 328
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H53A(+40+70)

<400> 328
ucauucaacu guugccuccg guucugaagg u 31

<210> 329
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H53A(+41+69)

<400> 329
cauucaacug uugccuccgg uucugaagg 29

<210> 330
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H53A(+43+69)

<400> 330
cauucaacug uugccuccgg uucugaa 27

<210> 331
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H53A(+69+98)

2010317599 06 Jan 2016



<400> 331
cagccauugu guugaauccu uuaacauuuc 30

<210> 332
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: Hint52(-47-23)

<400> 332
uauauaguag uaaaugcuag ucugg 25

<210> 333
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H53A(+27+59)

<400> 333
uugccuccgg uucugaaggu guucuuguac uuc 33

<210> 334
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H53A(+30+59)

<400> 334
uugccuccgg uucugaaggu guucuuguac 30

<210> 335
<211> 35
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(35)
<223> Exon: H53A(+30+64)

<400> 335
aacuguugcc uccgguucug aagguguucu uguac 35

<210> 336
<211> 40
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(40)
<223> Exon: H53A(+30+69)

<400> 336
cauucaacug uugccuccgg uucugaaggu guucuuguac 40

<210> 337
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H53A(+33+63)

<400> 337
acuguugccu ccgguucuga agguguucuu g 31

<210> 338
<211> 35
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(35)
<223> Exon: H53A(+33+67)

<400> 338
uucaacuguu gccuccgguu cugaaggugu ucuug 35

<210> 339
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H53A(+35+67)

<400> 339
uucaacuguu gccuccgguu cugaaggugu ucu 33

<210> 340
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H53A(+37+67)

<400> 340
uucaacuguu gccuccgguu cugaaggugu u 31

<210> 341
<211> 35
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(35)
<223> Exon: H53A(+36+70)

<400> 341
ucauucaacu guugccuccg guucugaagg uguuc 35

<210> 342
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H53A(+39+71)

<400> 342
uucauucaac uguugccucc gguucugaag gug 33

<210> 343
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H53A(+42+71)

<400> 343
uucauucaac uguugccucc gguucugaag 30

<210> 344
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H54A(+13+34)

<400> 344
uugucugcca cuggcggagg uc 22

<210> 345
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H54A(+60+90)

<400> 345
aucugcagaa uaaucccgga gaaguuucag 30

<210> 346
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H54A (+67+89)

<400> 346
ucugcagaau aaucccggag aag 23

<210> 347
<211> 30

2010317599 06 Jan 2016



<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H54A(+77+106)

<400> 347
ggacuuuucu gguaucaucu gcagaauaau 30

<210> 348
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H55A(-10+14)

<400> 348
cucgcucacu cacccugcaa agga 24

<210> 349
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H55A(+39 +61)

<400> 349
caggggggaac uguugcagua auc 23

<210> 350
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H55A(+41+71)

<400> 350
ucuuuuacuc ccuuggaguc uucuaggagc c 31

2010317599 06 Jan 2016



<210> 351
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H55A(+73+93)

<400> 351
ucuguaagcc aggcaagaaa c 21

<210> 352
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H55A(+107+137)

<400> 352
ccuuacgggu agcauccuga uggacauugg c 31

<210> 353
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H55A(+112 +136)

<400> 353
cuuacgggua gcauccugua ggaca 25

<210> 354
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H55A(+132 +161)

<400> 354
ccuuggaguc uucuaggagc cuuuccuuac 30

<210> 355
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H55A(+141 +160)

<400> 355
cuuggagucu ucuaggagcc 20

<210> 356
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H55A(+143 +171)

<400> 356
cucuuuuacu cccuuggagu cuucuaggag 30

<210> 357
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H55D(+11 -09)

<400> 357
ccugacuuac uugccauugu 20

<210> 358
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H56A(-06+23)

2010317599 06 Jan 2016



<400> 358
gcuucaauuu caccuuggag guccuacag 29

<210> 359
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H56A(-06+15)

<400> 359
uucaccuugg agguccuaca g 21

<210> 360
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H56A(+23 +44)

<400> 360
guugugauaa acaucugugu ga 22

<210> 361
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H56A(+56 +81)

<400> 361
ccagggaucu caggauuuuu uggcug 26

<210> 362
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)

2010317599 06 Jan 2016



<223> Exon: H56A(+67+91)

<400> 362
cggaaccuuc cagggaucuc aggau 25

<210> 363
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H56A(+102+126)

<400> 363
guuauccaaa cgucuuugua acagg 25

<210> 364
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H56A(+102+131)

<400> 364
uucauguuau ccaaacgucu uuguaacagg 30

<210> 365
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H56A(+117+146)

<400> 365
ucacuccacu ugaaguucau guuauccaaa 30

<210> 366
<211> 23
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016

<221> misc_feature
<222> (1)..(23)
<223> Exon: H56A(+121+143)

<400> 366
cuccacuuga aguucauguu auc 23

<210> 367
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H56D(+11-10)

<400> 367
cuuuuccuac caaauguuga g 21

<210> 368
<211> 33
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(33)
<223> Exon: H57A(-15+18)

<400> 368
cuggcuucca aaugggaccu gaaaaagaac agc 33

<210> 369
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H57A (-12 +18)

<400> 369
cuggcuucca aaugggaccu gaaaaagaac 30

<210> 370
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H57A(-06 +24)

<400> 370
ucagaacugg cuuccaaaug ggaccugaaa 30

<210> 371
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H57A(+21+44)

<400> 371
ggugcagacg cuuccacugg ucag 24

<210> 372
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H57A(+47 +77)

<400> 372
gcuguagcca caccagaagu uccugcagag a 31

<210> 373
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H57A(+79+103)

<400> 373
cugccggcuu aauucaucau cuuuc 25

<210> 374
<211> 27
<212> RNA

2010317599 06 Jan 2016



<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H57A(+105+131)

<400> 374
cugcuggaaa gucgccucca auaggug 27

<210> 375
<211> 22
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(22)
<223> Exon: H59A (−06 +16)

<400> 375
uccucaggag gcagcucuaa au 22

<210> 376
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H59A(+31 +61)

<400> 376
uccucgccug cuuucguaga agccgaguga 30

<210> 377
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H59A(+66+91)

<400> 377
agguucaauu uuucccacuc aguauu 26

<210> 378

2010317599 06 Jan 2016

<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H59A(+96+125)

<400> 378
cucaucuauu uuucucugcc agucagcgga 30

<210> 379
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H59A(+101 +132)

<400> 379
cagggucuca ucuauuuuuc ucugccaguc a 31

<210> 380
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+141 +165)

<400> 380
cauccguggc cucuugaagu uccug 25

<210> 381
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+151 +175)

<400> 381
agguccagcu cauccguggc cucuu 25

2010317599 06 Jan 2016

<210> 382
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+161 +185)

<400> 382
gcgcagcuug agguccagcu caucc 25

<210> 383
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H59A(+161+190)

<400> 383
gcuuggcgca gcuugagguc cagcucaucc 30

<210> 384
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H59A(+171+197)

<400> 384
caccucagcu uggcgcagcu ugagguc 27

<210> 385
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+181+205)

<400> 385

2010317599 06 Jan 2016



cccuugauca ccucagcuug gcgca 25

<210> 386
<211> 21
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(21)
<223> Exon: H59A(+200+220)

<400> 386
acgggcugcc aggaucccuu g 21

<210> 387
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H59A(+221+245)

<400> 387
gagagaguca augaggagau cgccc 25

<210> 388
<211> 34
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(34)
<223> Exon: H59A(+92+125)

<400> 388
cucaucuauu uuucucugcc agucagcgga gugc 34

<210> 389
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(-10+20)

2010317599 06 Jan 2016



<400> 389
gcaauuucuc cucgaagugc cugugugcaa 30

<210> 390
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H60A(-8+19)

<400> 390
caauuucucc ucgaagugcc ugugugc 27

<210> 391
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+29+58)

<400> 391
caaggucauu gacguggcuc acguucucuu 30

<210> 392
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+37+66)

<400> 392
cuggcgagca aggucauuga cguggcucac 30

<210> 393
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(28)
<223> Exon: H60A(+39+66)

<400> 393
cuggcgagca agguccuuga cguggcuc 28

<210> 394
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H60A(+43+73)

<400> 394
ugguaagcug gcgagcaagg uccuugacgu g 31

<210> 395
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H60A(+51+75)

<400> 395
agugguaagc uggcgugcaa gguca 25

<210> 396
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60A(+72+102)

<400> 396
uuauacggug agagcugaau gcccaaagug 30

<210> 397
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H60A(+75+105)

<400> 397
gagguuauac ggugagagcu gaaugcccaa a 31

<210> 398
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H60A(+80+109)

<400> 398
ugcugagguu auacggugag agcugaa 27

<210> 399
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H60D(+25-5)

<400> 399
cuuuccugca gaagcuucca ucugguguuc 30

<210> 400
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H61A(-7+19)

<400> 400
cucgguccuc gacggccacc ugggag 26

<210> 401
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H61A(+05+34)

<400> 401
caugcagcug ccugacucgg uccucgccgg 30

<210> 402
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H61A(+16+40)

<400> 402
gggcuucaug cagcugccug acucg 25

<210> 403
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H61A(+16+45)

<400> 403
ccugugggcu ucaugcagcu gccugacucg 30

<210> 404
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H61A(+42+67)

<400> 404
gcugagaugc uggaccaaag ucccug 26

<210> 405
<211> 26

2010317599 06 Jan 2016



<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H61D(+10-16)

<400> 405
gcugaaaaug acuuacugga aagaaa 26

<210> 406
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H62A(-15+15)

<400> 406
gacccuggac agacgcugaa aagaagggag 30

<210> 407
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H62A(-10+20)

<400> 407
ccagggaccc uggacagacg cugaaaagaa 30

<210> 408
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H62A(-05+15)

<400> 408
gacccuggac agacgcugaa 20

2010317599 06 Jan 2016



<210> 409
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H62A(-3+25)

<400> 409
cucucccagg gacccuggac agacgcug 28

<210> 410
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H62A(+01+30)

<400> 410
uggcucucuc ccagggaccc uggacagacg 30

<210> 411
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H62A(+8+34)

<400> 411
gagauggcuc ucucccaggg acccugg 27

<210> 412
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H62A(+13+43)

<400> 412
uuguuuggug agauggcucu cucccaggga c 31

2010317599 06 Jan 2016

<210> 413
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H62D(+17-03)

<400> 413
uacuugauau aguagggcac 20

<210> 414
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H62D(+25-5)

<400> 414
cuuacuugau auaguagggc acuuuguuug 30

<210> 415
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H63A(-14+11)

<400> 415
gagucucgug gcuaaaacac aaaac 25

<210> 416
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H63A(+11+35)

2010317599 06 Jan 2016

<400> 416
ugggaugguc ccagcaaguu guuug 25

<210> 417
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H63A(+33+57)

<400> 417
gacugguaga gcucugucau uuugg 25

<210> 418
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H63A(+40+62)

<400> 418
cuaaagacug guagagcucu guc 23

<210> 419
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H63D(+8-17)

<400> 419
cauggccaug uccuuaccua aagac 25

<210> 420
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)

<223> Exon: H64A(-3+27)

<400> 420
cugagaaucu gacauuauuc aggucagcug 30

<210> 421
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H64A(+43+72)

<400> 421
aaagggccuu cugcagucuu cggaguuuca 30

<210> 422
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H64A(+47+74)

<400> 422
gcaaagggcc uucugcaguc uucggag 27

<210> 423
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H64D(+15-10)

<400> 423
caauacuuac agcaaagggc cuucu 25

<210> 424
<211> 26
<212> RNA
<213> Homo sapiens

<220>

2010317599 06 Jan 2016



<221> misc_feature
<222> (1)..(26)
<223> Exon: H65A(+123+148)

<400> 424
uugaccaaau uguugugcuc uugcuc 26

<210> 425
<211> 28
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: H67A(+120+147)

<400> 425
agcuccggac acuuggcuca auguuacu 28

<210> 426
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H67A(+125+149)

<400> 426
gcagcuccgg acacuuggcu caaug 25

<210> 427
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H67D(+22-08)

<400> 427
uaacuuacaa auuggaagca gcuccggaca 30

<210> 428
<211> 25
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H68A(-4+21)

<400> 428
gaucucuggc uuauuauuag ccugc 25

<210> 429
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H68A(+22+48)

<400> 429
cauccagucu aggaagaggg ccgcuuc 27

<210> 430
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H68A(+74+103)

<400> 430
cagcagccac ucugugcagg acgggcagcc 30

<210> 431
<211> 31
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H69A(-12+19)

<400> 431
gugcuuuaga cuccuguacc ugauaaagag c 31

<210> 432
<211> 31
<212> RNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(31)
<223> Exon: H69A(+09 +39)

<400> 432
uggcagaugu cauaauuaaa gugcuuuaga c 31

<210> 433
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H69A(+29 +57)

<400> 433
ccagaaaaaa agcagcuuug gcagauguc 29

<210> 434
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H69A(+51+74)

<400> 434
ggccuuuugc aacucgacca gaaa 24

<210> 435
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H69A(+51 +80)

<400> 435
uuuuauggcc uuuugcaacu cgaccagaaa 30

<210> 436

2010317599 06 Jan 2016



<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H69D(+08-16)

<400> 436
cuggcgucaa acuuaccgga gugc 24

<210> 437
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H70A(-09+15)

<400> 437
uucuccugau guagucuaaa aggg 24

<210> 438
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H70A(-07 +23)

<400> 438
cgaacaucuu cuccugaugu agucuaaaag 30

<210> 439
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H70A(+16 +40)

<400> 439
guaccuuggc aaagucucga acauc 25

2010317599 06 Jan 2016

<210> 440
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H70A(+25 +48)

<400> 440
guuuuuuagu accuuggcaa aguc 24

<210> 441
<211> 29
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(29)
<223> Exon: H70A(+32+60)

<400> 441
gguucgaaau uuguuuuuua guaccuugg 29

<210> 442
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H70A(+64 +93)

<400> 442
gcccauucgg ggaugcuucg caaaauaccu 30

<210> 443
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H71A(-08+16)

<400> 443

gaucagagua acgggacugc aaaa 24

<210> 444
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H71A(+07+30)

<400> 444
acuggccaga aguugaucag agua 24

<210> 445
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H71A(+16+39)

<400> 445
gcagaaucua cuggccagaa guug 24

<210> 446
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H71D(+19-05)

<400> 446
cucacgcaga aucuacuggc caga 24

<210> 447
<211> 30
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H72A(-8+22)

2010317599 06 Jan 2016



<400> 447
aagcugaggg gacgaggcag gccuauaagg 30

<210> 448
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H72A(+02+28)

<400> 448
gugugaaagc ugaggggacg aggcagg 27

<210> 449
<211> 24
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(24)
<223> Exon: H72D(+14-10)

<400> 449
agucucauac cugcuagcau aaug 24

<210> 450
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H73A(+24+49)

<400> 450
augcuaucau uuagauaaga uccau 25

<210> 451
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature

2010317599 06 Jan 2016



<222> (1)..(26)
<223> Exon: H73A(-16+10)

<400> 451
uucugcuagc cugauaaaaa acguaa 26

<210> 452
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H73D(+23-02)

<400> 452
acaugcucuc auuaggagag augcu 25

<210> 453
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: HM73A(+19+44)

<400> 453
uaucauuuag auaagaucca uugcug 26

<210> 454
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: HM74A(+20+46)

<400> 454
guucaaacuu uggcaguaau gcuggau 27

<210> 455
<211> 28
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016

<220>
<221> misc_feature
<222> (1)..(28)
<223> Exon: HM74A(+50+77)

<400> 455
gacuacgagg cuggcucagg ggggaguc 28

<210> 456
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: HM74A(+96+122)

<400> 456
gcucccucu uuccucacuc ucuaagg 27

<210> 457
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H76A(-02+25)

<400> 457
cauucacuuu ggccucugcc uggggcu 27

<210> 458
<211> 27
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(27)
<223> Exon: H76A(+80+106)

<400> 458
gacugccaac cacucggagc agcauag 27

<210> 459
<211> 30
<212> RNA
<213> Homo sapiens

2010317599 06 Jan 2016



<220>
<221> misc_feature
<222> (1)..(30)
<223> Exon: H17A(-12 +18)

<400> 459
ggugacagcc ugugaaaucu gugagaagua 30

<210> 460
<211> 23
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(23)
<223> Exon: H17A(-07+16)

<400> 460
ugacagccug ugaaaucugu gag 23

<210> 461
<211> 26
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(26)
<223> Exon: H17A(+10 +35)

<400> 461
agugauggcu gagugguggu gacagc 26

<210> 462
<211> 20
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H17A(+31+50)

<400> 462
acaguugucu guguuaguga 20

<210> 463
<211> 20

2010317599 06 Jan 2016

<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(20)
<223> Exon: H17A(+144+163)

<400> 463
cagaauccac aguaaucugc 20

<210> 464
<211> 25
<212> RNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(25)
<223> Exon: H3A(+30+54)

<400> 464
gcgccuccca uccuguaggu cacug 25