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Van Deutekom et al.(10) **Pub. No.: US 2012/0046342 A1**(43) **Pub. Date: Feb. 23, 2012**(54) **OLIGONUCLEOTIDE COMPRISING AN
INOSINE FOR TREATING DMD**(75) Inventors: **Judith Christina Theodora Van
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The invention provides an oligonucleotide comprising an inosine, and/or a nucleotide containing a base able to form a wobble base pair or a functional equivalent thereof, wherein the oligonucleotide, or a functional equivalent thereof, comprises a sequence which is complementary to at least part of a dystrophin pre-m RNA exon or at least part of a non-exon region of a dystrophin pre-m RNA said part being a contiguous stretch comprising at least 8 nucleotides. The invention further provides the use of said oligonucleotide for preventing or treating DMD or BMD.

Fig 1

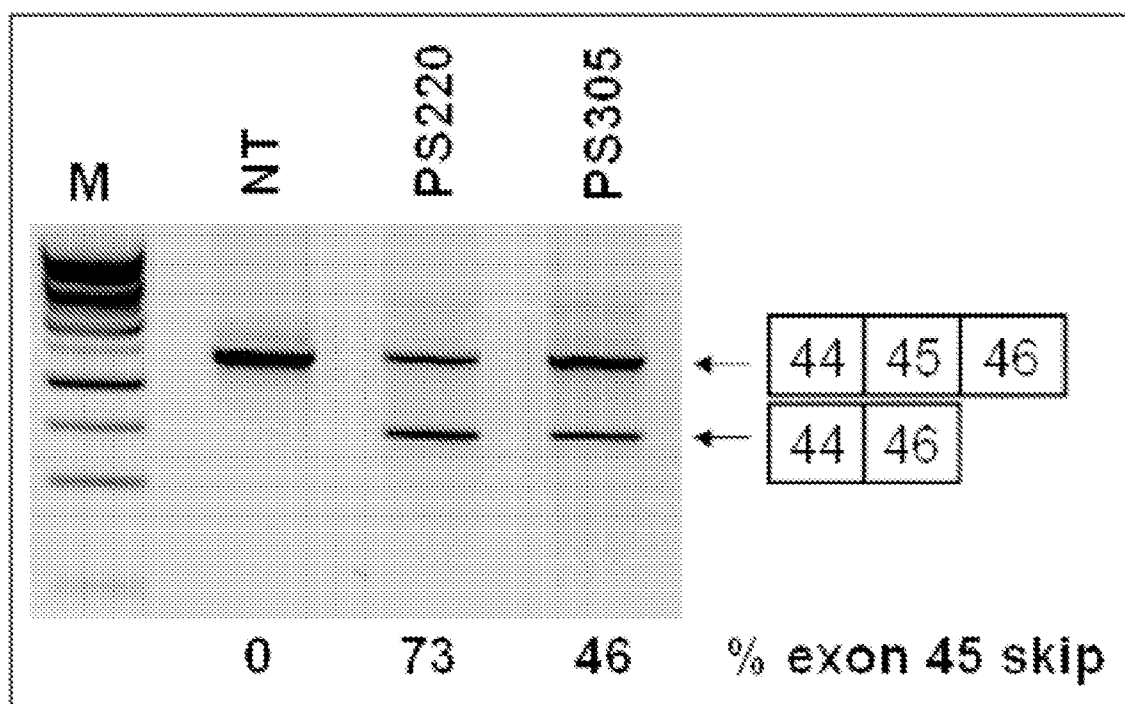
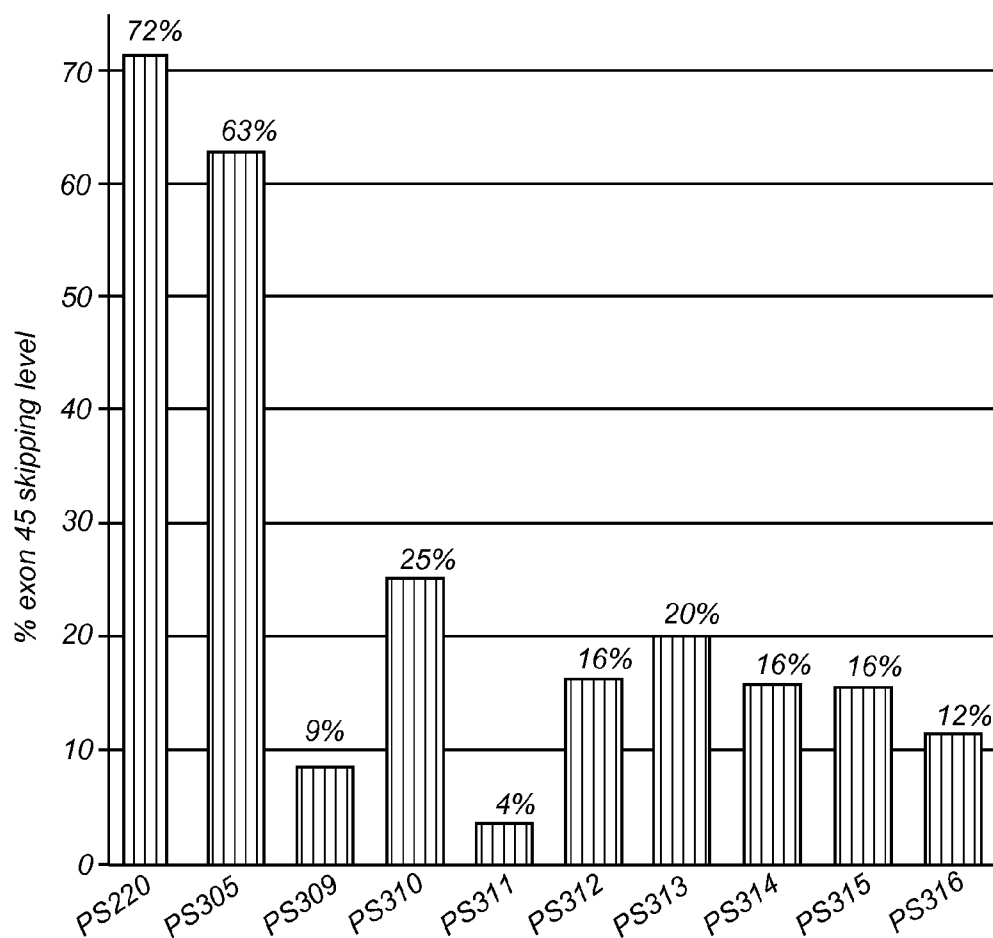


Fig 2

AON ID	Sequence (5' – 3')	SEQ ID NO
PS220	UUUGCCGCUGCCCAAUGCCAUCCUG	76
PS305	UUUGCCICUGCCCAAUGCCAUCCUG	557
PS309	UCAAUGUUCUGACAACAGUUUGCCI	based on 115
PS310	CAAUGUUCUGACAACAGUUUGCCIC	based on 116
PS311	AAUGUUCUGACAACAGUUUGCCICU	based on 117
PS312	AUGUUCUGACAACAGUUUGCCICUG	based on 118
PS313	UGUUCUGACAACAGUUUGCCICUGC	based on 119
PS314	GUUCUGACAACAGUUUGCCICUGCC	based on 120
PS315	UUCUGACAACAGUUUGCCICUGCCC	based on 121
PS316	UCUGACAACAGUUUGCCICUGCCCA	based on 122

OLIGONUCLEOTIDE COMPRISING AN INOSINE FOR TREATING DMD

FIELD OF THE INVENTION

[0001] The invention relates to the fields of molecular biology and medicine.

BACKGROUND OF THE INVENTION

[0002] A muscle disorder is a disease that usually has a significant impact on the life of an individual. A muscle disorder can have either a genetic cause or a non-genetic cause. An important group of muscle diseases with a genetic cause are Becker Muscular Dystrophy (BMD) and Duchenne Muscular Dystrophy (DMD). These disorders are caused by defects in a gene for a muscle protein.

[0003] Becker Muscular Dystrophy and Duchenne Muscular Dystrophy are genetic muscular dystrophies with a relatively high incidence. In both Duchenne and Becker muscular dystrophy the muscle protein dystrophin is affected. In Duchenne dystrophin is absent, whereas in Becker some dystrophin is present but its production is most often not sufficient and/or the dystrophin present is abnormally formed. Both diseases are associated with recessive X-linked inheritance. DMD results from a frameshift mutation in the DMD gene. The frameshift in the DMD gene's transcript (mRNA) results in the production of a truncated non-functional dystrophin protein, resulting in progressive muscle wasting and weakness. BMD occurs as a mutation does not cause a frame-shift in the DMD transcript (mRNA). As in BMD some partly to largely functional dystrophin is present in contrast to DMD where dystrophin is absent, BMD has generally less severe symptoms than DMD. The onset of DMD is earlier than BMD. DMD usually manifests itself in early childhood, BMD in the teens or in early adulthood. The progression of BMD is slower and less predictable than DMD. Patients with BMD can survive into mid to late adulthood. Patients with DMD rarely survive beyond their thirties.

[0004] Dystrophin plays an important structural role in the muscle fiber, connecting the extracellular matrix and the cytoskeleton. The N-terminal region binds actin, whereas the C-terminal end is part of the dystrophin glycoprotein complex (DGC), which spans the sarcolemma. In the absence of dystrophin, mechanical stress leads to sarcolemmal ruptures, causing an uncontrolled influx of calcium into the muscle fiber interior, thereby triggering calcium-activated proteases and fiber necrosis.

[0005] For most genetic muscular dystrophies no clinically applicable and effective therapies are currently available. Exon skipping techniques are nowadays explored in order to combat genetic muscular dystrophies. Promising results have recently been reported by us and others on a genetic therapy aimed at restoring the reading frame of the dystrophin pre-mRNA in cells from the mdx mouse, the GRMD dog (reference 59) and DMD patients¹⁻¹¹. By the targeted skipping of a specific exon, a DMD phenotype (lacking dystrophin) is converted into a milder BMD phenotype (partly to largely functional dystrophin). The skipping of an exon is preferably induced by the binding of antisense oligoribonucleotides (AONs) targeting either one or both of the splice sites, or exon-internal sequences. Since an exon will only be included in the mRNA when both the splice sites are recognised by the spliceosome complex, splice sites have been considered obvious targets for AONs. More preferably, one or more AONs are

used which are specific for at least part of one or more exonic sequences involved in correct splicing of the exon. Using exon-internal AONs specific for an exon 46 sequence, we were previously able to modulate the splicing pattern in cultured myotubes from two different DMD patients with an exon 45 deletion¹¹. Following AON treatment, exon 46 was skipped, which resulted in a restored reading frame and the induction of dystrophin synthesis in at least 75% of the cells. We have recently shown that exon skipping can also efficiently be induced in human control and patient muscle cells for 39 different DMD exons using exon-internal AONs^{1, 2, 11-15}.

[0006] Hence, exon skipping techniques applied on the dystrophin gene result in the generation of at least partially functional—albeit shorter—dystrophin protein in DMD patients. Since DMD is caused by a dysfunctional dystrophin protein, it would be expected that the symptoms of DMD are sufficiently alleviated once a DMD patient has been provided with functional dystrophin protein. However, the present invention provides the insight that, even though exon skipping techniques are capable of inducing dystrophin synthesis, the oligonucleotide used for exon skipping technique can be improved any further by incorporating an inosine and/or a nucleotide containing a base able to form a wobble base pair in said oligonucleotide.

DESCRIPTION OF THE INVENTION

Oligonucleotide

[0007] In a first aspect, there is provided an oligonucleotide comprising an inosine and/or a nucleotide containing a base able to form a wobble base pair or a functional equivalent thereof, wherein the oligonucleotide, or a functional equivalent thereof, comprises a sequence which is complementary to at least part of a dystrophin pre-mRNA exon or at least part of a non-exon region of a dystrophin pre-mRNA said part being a contiguous stretch comprising at least 8 nucleotides.

[0008] The use of an inosine and/or a nucleotide containing a base able to form a wobble base pair in an oligonucleotide of the invention is very attractive as explained below. Inosine for example is a known modified base which can pair with three bases: uracil, adenine, and cytosine. Inosine is a nucleoside that is formed when hypoxanthine is attached to a ribose ring (also known as a ribofuranose) via a β -N9-glycosidic bond. Inosine is commonly found in tRNAs and is essential for proper translation of the genetic code in wobble base pairs. A wobble base pair is a G-U and I-U/I-A/I-C pair fundamental in RNA secondary structure. Its thermodynamic stability is comparable to that of the Watson-Crick base pair. Wobble base pairs are critical for the proper translation of the genetic code. The genetic code makes up for disparities in the number of amino acids (20) for triplet codons (64), by using modified base pairs in the first base of the anti-codon. Similarly, when designing primers for polymerase chain reaction, inosine is useful in that it will indiscriminately pair with adenine, thymine, or cytosine. A first advantage of using such a base allows one to design a primer that spans a single nucleotide polymorphism (SNP), without worry that the polymorphism will disrupt the primer's annealing efficiency. Therefore in the invention, the use of such a base allows to design an oligonucleotide that may be used for an individual having a SNP within the dystrophin pre-mRNA stretch which is targeted by an oligonucleotide of the invention. A second advantage of using an inosine and/or a base able to form a

wobble base pair in an oligonucleotide of the invention is when said oligonucleotide would normally contain a CpG if one would have designed it as being complementary to at least part of a dystrophin pre-mRNA exon or at least part of a non-exon region of a dystrophin pre-mRNA said part being a contiguous stretch comprising at least 8 nucleotides. The presence of a CpG in an oligonucleotide is usually associated with an increased immunogenicity of said oligonucleotide (reference 60). This increased immunogenicity is undesired since it may induce the breakdown of muscle fibers. Replacing one, two or more CpG by the corresponding inosine and/or a base able to form a wobble base pair in said oligonucleotide is expected to provide an oligonucleotide with a decreased and/or acceptable level of immunogenicity. Immunogenicity may be assessed in an animal model by assessing the presence of CD4⁺ and/or CD8⁺ cells and/or inflammatory mononucleocyte infiltration in muscle biopsy of said animal.

[0009] Immunogenicity may also be assessed in blood of an animal or of a human being treated with an oligonucleotide of the invention by detecting the presence of a neutralizing antibody and/or an antibody recognizing said oligonucleotide using a standard immunoassay known to the skilled person.

[0010] An increase in immunogenicity preferably corresponds to a detectable increase of at least one of these cell types by comparison to the amount of each cell type in a corresponding muscle biopsy of an animal before treatment or treated with a corresponding oligonucleotide having at least one inosine and/or a base able to form a wobble base pair. Alternatively, an increase in immunogenicity may be assessed by detecting the presence or an increasing amount of a neutralizing antibody or an antibody recognizing said oligonucleotide using a standard immunoassay.

[0011] A decrease in immunogenicity preferably corresponds to a detectable decrease of at least one of these cell types by comparison to the amount of corresponding cell type in a corresponding muscle biopsy of an animal before treatment or treated with a corresponding oligonucleotide having no inosine and/or a base able to form a wobble base pair. Alternatively a decrease in immunogenicity may be assessed by the absence of or a decreasing amount of said compound and/or neutralizing antibodies using a standard immunoassay.

[0012] A third advantage of using an inosine and/or a base able to form a wobble base pair in an oligonucleotide of the invention is to avoid or decrease a potential multimerisation or aggregation of oligonucleotides. It is for example known that an oligonucleotide comprising a G-quartet motif has the tendency to form a quadruplex, a multimer or aggregate formed by the Hoogsteen base-pairing of four single-stranded oligonucleotides (reference 61), which is of course not desired: as a result the efficiency of the oligonucleotide is expected to be decreased. Multimerisation or aggregation is preferably assessed by standard polyacrylamid non-denaturing gel electrophoresis techniques known to the skilled person. In a preferred embodiment, less than 20% or 15%, 10%, 7%, 5% or less of a total amount of an oligonucleotide of the invention has the capacity to multimerize or aggregate assessed using the assay mentioned above.

[0013] A fourth advantage of using an inosine and/or a base able to form a wobble base pair in an oligonucleotide of the invention is thus also to avoid quadruplex structures which have been associated with antithrombotic activity (reference 62) as well as with the binding to, and inhibition of, the macrophage scavenger receptor (reference 63.).

[0014] A fifth advantage of using an inosine and/or a base able to form a wobble base pair in an oligonucleotide of the invention is to allow to design an oligonucleotide with improved RNA binding kinetics and/or thermodynamic properties. The RNA binding kinetics and/or thermodynamic properties are at least in part determined by the melting temperature of an oligonucleotide (T_m ; calculated with the oligonucleotide properties calculator (<http://www.unc.edu/~cail/biotool/oligo/index.html>) for single stranded RNA using the basic T_m and the nearest neighbour model), and/or the free energy of the AON-target exon complex (using RNA structure version 4.5). If a T_m is too high, the oligonucleotide is expected to be less specific. An acceptable T_m and free energy depend on the sequence of the oligonucleotide. Therefore, it is difficult to give preferred ranges for each of these parameters. An acceptable T_m may be ranged between 35 and 65° C. and an acceptable free energy may be ranged between 15 and 45 kcal/mol.

[0015] The skilled person may therefore first choose an oligonucleotide as a potential therapeutic compound. In a second step, he may use the invention to further optimise said oligonucleotide by decreasing its immunogenicity and/or avoiding aggregation and/or quadruplex formation and/or by optimizing its T_m and/or free energy of the AON-target complex. He may try to introduce at least one inosine and/or a base able to form a wobble base pair in said oligonucleotide at a suitable position and assess how the immunogenicity and/or aggregation and/or quadruplex formation and/or T_m and/or free energy of the AON-target complex have been altered by the presence of said inosine and/or a base able to form a wobble base pair. If the alteration does not provide the desired alteration or decrease of immunogenicity and/or aggregation and/or quadruplex formation and/or its T_m and/or free energy of the AON-target complex he may choose to introduce a further inosine and/or a base able to form a wobble base pair in said oligonucleotide and/or to introduce a given inosine and/or a base able to form a wobble base pair at a distinct suitable position within said oligonucleotide.

[0016] An oligonucleotide comprising an inosine and/or a base able to form a wobble base pair may be defined as an oligonucleotide wherein at least one nucleotide has been substituted with an inosine and/or a base able to form a wobble base pair. The skilled person knows how to test whether a nucleotide contains a base able to form a wobble base pair. Since for example inosine can form a base pair with uracil, adenine, and/or cytosine, it means that at least one nucleotide able to form a base pair with uracil, adenine and/or cytosine has been substituted with inosine. However, in order to safeguard specificity, the inosine containing oligonucleotide preferably comprises the substitution of at least one, two, three, four nucleotide(s) able to form a base pair with uracil or adenine or cytosine as long as an acceptable level of a functional activity of said oligonucleotide is retained as defined later herein.

[0017] An oligonucleotide comprising an inosine and/or a base able to form a wobble base pair is preferably an oligonucleotide, which is still able to exhibit an acceptable level of a functional activity of a corresponding oligonucleotide not comprising an inosine and/or a base able to form a wobble base pair. A functional activity of said oligonucleotide is preferably to provide an individual with a functional dystrophin protein and/or mRNA and/or at least in part decreasing the production of an aberrant dystrophin protein and/or mRNA. Each of these features are later defined herein. An

acceptable level of such a functional activity is preferably at least 50%, 60%, 70%, 80%, 90%, 95% or 100% of the functional activity of the corresponding oligonucleotide which does not comprise an inosine and/or a base able to form a wobble base pair. Such functional activity may be as measured in a muscular tissue or in a muscular cell of an individual or in vitro in a cell by comparison to the functional activity of a corresponding oligonucleotides not comprising an inosine and/or a base able to form a wobble base pair. The assessment of the functionality may be carried out at the mRNA level, preferably using RT-PCR. The assessment of the functionality may be carried out at the protein level, preferably using western blot analysis or immunofluorescence analysis of cross-sections.

[0018] Within the context of the invention, an inosine and/or a base able to form a wobble base pair as present in an oligonucleotide is/are present in a part of said oligonucleotide which is complementary to at least part of a dystrophin pre-mRNA exon or at least part of a non-exon region of a dystrophin pre-mRNA said part being a contiguous stretch comprising at least 8 nucleotides. Therefore, in a preferred embodiment, an oligonucleotide comprising an inosine and/or a nucleotide containing a base able to form a wobble base pair or a functional equivalent thereof, wherein the oligonucleotide, or a functional equivalent thereof, comprises a sequence which is complementary to at least part of a dystrophin pre-mRNA exon or at least part of a non-exon region of a dystrophin pre-mRNA said part being a contiguous stretch comprising at least 8 nucleotides and wherein said inosine and/or a nucleotide containing a base able is/are present within the oligonucleotide sequence which is complementary to at least part of a dystrophin pre-mRNA as defined in previous sentence.

[0019] However, as later defined herein such inosine and/or a base able to form a wobble base pair may also be present in a linking moiety present in an oligonucleotide of the invention. Preferred linking moieties are later defined herein.

[0020] In a preferred embodiment, such oligonucleotide is preferably a medicament. More preferably, said medicament is for preventing or treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual or a patient. As defined herein a DMD pre-mRNA preferably means the pre-mRNA of a DMD gene of a DMD or BMD patient. A patient is preferably intended to mean a patient having DMD or BMD or a patient susceptible to develop DMD or BMD due to his or her genetic background. In the case of a DMD patient, an oligonucleotide used will preferably correct at least one of the DMD mutations as present in the DMD gene of said patient and therefore will preferably create a dystrophin that will look like a BMD dystrophin: said dystrophin will preferably be a functional dystrophin as later defined herein.

[0021] In the case of a BMD patient, an oligonucleotide as used will preferably correct at least one of the BMD mutations as present in the DMD gene of said patient and therefore will preferably create a, or more of a, dystrophin, which will be more functional than the dystrophin which was originally present in said BMD patient. Even more preferably, said medicament provides an individual with a functional or more (of a) functional dystrophin protein and/or mRNA and/or at least in part decreases the production of an aberrant dystrophin protein and/or mRNA.

[0022] Preferably, a method of the invention by inducing and/or promoting skipping of at least one exon of the DMD pre-mRNA as identified herein in one or more cells, prefer-

ably muscle cells of a patient, provides said patient with an increased production of a more (of a) functional dystrophin protein and/or mRNA and/or decreases the production of an aberrant or less functional dystrophin protein and/or mRNA in said patient.

[0023] Providing a patient with a more functional dystrophin protein and/or mRNA and/or decreasing the production of an aberrant dystrophin protein and/or mRNA in said patient is typically applied in a DMD patient. Increasing the production of a more functional or functional dystrophin and/or mRNA is typically applied in a BMD patient.

[0024] Therefore a preferred method is a method, wherein a patient or one or more cells of said patient is provided with an increased production of a more functional or functional dystrophin protein and/or mRNA and/or wherein the production of an aberrant dystrophin protein and/or mRNA in said patient is decreased, wherein the level of said aberrant or more functional dystrophin protein and/or mRNA is assessed by comparison to the level of said dystrophin and/or mRNA in said patient at the onset of the method.

[0025] As defined herein, a functional dystrophin is preferably a wild type dystrophin corresponding to a protein having the amino acid sequence as identified in SEQ ID NO: 1. A functional dystrophin is preferably a dystrophin, which has an actin binding domain in its N terminal part (first 240 amino acids at the N terminus), a cystein-rich domain (amino acid 3361 till 3685) and a C terminal domain (last 325 amino acids at the C terminus) each of these domains being present in a wild type dystrophin as known to the skilled person. The amino acids indicated herein correspond to amino acids of the wild type dystrophin being represented by SEQ ID NO: 1. In another embodiment, a functional dystrophin is a dystrophin, which exhibits at least to some extent an activity of a wild type dystrophin. "At least to some extent" preferably means at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% of a corresponding activity of a wild type functional dystrophin. In this context, an activity of a wild type dystrophin is preferably binding to actin and to the dystrophin-associated glycoprotein complex (DGC)⁵⁶. Binding of dystrophin to actin and to the DGC complex may be visualized by either co-immunoprecipitation using total protein extracts or immunofluorescence analysis of cross-sections, from a biopsy of a muscle suspected to be dystrophic, as known to the skilled person.

[0026] Individuals suffering from Duchenne muscular dystrophy typically have a mutation in the gene encoding dystrophin that prevents synthesis of the complete protein, i.e a premature stop prevents the synthesis of the C-terminus of the protein. In Becker muscular dystrophy the dystrophin gene also comprises a mutation compared to the wild type but the mutation does typically not include a premature stop and the C-terminus of the protein is typically synthesized. As a result a functional dystrophin protein is synthesized that has at least the same activity in kind as a wild type protein, although not necessarily the same amount of activity. In a preferred embodiment, a functional dystrophin protein means an in frame dystrophin gene. The genome of a BMD individual typically encodes a dystrophin protein comprising the N terminal part (first 240 amino acids at the N terminus), a cystein-rich domain (amino acid 3361 till 3685) and a C terminal domain (last 325 amino acids at the C terminus) but its central rod shaped domain may be shorter than the one of a wild type dystrophin⁵⁶. Exon—skipping for the treatment of DMD is preferably but not exclusively directed to overcome a prema-

ture stop in the pre-mRNA by skipping an exon in the rod-domain shaped domain to correct the reading frame and allow synthesis of remainder of the dystrophin protein including the C-terminus, albeit that the protein is somewhat smaller as a result of a smaller rod domain. In a preferred embodiment, an individual having DMD and being treated using an oligonucleotide as defined herein will be provided a dystrophin, which exhibits at least to some extent an activity of a wild type dystrophin. More preferably, if said individual is a Duchenne patient or is suspected to be a Duchenne patient, a functional dystrophin is a dystrophin of an individual having BMD: preferably said dystrophin is able to interact with both actin and the DGC, but its central rod shaped domain may be shorter than the one of a wild type dystrophin (Aartsma-Rus et al (2006, ref 56). The central rod domain of wild type dystrophin comprises 24 spectrin-like repeats⁵⁶. For example, a central rod shaped domain of a dystrophin as provided herein may comprise 5 to 23, 10 to 22 or 12 to 18 spectrin-like repeats as long as it can bind to actin and to DGC. Decreasing the production of an aberrant dystrophin in said patient or in a cell of said patient may be assessed at the mRNA level and preferably means that 99%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or less of the initial amount of aberrant dystrophin mRNA, is still detectable by RT PCR. An aberrant dystrophin mRNA or protein is also referred to herein as a non-functional or less to non-functional or semi-functional dystrophin mRNA or protein. A non-functional pre-mRNA dystrophin is preferably leads to an out of frame dystrophin protein, which means that no dystrophin protein will be produced and/or detected. A non functional dystrophin protein is preferably a dystrophin protein which is not able to bind actin and/or members of the DGC protein complex. A non-functional dystrophin protein or dystrophin mRNA does typically not have, or does not encode a dystrophin protein with an intact C-terminus of the protein.

[0027] Increasing the production of a functional dystrophin in said patient or in a cell of said patient may be assessed at the mRNA level (by RT-PCR analysis) and preferably means that a detectable amount of a functional or in frame dystrophin mRNA is detectable by RT PCR. In another embodiment, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the detectable dystrophin mRNA is a functional or in frame dystrophin mRNA.

[0028] Increasing the production of a functional dystrophin in said patient or in a cell of said patient may be assessed at the protein level (by immunofluorescence and western blot analyses) and preferably means that a detectable amount of a functional dystrophin protein is detectable by immunofluorescence or western blot analysis. In another embodiment, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the detectable dystrophin protein is a functional dystrophin protein.

[0029] An increase or a decrease is preferably assessed in a muscular tissue or in a muscular cell of an individual or a patient by comparison to the amount present in said individual or patient before treatment with said molecule or composition of the invention. Alternatively, the comparison can be made with a muscular tissue or cell of said individual or patient, which has not yet been treated with said oligonucleotide or composition in case the treatment is local.

[0030] In a preferred method, one or more symptom(s) from a DMD or a BMD patient is/are alleviated and/or one or more characteristic(s) of a muscle cell or tissue from a DMD

or a BMD patient is/are alleviated using a molecule or a composition of the invention. Such symptoms may be assessed on the patient self. Such characteristics may be assessed at the cellular, tissue level of a given patient. An alleviation of one or more characteristics may be assessed by any of the following assays on a myogenic cell or muscle cell from a patient: reduced calcium uptake by muscle cells, decreased collagen synthesis, altered morphology, altered lipid biosynthesis, decreased oxidative stress, and/or improved muscle fiber function, integrity, and/or survival. These parameters are usually assessed using immunofluorescence and/or histochemical analyses of cross sections of muscle biopsies.

[0031] Alleviating one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual using a molecule or a composition of the invention may be assessed by any of the following assays: prolongation of time to loss of walking, improvement of muscle strength, improvement of the ability to lift weight, improvement of the time taken to rise from the floor, improvement in the nine-meter walking time, improvement in the time taken for four-stairs climbing, improvement of the leg function grade, improvement of the pulmonary function, improvement of cardiac function, improvement of the quality of life. Each of these assays is known to the skilled person. As an example, the publication of Manzur et al (2008, ref 58) gives an extensive explanation of each of these assays. For each of these assays, as soon as a detectable improvement or prolongation of a parameter measured in an assay has been found, it will preferably mean that one or more symptoms of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy has been alleviated in an individual using a molecule or composition of the invention. Detectable improvement or prolongation is preferably a statistically significant improvement or prolongation as described in Hodgetts et al (2006, ref 57). Alternatively, the alleviation of one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy may be assessed by measuring an improvement of a muscle fiber function, integrity and/or survival as later defined herein.

[0032] An oligonucleotide as used herein preferably comprises an antisense oligonucleotide or antisense oligoribonucleotide. In a preferred embodiment an exon skipping technique is applied. Exon skipping interferes with the natural splicing processes occurring within a eukaryotic cell. In higher eukaryotes the genetic information for proteins in the DNA of the cell is encoded in exons which are separated from each other by intronic sequences. These introns are in some cases very long. The transcription machinery of eukaryotes generates a pre-mRNA which contains both exons and introns, while the splicing machinery, often already during the production of the pre-mRNA, generates the actual coding region for the protein by splicing together the exons present in the pre-mRNA.

[0033] Exon-skipping results in mature mRNA that lacks at least one skipped exon. Thus, when said exon codes for amino acids, exon skipping leads to the expression of an altered product. Technology for exon-skipping is currently directed towards the use of antisense oligonucleotides (AONs). Much of this work is done in the mdx mouse model for Duchenne muscular dystrophy. The mdx mouse carries a nonsense mutation in exon 23. Despite the mdx mutation, which should preclude the synthesis of a functional dystrophin protein, rare, naturally occurring dystrophin positive fibers have been

observed in mdx muscle tissue. These dystrophin-positive fibers are thought to have arisen from an apparently naturally occurring exon-skipping mechanism, either due to somatic mutations or through alternative splicing. AONs directed to, respectively, the 3' and/or 5' splice sites of introns 22 and 23 in dystrophin pre-mRNA, have been shown to interfere with factors normally involved in removal of intron 23 so that also exon 23 was removed from the mRNA^{3, 5, 6, 39, 40}.

[0034] By the targeted skipping of a specific exon, a DMD phenotype is converted into a milder BMD phenotype. The skipping of an exon is preferably induced by the binding of AONs targeting either one or both of the splice sites, or exon-internal sequences. An oligonucleotide directed toward an exon internal sequence typically exhibits no overlap with non-exon sequences. It preferably does not overlap with the splice sites at least not insofar, as these are present in the intron. An oligonucleotide directed toward an exon internal sequence preferably does not contain a sequence complementary to an adjacent intron. Further provided is thus an oligonucleotide according to the invention, wherein said oligonucleotide, or a functional equivalent thereof, is for inhibiting inclusion of an exon of a dystrophin pre-mRNA into mRNA produced from splicing of said pre-mRNA. An exon skipping technique is preferably applied such that the absence of an exon from mRNA produced from dystrophin pre-mRNA generates a coding region for a more functional—albeit shorter—dystrophin protein. In this context, inhibiting inclusion of an exon preferably means that the detection of the original, aberrant dystrophin mRNA and/or protein is decreased as earlier defined herein.

[0035] Since an exon of a dystrophin pre-mRNA will only be included into the resulting mRNA when both the splice sites are recognised by the spliceosome complex, splice sites have been obvious targets for AONs. One embodiment therefore provides an oligonucleotide, or a functional equivalent thereof, comprising a sequence which is complementary to a non-exon region of a dystrophin pre mRNA. In one embodiment an AON is used which is solely complementary to a non-exon region of a dystrophin pre mRNA. This is however not necessary: it is also possible to use an AON which comprises an intron-specific sequence as well as exon-specific sequence. Such AON comprises a sequence which is complementary to a non-exon region of a dystrophin pre mRNA, as well as a sequence which is complementary to an exon region of a dystrophin pre mRNA. Of course, an AON is not necessarily complementary to the entire sequence of a dystrophin exon or intron. AONs, which are complementary to a part of such exon or intron are preferred. An AON is preferably complementary to at least part of a dystrophin exon and/or intron, said part having at least 8, 10, 13, 15, 20 nucleotides.

[0036] Splicing of a dystrophin pre-mRNA occurs via two sequential transesterification reactions. First, the 2'OH of a specific branch-point nucleotide within the intron that is defined during spliceosome assembly performs a nucleophilic attack on the first nucleotide of the intron at the 5' splice site forming the lariat intermediate. Second, the 3'OH of the released 5' exon then performs a nucleophilic attack at the last nucleotide of the intron at the 3' splice site thus joining the exons and releasing the intron lariat. The branch point and splice sites of an intron are thus involved in a splicing event. Hence, an oligonucleotide comprising a sequence, which is complementary to such branch point and/or splice site is preferably used for exon skipping. Further provided is therefore an oligonucleotide, or a functional equivalent thereof,

which comprises a sequence which is complementary to a splice site and/or branch point of a dystrophin pre mRNA.

[0037] Since splice sites contain consensus sequences, the use of an oligonucleotide or a functional equivalent thereof (herein also called an AON) comprising a sequence which is complementary of a splice site involves the risk of promiscuous hybridization. Hybridization of AONs to other splice sites than the sites of the exon to be skipped could easily interfere with the accuracy of the splicing process. To overcome these and other potential problems related to the use of AONs which are complementary to an intron sequence, one preferred embodiment provides an oligonucleotide, or a functional equivalent thereof, comprising a sequence which is complementary to a dystrophin pre-mRNA exon. Preferably, said AON is capable of specifically inhibiting an exon inclusion signal of at least one exon in said dystrophin pre-mRNA. Interfering with an exon inclusion signal (EIS) has the advantage that such elements are located within the exon. By providing an AON for the interior of the exon to be skipped, it is possible to interfere with the exon inclusion signal thereby effectively masking the exon from the splicing apparatus. The failure of the splicing apparatus to recognize the exon to be skipped thus leads to exclusion of the exon from the final mRNA. This embodiment does not interfere directly with the enzymatic process of the splicing machinery (the joining of the exons). It is thought that this allows the method to be more specific and/or reliable. It is thought that an EIS is a particular structure of an exon that allows splice acceptor and donor to assume a particular spatial conformation. In this concept, it is the particular spatial conformation that enables the splicing machinery to recognize the exon. However, the invention is certainly not limited to this model. In a preferred embodiment, use is made of an oligonucleotide, which is capable of binding to an exon and is capable of inhibiting an EIS. An AON may specifically contact said exon at any point and still be able to specifically inhibit said EIS.

[0038] Within the context of the invention, a functional equivalent of an oligonucleotide preferably means an oligonucleotide as defined herein wherein one or more nucleotides have been substituted and wherein an activity of said functional equivalent is retained to at least some extent. Preferably, an activity of said functional equivalent is providing a functional dystrophin protein. Said activity of said functional equivalent is therefore preferably assessed by quantifying the amount of a functional dystrophin protein or by quantifying the amount of a functional dystrophin mRNA. A functional dystrophin protein (or a functional dystrophin mRNA) is herein preferably defined as being a dystrophin protein (or a dystrophin protein encoded by said mRNA) able to bind actin and members of the DGC protein. The assessment of said activity of an oligonucleotide is preferably done by RT-PCR (mRNA) or by immunofluorescence or Western blot analyses (protein). Said activity is preferably retained to at least some extent when it represents at least 50%, or at least 60%, or at least 70% or at least 80% or at least 90% or at least 95% or more of corresponding activity of said oligonucleotide the functional equivalent derives from. Such activity may be measured in a muscular tissue or in a muscular cell of an individual or in vitro in a cell by comparison to an activity of a corresponding oligonucleotide of said oligonucleotide the functional equivalent derives from. Throughout this application, when the word oligonucleotide is used it may be replaced by a functional equivalent thereof as defined herein.

[0039] Hence, an oligonucleotide, or a functional equivalent thereof, comprising or consisting of a sequence which is complementary to a dystrophin pre-mRNA exon provides good DMD therapeutic results. In one preferred embodiment an oligonucleotide, or a functional equivalent thereof, is used which comprises or consists of a sequence which is complementary to at least part of either dystrophin pre-mRNA exons 2 to 75 said part having or comprising at least 13 nucleotides. However, said part may also have at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 nucleotides. A part of dystrophin pre-mRNA to which an oligonucleotide is complementary may also be called a contiguous stretch of dystrophin pre-mRNA.

[0040] Most preferably an AON is used which comprises or consists of a sequence which is complementary to at least part of dystrophin pre-mRNA exon 51, 45, 53, 44, 46, 52, 50, 43, 6, 7, 8, 55, 2, 11, 17, 19, 21, 57, 59, 62, 63, 65, 66, 69, and/or 75 said part having or comprising at least 13 nucleotides. However, said part may also have at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 nucleotides. More preferred oligonucleotides are represented by a sequence that comprises or consists of each of the following sequences SEQ ID NO: 2 to SEQ ID NO:539 wherein at least one inosine and/or a base able to form a wobble base pair is present in said sequence. Preferably, an inosine has been introduced in one of these sequences to replace a guanosine, adenine, or a uracil. Accordingly, an even more preferred oligonucleotide as used herein is represented by a sequence that comprises or consists of SEQ ID NO:2 to SEQ ID NO:486 or SEQ ID NO:539, even more preferably SEQ ID NO:2 to NO 237 or SEQ ID NO:539, most preferably SEQ ID NO:76 wherein at least one inosine and/or a base able to form a wobble base pair is present in said sequence. Preferably, an inosine has been introduced in one of these sequences to replace a guanosine, adenine, or a uracil.

[0041] Accordingly, in another preferred embodiment, an oligonucleotide as used herein is represented by a sequence that comprises or consists of SEQ ID NO:540 to SEQ ID NO:576. More preferably, an oligonucleotide as used herein is represented by a sequence that comprises or consists of SEQ ID NO:557.

[0042] Said exons are listed in decreasing order of patient population applicability. Hence, the use of an AON comprising a sequence, which is complementary to at least part of dystrophin pre-mRNA exon 51 is suitable for use in a larger part of the DMD patient population as compared to an AON comprising a sequence which is complementary to dystrophin pre-mRNA exon 44, et cetera.

[0043] In a preferred embodiment, an oligonucleotide of the invention, which comprises a sequence that is complementary to part of dystrophin pre-mRNA is such that the complementary part is at least 50% of the length of the oligonucleotide of the invention, more preferably at least 60%, even more preferably at least 70%, even more preferably at least 80%, even more preferably at least 90% or even more preferably at least 95%, or even more preferably 98% or even more preferably at least 99%, or even more preferably 100%. In a most preferred embodiment, the oligonucleotide of the invention consists of a sequence that is complementary to part of dystrophin pre-mRNA as defined herein. As an example, an oligonucleotide may comprise a sequence that is complementary to part of dystrophin pre-mRNA as defined herein

and additional flanking sequences. In a more preferred embodiment, the length of said complementary part of said oligonucleotide is of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 nucleotides. Preferably, additional flanking sequences are used to modify the binding of a protein to the oligonucleotide, or to modify a thermodynamic property of the oligonucleotide, more preferably to modify target RNA binding affinity.

[0044] One preferred embodiment provides an oligonucleotide, or a functional equivalent thereof which comprises:

[0045] a sequence which is complementary to a region of a dystrophin pre-mRNA exon that is hybridized to another part of a dystrophin pre-mRNA exon (closed structure), and

[0046] a sequence which is complementary to a region of a dystrophin pre-mRNA exon that is not hybridized in said dystrophin pre-mRNA (open structure).

[0047] For this embodiment, reference is made to WO 2004/083432, which is incorporated by reference in its entirety. RNA molecules exhibit strong secondary structures, mostly due to base pairing of complementary or partly complementary stretches within the same RNA. It has long since been thought that structures in the RNA play a role in the function of the RNA. Without being bound by theory, it is believed that the secondary structure of the RNA of an exon plays a role in structuring the splicing process. The structure of an exon is one parameter which is believed to direct its inclusion into the mRNA. However, other parameters may also play a role therein. Herein this signalling function is referred to as an exon inclusion signal. A complementary oligonucleotide of this embodiment is capable of interfering with the structure of the exon and thereby capable of interfering with the exon inclusion signal of the exon. It has been found that many complementary oligonucleotides indeed comprise this capacity, some more efficient than others. Oligonucleotides of this preferred embodiment, i.e. those with the said overlap directed towards open and closed structures in the native exon RNA, are a selection from all possible oligonucleotides. The selection encompasses oligonucleotides that can efficiently interfere with an exon inclusion signal. Without being bound by theory it is thought that the overlap with an open structure improves the invasion efficiency of the oligonucleotide and prevents the binding of splicing factors (i.e. increases the efficiency with which the oligonucleotide can enter the structure), whereas the overlap with the closed structure subsequently increases the efficiency of interfering with the secondary structure of the RNA of the exon, and thereby interfere with the exon inclusion signal. It is found that the length of the partial complementarity to both the closed and the open structure is not extremely restricted. We have observed high efficiencies with oligonucleotides with variable lengths of complementarity in either structure. The term complementarity is used herein to refer to a stretch of nucleic acids that can hybridise to another stretch of nucleic acids under physiological conditions. It is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand. For instance, when designing the oligonucleotide one may want to incorporate for instance a residue that does not base pair with the base on the complementary strand. Mismatches may, to some extent, be allowed, if under the circumstances in the cell, the stretch of nucleotides is sufficiently capable of hybridising to the complementary part. In this context, "sufficiently" preferably means that using a

gel mobility shift assay as described in example 1 of EP 1 619 249, binding of an oligonucleotide is detectable. Optionally, said oligonucleotide may further be tested by transfection into muscle cells of patients. Skipping of the targeted exon may be assessed by RT-PCR (as described in EP 1 619 249). The complementary regions are preferably designed such that, when combined, they are specific for the exon in the pre-mRNA. Such specificity may be created with various lengths of complementary regions as this depends on the actual sequences in other (pre-)mRNA in the system. The risk that also one or more other pre-mRNA will be able to hybridise to the oligonucleotide decreases with increasing size of the oligonucleotide. It is clear that oligonucleotides comprising mismatches in the region of complementarity but that retain the capacity to hybridise to the targeted region(s) in the pre-mRNA, can be used in the present invention. However, preferably at least the complementary parts do not comprise such mismatches as these typically have a higher efficiency and a higher specificity, than oligonucleotides having such mismatches in one or more complementary regions. It is thought, that higher hybridisation strengths, (i.e. increasing number of interactions with the opposing strand) are favourable in increasing the efficiency of the process of interfering with the splicing machinery of the system. Preferably, the complementarity is between 90 and 100%. In general this allows for approximately 1 or 2 mismatch(es) in an oligonucleotide of around 20 nucleotides

[0048] The secondary structure is best analysed in the context of the pre-mRNA wherein the exon resides. Such structure may be analysed in the actual RNA. However, it is currently possible to predict the secondary structure of an RNA molecule (at lowest energy costs) quite well using structure-modelling programs. A non-limiting example of a suitable program is RNA mfold version 3.1 server⁴¹. A person skilled in the art will be able to predict, with suitable reproducibility, a likely structure of the exon, given the nucleotide sequence. Best predictions are obtained when providing such modelling programs with both the exon and flanking intron sequences. It is typically not necessary to model the structure of the entire pre-mRNA.

[0049] The open and closed structure to which the oligonucleotide is directed, are preferably adjacent to one another. It is thought, that in this way the annealing of the oligonucleotide to the open structure induces opening of the closed structure whereupon annealing progresses into this closed structure. Through this action the previously closed structure assumes a different conformation. The different conformation results in the disruption of the exon inclusion signal. However, when potential (cryptic) splice acceptor and/or donor sequences are present within the targeted exon, occasionally a new exon inclusion signal is generated defining a different (neo) exon, i.e. with a different 5' end, a different 3' end, or both. This type of activity is within the scope of the present invention as the targeted exon is excluded from the mRNA. The presence of a new exon, containing part of the targeted exon, in the mRNA does not alter the fact that the targeted exon, as such, is excluded. The inclusion of a neo-exon can be seen as a side effect, which occurs only occasionally. There are two possibilities when exon skipping is used to restore (part of) an open reading frame of dystrophin that is disrupted as a result of a mutation. One is that the neo-exon is functional in the restoration of the reading frame, whereas in the other case the reading frame is not restored. When selecting oligonucleotides for restoring dystrophin

reading frames by means of exon-skipping it is of course clear that under these conditions only those oligonucleotides are selected that indeed result in exon-skipping that restores the dystrophin open reading frame, with or without a neo-exon.

[0050] Further provided is an oligonucleotide, or a functional equivalent thereof, comprising a sequence that is complementary to a binding site for a serine-arginine (SR) protein in RNA of an exon of a dystrophin pre-mRNA. In WO 2006/112705 we have disclosed the presence of a correlation between the effectivity of an exon-internal antisense oligonucleotide (AON) in inducing exon skipping and the presence of a (for example by ESE finder) predicted SR binding site in the target pre-mRNA site of said AON.

[0051] Therefore, in one embodiment an oligonucleotide is generated comprising determining a (putative) binding site for an SR (Ser-Arg) protein in RNA of a dystrophin exon and producing an oligonucleotide that is complementary to said RNA and that at least partly overlaps said (putative) binding site. The term "at least partly overlaps" is defined herein as to comprise an overlap of only a single nucleotide of an SR binding site as well as multiple nucleotides of said binding site as well as a complete overlap of said binding site. This embodiment preferably further comprises determining from a secondary structure of said RNA, a region that is hybridised to another part of said RNA (closed structure) and a region that is not hybridised in said structure (open structure), and subsequently generating an oligonucleotide that at least partly overlaps said (putative) binding site and that overlaps at least part of said closed structure and overlaps at least part of said open structure. In this way we increase the chance of obtaining an oligonucleotide that is capable of interfering with the exon inclusion from the pre-mRNA into mRNA. It is possible that a first selected SR-binding region does not have the requested open-closed structure in which case another (second) SR protein binding site is selected which is then subsequently tested for the presence of an open-closed structure. This process is continued until a sequence is identified which contains an SR protein binding site as well as a(n) (partly overlapping) open-closed structure. This sequence is then used to design an oligonucleotide which is complementary to said sequence.

[0052] Such a method, for generating an oligonucleotide, is also performed by reversing the described order, i.e. first generating an oligonucleotide comprising determining, from a secondary structure of RNA from a dystrophin exon, a region that assumes a structure that is hybridised to another part of said RNA (closed structure) and a region that is not hybridised in said structure (open structure), and subsequently generating an oligonucleotide, of which at least a part of said oligonucleotide is complementary to said closed structure and of which at least another part of said oligonucleotide is complementary to said open structure. This is then followed by determining whether an SR protein binding site at least overlaps with said open/closed structure. In this way the method of WO 2004/083432 is improved. In yet another embodiment the selections are performed simultaneously.

[0053] Without wishing to be bound by any theory it is currently thought that use of an oligonucleotide directed to an SR protein binding site results in (at least partly) impairing the binding of an SR protein to the binding site of an SR protein which results in disrupted or impaired splicing.

[0054] Preferably, an open/closed structure and an SR protein binding site partly overlap and even more preferred an open/closed structure completely overlaps an SR protein

binding site or an SR protein binding site completely overlaps an open/closed structure. This allows for an improved disruption of exon inclusion.

[0055] Besides consensus splice sites sequences, many (if not all) exons contain splicing regulatory sequences such as exonic splicing enhancer (ESE) sequences to facilitate the recognition of genuine splice sites by the spliceosome^{42, 43}. A subgroup of splicing factors, called the SR proteins, can bind to these ESEs and recruit other splicing factors, such as U1 and U2AF to (weakly defined) splice sites. The binding sites of the four most abundant SR proteins (SF2/ASF, SC35, SRp40 and SRp55) have been analyzed in detail and these results are implemented in ESE finder, a web source that predicts potential binding sites for these SR proteins^{42, 43}. There is a correlation between the effectiveness of an AON and the presence/absence of an SF2/ASF, SC35 and SRp40 binding site. In a preferred embodiment, the invention thus provides a combination as described above, wherein said SR protein is SF2/ASF or SC35 or SRp40.

[0056] In one embodiment an oligonucleotide, or a functional equivalent thereof is capable of specifically binding a regulatory RNA sequence which is required for the correct splicing of a dystrophin exon in a transcript. Several cis-acting RNA sequences are required for the correct splicing of exons in a transcript. In particular, supplementary elements such as intronic or exonic splicing enhancers (ISEs and ESEs) or silencers (ISSs and ESSs) are identified to regulate specific and efficient splicing of constitutive and alternative exons. Using sequence-specific antisense oligonucleotides (AONs) that bind to the elements, their regulatory function is disturbed so that the exon is skipped, as shown for DMD. Hence, in one preferred embodiment an oligonucleotide or functional equivalent thereof is used which is complementary to an intronic splicing enhancer (ISE), an exonic splicing enhancer (ESE), an intronic splicing silencer (ISS) and/or an exonic splicing silencer (ESS). As already described herein before, a dystrophin exon is in one preferred embodiment skipped by an agent capable of specifically inhibiting an exon inclusion signal of said exon, so that said exon is not recognized by the splicing machinery as a part that needs to be included in the mRNA. As a result, a mRNA without said exon is formed.

[0057] An AON used herein is preferably complementary to a consecutive part or a contiguous stretch of between 8 and 50 nucleotides of dystrophin exon RNA or dystrophin intron RNA. In one embodiment an AON used herein is complementary to a consecutive part or a contiguous stretch of between 14 and 50 nucleotides of a dystrophin exon RNA or dystrophin intron RNA. Preferably, said AON is complementary to a consecutive part or contiguous stretch of between 14 and 25 nucleotides of said exon RNA. More preferably, an AON is used which comprises a sequence which is complementary to a consecutive part or a contiguous stretch of between 20 and 25 nucleotides of a dystrophin exon RNA or a dystrophin intron RNA.

[0058] Different types of nucleic acid may be used to generate an oligonucleotide. Preferably, said oligonucleotide comprises RNA, as RNA/RNA hybrids are very stable. Since one of the aims of the exon skipping technique is to direct splicing in subjects it is preferred that the oligonucleotide RNA comprises a modification providing the RNA with an additional property, for instance resistance to endonucleases, exonucleases, and RNaseH, additional hybridisation strength, increased stability (for instance in a bodily fluid), increased or decreased flexibility, reduced toxicity, increased

intracellular transport, tissue-specificity, etc. Preferably, said modification comprises a 2'-O-methyl-phosphorothioate oligoribonucleotide modification. Preferably, said modification comprises a 2'-O-methyl-phosphorothioate oligodeoxyribonucleotide modification. One embodiment thus provides an oligonucleotide is used which comprises RNA which contains a modification, preferably a 2'-O-methyl modified ribose (RNA) or deoxyribose (DNA) modification.

[0059] In one embodiment the invention provides a hybrid oligonucleotide comprising an oligonucleotide comprising a 2'-O-methyl-phosphorothioate oligo(deoxy)ribonucleotide modification and locked nucleic acid. This particular oligonucleotide comprises better sequence specificity compared to an equivalent consisting of locked nucleic acid, and comprises improved effectivity when compared with an oligonucleotide consisting of 2'-O-methyl-phosphorothioate oligo (deoxy)ribonucleotide modification.

[0060] With the advent of nucleic acid mimicking technology it has become possible to generate molecules that have a similar, preferably the same hybridisation characteristics in kind not necessarily in amount as nucleic acid itself. Such functional equivalents are of course also suitable for use in the invention. Preferred examples of functional equivalents of an oligonucleotide are peptide nucleic acid and/or locked nucleic acid. Most preferably, a morpholino phosphorodiamidate is used. Suitable but non-limiting examples of equivalents of oligonucleotides of the invention can be found in⁴⁴⁻⁵⁰. Hybrids between one or more of the equivalents among each other and/or together with nucleic acid are of course also suitable. In a preferred embodiment locked nucleic acid is used as a functional equivalent of an oligonucleotide, as locked nucleic acid displays a higher target affinity and reduced toxicity and therefore shows a higher efficiency of exon skipping.

[0061] In one embodiment an oligonucleotide, or a functional equivalent thereof, which is capable of inhibiting inclusion of a dystrophin exon into dystrophin mRNA is combined with at least one other oligonucleotide, or functional equivalent thereof, that is capable of inhibiting inclusion of another dystrophin exon into dystrophin mRNA. This way, inclusion of two or more exons of a dystrophin pre-mRNA in mRNA produced from this pre-mRNA is prevented. This embodiment is further referred to as double- or multi-exon skipping^{2, 15}. In most cases double-exon skipping results in the exclusion of only the two targeted exons from the dystrophin pre-mRNA. However, in other cases it was found that the targeted exons and the entire region in between said exons in said pre-mRNA were not present in the produced mRNA even when other exons (intervening exons) were present in such region. This multi-exon skipping was notably so for the combination of oligonucleotides derived from the DMD gene, wherein one oligonucleotide for exon 45 and one oligonucleotide for exon 51 was added to a cell transcribing the DMD gene. Such a set-up resulted in mRNA being produced that did not contain exons 45 to 51. Apparently, the structure of the pre-mRNA in the presence of the mentioned oligonucleotides was such that the splicing machinery was stimulated to connect exons 44 and 52 to each other. Other preferred examples of multi-exon skipping are:

[0062] the use of an oligonucleotide targeting exon 17, and a second one exon 48 which may result in the skipping of said both exons or of the entire region between exon 17 and exon 48.

- [0063] the use of an oligonucleotide targeting exon 17, and a second one exon 51 which may result in the skipping of said both exons or of the entire region between exon 17 and exon 51.
- [0064] the use of an oligonucleotide targeting exon 42, and a second one exon 55 which may result in the skipping of said both exons or of the entire region between exon 42 and exon 55.
- [0065] the use of an oligonucleotide targeting exon 43, and a second one exon 51 which may result in the skipping of said both exons or of the entire region between exon 43 and exon 51.
- [0066] the use of an oligonucleotide targeting exon 43, and a second one exon 55 which may result in the skipping of said both exons or of the entire region between exon 43 and exon 55.
- [0067] the use of an oligonucleotide targeting exon 45, and a second one exon 55 which may result in the skipping of said both exons or of the entire region between exon 45 and exon 55.
- [0068] the use of an oligonucleotide targeting exon 45, and a second one exon 59 which may result in the skipping of said both exons or of the entire region between exon 45 and exon 59.
- [0069] the use of an oligonucleotide targeting exon 48, and a second one exon 59 which may result in the skipping of said both exons or of the entire region between exon 48 and exon 59.
- [0070] the use of an oligonucleotide targeting exon 50, and a second one exon 51 which may result in the skipping of said both exons.
- [0071] the use of an oligonucleotide targeting exon 51, and a second one exon 52 which may result in the skipping of said both exons.
- [0072] Further provided is therefore an oligonucleotide which comprises at least 8, preferably between 16 to 80, consecutive nucleotides that are complementary to a first exon of a dystrophin pre-mRNA and wherein a nucleotide sequence is used which comprises at least 8, preferably between 16 to 80, consecutive nucleotides that are complementary to a second exon of said dystrophin pre-mRNA. Said first and said second exon may be the same.
- [0073] In one preferred embodiment said first and said second exon are separated in said dystrophin pre-mRNA by at least one exon to which said oligonucleotide is not complementary. Alternatively, said first and said second exon are adjacent.
- [0074] It is possible to specifically promote the skipping of also the intervening exons by providing a linkage between the two complementary oligonucleotides. Hence, in one embodiment stretches of nucleotides complementary to at least two dystrophin exons are separated by a linking moiety. The at least two stretches of nucleotides are thus linked in this embodiment so as to form a single molecule. Further provided is therefore an oligonucleotide, or functional equivalent thereof which is complementary to at least two exons in a dystrophin pre-mRNA, said oligonucleotide or functional equivalent comprising at least two parts wherein a first part comprises an oligonucleotide having at least 8, preferably between 16 to 80, consecutive nucleotides that are complementary to a first of said at least two exons and wherein a second part comprises an oligonucleotide having at least 8, preferably between 16 to 80, consecutive nucleotides that are complementary to a second exon in said dystrophin pre-

mRNA. The linkage may be through any means, but is preferably accomplished through a nucleotide linkage. In the latter case, the number of nucleotides that do not contain an overlap between one or the other complementary exon can be zero, but is preferably between 4 to 40 nucleotides. The linking moiety can be any type of moiety capable of linking oligonucleotides. Preferably, said linking moiety comprises at least 4 uracil nucleotides. Currently, many different compounds are available that mimic hybridisation characteristics of oligonucleotides. Such a compound, called herein a functional equivalent of an oligonucleotide, is also suitable for the present invention if such equivalent comprises similar hybridisation characteristics in kind not necessarily in amount. Suitable functional equivalents are mentioned earlier in this description. As mentioned, oligonucleotides of the invention do not have to consist of only oligonucleotides that contribute to hybridisation to the targeted exon. There may be additional material and/or nucleotides added.

[0075] The DMD gene is a large gene, with many different exons. Considering that the gene is located on the X-chromosome, it is mostly boys that are affected, although girls can also be affected by the disease, as they may receive a bad copy of the gene from both parents, or are suffering from a particularly biased inactivation of the functional allele due to a particularly biased X chromosome inactivation in their muscle cells. The protein is encoded by a plurality of exons (79) over a range of at least 2.4 Mb. Defects may occur in any part of the DMD gene. Skipping of a particular exon or particular exons can, very often, result in a restructured mRNA that encodes a shorter than normal but at least partially functional dystrophin protein. A practical problem in the development of a medicament based on exon-skipping technology is the plurality of mutations that may result in a deficiency in functional dystrophin protein in the cell. Despite the fact that already multiple different mutations can be corrected for by the skipping of a single exon, this plurality of mutations, requires the generation of a series of different pharmaceuticals as for different mutations different exons need to be skipped. An advantage of an oligonucleotide or of a composition comprising at least two distinct oligonucleotide as later defined herein capable of inducing skipping of two or more exons, is that more than one exon can be skipped with a single pharmaceutical. This property is not only practically very useful in that only a limited number of pharmaceuticals need to be generated for treating many different DMD or particular, severe BMD mutations. Another option now open to the person skilled in the art is to select particularly functional restructured dystrophin proteins and produce compounds capable of generating these preferred dystrophin proteins. Such preferred end results are further referred to as mild phenotype dystrophins.

[0076] Dose ranges of oligonucleotide according to the invention are preferably designed on the basis of rising dose studies in clinical trials (in vivo use) for which rigorous protocol requirements exist. A molecule or an oligonucleotide as defined herein may be used at a dose which is ranged between 0.1 and 20 mg/kg, preferably 0.5 and 10 mg/kg.

[0077] In a preferred embodiment, a concentration of an oligonucleotide as defined herein, which is ranged between 0.1 nM and 1 μ M is used. Preferably, this range is for in vitro use in a cellular model such as muscular cells or muscular tissue. More preferably, the concentration used is ranged between 0.3 to 400 nM, even more preferably between 1 to 200 nM. If several oligonucleotides are used, this concentra-

tion or dose may refer to the total concentration or dose of oligonucleotides or the concentration or dose of each oligonucleotide added.

[0078] The ranges of concentration or dose of oligonucleotide(s) as given above are preferred concentrations or doses for in vitro or ex vivo uses. The skilled person will understand that depending on the oligonucleotide(s) used, the target cell to be treated, the gene target and its expression levels, the medium used and the transfection and incubation conditions, the concentration or dose of oligonucleotide(s) used may further vary and may need to be optimised any further.

[0079] An oligonucleotide as defined herein for use according to the invention may be suitable for administration to a cell, tissue and/or an organ in vivo of individuals affected by or at risk of developing DMD or BMD, and may be administered in vivo, ex vivo or in vitro. Said oligonucleotide may be directly or indirectly administered to a cell, tissue and/or an organ in vivo of an individual affected by or at risk of developing DMD or BMD, and may be administered directly or indirectly in vivo, ex vivo or in vitro. As Duchenne and Becker muscular dystrophy have a pronounced phenotype in muscle cells, it is preferred that said cells are muscle cells, it is further preferred that said tissue is a muscular tissue and/or it is further preferred that said organ comprises or consists of a muscular tissue. A preferred organ is the heart. Preferably, said cells comprise a gene encoding a mutant dystrophin protein. Preferably, said cells are cells of an individual suffering from DMD or BMD.

[0080] An oligonucleotide of the invention may be indirectly administered using suitable means known in the art. An oligonucleotide may for example be provided to an individual or a cell, tissue or organ of said individual in the form of an expression vector wherein the expression vector encodes a transcript comprising said oligonucleotide. The expression vector is preferably introduced into a cell, tissue, organ or individual via a gene delivery vehicle. In a preferred embodiment, there is provided a viral-based expression vector comprising an expression cassette or a transcription cassette that drives expression or transcription of a molecule as identified herein. A preferred delivery vehicle is a viral vector such as an adeno-associated virus vector (AAV), or a retroviral vector such as a lentivirus vector^{4, 51, 52} and the like. Also, plasmids, artificial chromosomes, plasmids suitable for targeted homologous recombination and integration in the human genome of cells may be suitably applied for delivery of an oligonucleotide as defined herein. Preferred for the current invention are those vectors wherein transcription is driven from PolIII promoters, and/or wherein transcripts are in the form fusions with U1 or U7 transcripts, which yield good results for delivering small transcripts. It is within the skill of the artisan to design suitable transcripts. Preferred are PolIII driven transcripts. Preferably, in the form of a fusion transcript with an U1 or U7 transcript^{4, 51, 52}. Such fusions may be generated as described^{53, 54}. The oligonucleotide may be delivered as is. However, the oligonucleotide may also be encoded by the viral vector. Typically, this is in the form of an RNA transcript that comprises the sequence of the oligonucleotide in a part of the transcript.

[0081] Improvements in means for providing an individual or a cell, tissue, organ of said individual with an oligonucleotide and/or an equivalent thereof, are anticipated considering the progress that has already thus far been achieved. Such future improvements may of course be incorporated to achieve the mentioned effect on restructuring of mRNA using

a method of the invention. An oligonucleotide and/or an equivalent thereof can be delivered as is to an individual, a cell, tissue or organ of said individual. When administering an oligonucleotide and/or an equivalent thereof, it is preferred that an oligonucleotide and/or an equivalent thereof is dissolved in a solution that is compatible with the delivery method. For intravenous, subcutaneous, intramuscular, intrathecal and/or intraventricular administration it is preferred that the solution is a physiological salt solution. Particularly preferred in the invention is the use of an excipient that will aid in delivery of each of the constituents as defined herein to a cell and/or into a cell, preferably a muscle cell. Preferred are excipients capable of forming complexes, nanoparticles, micelles, vesicles and/or liposomes that deliver each constituent as defined herein, complexed or trapped in a vesicle or liposome through a cell membrane. Many of these excipients are known in the art. Suitable excipients comprise polyethylenimine (PEI), or similar cationic polymers, including polypropyleneimine or polyethylenimine copolymers (PECs) and derivatives,

synthetic amphiphils (SAINT-18), Lipofectin™, DOTAP and/or viral capsid proteins that are capable of self assembly into particles that can deliver each constituent as defined herein to a cell, preferably a muscle cell. Such excipients have been shown to efficiently deliver an oligonucleotide such as antisense nucleic acids to a wide variety of cultured cells, including muscle cells. Their high transfection potential is combined with an excepted low to moderate toxicity in terms of overall cell survival. The ease of structural modification can be used to allow further modifications and the analysis of their further (in vivo) nucleic acid transfer characteristics and toxicity.

[0082] Lipofectin represents an example of a liposomal transfection agent. It consists of two lipid components, a cationic lipid N-[1-(2,3 dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) (cp. DOTAP which is the methylsulfate salt) and a neutral lipid dioleoylphosphatidylethanolamine (DOPE). The neutral component mediates the intracellular release. Another group of delivery systems are polymeric nanoparticles.

[0083] Polycations such like diethylaminoethylaminoethyl (DEAE)-dextran, which are well known as DNA transfection reagent can be combined with butylcyanoacrylate (BCA) and hexylcyanoacrylate (PHCA) to formulate cationic nanoparticles that can deliver each constituent as defined herein, preferably an oligonucleotide across cell membranes into cells.

[0084] In addition to these common nanoparticle materials, the cationic peptide protamine offers an alternative approach to formulate an oligonucleotide with colloids. This colloidal nanoparticle system can form so called proticles, which can be prepared by a simple self-assembly process to package and mediate intracellular release of an oligonucleotide. The skilled person may select and adapt any of the above or other commercially available alternative excipients and delivery systems to package and deliver an oligonucleotide for use in the current invention to deliver it for the treatment of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in humans.

[0085] In addition, an oligonucleotide could be covalently or non-covalently linked to a targeting ligand specifically designed to facilitate the uptake in to the cell, cytoplasm and/or its nucleus. Such ligand could comprise (i) a compound (including but not limited to peptide(-like) structures)

recognising cell, tissue or organ specific elements facilitating cellular uptake and/or (ii) a chemical compound able to facilitate the uptake in to cells and/or the intracellular release of an oligonucleotide from vesicles, e.g. endosomes or lysosomes.

[0086] Therefore, in a preferred embodiment, an oligonucleotide is formulated in a composition or a medicament or a composition, which is provided with at least an excipient and/or a targeting ligand for delivery and/or a delivery device thereof to a cell and/or enhancing its intracellular delivery. Accordingly, the invention also encompasses a pharmaceutically acceptable composition comprising an oligonucleotide and further comprising at least one excipient and/or a targeting ligand for delivery and/or a delivery device of said oligonucleotide to a cell and/or enhancing its intracellular delivery. It is to be understood that if a composition comprises an additional constituent such as an adjunct compound as later defined herein, each constituent of the composition may not be formulated in one single combination or composition or preparation. Depending on their identity, the skilled person will know which type of formulation is the most appropriate for each constituent as defined herein. In a preferred embodiment, the invention provides a composition or a preparation which is in the form of a kit of parts comprising an oligonucleotide and a further adjunct compound as later defined herein.

[0087] A preferred oligonucleotide is for preventing or treating Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) in an individual. An individual, which may be treated using an oligonucleotide of the invention may already have been diagnosed as having a DMD or a BMD. Alternatively, an individual which may be treated using an oligonucleotide of the invention may not have yet been diagnosed as having a DMD or a BMD but may be an individual having an increased risk of developing a DMD or a BMD in the future given his or her genetic background. A preferred individual is a human being.

Composition

[0088] In a further aspect, there is provided a composition comprising an oligonucleotide as defined herein. Preferably, said composition comprises at least two distinct oligonucleotides as defined herein. More preferably, these two distinct oligonucleotides are designed to skip distinct two or more exons as earlier defined herein for multi-exon skipping.

[0089] In a preferred embodiment, said composition being preferably a pharmaceutical composition said pharmaceutical composition comprising a pharmaceutically acceptable carrier, adjuvant, diluent and/or excipient. Such a pharmaceutical composition may comprise any pharmaceutically acceptable carrier, filler, preservative, adjuvant, solubilizer, diluent and/or excipient is also provided. Such pharmaceutically acceptable carrier, filler, preservative, adjuvant, solubilizer, diluent and/or excipient may for instance be found in Remington: The Science and Practice of Pharmacy, 20th Edition. Baltimore, Md.: Lippincott Williams & Wilkins, 2000. Each feature of said composition has earlier been defined herein.

[0090] If several oligonucleotides are used, concentration or dose already defined herein may refer to the total concentration or dose of all oligonucleotides used or the concentration or dose of each oligonucleotide used or added. Therefore in one embodiment, there is provided a composition wherein each or the total amount of oligonucleotide used is dosed in an amount ranged between 0.5 mg/kg and 10 mg/kg.

[0091] A preferred composition additionally comprises:

[0092] a) an adjunct compound for reducing inflammation, preferably for reducing muscle tissue inflammation, and/or

[0093] b) an adjunct compound for improving muscle fiber function, integrity and/or survival and/or

[0094] c) a compound exhibiting readthrough activity.

[0095] It has surprisingly been found that the skipping frequency of a dystrophin exon from a pre-mRNA comprising said exon, when using an oligonucleotide directed toward the exon or to one or both splice sites of said exon, is enhanced if cells expressing said pre-mRNA are also provided with an adjunct compound for reducing inflammation, preferably for reducing muscle tissue inflammation, and/or an adjunct compound for improving muscle fiber function, integrity and/or survival. The enhanced skipping frequency also increases the level of functional dystrophin protein produced in a muscle cell of a DMD or BMD individual.

[0096] According to the present invention, even when a dystrophin protein deficiency has been restored in a DMD patient by administering an oligonucleotide of the invention, the presence of tissue inflammation and damaged muscle cells still continues to contribute to the symptoms of DMD. Hence, even though the cause of DMD—i.e. a dysfunctional dystrophin protein—is alleviated, treatment of DMD is still further improved by additionally using an adjunct therapy according to the present invention. Furthermore, the present invention provides the insight that a reduction of inflammation does not result in significant reduction of AON uptake by muscle cells. This is surprising because, in general, inflammation enhances the trafficking of cells, blood and other compounds. As a result, AON uptake/delivery is also enhanced during inflammation. Hence, before the present invention it would be expected that an adjunct therapy counteracting inflammation involves the risk of negatively influencing AON therapy. This, however, appears not to be the case.

[0097] An adjunct compound for reducing inflammation comprises any therapy which is capable of at least in part reducing inflammation, preferably inflammation caused by damaged muscle cells. Said adjunct compound is most preferably capable of reducing muscle tissue inflammation. Inflammation is preferably assessed by detecting an increase in the number of infiltrating immune cells such as neutrophils and/or mast cells and/or dendritic cells and/or lymphocytes in muscle tissue suspected to be dystrophic. This assessment is preferably carried out in cross-sections of a biopsy⁵⁷ of muscle tissue suspected to be dystrophic after having specifically stained immune cells as identified above. The quantification is preferably carried out under the microscope. Reducing inflammation is therefore preferably assessed by detecting a decrease in the number of immune cells in a cross-section of muscle tissue suspected to be dystrophic. Detecting a decrease preferably means that the number of at least one sort of immune cells as identified above is decreased of at least 1%, 2%, 3%, 5%, 7%, 10%, 12%, 15%, 17%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more compared to the number of a corresponding immune cell in a same individual before treatment. Most preferably, no infiltrating immune cells are detected in cross-sections of said biopsy.

[0098] An adjunct compound for improving muscle fiber function, integrity and/or survival comprises any therapy, which is capable of measurably enhancing muscle fiber function, integrity and/or survival as compared to an otherwise

similar situation wherein said adjunct compound is not present. The improvement of muscle fiber function, integrity and/or survival may be assessed using at least one of the following assays: a detectable decrease of creatine kinase in blood, a detectable decrease of necrosis of muscle fibers in a biopsy cross-section of a muscle suspected to be dystrophic, and/or a detectable increase of the homogeneity of the diameter of muscle fibers in a biopsy cross-section of a muscle suspected to be dystrophic. Each of these assays is known to the skilled person.

[0099] Creatine kinase may be detected in blood as described in 57. A detectable decrease in creatine kinase may mean a decrease of 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more compared to the concentration of creatine kinase in a same individual before treatment.

[0100] A detectable decrease of necrosis of muscle fibers is preferably assessed in a muscle biopsy, more preferably as described in 57 using biopsy cross-sections. A detectable decrease of necrosis may be a decrease of 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the area wherein necrosis has been identified using biopsy cross-sections. The decrease is measured by comparison to the necrosis as assessed in a same individual before treatment.

[0101] A detectable increase of the homogeneity of the diameter of a muscle fiber is preferably assessed in a muscle biopsy cross-section, more preferably as described in 57.

[0102] In one embodiment, an adjunct compound for increasing turnover of damaged muscle cells is used. An adjunct compound for increasing turnover of damaged muscle cells comprises any therapy, which is capable of at least in part inducing and/or increasing turnover of damaged muscle cells. Damaged muscle cells are muscle cells, which have significantly less clinically measurable functionality than a healthy, intact muscle cell. In the absence of dystrophin, mechanical stress leads to sarcolemmal ruptures, causing an uncontrolled influx of calcium into the muscle fiber interior, thereby triggering calcium-activated proteases and fiber necrosis, resulting in damaged muscle cells. Increasing turnover of damaged muscle cells means that damaged muscle cells are more quickly broken down and/or removed as compared to a situation wherein turnover of damaged muscle cells is not increased. Turnover of damaged muscle cells is preferably assessed in a muscle biopsy, more preferably as described in 57 using a cross-section of a biopsy. A detectable increase of turnover may be an increase of 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the area wherein turnover has been identified using a biopsy cross-section. The increase is measured by comparison to the turnover as assessed in a same individual before treatment.

[0103] Without wishing to be bound to theory, it is believed that increasing turnover of muscle cells is preferred because this reduces inflammatory responses.

[0104] According to the present invention, a composition of the invention further comprising an adjunct therapy for reducing inflammation, preferably for reducing muscle tissue inflammation in an individual, is particularly suitable for use as a medicament. Such composition is even better capable of alleviating one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy as compared to a combination not comprising said adjunct compound. This embodiment also enhances the skipping frequency of a dystrophin exon from a pre-mRNA comprising said exon, when using an oligonucleotide directed toward the exon or to one or both splice sites of said exon. The enhanced skipping fre-

quency also increases the level of functional dystrophin protein produced in a muscle cell of a DMD or BMD individual.

[0105] Further provided is therefore a composition further comprising an adjunct compound for reducing inflammation, preferably for reducing muscle tissue inflammation in said individual, for use as a medicament, preferably for treating or preventing counteracting DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein or altered or truncated dystrophin mRNA or protein is formed which is not sufficiently functional.

[0106] Preferred adjunct compound for reducing inflammation include a steroid, a $\text{TNF}\alpha$ inhibitor, a source of mIGF-1 and/or an antioxidant. However, any other compound able to reduce inflammation as defined herein is also encompassed within the present invention. Each of these compounds is later on extensively presented. Each of the compounds extensively presented may be used separately or in combination with each other and/or in combination with one or more of the adjunct compounds used for improving muscle fiber function, integrity and/or survival.

[0107] Furthermore, a composition comprising an adjunct therapy for improving muscle fiber function, integrity and/or survival in an individual is particularly suitable for use as a medicament, preferably for treating or preventing DMD. Such composition is even better capable of alleviating one or more symptom(s) of Duchenne Muscular Dystrophy as compared to a composition not comprising said adjunct compound.

[0108] Preferred adjunct compounds for improving muscle fiber function, integrity and/or survival include an ion channel inhibitor, a protease inhibitor, L-arginine and/or an angiotensin II type I receptor blocker. However, any other compound able to improving muscle fiber function, integrity and/or survival as defined herein is also encompassed within the present invention. Each of these compounds is later on extensively presented. Each of the compounds extensively presented may be used separately or in combination with each other and/or in combination with one or more of the adjunct compounds used for reducing inflammation.

[0109] In a particularly preferred embodiment, a composition further comprises a steroid. Such composition results in significant alleviation of DMD symptoms. This embodiment also enhances the skipping frequency of a dystrophin exon from a pre-mRNA comprising said exon, when using an oligonucleotide directed toward the exon or to one or both splice sites of said exon. The enhanced skipping frequency also increases the level of functional dystrophin protein produced in a muscle cell of a DMD or BMD individual.

[0110] In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional.

[0111] A steroid is a terpenoid lipid characterized by a carbon skeleton with four fused rings, generally arranged in a 6-6-6-5 fashion. Steroids vary by the functional groups attached to these rings and the oxidation state of the rings. Steroids include hormones and drugs, which are usually used to relieve swelling and inflammation, such as for instance prednisone, dexamethasone and vitamin D.

[0112] According to the present invention, supplemental effects of adjunct steroid therapy in DMD patients include reduction of tissue inflammation, suppression of cytotoxic cells, and improved calcium homeostasis. Most positive

results are obtained in younger boys. Preferably, the steroid is a corticosteroid, more preferably, a glucocorticosteroid. Preferably, prednisone steroids such as prednisone, prednisolone or deflazacort are used in a combination according to the invention²¹. Dose ranges of steroid or of a glucocorticosteroid to be used in the therapeutic applications as described herein are designed on the basis of rising dose studies in clinical trials for which rigorous protocol requirements exist. The usual doses are 0.5-1.0 mg/kg/day, preferably 0.75 mg/kg/day for prednisone and prednisolone, and 0.4-1.4 mg/kg/day, preferably 0.9 mg/kg/day for deflazacort.

[0113] In one embodiment, a steroid is administered to said individual prior to administering a composition as earlier defined herein. In this embodiment, it is preferred that said steroid is administered at least one day, more preferred at least one week, more preferred at least two weeks, more preferred at least three weeks prior to administering said composition.

[0114] In another preferred embodiment, a combination further comprises a tumour necrosis factor- α (TNF α) inhibitor. Tumour necrosis factor- α (TNF α) is a pro-inflammatory cytokine that stimulates the inflammatory response. Pharmacological blockade of TNF α activity with the neutralizing antibody infliximab (Remicade) is highly effective clinically at reducing symptoms of inflammatory diseases. In mdx mice, both infliximab and etanercept delay and reduce the necrosis of dystrophic muscle^{24, 25}, with additional physiological benefits on muscle strength, chloride channel function and reduced CK levels being demonstrated in chronically treated exercised adult mdx mice²⁶. Such highly specific anti-inflammatory drugs designed for use in other clinical conditions, are attractive alternatives to the use of steroids for DMD. In one embodiment, the use of a TNF α inhibitor is limited to periods of intensive muscle growth in boys when muscle damage and deterioration are especially pronounced.

[0115] A composition further comprising a TNF α inhibitor for use as a medicament is also provided. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. A preferred TNF α inhibitor is a dimeric fusion protein consisting of the extracellular ligand-binding domain of the human p75 receptor of TNF α linked to the Fc portion of human IgG1. A more preferred TNF α inhibitor is etanercept (Amgen, America)²⁶. The usual doses of etanercept is about 0.2 mg/kg, preferably about 0.5 mg/kg twice a week. The administration is preferably subcutaneous.

[0116] In another preferred embodiment, a composition of the invention further comprises a source of mIGF-1. As defined herein, a source of IGF-1 preferably encompasses mIGF-1 itself, a compound able of enhancing mIGF-1 expression and/or activity. Enhancing is herein synonymous with increasing. Expression of mIGF-1 is synonymous with amount of mIGF-1. mIGF-1 promotes regeneration of muscles through increase in satellite cell activity, and reduces inflammation and fibrosis²⁷. Local injury of muscle results in increased mIGF-1 expression. In transgenic mice with extra IGF-1 genes, muscle hypertrophy and enlarged muscle fibers are observed²⁷. Similarly, transgenic mdx mice show reduced muscle fiber degeneration²⁸. Upregulation of the mIGF-1 gene and/or administration of extra amounts of mIGF-1 protein or a functional equivalent thereof (especially the mIGF-1 Ea isoform [as described in 27, human homolog IGF-1 isoform 4: SEQ ID NO: 577]) thus promotes the effect of other,

preferably genetic, therapies for DMD, including antisense-induced exon skipping. The additional mIGF-1 levels in the above mentioned transgenic mice do not induce cardiac problems nor promote cancer, and have no pathological side effects. As stated before, the amount of mIGF-1 is for instance increased by enhancing expression of the mIGF-1 gene and/or by administration of mIGF-1 protein and/or a functional equivalent thereof (especially the mIGF-1 Ea isoform [as described in 27, human homolog IGF-1 isoform 4: SEQ ID NO: 577]). A composition of the invention further preferably comprises mIGF-1, a compound capable of enhancing mIGF-1 expression and/or an mIGF-1 activity, for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, such composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional.

[0117] Within the context of the invention, an increased amount or activity of mIGF-1 may be reached by increasing the gene expression level of an IGF-1 gene, by increasing the amount of a corresponding IGF-1 protein and/or by increasing an activity of an IGF1-protein. A preferred mIGF-1 protein has been earlier defined herein. An increase of an activity of said protein is herein understood to mean any detectable change in a biological activity exerted by said protein or in the steady state level of said protein as compared to said activity or steady-state in a individual who has not been treated. Increased amount or activity of mIGF-1 is preferably assessed by detection of increased expression of muscle hypertrophy biomarker GATA-2 (as described in 27).

[0118] Gene expression level is preferably assessed using classical molecular biology techniques such as (real time) PCR, arrays or Northern analysis. A steady state level of a protein is determined directly by quantifying the amount of a protein. Quantifying a protein amount may be carried out by any known technique such as Western blotting or immunoassay using an antibody raised against a protein. The skilled person will understand that alternatively or in combination with the quantification of a gene expression level and/or a corresponding protein, the quantification of a substrate of a corresponding protein or of any compound known to be associated with a function or activity of a corresponding protein or the quantification of said function or activity of a corresponding protein using a specific assay may be used to assess the alteration of an activity or steady state level of a protein.

[0119] In the invention, an activity or steady-state level of a said protein may be altered at the level of the protein itself, e.g. by providing a protein to a cell from an exogenous source.

[0120] Preferably, an increase or an up-regulation of the expression level of a said gene means an increase of at least 5% of the expression level of said gene using arrays. More preferably, an increase of the expression level of said gene means an increase of at least 10%, even more preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 90%, at least 150% or more. In another preferred embodiment, an increase of the expression level of said protein means an increase of at least 5% of the expression level of said protein using Western blotting and/or using ELISA or a suitable assay. More preferably, an increase of the expression level of a protein means an increase of at least 10%, even more preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 90%, at least 150% or more.

[0121] In another preferred embodiment, an increase of a polypeptide activity means an increase of at least 5% of a polypeptide activity using a suitable assay. More preferably, an increase of a polypeptide activity means an increase of at least 10%, even more preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, at least 90%, at least 150% or more. The increase is preferably assessed by comparison to corresponding activity in the individual before treatment.

[0122] A preferred way of providing a source of mIGF1 is to introduce a transgene encoding mIGF1, preferably an mIGF-1 Ea isoform (as described in 27, human homolog IGF-1 isoform 4: SEQ ID NO: 577), more preferably in an AAV vector as later defined herein. Such source of mIGF1 is specifically expressed in muscle tissue as described in mice in 27.

[0123] In another preferred embodiment, a composition further comprises an antioxidant. Oxidative stress is an important factor in the progression of DMD and promotes chronic inflammation and fibrosis²⁹. The most prevalent products of oxidative stress, the peroxidized lipids, are increased by an average of 35% in Duchenne boys. Increased levels of the enzymes superoxide dismutase and catalase reduce the excessive amount of free radicals causing these effects. In fact, a dietary supplement Protandim® (LifeVantage) was clinically tested and found to increase levels of superoxide dismutase (up to 30%) and catalase (up to 54%), which indeed significantly inhibited the peroxidation of lipids in 29 healthy persons³⁰. Such effective management of oxidative stress thus preserves muscle quality and so promotes the positive effect of DMD therapy. Idebenone is another potent antioxidant with a chemical structure derived from natural coenzyme Q10. It protects mitochondria where adenosine triphosphate, ATP, is generated by oxidative phosphorylation. The absence of dystrophin in DMD negatively affects this process in the heart, and probably also in skeletal muscle. Idebenone was recently applied in clinical trials in the US and Europe demonstrating efficacy on neurological aspects of Friedreich's Ataxia³¹. A phase-IIa double-blind, placebo-controlled randomized clinical trial with Idebenone has recently been started in Belgium, including 21 Duchenne boys at 8 to 16 years of age. The primary objective of this study is to determine the effect of Idebenone on heart muscle function. In addition, several different tests will be performed to detect the possible functional benefit on muscle strength in the patients. When effective, Idebenone is a preferred adjunct compound for use in a combination according to the present invention in order to enhance the therapeutic effect of DMD therapy, especially in the heart. A composition further comprising an antioxidant for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. Depending on the identity of the antioxidant, the skilled person will know which quantities are preferably used. An antioxidant may include bacoside, silymarin, curcumin and/or a polyphenol. Preferably, a polyphenol is or comprises epigallocatechin-3-gallate (EGCG). Preferably, an antioxidant is a mixture of antioxidants as the dietary supplement Protandim® (LifeVantage). A daily capsule of 675 mg of Protandim® comprises 150 mg of *B. monniera* (45% bacosides), 225 mg of *S. marianum* (70-80% silymarin), 150 mg of *W. somnifera* pow-

der, 75 mg green tea (98% polyphenols wherein 45% EGCG) and 75 mg turmeric (95% curcumin).

[0124] In another preferred embodiment, a composition further comprises an ion channel inhibitor. The presence of damaged muscle membranes in DMD disturbs the passage of calcium ions into the myofibers, and the consequently disrupted calcium homeostasis activates many enzymes, e.g. proteases, that cause additional damage and muscle necrosis. Ion channels that directly contribute to the pathological accumulation of calcium in dystrophic muscle are potential targets for adjunct compounds to treat DMD. There is evidence that some drugs, such as pentoxifylline, block exercise-sensitive calcium channels³² and antibiotics that block stretch activated channels reduce myofibre necrosis in mdx mice and CK levels in DMD boys³³. A composition further comprising an ion channel inhibitor for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional.

[0125] Preferably, an ion channel inhibitor of the class of xanthines is used. More preferably, said xanthines are derivatives of methylxanthines, and most preferably, said methylxanthine derivatives are chosen from the group consisting of pentoxifylline, furafylline, lisofylline, propentofylline, pentifylline, theophylline, torbafylline, albigylline, enprofylline and derivatives thereof. Most preferred is the use of pentoxifylline. Ion channel inhibitors of the class of xanthines enhance the skipping frequency of a dystrophin exon from a pre-mRNA comprising said exon, when using an oligonucleotide directed toward the exon or to one or both splice sites of said exon. The enhanced skipping frequency also increases the level of functional dystrophin protein produced in a muscle cell of a DMD or BMD individual.

[0126] Depending on the identity of the ion channel inhibitor, the skilled person will know which quantities are preferably used. Suitable dosages of pentoxifylline are between 1 mg/kg/day to 100 mg/kg/day, preferred dosages are between 10 mg/kg/day to 50 mg/kg/day. Typical dosages used in humans are 20 mg/kg/day.

[0127] In one embodiment, an ion channel inhibitor is administered to said individual prior to administering a composition comprising an oligonucleotide. In this embodiment, it is preferred that said ion channel inhibitor is administered at least one day, more preferred at least one week, more preferred at least two weeks, more preferred at least three weeks prior to administering a composition comprising an oligonucleotide.

[0128] In another preferred embodiment, a composition further comprises a protease inhibitor. Calpains are calcium-activated proteases that are increased in dystrophic muscle and account for myofiber degeneration. Calpain inhibitors such as calpastatin, leupeptin³⁴, calpeptin, calpain inhibitor III, or PD150606 are therefore applied to reduce the degeneration process. A new compound, BN 82270 (Ipsen) that has dual action as both a calpain inhibitor and an antioxidant increased muscle strength, decreased serum CK and reduced fibrosis of the mdx diaphragm, indicating a therapeutic effect with this new compound³⁵. Another compound of Leupeptin/Carnitine (Myodur) has recently been proposed for clinical trials in DMD patients.

[0129] MG132 is another proteasomal inhibitor that has shown to reduce muscle membrane damage, and to amelio-

rate the histopathological signs of muscular dystrophy³⁶. MG-132 (CBZ-leucyl-leucyl-leucinal) is a cell-permeable, proteasomal inhibitor ($K_i=4$ nM), which inhibits NF κ B activation by preventing IkappaB degradation ($IC_{50}=3$ μ M). In addition, it is a peptide aldehyde that inhibits ubiquitin-mediated proteolysis by binding to and inactivating 20S and 26S proteasomes. MG-132 has shown to inhibit the proteasomal degradation of dystrophin-associated proteins in the dystrophic mdx mouse model³⁶. This compound is thus also suitable for use as an adjunct pharmacological compound for DMD. A composition further comprising a protease inhibitor for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said combination is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. Depending on the identity of the protease inhibitor, the skilled person will know which quantities are preferably used.

[0130] In another preferred embodiment, a composition further comprises L-arginine. Dystrophin-deficiency is associated with the loss of the DGC-complex at the fiber membranes, including neuronal nitric oxide synthase (nNOS). Expression of a nNOS transgene in mdx mice greatly reduced muscle membrane damage. Similarly, administration of L-arginine (the substrate for nitric oxide synthase) increased NO production and upregulated utrophin expression in mdx mice. Six weeks of L-arginine treatment improved muscle pathology and decreased serum CK in mdx mice³⁷. The use of L-arginine as a further constituent in a composition of the invention has not been disclosed.

[0131] A composition further comprising L-arginine for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional.

[0132] In another preferred embodiment, a composition further comprises angiotensin II type 1 receptor blocker Losartan, which normalizes muscle architecture, repair and function, as shown in the dystrophin-deficient mdx mouse model²³. A composition further comprising angiotensin II type 1 receptor blocker Losartan for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. Depending on the identity of the angiotensin II type 1 receptor blocker, the skilled person will know which quantities are preferably used.

[0133] In another preferred embodiment, a composition further comprises an angiotensin-converting enzyme (ACE) inhibitor, preferably perindopril. ACE inhibitors are capable of lowering blood pressure. Early initiation of treatment with perindopril is associated with a lower mortality in DMD patients²². A composition further comprising an ACE inhibitor, preferably perindopril for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. The

usual doses of an ACE inhibitor, preferably perindopril are about 2 to 4 mg/day²². In a more preferred embodiment, an ACE inhibitor is combined with at least one of the previously identified adjunct compounds.

[0134] In another preferred embodiment, a composition further comprises a compound exhibiting a readthrough activity. A compound exhibiting a readthrough activity may be any compound, which is able to suppress a stop codon. For 20% of DMD patients, the mutation in the dystrophin gene is comprising a point mutation, of which 13% is a nonsense mutation. A compound exhibiting a readthrough activity or which is able to suppress a stop codon is a compound which is able to provide an increased amount of a functional dystrophin mRNA or protein and/or a decreased amount of an aberrant or truncated dystrophin mRNA or protein. Increased preferably means increased of at least 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100% or more. Decreased preferably means decreased of at least 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100% or more. An increase or a decrease of said protein is preferably assessed in a muscular tissue or in a muscular cell of an individual by comparison to the amount present in said individual before treatment with said compound exhibiting a readthrough activity. Alternatively, the comparison can be made with a muscular tissue or cell of said individual, which has not yet been treated with said compound in case the treatment is local. The assessment of an amount at the protein level is preferably carried out using western blot analysis.

[0135] Preferred compounds exhibiting a readthrough activity comprise or consist of aminoglycosides, including, but not limited to, geneticin (G418), paromomycin, gentamycin and/or 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid, and derivatives thereof (references 64, 65).

[0136] A more preferred compound exhibiting a readthrough activity comprises or consists of PTC124TM, and/or a functional equivalent thereof. PTC124TM is a registered trademark of PTC Therapeutics, Inc. South Plainfield, N.J. 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid also known as PTC124TM (references 16, 17) belongs to a new class of small molecules that mimics at lower concentrations the readthrough activity of gentamicin (reference 55). A functional equivalent of 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid or of gentamicin is a compound which is able to exhibit a readthrough activity as earlier defined herein. Most preferably, a compound exhibiting a readthrough activity comprises or consists of gentamycin and/or 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid also known as PTC124TM. A composition further comprising a compound exhibiting a readthrough activity, preferably comprising or consisting of gentamycin and/or 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. The usual doses of a compound exhibiting a readthrough activity, preferably 3-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)benzoic acid or of gentamicin are ranged between 3 mg/kg/day to 200 mg/kg/day, preferred dosages are between 10 mg/kg to 50 mg/kg per day or twice a day.

[0137] In a more preferred embodiment, a compound exhibiting a readthrough activity is combined with at least one of the previously identified adjunct compounds.

[0138] In another preferred embodiment, a composition further comprises a compound, which is capable of enhancing exon skipping and/or inhibiting spliceosome assembly and/or splicing. Small chemical compounds, such as for instance specific indole derivatives, have been shown to selectively inhibit spliceosome assembly and splicing³⁸, for instance by interfering with the binding of serine- and arginine-rich (SR) proteins to their cognate splicing enhancers (ISEs or ESEs) and/or by interfering with the binding of splicing repressors to silencer sequences (ESSs or ISSs). These compounds are therefore suitable for applying as adjunct compounds that enhance exon skipping. A composition further comprising a compound for enhancing exon skipping and/or inhibiting spliceosome assembly and/or splicing for use as a medicament is also provided. Said medicament is preferably for alleviating one or more symptom(s) of DMD. In one embodiment, said composition is used in order to alleviate one or more symptom(s) of a severe form of BMD wherein a very short dystrophin protein is formed which is not sufficiently functional. Depending on the identity of the compound, which is capable of enhancing exon skipping and/or inhibiting spliceosome assembly and/or splicing, the skilled person will know which quantities are preferably used. In a more preferred embodiment, a compound for enhancing exon skipping and/or inhibiting spliceosome assembly and/or splicing is combined with a ACE inhibitor and/or with any adjunct compounds as identified earlier herein.

[0139] The invention thus provides a composition further comprising an adjunct compound, wherein said adjunct compound comprises a steroid, an ACE inhibitor (preferably perindopril), angiotensin II type 1 receptor blocker Losartan, a tumour necrosis factor-alpha (TNF α) inhibitor, a source of mIGF-1, preferably mIGF-1, a compound for enhancing mIGF-1 expression, a compound for enhancing mIGF-1 activity, an antioxidant, an ion channel inhibitor, a protease inhibitor, L-arginine, a compound exhibiting a readthrough activity and/or inhibiting spliceosome assembly and/or splicing.

[0140] In one embodiment an individual is further provided with a functional dystrophin protein using a vector, preferably a viral vector, comprising a micro-mini-dystrophin gene. Most preferably, a recombinant adeno-associated viral (rAAV) vector is used. AAV is a single-stranded DNA parvovirus that is non-pathogenic and shows a helper-dependent life cycle. In contrast to other viruses (adenovirus, retrovirus, and herpes simplex virus), rAAV vectors have demonstrated to be very efficient in transducing mature skeletal muscle. Application of rAAV in classical DMD "gene addition" studies has been hindered by its restricted packaging limits (<5 kb). Therefore, rAAV is preferably applied for the efficient delivery of a much smaller micro- or mini-dystrophin gene. Administration of such micro- or mini-dystrophin gene results in the presence of an at least partially functional dystrophin protein. Reference is made to¹⁸⁻²⁰.

[0141] Each constituent of a composition can be administered to an individual in any order. In one embodiment, each constituent is administered simultaneously (meaning that each constituent is administered within 10 hours, preferably within one hour). This is however not necessary. In one embodiment at least one adjunct compound is administered to an individual in need thereof before administration of an

oligonucleotide. Alternatively, an oligonucleotide is administered to an individual in need thereof before administration of at least one adjunct compound.

Use

[0142] In a further aspect, there is provided the use of a oligonucleotide or of a composition as defined herein for the manufacture of a medicament for preventing or treating Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual. Each feature of said use has earlier been defined herein.

[0143] A treatment in a use or in a method according to the invention is at least one week, at least one month, at least several months, at least one year, at least 2, 3, 4, 5, 6 years or more. Each molecule or oligonucleotide or equivalent thereof as defined herein for use according to the invention may be suitable for direct administration to a cell, tissue and/or an organ in vivo of individuals affected by or at risk of developing DMD or BMD, and may be administered directly in vivo, ex vivo or in vitro. The frequency of administration of an oligonucleotide, composition, compound or adjunct compound of the invention may depend on several parameters such as the age of the patient, the mutation of the patient, the number of molecules (i.e. dose), the formulation of said molecule. The frequency may be ranged between at least once in two weeks, or three weeks or four weeks or five weeks or a longer time period.

Method

[0144] In a further aspect, there is provided a method for alleviating one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual or alleviate one or more characteristic(s) of a myogenic or muscle cell of said individual, the method comprising administering to said individual an oligonucleotide or a composition as defined herein.

[0145] There is further provided a method for enhancing, inducing or promoting skipping of an exon from a dystrophin pre-mRNA in a cell expressing said pre-mRNA in an individual suffering from Duchenne Muscular Dystrophy or Becker Muscular Dystrophy, the method comprising administering to said individual an oligonucleotide or a composition as defined herein. Further provided is a method for increasing the production of a functional dystrophin protein and/or decreasing the production of an aberrant dystrophin protein in a cell, said cell comprising a pre-mRNA of a dystrophin gene encoding an aberrant dystrophin protein, the method comprising providing said cell with an oligonucleotide or composition of the invention and allowing translation of mRNA produced from splicing of said pre-mRNA. In one embodiment, said method is performed in vitro, for instance using a cell culture. Preferably, said method is in vivo.

[0146] In this context, increasing the production of a functional dystrophin protein has been earlier defined herein.

[0147] Unless otherwise indicated each embodiment as described herein may be combined with another embodiment as described herein.

[0148] In this document and in its claims, the verb "to comprise" and its conjugations is used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition the verb "to consist" may be replaced by "to consist essentially of" meaning that a compound or adjunct compound as

defined herein may comprise additional component(s) than the ones specifically identified, said additional component(s) not altering the unique characteristic of the invention.

[0149] In addition, reference to an element by the indefinite article “a” or “an” does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article “a” or “an” thus usually means “at least one”.

[0150] The word “approximately” or “about” when used in association with a numerical value (approximately 10, about 10) preferably means that the value may be the given value of 10 more or less 1% of the value.

[0151] All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety. Each embodiment as identified herein may be combined together unless otherwise indicated.

[0152] The invention is further explained in the following examples. These examples do not limit the scope of the invention, but merely serve to clarify the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0153] FIG. 1. In human control myotubes, PS220 and PS305 both targeting an identical sequence within exon 45, were directly compared for relative skipping efficiencies. PS220 reproducibly induced highest levels of exon 45 skipping (up to 73%), whereas with PS305 maximum exon 45 skipping levels of up to 46% were obtained. No exon 45 skipping was observed in non-treated cells. (M: DNA size marker; NT: non-treated cells)

[0154] FIG. 2. Graph showing relative exon 45 skipping levels of inosine-containing AONs as assessed by RT-PCR analysis. In human control myotubes, a series of new AONs, all targeting exon 45 and containing one inosine for guanosine substitution were tested for relative exon 45 skipping efficiencies when compared with PS220 and PS305 (see FIG. 1). All new inosine-containing AONs were effective, albeit at variable levels (between 4% and 25%). PS220 induced highest levels of exon 45 skipping (up to 72%), whereas with PS305 maximum exon 45 skipping levels of up to 63% were obtained. No exon 45 skipping was observed in non-treated cells. (M: DNA size marker; NT: non-treated cells).

EXAMPLES

Example 1

Materials and Methods

[0155] AON design was based on (partly) overlapping open secondary structures of the target exon RNA as predicted by the m-fold program, on (partly) overlapping putative SR-protein binding sites as predicted by the ESE-finder software. AONs were synthesized by Prosensa Therapeutics B.V. (Leiden, Netherlands), and contain 2'-O-methyl RNA and full-length phosphorothioate (PS) backbones.

Tissue Culturing, Transfection and RT-PCR Analysis

[0156] Myotube cultures derived from a healthy individual (“human control”) (examples 1, 3, and 4; exon 43, 50, 52 skipping) or a DMD patient carrying an exon 45 deletion (example 2; exon 46 skipping) were processed as described previously (Aartsma-Rus et al., *Neuromuscul. Disord.* 2002; 12: S71-77 and *Hum Mol Genet.* 2003; 12(8): 907-14). For the screening of AONs, myotube cultures were transfected

with 200 nM for each AON (PS220 and PS305). Transfection reagent UNIFectylin (Prosensa Therapeutics BV, Netherlands) was used, with 2 µl UNIFectylin per µg AON. Exon skipping efficiencies were determined by nested RT-PCR analysis using primers in the exons flanking the targeted exon 45. PCR fragments were isolated from agarose gels for sequence verification. For quantification, the PCR products were analyzed using the DNA 1000 LabChip Kit on the Agilent 2100 bioanalyzer (Agilent Technologies, USA).

Results

[0157] DMD exon 45 skipping.

[0158] Two AONs, PS220 (SEQ ID NO: 76; 5'-UUUGC-CGCUGCCCAUGCCAUCUG-3') and PS305 (SEQ ID NO: 557; 5'-UUUGCCICUGCCCAUGCCAUCUG-3') both targeting an identical sequence within exon 45, were directly compared for relative skipping efficiencies in healthy control myotube cultures. Subsequent RT-PCR and sequence analysis of isolated RNA demonstrated that both AONs were indeed capable of inducing exon 45 skipping. PS220, consisting a GCCGC stretch, reproducibly induced highest levels of exon 45 skipping (up to 73%), as shown in FIG. 1. However, PS305, which is identical to PS220 but containing an inosine for a G substitution at position 4 within that stretch is also effective and leading to exon 45 skipping levels of up to 46%. No exon 45 skipping was observed in non-treated cells (NT).

Example 2

[0159] Materials and Methods

[0160] AON design was based on (partly) overlapping open secondary structures of the target exon 45 RNA as predicted by the m-fold program, on (partly) overlapping putative SR-protein binding sites as predicted by the ESE-finder software. AONs were synthesized by Prosensa Therapeutics B.V. (Leiden, Netherlands), and contain 2'-O-methyl RNA, full-length phosphorothioate (PS) backbones and one inosine for guanosine substitution.

Tissue Culturing, Transfection and RT-PCR Analysis

[0161] Myotube cultures derived from a healthy individual (“human control”) were processed as described previously (Aartsma-Rus et al., *Neuromuscul. Disord.* 2002; 12: S71-77 and *Hum Mol Genet.* 2003; 12(8): 907-14). For the screening of AONs, myotube cultures were transfected with 200 nM for each AON. Transfection reagent UNIFectylin (Prosensa Therapeutics BV, Netherlands) was used, with 2 µl UNIFectylin per µg AON. Exon skipping efficiencies were determined by nested RT-PCR analysis using primers in the exons flanking the targeted exon 45. PCR fragments were isolated from agarose gels for sequence verification. For quantification, the PCR products were analyzed using the DNA 1000 LabChip Kit on the Agilent 2100 bioanalyzer (Agilent Technologies, USA).

Results

[0162] DMD exon 45 skipping.

[0163] An additional series of AONs targeting exon 45 and containing one inosine-substitution were tested in healthy control myotube cultures for exon 45 skipping efficiencies, and directly compared to PS220 (without inosine; SEQ ID NO: 76) and PS305 (identical sequence as PS220 but with inosine substitution; SEQ ID NO: 557). Subsequent RT-PCR and sequence analysis of isolated RNA demonstrated that all

new AONs (PS309 to PS316) were capable of inducing exon 45 skipping between 4% (PS311) and 25% (PS310) as shown in FIG. 2. When compared to PS220 and PS305, PS220 induced highest levels of exon 45 skipping (up to 72%). Of the new inosine-containing AONs PS305 was most effective, showing exon 45 skipping levels of up to 63%. No exon 45 skipping was observed in non-treated cells (NT).

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Sequence listing

DMD gene amino acid sequence

SEQ ID NO 1:

MLWWEVEDCYEREDVQKKTFTKWVNAQFSKFGKQHIEENLFSDLQDGRRLDLDLEGL
TGQKLPEKEKGSTRAVHALNNVNKALRVLQNNVNDLVNIGSTDIVDGNHKLTLGLIWNIIIL
HWQVKNVMKNIMAGLQQTNSEKILLSWVRQSTRNYPQVNVINFTTSWSDGLALNALIH
SHRPDLFDWNSVVCQQSATORLEHAFNIARYQLGIEKLLDPEDVDTTYPDKKSILMYIT
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SEQ ID UUCCAGGUUCAAGUGGGGAUACUAGC NO 263	SEQ ID UGUUAUCUGCUUCCUCCAACCAUAA NO 290
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DMD Gene Exon 52	
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SEQ ID UCUUGAUUGCUGGUCUUGUUUUUCA NO 296	SEQ ID CAGCGGUAAUGAGUUCUCCAACUG NO 331
SEQ ID CUUGAUUGCUGGUCUUGUUUUUCAA NO 297	SEQ ID AGCGGUAAUGAGUUCUCCAACUGG NO 332
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SEQ ID AUUGCUGGUCUUGUUUUUCAAAUUU NO 302	SEQ ID GUAAUGAGUUCUCCAACUGGGGAC NO 337
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DMD Gene Exon 50			
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DMD Gene Exon 43	
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SEQ ID ACAGGCGUUGCACUUUGCAAUGCUG NO 414	SEQ ID UUCUUGCUAUGAAUAAUGUCAAUCC NO 445
SEQ ID CAGGCGUUGCACUUUGCAAUGCUGC NO 415	SEQ ID UCUUGCUAUGAAUAAUGUCAAUCCG NO 446
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SEQ ID NO 421	GUUGCACUUUGCAAUGCUGCUGUCU	SEQ ID NO 452	UAUGAAUAAUGUCAAUCCGACCUGA
SEQ ID NO 422	UUGCACUUUGCAAUGCUGCUGUCUU	SEQ ID NO 453	AUGAAUAAUGUCAAUCCGACCUGAG
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SEQ ID NO 426	ACUUUGCAAUGCUGCUGUCUUCUUG	SEQ ID NO 457	AUAUGUCAAUCCGACCUGAGCUUU
SEQ ID NO 427	CUUUGCAAUGCUGCUGUCUUUCUUGC	SEQ ID NO 458	UAAUGUCAAUCCGACCUGAGCUUUG
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SEQ ID NO 438	UGCUGUCUUUCUUGCUAUGAAUAAUG	SEQ ID NO 469	CGACCUGAGCUUUGUUGUAG
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SEQ ID NO 440	CUGUCUUUCUUGCUAUGAAUAAUGUC	SEQ ID NO 471	GACCUGAGCUUUGUUGUAGACUAUC
SEQ ID NO 441	UGUCUUUCUUGCUAUGAAUAAUGUCA	SEQ ID NO 472	ACCUGAGCUUUGUUGUAGACUAUCA
SEQ ID NO 442	GUCUUUCUUGCUAUGAAUAAUGUCA	SEQ ID NO 473	CCUGA GCUUU GUUGU AGAC- U AUC

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DMD Gene Exon 6

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SEQ ID AUUUUUGACCUACAUGGGAAA G
NO 479

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NO 475

SEQ ID UACGAGUUGAUUGUCGGACCCAG
NO 480

SEQ ID UACAUUUUUGACCUACAUGUGGAAA
NO 476 G

SEQ ID GUGGUCUCCUUACCUAUGACUGUGG
NO 481

SEQ ID GGUUCUCCUUACCUAUGA
NO 477

SEQ ID UGUCUCAGUAAUUCUUACCUAU
NO 482

SEQ ID UCUUACCUAUGACUAUGGAUGAGA
NO 478

DMD Gene Exon 7

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NO 483

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NO 485

SEQ ID CACUAUCCAGUCAAAUAGGUCUGG
NO 484

SEQ ID GGCCUAAAACACAUACACAU
NO 486

DMD Gene Exon 8

SEQ ID GAUAGGUGGUUAUCAACAUUGUAA
NO 487

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NO 490

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NO 489

DMD Gene Exon 55

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NO 492

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NO 494

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NO 497

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NO 498 AACAUC

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SEQ ID CCCAUUUUGUGAAUGUUUUCUUUU
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SEQ ID UUGUGCAUUUACCAUUUUUGUG
NO 501

DMD Gene Exon 11

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NO 504

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DMD Gene Exon 17

SEQ ID CCAUUACAGUUGUCUGUGUU
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NO 507

DMD Gene Exon 19

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NO 510

SEQ ID UCUGCUGGCAUCUUGC
NO 512

DMD Gene Exon 21

SEQ ID GCCGGUUGACUUAUCCUGUGC
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SEQ ID CUGCAUCCAGGAACAUGGGUCC
NO 516

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NO 514 NO 517

SEQ ID UACUUACUGUCUGUAGCUCUUUCU
NO 515

DMD Gene Exon 57
SEQ ID UAGGUGCCUGCCGGCCUU SEQ ID CUGAACUGCUGGAAAGUCGCC
NO 518 NO 520

SEQ ID UUCAGCUGUAGCCACACC SEQ ID CUGGCUUCCAAAUGGGACCUGAAAAA
NO 519 NO 521 GAAC

DMD Gene Exon 59
SEQ ID CAAUUUUUCCACUCAGUAUU SEQ ID UCCUCAGGAGGCAGCUCUAAAU
NO 522 NO 524

SEQ ID UUGAAGUUCUGGAGUCUU
NO 523

DMD Gene Exon 62
SEQ ID UGGCUCUCUCCAGGG SEQ ID GGGCACUUUGUUUGGCG
NO 525 NO 527

SEQ ID GAGAUGGCUCUCUCCAGGGACCCU
NO 526 GG

DMD Gene Exon 63
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NO 528 NO 530

SEQ ID UGGGAUGGUCCAGCAAGUUGUUUG
NO 529

DMD Gene Exon 65
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SEQ ID GCCAUACGUACGUAUCAUAAACAUU
NO 532 C

DMD Gene Exon 66
SEQ ID GAUCCUCCUGUUCGUCCCCUAUUA
NO 534 UG

DMD Gene Exon 69
SEQ ID UGCUUUAGACUCCUGUACCUGAUA
NO 535

DMD Gene Exon 75
SEQ ID GGCGGCCUUUGUGUUGAC SEQ ID CCUUUAUGUUCGUGCUGCU
NO 536 NO 538

SEQ ID GGACAGGCCUUUAUGUUCGUGCUGC
NO 537

Human IGF-1 Isoform 4 amino acid sequence
SEQ ID NO 577:
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SEQUENCE LISTING

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<210> SEQ ID NO 1
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<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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 20          25          30
Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
 35          40          45
Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
 50          55          60
Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
 65          70          75          80
Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
 85          90          95
Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
100          105          110
Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
115          120          125
Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
130          135          140
Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145          150          155          160
Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
165          170          175
Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
180          185          190
Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
195          200          205
Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
210          215          220
Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225          230          235          240
Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
245          250          255
Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
260          265          270
His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
275          280          285
Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
290          295          300
Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305          310          315          320
His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
325          330          335
Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
340          345          350
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355          360          365
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370          375          380

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Tyr	Met	Met	Asp	Leu	Thr	Ala	His	Gln	Gly	Arg	Val	Gly	Asn	Ile	Leu	385	390	395	400
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Glu	Thr	Glu	Val	Gln	Glu	Gln	Met	Asn	Leu	Leu	Asn	Ser	Arg	Trp	Glu	420	425	430	
Cys	Leu	Arg	Val	Ala	Ser	Met	Glu	Lys	Gln	Ser	Asn	Leu	His	Arg	Val	435	440	445	
Leu	Met	Asp	Leu	Gln	Asn	Gln	Lys	Leu	Lys	Glu	Leu	Asn	Asp	Trp	Leu	450	455	460	
Thr	Lys	Thr	Glu	Glu	Arg	Thr	Arg	Lys	Met	Glu	Glu	Glu	Pro	Leu	Gly	465	470	475	480
Pro	Asp	Leu	Glu	Asp	Leu	Lys	Arg	Gln	Val	Gln	Gln	His	Lys	Val	Leu	485	490	495	
Gln	Glu	Asp	Leu	Glu	Gln	Glu	Gln	Val	Arg	Val	Asn	Ser	Leu	Thr	His	500	505	510	
Met	Val	Val	Val	Val	Asp	Glu	Ser	Ser	Gly	Asp	His	Ala	Thr	Ala	Ala	515	520	525	
Leu	Glu	Glu	Gln	Leu	Lys	Val	Leu	Gly	Asp	Arg	Trp	Ala	Asn	Ile	Cys	530	535	540	
Arg	Trp	Thr	Glu	Asp	Arg	Trp	Val	Leu	Leu	Gln	Asp	Ile	Leu	Leu	Lys	545	550	555	560
Trp	Gln	Arg	Leu	Thr	Glu	Glu	Gln	Cys	Leu	Phe	Ser	Ala	Trp	Leu	Ser	565	570	575	
Glu	Lys	Glu	Asp	Ala	Val	Asn	Lys	Ile	His	Thr	Thr	Gly	Phe	Lys	Asp	580	585	590	
Gln	Asn	Glu	Met	Leu	Ser	Ser	Leu	Gln	Lys	Leu	Ala	Val	Leu	Lys	Ala	595	600	605	
Asp	Leu	Glu	Lys	Lys	Lys	Gln	Ser	Met	Gly	Lys	Leu	Tyr	Ser	Leu	Lys	610	615	620	
Gln	Asp	Leu	Leu	Ser	Thr	Leu	Lys	Asn	Lys	Ser	Val	Thr	Gln	Lys	Thr	625	630	635	640
Glu	Ala	Trp	Leu	Asp	Asn	Phe	Ala	Arg	Cys	Trp	Asp	Asn	Leu	Val	Gln	645	650	655	
Lys	Leu	Glu	Lys	Ser	Thr	Ala	Gln	Ile	Ser	Gln	Ala	Val	Thr	Thr	Thr	660	665	670	
Gln	Pro	Ser	Leu	Thr	Gln	Thr	Thr	Val	Met	Glu	Thr	Val	Thr	Thr	Val	675	680	685	
Thr	Thr	Arg	Glu	Gln	Ile	Leu	Val	Lys	His	Ala	Gln	Glu	Glu	Leu	Pro	690	695	700	
Pro	Pro	Pro	Pro	Gln	Lys	Lys	Arg	Gln	Ile	Thr	Val	Asp	Ser	Glu	Ile	705	710	715	720
Arg	Lys	Arg	Leu	Asp	Val	Asp	Ile	Thr	Glu	Leu	His	Ser	Trp	Ile	Thr	725	730	735	
Arg	Ser	Glu	Ala	Val	Leu	Gln	Ser	Pro	Glu	Phe	Ala	Ile	Phe	Arg	Lys	740	745	750	
Glu	Gly	Asn	Phe	Ser	Asp	Leu	Lys	Glu	Lys	Val	Asn	Ala	Ile	Glu	Arg	755	760	765	
Glu	Lys	Ala	Glu	Lys	Phe	Arg	Lys	Leu	Gln	Asp	Ala	Ser	Arg	Ser	Ala	770	775	780	
Gln	Ala	Leu	Val	Glu	Gln	Met	Val	Asn	Glu	Gly	Val	Asn	Ala	Asp	Ser				

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Gln Leu Leu Ser Glu Arg	Leu Asn Trp Leu Glu Tyr	Gln Asn Asn Ile	
	820	825	830
Ile Ala Phe Tyr Asn Gln	Leu Gln Gln Leu Glu Gln Met Thr Thr Thr		
	835	840	845
Ala Glu Asn Trp Leu Lys	Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr		
	850	855	860
Ala Ile Lys Ser Gln Leu Lys	Ile Cys Lys Asp Glu Val Asn Arg Leu		
	865	870	875
Ser Gly Leu Gln Pro Gln	Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala		
	885	890	895
Leu Lys Glu Lys Gly Gln Gly	Pro Met Phe Leu Asp Ala Asp Phe Val		
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Ala Phe Thr Asn His Phe Lys	Gln Val Phe Ser Asp Val Gln Ala Arg		
	915	920	925
Glu Lys Glu Leu Gln Thr	Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr		
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Gln Glu Thr Met Ser Ala	Ile Arg Thr Trp Val Gln Gln Ser Glu Thr		
	945	950	955
Lys Leu Ser Ile Pro Gln	Leu Ser Val Thr Asp Tyr Glu Ile Met Glu		
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Gln Arg Leu Gly Glu Leu	Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln		
	980	985	990
Gln Ser Gly Leu Tyr Tyr	Leu Ser Thr Thr Val Lys Glu Met Ser Lys		
	995	1000	1005
Lys Ala Pro Ser Glu Ile	Ser Arg Lys Tyr Gln Ser Glu Phe Glu		
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Glu Ile Glu Gly Arg Trp	Lys Lys Leu Ser Ser Gln Leu Val Glu		
	1025	1030	1035
His Cys Gln Lys Leu Glu	Glu Gln Met Asn Lys Leu Arg Lys Ile		
	1040	1045	1050
Gln Asn His Ile Gln Thr	Leu Lys Lys Trp Met Ala Glu Val Asp		
	1055	1060	1065
Val Phe Leu Lys Glu Glu	Trp Pro Ala Leu Gly Asp Ser Glu Ile		
	1070	1075	1080
Leu Lys Lys Gln Leu Lys	Gln Cys Arg Leu Leu Val Ser Asp Ile		
	1085	1090	1095
Gln Thr Ile Gln Pro Ser	Leu Asn Ser Val Asn Glu Gly Gly Gln		
	1100	1105	1110
Lys Ile Lys Asn Glu Ala	Glu Pro Glu Phe Ala Ser Arg Leu Glu		
	1115	1120	1125
Thr Glu Leu Lys Glu Leu	Asn Thr Gln Trp Asp His Met Cys Gln		
	1130	1135	1140
Gln Val Tyr Ala Arg Lys	Glu Ala Leu Lys Gly Gly Leu Glu Lys		
	1145	1150	1155
Thr Val Ser Leu Gln Lys	Asp Leu Ser Glu Met His Glu Trp Met		
	1160	1165	1170
Thr Gln Ala Glu Glu Glu	Tyr Leu Glu Arg Asp Phe Glu Tyr Lys		
	1175	1180	1185

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Thr	Pro	Asp	Glu	Leu	Gln	Lys	Ala	Val	Glu	Glu	Met	Lys	Arg	Ala
1190						1195					1200			
Lys	Glu	Glu	Ala	Gln	Gln	Lys	Glu	Ala	Lys	Val	Lys	Leu	Leu	Thr
1205						1210					1215			
Glu	Ser	Val	Asn	Ser	Val	Ile	Ala	Gln	Ala	Pro	Pro	Val	Ala	Gln
1220						1225					1230			
Glu	Ala	Leu	Lys	Lys	Glu	Leu	Glu	Thr	Leu	Thr	Thr	Asn	Tyr	Gln
1235						1240					1245			
Trp	Leu	Cys	Thr	Arg	Leu	Asn	Gly	Lys	Cys	Lys	Thr	Leu	Glu	Glu
1250						1255					1260			
Val	Trp	Ala	Cys	Trp	His	Glu	Leu	Leu	Ser	Tyr	Leu	Glu	Lys	Ala
1265						1270					1275			
Asn	Lys	Trp	Leu	Asn	Glu	Val	Glu	Phe	Lys	Leu	Lys	Thr	Thr	Glu
1280						1285					1290			
Asn	Ile	Pro	Gly	Gly	Ala	Glu	Glu	Ile	Ser	Glu	Val	Leu	Asp	Ser
1295						1300					1305			
Leu	Glu	Asn	Leu	Met	Arg	His	Ser	Glu	Asp	Asn	Pro	Asn	Gln	Ile
1310						1315					1320			
Arg	Ile	Leu	Ala	Gln	Thr	Leu	Thr	Asp	Gly	Gly	Val	Met	Asp	Glu
1325						1330					1335			
Leu	Ile	Asn	Glu	Glu	Leu	Glu	Thr	Phe	Asn	Ser	Arg	Trp	Arg	Glu
1340						1345					1350			
Leu	His	Glu	Glu	Ala	Val	Arg	Arg	Gln	Lys	Leu	Leu	Glu	Gln	Ser
1355						1360					1365			
Ile	Gln	Ser	Ala	Gln	Glu	Thr	Glu	Lys	Ser	Leu	His	Leu	Ile	Gln
1370						1375					1380			
Glu	Ser	Leu	Thr	Phe	Ile	Asp	Lys	Gln	Leu	Ala	Ala	Tyr	Ile	Ala
1385						1390					1395			
Asp	Lys	Val	Asp	Ala	Ala	Gln	Met	Pro	Gln	Glu	Ala	Gln	Lys	Ile
1400						1405					1410			
Gln	Ser	Asp	Leu	Thr	Ser	His	Glu	Ile	Ser	Leu	Glu	Glu	Met	Lys
1415						1420					1425			
Lys	His	Asn	Gln	Gly	Lys	Glu	Ala	Ala	Gln	Arg	Val	Leu	Ser	Gln
1430						1435					1440			
Ile	Asp	Val	Ala	Gln	Lys	Lys	Leu	Gln	Asp	Val	Ser	Met	Lys	Phe
1445						1450					1455			
Arg	Leu	Phe	Gln	Lys	Pro	Ala	Asn	Phe	Glu	Gln	Arg	Leu	Gln	Glu
1460						1465					1470			
Ser	Lys	Met	Ile	Leu	Asp	Glu	Val	Lys	Met	His	Leu	Pro	Ala	Leu
1475						1480					1485			
Glu	Thr	Lys	Ser	Val	Glu	Gln	Glu	Val	Val	Gln	Ser	Gln	Leu	Asn
1490						1495					1500			
His	Cys	Val	Asn	Leu	Tyr	Lys	Ser	Leu	Ser	Glu	Val	Lys	Ser	Glu
1505						1510					1515			
Val	Glu	Met	Val	Ile	Lys	Thr	Gly	Arg	Gln	Ile	Val	Gln	Lys	Lys
1520						1525					1530			
Gln	Thr	Glu	Asn	Pro	Lys	Glu	Leu	Asp	Glu	Arg	Val	Thr	Ala	Leu
1535						1540					1545			
Lys	Leu	His	Tyr	Asn	Glu	Leu	Gly	Ala	Lys	Val	Thr	Glu	Arg	Lys
1550						1555					1560			

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Gln 1565	Gln	Leu	Glu	Lys	Cys	Leu 1570	Lys	Leu	Ser	Arg	Lys 1575	Met	Arg	Lys
Glu 1580	Met	Asn	Val	Leu	Thr	Glu 1585	Trp	Leu	Ala	Ala	Thr 1590	Asp	Met	Glu
Leu 1595	Thr	Lys	Arg	Ser	Ala	Val 1600	Glu	Gly	Met	Pro	Ser 1605	Asn	Leu	Asp
Ser 1610	Glu	Val	Ala	Trp	Gly	Lys 1615	Ala	Thr	Gln	Lys	Glu 1620	Ile	Glu	Lys
Gln 1625	Lys	Val	His	Leu	Lys	Ser 1630	Ile	Thr	Glu	Val	Gly 1635	Glu	Ala	Leu
Lys 1640	Thr	Val	Leu	Gly	Lys	Lys 1645	Glu	Thr	Leu	Val	Glu 1650	Asp	Lys	Leu
Ser 1655	Leu	Leu	Asn	Ser	Asn	Trp 1660	Ile	Ala	Val	Thr	Ser 1665	Arg	Ala	Glu
Glu 1670	Trp	Leu	Asn	Leu	Leu	Leu 1675	Glu	Tyr	Gln	Lys	His 1680	Met	Glu	Thr
Phe 1685	Asp	Gln	Asn	Val	Asp	His 1690	Ile	Thr	Lys	Trp	Ile 1695	Ile	Gln	Ala
Asp 1700	Thr	Leu	Leu	Asp	Glu	Ser 1705	Glu	Lys	Lys	Lys	Pro 1710	Gln	Gln	Lys
Glu 1715	Asp	Val	Leu	Lys	Arg	Leu 1720	Lys	Ala	Glu	Leu	Asn 1725	Asp	Ile	Arg
Pro 1730	Lys	Val	Asp	Ser	Thr	Arg 1735	Asp	Gln	Ala	Ala	Asn 1740	Leu	Met	Ala
Asn 1745	Arg	Gly	Asp	His	Cys	Arg 1750	Lys	Leu	Val	Glu	Pro 1755	Gln	Ile	Ser
Glu 1760	Leu	Asn	His	Arg	Phe	Ala 1765	Ala	Ile	Ser	His	Arg 1770	Ile	Lys	Thr
Gly 1775	Lys	Ala	Ser	Ile	Pro	Leu 1780	Lys	Glu	Leu	Glu	Gln 1785	Phe	Asn	Ser
Asp 1790	Ile	Gln	Lys	Leu	Leu	Glu 1795	Pro	Leu	Glu	Ala	Glu 1800	Ile	Gln	Gln
Gly 1805	Val	Asn	Leu	Lys	Glu	Glu 1810	Asp	Phe	Asn	Lys	Asp 1815	Met	Asn	Glu
Asp 1820	Asn	Glu	Gly	Thr	Val	Lys 1825	Glu	Leu	Leu	Gln	Arg 1830	Gly	Asp	Asn
Leu 1835	Gln	Gln	Arg	Ile	Thr	Asp 1840	Glu	Arg	Lys	Arg	Glu 1845	Glu	Ile	Lys
Ile 1850	Lys	Gln	Gln	Leu	Leu	Gln 1855	Thr	Lys	His	Asn	Ala 1860	Leu	Lys	Asp
Leu 1865	Arg	Ser	Gln	Arg	Arg	Lys 1870	Lys	Ala	Leu	Glu	Ile 1875	Ser	His	Gln
Trp 1880	Tyr	Gln	Tyr	Lys	Arg	Gln 1885	Ala	Asp	Asp	Leu	Leu 1890	Lys	Cys	Leu
Asp 1895	Asp	Ile	Glu	Lys	Lys	Leu 1900	Ala	Ser	Leu	Pro	Glu 1905	Pro	Arg	Asp
Glu 1910	Arg	Lys	Ile	Lys	Glu	Ile 1915	Asp	Arg	Glu	Leu	Gln 1920	Lys	Lys	Lys
Glu 1925	Glu	Leu	Asn	Ala	Val	Arg 1930	Arg	Gln	Ala	Glu	Gly 1935	Leu	Ser	Glu
Asp 1940	Gly	Ala	Ala	Met	Ala	Val	Glu	Pro	Thr	Gln	Ile	Gln	Leu	Ser

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1940	1945	1950
Lys Arg Trp Arg Glu Ile 1955	Glu Ser Lys Phe Ala 1960	Gln Phe Arg Arg 1965
Leu Asn Phe Ala Gln Ile 1970	His Thr Val Arg Glu 1975	Glu Thr Met Met 1980
Val Met Thr Glu Asp Met 1985	Pro Leu Glu Ile Ser 1990	Tyr Val Pro Ser 1995
Thr Tyr Leu Thr Glu Ile 2000	Thr His Val Ser Gln 2005	Ala Leu Leu Glu 2010
Val Glu Gln Leu Leu Asn 2015	Ala Pro Asp Leu Cys 2020	Ala Lys Asp Phe 2025
Glu Asp Leu Phe Lys Gln 2030	Glu Glu Ser Leu Lys 2035	Asn Ile Lys Asp 2040
Ser Leu Gln Gln Ser Ser 2045	Gly Arg Ile Asp Ile 2050	Ile His Ser Lys 2055
Lys Thr Ala Ala Leu Gln 2060	Ser Ala Thr Pro Val 2065	Glu Arg Val Lys 2070
Leu Gln Glu Ala Leu Ser 2075	Gln Leu Asp Phe Gln 2080	Trp Glu Lys Val 2085
Asn Lys Met Tyr Lys Asp 2090	Arg Gln Gly Arg Phe 2095	Asp Arg Ser Val 2100
Glu Lys Trp Arg Arg Phe 2105	His Tyr Asp Ile Lys 2110	Ile Phe Asn Gln 2115
Trp Leu Thr Glu Ala Glu 2120	Gln Phe Leu Arg Lys 2125	Thr Gln Ile Pro 2130
Glu Asn Trp Glu His Ala 2135	Lys Tyr Lys Trp Tyr 2140	Leu Lys Glu Leu 2145
Gln Asp Gly Ile Gly Gln 2150	Arg Gln Thr Val Val 2155	Arg Thr Leu Asn 2160
Ala Thr Gly Glu Glu Ile 2165	Ile Gln Gln Ser Ser 2170	Lys Thr Asp Ala 2175
Ser Ile Leu Gln Glu Lys 2180	Leu Gly Ser Leu Asn 2185	Leu Arg Trp Gln 2190
Glu Val Cys Lys Gln Leu 2195	Ser Asp Arg Lys Lys 2200	Arg Leu Glu Glu 2205
Gln Lys Asn Ile Leu Ser 2210	Glu Phe Gln Arg Asp 2215	Leu Asn Glu Phe 2220
Val Leu Trp Leu Glu Glu 2225	Ala Asp Asn Ile Ala 2230	Ser Ile Pro Leu 2235
Glu Pro Gly Lys Glu Gln 2240	Gln Leu Lys Glu Lys 2245	Leu Glu Gln Val 2250
Lys Leu Leu Val Glu Glu 2255	Leu Pro Leu Arg Gln 2260	Gly Ile Leu Lys 2265
Gln Leu Asn Glu Thr Gly 2270	Gly Pro Val Leu Val 2275	Ser Ala Pro Ile 2280
Ser Pro Glu Glu Gln Asp 2285	Lys Leu Glu Asn Lys 2290	Leu Lys Gln Thr 2295
Asn Leu Gln Trp Ile Lys 2300	Val Ser Arg Ala Leu 2305	Pro Glu Lys Gln 2310
Gly Glu Ile Glu Ala Gln 2315	Ile Lys Asp Leu Gly 2320	Gln Leu Glu Lys 2325

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Lys Leu	Glu Asp	Leu Glu	Glu	Gln Leu	Asn His	Leu	Leu Leu	Trp
2330			2335			2340		
Leu Ser	Pro Ile	Arg Asn	Gln	Leu Glu	Ile Tyr	Asn	Gln Pro	Asn
2345			2350			2355		
Gln Glu	Gly Pro	Phe Asp	Val	Gln Glu	Thr Glu	Ile	Ala Val	Gln
2360			2365			2370		
Ala Lys	Gln Pro	Asp Val	Glu	Glu Ile	Leu Ser	Lys	Gly Gln	His
2375			2380			2385		
Leu Tyr	Lys Glu	Lys Pro	Ala	Thr Gln	Pro Val	Lys	Arg Lys	Leu
2390			2395			2400		
Glu Asp	Leu Ser	Ser Glu	Trp	Lys Ala	Val Asn	Arg	Leu Leu	Gln
2405			2410			2415		
Glu Leu	Arg Ala	Lys Gln	Pro	Asp Leu	Ala Pro	Gly	Leu Thr	Thr
2420			2425			2430		
Ile Gly	Ala Ser	Pro Thr	Gln	Thr Val	Thr Leu	Val	Thr Gln	Pro
2435			2440			2445		
Val Val	Thr Lys	Glu Thr	Ala	Ile Ser	Lys Leu	Glu	Met Pro	Ser
2450			2455			2460		
Ser Leu	Met Leu	Glu Val	Pro	Ala Leu	Ala Asp	Phe	Asn Arg	Ala
2465			2470			2475		
Trp Thr	Glu Leu	Thr Asp	Trp	Leu Ser	Leu Leu	Asp	Gln Val	Ile
2480			2485			2490		
Lys Ser	Gln Arg	Val Met	Val	Gly Asp	Leu Glu	Asp	Ile Asn	Glu
2495			2500			2505		
Met Ile	Ile Lys	Gln Lys	Ala	Thr Met	Gln Asp	Leu	Glu Gln	Arg
2510			2515			2520		
Arg Pro	Gln Leu	Glu Glu	Leu	Ile Thr	Ala Ala	Gln	Asn Leu	Lys
2525			2530			2535		
Asn Lys	Thr Ser	Asn Gln	Glu	Ala Arg	Thr Ile	Ile	Thr Asp	Arg
2540			2545			2550		
Ile Glu	Arg Ile	Gln Asn	Gln	Trp Asp	Glu Val	Gln	Glu His	Leu
2555			2560			2565		
Gln Asn	Arg Arg	Gln Gln	Leu	Asn Glu	Met Leu	Lys	Asp Ser	Thr
2570			2575			2580		
Gln Trp	Leu Glu	Ala Lys	Glu	Glu Ala	Glu Gln	Val	Leu Gly	Gln
2585			2590			2595		
Ala Arg	Ala Lys	Leu Glu	Ser	Trp Lys	Glu Gly	Pro	Tyr Thr	Val
2600			2605			2610		
Asp Ala	Ile Gln	Lys Lys	Ile	Thr Glu	Thr Lys	Gln	Leu Ala	Lys
2615			2620			2625		
Asp Leu	Arg Gln	Trp Gln	Thr	Asn Val	Asp Val	Ala	Asn Asp	Leu
2630			2635			2640		
Ala Leu	Lys Leu	Leu Arg	Asp	Tyr Ser	Ala Asp	Asp	Thr Arg	Lys
2645			2650			2655		
Val His	Met Ile	Thr Glu	Asn	Ile Asn	Ala Ser	Trp	Arg Ser	Ile
2660			2665			2670		
His Lys	Arg Val	Ser Glu	Arg	Glu Ala	Ala Leu	Glu	Glu Thr	His
2675			2680			2685		
Arg Leu	Leu Gln	Gln Phe	Pro	Leu Asp	Leu Glu	Lys	Phe Leu	Ala
2690			2695			2700		

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Trp Leu	Thr Glu Ala Glu	Thr	Thr Ala Asn Val	Leu Gln Asp Ala
2705		2710		2715
Thr Arg	Lys Glu Arg Leu	Leu Glu Asp Ser Lys Gly	Val Lys Glu	
2720		2725		2730
Leu Met	Lys Gln Trp Gln	Asp Leu Gln Gly Glu Ile	Glu Ala His	
2735		2740		2745
Thr Asp	Val Tyr His Asn	Leu Asp Glu Asn Ser Gln	Lys Ile Leu	
2750		2755		2760
Arg Ser	Leu Glu Gly Ser	Asp Asp Ala Val Leu Leu	Gln Arg Arg	
2765		2770		2775
Leu Asp	Asn Met Asn Phe	Lys Trp Ser Glu Leu Arg	Lys Lys Ser	
2780		2785		2790
Leu Asn	Ile Arg Ser His	Leu Glu Ala Ser Ser Asp	Gln Trp Lys	
2795		2800		2805
Arg Leu	His Leu Ser Leu	Gln Glu Leu Val Trp	Leu Gln Leu	
2810		2815		2820
Lys Asp	Asp Glu Leu Ser	Arg Gln Ala Pro Ile Gly	Gly Asp Phe	
2825		2830		2835
Pro Ala	Val Gln Lys Gln	Asn Asp Val His Arg Ala	Phe Lys Arg	
2840		2845		2850
Glu Leu	Lys Thr Lys Glu	Pro Val Ile Met Ser Thr	Leu Glu Thr	
2855		2860		2865
Val Arg	Ile Phe Leu Thr	Glu Gln Pro Leu Glu Gly	Leu Glu Lys	
2870		2875		2880
Leu Tyr	Gln Glu Pro Arg	Glu Leu Pro Pro Glu Glu	Arg Ala Gln	
2885		2890		2895
Asn Val	Thr Arg Leu Leu	Arg Lys Gln Ala Glu Glu	Val Asn Thr	
2900		2905		2910
Glu Trp	Glu Lys Leu Asn	Leu His Ser Ala Asp Trp	Gln Arg Lys	
2915		2920		2925
Ile Asp	Glu Thr Leu Glu	Arg Leu Gln Glu Leu Gln	Glu Ala Thr	
2930		2935		2940
Asp Glu	Leu Asp Leu Lys	Leu Arg Gln Ala Glu Val	Ile Lys Gly	
2945		2950		2955
Ser Trp	Gln Pro Val Gly	Asp Leu Leu Ile Asp Ser	Leu Gln Asp	
2960		2965		2970
His Leu	Glu Lys Val Lys	Ala Leu Arg Gly Glu Ile	Ala Pro Leu	
2975		2980		2985
Lys Glu	Asn Val Ser His	Val Asn Asp Leu Ala Arg	Gln Leu Thr	
2990		2995		3000
Thr Leu	Gly Ile Gln Leu	Ser Pro Tyr Asn Leu Ser	Thr Leu Glu	
3005		3010		3015
Asp Leu	Asn Thr Arg Trp	Lys Leu Leu Gln Val Ala	Val Glu Asp	
3020		3025		3030
Arg Val	Arg Gln Leu His	Glu Ala His Arg Asp Phe	Gly Pro Ala	
3035		3040		3045
Ser Gln	His Phe Leu Ser	Thr Ser Val Gln Gly Pro	Trp Glu Arg	
3050		3055		3060
Ala Ile	Ser Pro Asn Lys	Val Pro Tyr Tyr Ile Asn	His Glu Thr	
3065		3070		3075
Gln Thr	Thr Cys Trp Asp	His Pro Lys Met Thr Glu	Leu Tyr Gln	

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3080	3085	3090
Ser Leu Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr		
3095	3100	3105
Ala Met Lys Leu Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu		
3110	3115	3120
Leu Ser Leu Ser Ala Ala Cys Asp Ala Leu Asp Gln His Asn Leu		
3125	3130	3135
Lys Gln Asn Asp Gln Pro Met Asp Ile Leu Gln Ile Ile Asn Cys		
3140	3145	3150
Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu His Asn Asn Leu		
3155	3160	3165
Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn Trp Leu Leu		
3170	3175	3180
Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val Leu Ser		
3185	3190	3195
Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu Asp		
3200	3205	3210
Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe		
3215	3220	3225
Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln		
3230	3235	3240
Ile Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn		
3245	3250	3255
Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys		
3260	3265	3270
Pro Glu Ile Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu		
3275	3280	3285
Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg Val Ala Ala		
3290	3295	3300
Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile Cys Lys Glu		
3305	3310	3315
Cys Pro Ile Ile Gly Phe Arg Tyr Arg Ser Leu Lys His Phe Asn		
3320	3325	3330
Tyr Asp Ile Cys Gln Ser Cys Phe Phe Ser Gly Arg Val Ala Lys		
3335	3340	3345
Gly His Lys Met His Tyr Pro Met Val Glu Tyr Cys Thr Pro Thr		
3350	3355	3360
Thr Ser Gly Glu Asp Val Arg Asp Phe Ala Lys Val Leu Lys Asn		
3365	3370	3375
Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys His Pro Arg Met Gly		
3380	3385	3390
Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn Met Glu Thr		
3395	3400	3405
Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser Ala Pro Ala		
3410	3415	3420
Ser Ser Pro Gln Leu Ser His Asp Asp Thr His Ser Arg Ile Glu		
3425	3430	3435
His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn Ser Asn Gly Ser		
3440	3445	3450
Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile Asp Asp Glu		
3455	3460	3465

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His Leu	Leu Ile	Gln His	Tyr	Cys Gln	Ser Leu	Asn	Gln Asp	Ser	
3470			3475			3480			
Pro Leu	Ser Gln	Pro Arg	Ser	Pro Ala	Gln Ile	Leu	Ile Ser	Leu	
3485			3490			3495			
Glu Ser	Glu Glu	Arg Gly	Glu	Leu Glu	Arg Ile	Leu	Ala Asp	Leu	
3500			3505			3510			
Glu Glu	Glu Asn	Arg Asn	Leu	Gln Ala	Glu Tyr	Asp	Arg Leu	Lys	
3515			3520			3525			
Gln Gln	His Glu	His Lys	Gly	Leu Ser	Pro Leu	Pro	Ser Pro	Pro	
3530			3535			3540			
Glu Met	Met Pro	Thr Ser	Pro	Gln Ser	Pro Arg	Asp	Ala Glu	Leu	
3545			3550			3555			
Ile Ala	Glu Ala	Lys Leu	Leu	Arg Gln	His Lys	Gly	Arg Leu	Glu	
3560			3565			3570			
Ala Arg	Met Gln	Ile Leu	Glu	Asp His	Asn Lys	Gln	Leu Glu	Ser	
3575			3580			3585			
Gln Leu	His Arg	Leu Arg	Gln	Leu Leu	Glu Gln	Pro	Gln Ala	Glu	
3590			3595			3600			
Ala Lys	Val Asn	Gly Thr	Thr	Val Ser	Ser Pro	Ser	Thr Ser	Leu	
3605			3610			3615			
Gln Arg	Ser Asp	Ser Ser	Gln	Pro Met	Leu Leu	Arg	Val Val	Gly	
3620			3625			3630			
Ser Gln	Thr Ser	Asp Ser	Met	Gly Glu	Glu Asp	Leu	Leu Ser	Pro	
3635			3640			3645			
Pro Gln	Asp Thr	Ser Thr	Gly	Leu Glu	Glu Val	Met	Glu Gln	Leu	
3650			3655			3660			
Asn Asn	Ser Phe	Pro Ser	Ser	Arg Gly	Arg Asn	Thr	Pro Gly	Lys	
3665			3670			3675			
Pro Met	Arg Glu	Asp Thr	Met						
3680			3685						

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 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 2

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25

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 <213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

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<211> LENGTH: 25

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

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uccaacauc aaggaagau gcauu 25

<210> SEQ ID NO 8

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 8

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<210> SEQ ID NO 9

<211> LENGTH: 25

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aacaucaagg aagauggcau uucua 25

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acaucaagga agauggcauu ucuag 25

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caucaaggaa gauggcauuu cuagu 25

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aucaaggaag auggcauuuc uaguu 25

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ucaaggaaga uggcauuuc aguuu 25

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caaggaagau ggcauuucua guuug 25

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agauggcauu ucuaguuuugg agaag 25

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uucuaguug gagauggcag uuucc 25

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gagauggcag uuuccuuagu aacca 25

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agauggcagu uuuccuagua accac 25

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aguuuccuua guaaccacag guugu 25

<210> SEQ ID NO 48

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<223> OTHER INFORMATION: oligonucleotide

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guuuccuuag uaaccacagg uugug 25

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uuuccuuagu aaccacaggu ugugu 25

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cuuaguaacc acagguugug ucacc 25

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uuaguaacca cagguugugu cacca 25

<210> SEQ ID NO 55

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guaaccacag guugugucac cagag 25

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uaaccacagg uugugucacc agagu 25

<210> SEQ ID NO 59
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<223> OTHER INFORMATION: oligonucleotide

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ccacagguug ugucaccaga gaaac

25

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cacagguugu gucaccagag aaaca

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<212> TYPE: RNA

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25

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agguuguguc accagaguaa caguc

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<210> SEQ ID NO 66

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gguguguca ccagaguac agucu

25

<210> SEQ ID NO 67

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<223> OTHER INFORMATION: oligonucleotide

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guugugucac cagaguaaca gucug 25

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<400> SEQUENCE: 68

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<210> SEQ ID NO 69
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gugucaccag aguaacaguc ugaug 25

<210> SEQ ID NO 71
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ugucaccaga guaacagucu gagua 25

<210> SEQ ID NO 72
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gucaccagag uaacagucug aguag 25

<210> SEQ ID NO 73
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ucaccagagu aacagucuga guagg 25

<210> SEQ ID NO 74

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<211> LENGTH: 25
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accagaguua cagucugagu aggag 25

<210> SEQ ID NO 76
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<212> TYPE: RNA
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auucaauguu cugacaacag uuugc 25

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<211> LENGTH: 25
<212> TYPE: RNA
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

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<210> SEQ ID NO 81

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<212> TYPE: RNA

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gauugcugaa uuauuucuuc c 21

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<211> LENGTH: 25

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<212> TYPE: RNA

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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ugcugaauua uuucuucccc aguug 25

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<211> LENGTH: 25

<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 86

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<212> TYPE: RNA
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cugaaauauu ucuuccccag uugca 25

<210> SEQ ID NO 88
<211> LENGTH: 25
<212> TYPE: RNA
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ugaaauauuu cuuccccagu ugcau 25

<210> SEQ ID NO 89
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<212> TYPE: RNA
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gaauuauuuc uuccccaguu gcauu 25

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<211> LENGTH: 25
<212> TYPE: RNA
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aaauuauuuc uccccaguug cauuc 25

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<212> TYPE: RNA
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<210> SEQ ID NO 93

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uauuucuucc ccaguugcau ucaau 25

<210> SEQ ID NO 94
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<212> TYPE: RNA
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auuucuuccc caguugcauu caaug 25

<210> SEQ ID NO 95
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<212> TYPE: RNA
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uuucuucccc aguugcauuc aaugu 25

<210> SEQ ID NO 96
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<212> TYPE: RNA
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<400> SEQUENCE: 96

uucuucccca guugcauua auguu 25

<210> SEQ ID NO 97
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<223> OTHER INFORMATION: oligonucleotide

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ucuuccccag uugcaucaa uguuc 25

<210> SEQ ID NO 98
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cuuccccagu ugcaucaa guucu 25

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<211> LENGTH: 25
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<223> OTHER INFORMATION: oligonucleotide

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uccccaguug cauucaaugu ucuga 25

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ccccaguugc auucaauguu cugac 25

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cccaguugca uucaauguuc ugaca 25

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<212> TYPE: RNA

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<400> SEQUENCE: 103

ccaguugcau ucaauguucu gacaa 25

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 104

caguugcauu caaaguucug acaac 25

<210> SEQ ID NO 105

<211> LENGTH: 25

<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 105

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aguugcauuc aauguucuga caaca 25

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uccuguagaa uacuggcauc 20

<210> SEQ ID NO 107
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<212> TYPE: RNA
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ugcagaccuc cugccaccgc agauuca 27

<210> SEQ ID NO 108
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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uugcagaccu ccugccaccg cagauucagg cuuc 34

<210> SEQ ID NO 109
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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guugcauua auguucugac aacag 25

<210> SEQ ID NO 110
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<212> TYPE: RNA
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<210> SEQ ID NO 112

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<211> LENGTH: 25
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gcauucaaug uucugacaac aguuu 25

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<212> TYPE: RNA
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cauucaaugu ucugacaaca guuug 25

<210> SEQ ID NO 114
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 114

auucaauguu cugacaacag uuugc 25

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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ucaauguucu gacaacaguu ugccg 25

<210> SEQ ID NO 116
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 116

caaguucug acaacaguuu gccgc 25

<210> SEQ ID NO 117
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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aaguucuga caacaguuug ccgcu 25

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 118

auguucugac aacaguugc cgcug 25

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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uguucugaca acaguugcc gcugc 25

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guucugacaa caguugccg cugcc 25

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uucugacaac aguugccgc ugccc 25

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ucugacaaca guuugccgc gccca 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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cugacaacag uuugccgcug cccaa 25

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 124

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ugacaacagu uugccgcugc ccaau 25

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gacaacaguu ugccgcugcc caaug 25

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<400> SEQUENCE: 126

acaacaguuu gccgcugccc aaugc 25

<210> SEQ ID NO 127
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<400> SEQUENCE: 127

caacaguug ccgcugccca augcc 25

<210> SEQ ID NO 128
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<212> TYPE: RNA
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<400> SEQUENCE: 128

aacaguugc cgcugcccaa ugcca 25

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acaguugcc gcugcccaau gccau 25

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caguugccg cugcccaaug ccauc 25

<210> SEQ ID NO 131

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<400> SEQUENCE: 131

aguuugccgc ugcccaugc caucc 25

<210> SEQ ID NO 132
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<212> TYPE: RNA
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<400> SEQUENCE: 132

guuugccgcg gcccaaugcc auccu 25

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uuugccgcug cccaugcca uccug 25

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<400> SEQUENCE: 134

uugccgcugc ccaaugccau ccugg 25

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<212> TYPE: RNA
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ugccgcugcc caaugccauc cugga 25

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<400> SEQUENCE: 136

gccgcugccc aaugccauc uggag 25

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 137

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<211> LENGTH: 25

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<220> FEATURE:

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<212> TYPE: RNA

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<220> FEATURE:

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<400> SEQUENCE: 139

uguuuuugag gauugcugaa 20

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<211> LENGTH: 40

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 140

uguucugaca acaguugcc gcugcccaau gccauccugg 40

<210> SEQ ID NO 141

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 141

cucuggccug uccuaagacc ugcuc 25

<210> SEQ ID NO 142

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 142

ucuggccugu ccuaagaccu gcua 25

<210> SEQ ID NO 143

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 143

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cuggccuguc cuaagaccug cucag 25

<210> SEQ ID NO 144
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 144

uggccugucc uaagaccugc ucagc 25

<210> SEQ ID NO 145
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 145

ggccuguccu aagaccugcu cagcu 25

<210> SEQ ID NO 146
<211> LENGTH: 25
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<400> SEQUENCE: 146

gccuguccua agaccugcuc agcuu 25

<210> SEQ ID NO 147
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 147

ccuguccuaa gaccugcuca gcuuc 25

<210> SEQ ID NO 148
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 148

cuguccuaag accugcucag cuucu 25

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<400> SEQUENCE: 149

uguccuaaga ccugcucagc uucuu 25

<210> SEQ ID NO 150

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<211> LENGTH: 25
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<400> SEQUENCE: 150

guccuaagac cugcucagcu ucuuc 25

<210> SEQ ID NO 151
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<212> TYPE: RNA
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<400> SEQUENCE: 151

uccuaagacc ugcucagcuu cuucc 25

<210> SEQ ID NO 152
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<212> TYPE: RNA
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<400> SEQUENCE: 152

ccuaagaccu gcucagcuuc uuccu 25

<210> SEQ ID NO 153
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<212> TYPE: RNA
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<400> SEQUENCE: 153

cuaagaccug cucagcuuc uccu 25

<210> SEQ ID NO 154
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<212> TYPE: RNA
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<400> SEQUENCE: 154

uaagaccugc ucagcuucuu ccua 25

<210> SEQ ID NO 155
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 155

aagaccugcu cagcuucuu cuuag 25

<210> SEQ ID NO 156
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 156

agaccugcuc agcuucucc uuagc 25

<210> SEQ ID NO 157

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 157

gaccugcuca gcuucuccu uagcu 25

<210> SEQ ID NO 158

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 158

accugcucag cuucuccuu agcuu 25

<210> SEQ ID NO 159

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 159

ccugcucagc uucuccuua gcuuc 25

<210> SEQ ID NO 160

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 160

cugcucageu ucuuccuag cuucc 25

<210> SEQ ID NO 161

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 161

ugcucagcuu cuuccuagc uucca 25

<210> SEQ ID NO 162

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 162

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gcucagcuuc uuccuuagcu uccag 25

<210> SEQ ID NO 163
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 163

cucagcuucu uccuuagcuu ccagc 25

<210> SEQ ID NO 164
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 164

ucagcuucuu ccuuagcuuc cagcc 25

<210> SEQ ID NO 165
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<212> TYPE: RNA
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<400> SEQUENCE: 165

cagcuucuuuc cuuagcuucc agcca 25

<210> SEQ ID NO 166
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 166

agcuucuuucc uuagcuucca gccau 25

<210> SEQ ID NO 167
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 167

gcuucuuuccu uagcuuccag ccauu 25

<210> SEQ ID NO 168
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<212> TYPE: RNA
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<400> SEQUENCE: 168

cuucuuuccuu agcuuccagc cauug 25

<210> SEQ ID NO 169

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<211> LENGTH: 25
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<213> ORGANISM: Artificial
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<400> SEQUENCE: 169

uucuuuccua gcuuccagcc auugu 25

<210> SEQ ID NO 170
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 170

ucuuuccuag cuuccagcca uugug 25

<210> SEQ ID NO 171
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 171

cuuccuuagc uuccagccau ugugu 25

<210> SEQ ID NO 172
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 172

uuccuuagcu uccagccauu guguu 25

<210> SEQ ID NO 173
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 173

uccuuagcuu ccagccauug uguug 25

<210> SEQ ID NO 174
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 174

ccuuagcuuc cagccauugu guuga 25

<210> SEQ ID NO 175
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 175

cuuagcuucc agccauugug uugaa 25

<210> SEQ ID NO 176

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 176

uuagcuucca gccauugugu ugaau 25

<210> SEQ ID NO 177

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 177

uagcuuccag ccuuguguu gaau 25

<210> SEQ ID NO 178

<211> LENGTH: 25

<212> TYPE: RNA

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<220> FEATURE:

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<400> SEQUENCE: 178

agcuuccagc cauugugug aauc 25

<210> SEQ ID NO 179

<211> LENGTH: 25

<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 179

gcuuccagcc auuguguuga auccu 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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<400> SEQUENCE: 180

cuuccagcca uuguguugaa uccuu 25

<210> SEQ ID NO 181

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 181

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uuccagccau uguugaau ccuuu 25

<210> SEQ ID NO 182
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 182

uccagccauu guguugauc cuuua 25

<210> SEQ ID NO 183
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 183

ccagccauug uguugaaucc uuuaa 25

<210> SEQ ID NO 184
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 184

cagccauugu guugaauccu uuaac 25

<210> SEQ ID NO 185
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 185

agccauugug uugaauccuu uaaca 25

<210> SEQ ID NO 186
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 186

gccauugugu ugaauccuuu aacau 25

<210> SEQ ID NO 187
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 187

ccauuguguu gaaucuuua acauu 25

<210> SEQ ID NO 188

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 188

caugugugug aaucuuuaa cauu 25

<210> SEQ ID NO 189
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<400> SEQUENCE: 189

ucagcuucug uuagccacug 20

<210> SEQ ID NO 190
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 190

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<210> SEQ ID NO 191
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 191

uucagcuucu guuagccacu g 21

<210> SEQ ID NO 192
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 192

ucagcuucug uuagccacug a 21

<210> SEQ ID NO 193
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 193

uucagcuucu guuagccacu ga 22

<210> SEQ ID NO 194
<211> LENGTH: 21
<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 194

ucagcuucug uuagccacug a 21

<210> SEQ ID NO 195

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 195

uucagcuucu guuagccacu ga 22

<210> SEQ ID NO 196

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 196

ucagcuucug uuagccacug au 22

<210> SEQ ID NO 197

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 197

uucagcuucu guuagccacu gau 23

<210> SEQ ID NO 198

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

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ucagcuucug uuagccacug auu 23

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 199

uucagcuucu guuagccacu gauu 24

<210> SEQ ID NO 200

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 200

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ucagcuucug uuagccacug auua 24

<210> SEQ ID NO 201
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 201

uucagcuucu guuagccacu gaua 24

<210> SEQ ID NO 202
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 202

ucagcuucug uuagccacug auuaa 25

<210> SEQ ID NO 203
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 203

uucagcuucu guuagccacu gauuaa 26

<210> SEQ ID NO 204
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 204

ucagcuucug uuagccacug auuaaa 26

<210> SEQ ID NO 205
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 205

uucagcuucu guuagccacu gauuaaa 27

<210> SEQ ID NO 206
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 206

cagcuucugu uagccacug 19

<210> SEQ ID NO 207

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<211> LENGTH: 21
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<213> ORGANISM: Artificial
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<400> SEQUENCE: 207

cagcuucugu uagccacuga u 21

<210> SEQ ID NO 208
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 208

agcuucuguu agccacugau u 21

<210> SEQ ID NO 209
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<212> TYPE: RNA
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<400> SEQUENCE: 209

cagcuucugu uagccacuga uu 22

<210> SEQ ID NO 210
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 210

agcuucuguu agccacugau ua 22

<210> SEQ ID NO 211
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 211

cagcuucugu uagccacuga uua 23

<210> SEQ ID NO 212
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
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cagcuucugu uagccacuga uaaaa 25

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agcuucuguu agccacugau uaaa 24

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agcuucuguu agccacugau 20

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agcuucuguu agccacugau ua 22

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gcuucugua gccacugau aa 22

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agcuucuguu agccacugau uaa 23

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gcuucugua gccacugau aaa 23

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agcuucuguu agccacugau uaaa 24

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gcuucuguaa gccacugauu aaa 23

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ccaauuguaa uuagcauguu ccc 23

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agauaccauu uguauuuagc 20

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gccauuucuc aacagaucu 19

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gccauuucuc aacagaucug uca 23

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auucucagga auuugugucu uuc 23

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<400> SEQUENCE: 232

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guucagcuuc uguuagcc 18

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<223> OTHER INFORMATION: oligonucleotide

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gccgccauu cucaacag 18

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guauuuagca uguucca 18

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caggauuug ugucuuuc 18

<210> SEQ ID NO 238

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 238

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gcuuuucuuu uaguugcugc uuuu 25

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cuuuucuuuu aguugcugcu cuuu 25

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uuuuuuuuu guugcugcuc uuuc 25

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uuuuuuuag uugcugcucu uuucc 25

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uucuuuuagu ugcugcucu uuca 25

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ucuuuuaguu gcugcucu uccag 25

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cuuuuaguug cugcucu uccagg 25

<210> SEQ ID NO 245

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uuuuaguugc ugcucuuuuc caggu 25

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uuuaguugcu gcucuuuucc agguu 25

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uuaguugcug cucuuuucca gguuc 25

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uaguugcugc ucuuuuccag guuca 25

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aguugcugcu cuuuuccagg uucaa 25

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guugcugcuc uuuuuccaggu ucaag 25

<210> SEQ ID NO 251
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

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<400> SEQUENCE: 252

ugcugcucu uuccagguuc aagug 25

<210> SEQ ID NO 253

<211> LENGTH: 25

<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 253

gcugcucuuu uccagguuca agugg 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 254

cugcucuuuu ccagguuca guggg 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

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ugcucuuuuc cagguucaag uggga 25

<210> SEQ ID NO 256

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 256

gcucuuuucc agguucaagu gggac 25

<210> SEQ ID NO 257

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 257

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cucuuuucca gguucaagug ggaua 25

<210> SEQ ID NO 258
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<400> SEQUENCE: 258

ucuuuuccag guucaagugg gauac 25

<210> SEQ ID NO 259
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 259

ucuuuuccag guucaagugg 20

<210> SEQ ID NO 260
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<212> TYPE: RNA
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cuuuuccagg uucaaguggg auacu 25

<210> SEQ ID NO 261
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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uuuuccaggu ucaaguggga uacua 25

<210> SEQ ID NO 262
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<213> ORGANISM: Artificial
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uuuccagguu caagugggau acuag 25

<210> SEQ ID NO 263
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uuccagguuc aagugggau cuagc 25

<210> SEQ ID NO 264

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<211> LENGTH: 25
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<400> SEQUENCE: 264

uccagguuca agugggauac uagca 25

<210> SEQ ID NO 265
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<212> TYPE: RNA
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ccagguucaa gugggauacu agcaa 25

<210> SEQ ID NO 266
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<212> TYPE: RNA
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<400> SEQUENCE: 266

cagguucaag ugggauacua gcaau 25

<210> SEQ ID NO 267
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 267

agguucaagu gggauacuag caaug 25

<210> SEQ ID NO 268
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 268

gguucaagug ggauacuagc aaugu 25

<210> SEQ ID NO 269
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<212> TYPE: RNA
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guucaagugg gauacuagca auguu 25

<210> SEQ ID NO 270
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 270

uucaaguggg auacuagcaa uguua 25

<210> SEQ ID NO 271

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 271

ucaaguggga uacuagcaau guuau 25

<210> SEQ ID NO 272

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 272

caagugggau acuagcaaug uuau 25

<210> SEQ ID NO 273

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 273

aagugggaua cuagcaaugu uaucu 25

<210> SEQ ID NO 274

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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<400> SEQUENCE: 274

agugggauac uagcaauguu aucug 25

<210> SEQ ID NO 275

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: oligonucleotide

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gugggauacu agcaauguua ucugc 25

<210> SEQ ID NO 276

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<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 276

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<210> SEQ ID NO 277
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<400> SEQUENCE: 277

gggauacuag caauguuau ugcuu 25

<210> SEQ ID NO 278
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 278

ggauacuagc aauguuau cuuc 25

<210> SEQ ID NO 279
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 279

gauacuagca auguuau cuucc 25

<210> SEQ ID NO 280
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 280

auacuagcaa uguuau cuccu 25

<210> SEQ ID NO 281
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 281

uacuagcaau guuau cuccu 25

<210> SEQ ID NO 282
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<212> TYPE: RNA
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acuagcaaug uuau cuccu 25

<210> SEQ ID NO 283

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<211> LENGTH: 25
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<400> SEQUENCE: 283

cuagcaaugu uaucugcuuc cucca 25

<210> SEQ ID NO 284
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<212> TYPE: RNA
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uagcaauguu aucugcuucc uccaa 25

<210> SEQ ID NO 285
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 285

agcaauguua ucugcuuccu ccaac 25

<210> SEQ ID NO 286
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<212> TYPE: RNA
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gcaauguauu cugcuuccuc caacc 25

<210> SEQ ID NO 287
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<212> TYPE: RNA
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caauguuauc ugcuccucc aacca 25

<210> SEQ ID NO 288
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<212> TYPE: RNA
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aauguuauu gcuuccucca accau 25

<210> SEQ ID NO 289
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<223> OTHER INFORMATION: oligonucleotide

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auguauaucug cuuccuccaa ccaua 25

<210> SEQ ID NO 290

<211> LENGTH: 25

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uguuauaucugc uuccuccaac cauaa 25

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<212> TYPE: RNA

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agccucuuga uugcuggucu uguuu 25

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<211> LENGTH: 25

<212> TYPE: RNA

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<400> SEQUENCE: 292

gccucuugau ugcuggucuu guuuu 25

<210> SEQ ID NO 293

<211> LENGTH: 25

<212> TYPE: RNA

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<220> FEATURE:

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<400> SEQUENCE: 293

ccucuugauu gcuggucug uuuuu 25

<210> SEQ ID NO 294

<211> LENGTH: 20

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 294

ccucuugauu gcuggucug 20

<210> SEQ ID NO 295

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 295

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cucuugauug cuggucuugu uuuc 25

<210> SEQ ID NO 296
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 296

ucuugauugc uggucuuguu uuca 25

<210> SEQ ID NO 297
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 297

cuugauugcu ggucuuguuu uuca 25

<210> SEQ ID NO 298
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 298

uugauugcug gucuuguuuu ucaa 25

<210> SEQ ID NO 299
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 299

ugauugcugg ucuuguuuuu caaau 25

<210> SEQ ID NO 300
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 300

gauugcuggu cuuguuuuuc aaau 25

<210> SEQ ID NO 301
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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gauugcuggu cuuguuuuuc 20

<210> SEQ ID NO 302

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<211> LENGTH: 25
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<400> SEQUENCE: 302

auugcugguc uguuuuuuca aauiu 25

<210> SEQ ID NO 303
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 303

uugcuggucu uguuuuucaa aauiu 25

<210> SEQ ID NO 304
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 304

ugcuggucuu guuuuucaaa uuug 25

<210> SEQ ID NO 305
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 305

gcuggucuug uuuuucaaa uuug 25

<210> SEQ ID NO 306
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 306

cuggucuugu uuuucaaau uugg 25

<210> SEQ ID NO 307
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 307

uggucuugu uuucaaaau uggg 25

<210> SEQ ID NO 308
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

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ggucuuguuu uucaaaaauuu gggca 25

<210> SEQ ID NO 309

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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<400> SEQUENCE: 309

gucuuguuuu ucaaaaauuug ggcag 25

<210> SEQ ID NO 310

<211> LENGTH: 25

<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

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<213> ORGANISM: Artificial

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: oligonucleotide

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<213> ORGANISM: Artificial

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<223> OTHER INFORMATION: oligonucleotide

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guuuuucaaa uuugggcgag cggua 25

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uuuuucaaau uuugggcgagc gguaa 25

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uuuucaaaau uuugggcgagc gguaa 25

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uuucaaaaau ugggcgagcgg uaaug 25

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uucaaaaauu gggcgagcgg uauga 25

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ucaaauuuug ggcagcgua augag 25

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caaaauuuug gcagcgguaa ugagu 25

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<211> LENGTH: 25
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aaaauuuuggg cagcgguauu gaguu 25

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auuuuugggca gcgguuauu guuuc 25

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uuuugggcag cgguuauu uucuu 25

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uugggcagcg guuauuagu cuucc 25

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<223> OTHER INFORMATION: oligonucleotide

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<210> SEQ ID NO 332

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<212> TYPE: RNA

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<400> SEQUENCE: 332

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<212> TYPE: RNA

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cgguaaugag uucuuccaac ugggg 25

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gguaaugagu ucuuccaacu gg 22

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<400> SEQUENCE: 337

guaaagaguu cuuccaacug gggac 25

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<400> SEQUENCE: 338

uaaagaguuc uuccaacugg ggacg 25

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aaugaguucu uccaacuggg gacgc 25

<210> SEQ ID NO 340

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<400> SEQUENCE: 340

augaguucuu ccaacugggg acgcc 25

<210> SEQ ID NO 341
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<400> SEQUENCE: 341

ugaguucuu ccaacugggga cgccu 25

<210> SEQ ID NO 342
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<212> TYPE: RNA
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<400> SEQUENCE: 342

gaguucuu cc aacuggggac gccuc 25

<210> SEQ ID NO 343
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<212> TYPE: RNA
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<400> SEQUENCE: 343

aguucuucca acuggggacg ccucu 25

<210> SEQ ID NO 344
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<212> TYPE: RNA
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<400> SEQUENCE: 344

guucuuccaa cuggggacgc cucug 25

<210> SEQ ID NO 345
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<212> TYPE: RNA
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<400> SEQUENCE: 345

uucuuccaac uggggacgcc ucugu 25

<210> SEQ ID NO 346
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

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ucuuccaacu ggggacgccu cuguu 25

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<211> LENGTH: 25

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<213> ORGANISM: Artificial

<220> FEATURE:

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<400> SEQUENCE: 347

cuuccaacug gggacgccuc uguuc 25

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 348

uuccaacugg ggacgccucu guucc 25

<210> SEQ ID NO 349

<211> LENGTH: 25

<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 349

uccaacuggg gacgccucug uucca 25

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<211> LENGTH: 25

<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 350

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 351

caacugggga cgccucuguu caaa 25

<210> SEQ ID NO 352

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 352

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aacuggggac gccucuguuc caaau 25

<210> SEQ ID NO 353
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<400> SEQUENCE: 353

acuggggacg ccucuguucc aaauc 25

<210> SEQ ID NO 354
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 354

cuggggacgc cucuguucca aauc 25

<210> SEQ ID NO 355
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 355

uggggacgcc ucuguuccaa auccu 25

<210> SEQ ID NO 356
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<212> TYPE: RNA
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<400> SEQUENCE: 356

ggggacgccu cuguuccaaa uccug 25

<210> SEQ ID NO 357
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 357

gggacgccuc uguuccaaau ccugc 25

<210> SEQ ID NO 358
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<212> TYPE: RNA
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<400> SEQUENCE: 358

ggacgccucu guuccaaauc cugca 25

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<211> LENGTH: 25
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gacgccucug uucaaaaucc ugcau 25

<210> SEQ ID NO 360
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<212> TYPE: RNA
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<400> SEQUENCE: 360

ccaauagugg ucaguccagg agcua 25

<210> SEQ ID NO 361
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 361

caauaguggu caguccagga gcuag 25

<210> SEQ ID NO 362
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 362

aaauagugguc aguccaggag cuagg 25

<210> SEQ ID NO 363
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 363

auagugguca guccaggagc uaggu 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 364

auagugguca guccaggagc u 21

<210> SEQ ID NO 365
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 365

uaguggucag uccaggagcu agguc 25

<210> SEQ ID NO 366

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 366

aguggucagu ccaggagcua gguca 25

<210> SEQ ID NO 367

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 367

guggucaguc caggagcuag gucag 25

<210> SEQ ID NO 368

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 368

uggucagucc aggagcuagg ucagg 25

<210> SEQ ID NO 369

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 369

ggucagucca ggagcuaggu caggc 25

<210> SEQ ID NO 370

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 370

gucaguccag gagcuagguc aggc 25

<210> SEQ ID NO 371

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 371

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ucaguccagg agcuagguca ggcug 25

<210> SEQ ID NO 372
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 372

caguccagga gcuaggucag gcugc 25

<210> SEQ ID NO 373
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 373

aguccaggag cuaggucagg cugcu 25

<210> SEQ ID NO 374
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 374

guccaggagc uaggucaggc ugcuu 25

<210> SEQ ID NO 375
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 375

uccaggagcu aggucaggcu gcuuu 25

<210> SEQ ID NO 376
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 376

ccaggagcua ggucaggcug cuuug 25

<210> SEQ ID NO 377
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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caggagcuag gucaggcugc uuugc 25

<210> SEQ ID NO 378

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 378

aggagcuagg ucaggcugcu uugcc 25

<210> SEQ ID NO 379
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 379

ggagcuaggu caggcugcuu ugccc 25

<210> SEQ ID NO 380
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<220> FEATURE:
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<400> SEQUENCE: 380

gagcuagguc aggcugcuuu gcccc 25

<210> SEQ ID NO 381
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 381

agcuagguca ggcugcuuug cccuc 25

<210> SEQ ID NO 382
<211> LENGTH: 25
<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 382

gcuaggucag gcugcuuugc ccuca 25

<210> SEQ ID NO 383
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 383

cucagcucu gaaguaaacg guuua 25

<210> SEQ ID NO 384
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 384

cagcucuuga aguaaacggu uuacc 25

<210> SEQ ID NO 385

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 385

gcucuugaag uaaacgguu accgc 25

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cuaggucagg cugcuugcc cucag 25

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<213> ORGANISM: Artificial

<220> FEATURE:

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<400> SEQUENCE: 387

uaggucaggc ugcuuugccc ucagc 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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<400> SEQUENCE: 388

aggucaggeu gcuuugcccu cagcu 25

<210> SEQ ID NO 389

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 389

ggucaggcug cuuugcccuc agcuc 25

<210> SEQ ID NO 390

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 390

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<210> SEQ ID NO 391
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<400> SEQUENCE: 391

ucaggcugcu uugccucag cucuu 25

<210> SEQ ID NO 392
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 392

caggcugcuu ugcccucagc ucuug 25

<210> SEQ ID NO 393
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 393

aggcugcuuu gccucagcu cuuga 25

<210> SEQ ID NO 394
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 394

ggcugcuuug ccucagcuc uugaa 25

<210> SEQ ID NO 395
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 395

gcugcuuugc ccucagcucu ugaag 25

<210> SEQ ID NO 396
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 396

cugcuuugcc cucagcucu gaagu 25

<210> SEQ ID NO 397

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 397

ugcuuugccc ucagcucuug aagua 25

<210> SEQ ID NO 398
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 398

gcuuugcccu cagcucuuga aguaa 25

<210> SEQ ID NO 399
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<212> TYPE: RNA
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<400> SEQUENCE: 399

cuuugccuc agcucuugaa guaaa 25

<210> SEQ ID NO 400
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 400

uuugcccuca gcucuugaag uaaac 25

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 401

uugccucag cucuugaagu aaacg 25

<210> SEQ ID NO 402
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 402

ugccucagc ucuugaagua aacgg 25

<210> SEQ ID NO 403
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 403

gccucagcu cuugaagaaa acggu 25

<210> SEQ ID NO 404

<211> LENGTH: 25

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<220> FEATURE:

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<400> SEQUENCE: 407

cucagcucu gaagaaacg 20

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<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 408

ccucagcucu ugaagaaac gguuu 25

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 409

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ucagcucuug aaguaaacgg uuuac 25

<210> SEQ ID NO 410
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 410

agcucuugaa guaaacgguu uaccg 25

<210> SEQ ID NO 411
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 411

cucuugaagu aaacgguuua ccgcc 25

<210> SEQ ID NO 412
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 412

ccacaggcgu ugcacuuugc aaugc 25

<210> SEQ ID NO 413
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<400> SEQUENCE: 413

cacaggcguu gcacuuugca augcu 25

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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acaggcguug cacuuugcaa ugcug 25

<210> SEQ ID NO 415
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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caggcguugc acuuugcaau gcugc 25

<210> SEQ ID NO 416

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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aggcgugca cuuugcaaug cugcu 25

<210> SEQ ID NO 417
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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ggcgugcac uuugcaaugc ugcug 25

<210> SEQ ID NO 418
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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gcgugcacu uugcaaugcu gcugu 25

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 419

cguugcacuu ugcaaugcug cuguc 25

<210> SEQ ID NO 420
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 420

cguugcacuu ugcaaugcug cug 23

<210> SEQ ID NO 421
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 421

guugcacuuu gcaaugcugc ugucu 25

<210> SEQ ID NO 422
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 422

uugcacuuug caaugcugcu gucuu 25

<210> SEQ ID NO 423

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 423

ugcacuuugc aaugcugcug ucuuc 25

<210> SEQ ID NO 424

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 424

gcacuuugca augcugcugu cuucu 25

<210> SEQ ID NO 425

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 425

cacuuugcaa ugcugcuguc uucuu 25

<210> SEQ ID NO 426

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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acuuugcaau gcugcugucu ucuug 25

<210> SEQ ID NO 427

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

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<400> SEQUENCE: 427

cuuugcaaug cugcugucuu cuugc 25

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<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

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uuugcaaugc ugcugucuuc uugcu 25

<210> SEQ ID NO 429
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uugcaaugcu gcugucuucu ugcua 25

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<211> LENGTH: 25
<212> TYPE: RNA
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ugcaaugcug cugucuucuu gcua 25

<210> SEQ ID NO 431
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<212> TYPE: RNA
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<400> SEQUENCE: 431

gcaaugcugc ugucuucug cuaug 25

<210> SEQ ID NO 432
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 432

caaugcugcu gucuucugc uauga 25

<210> SEQ ID NO 433
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 433

aaugcugcug ucuucugcu augaa 25

<210> SEQ ID NO 434
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 434

augcugcugu cuucugcua ugaau 25

<210> SEQ ID NO 435

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<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 435

ugcugcuguc uucuugcuau gaaua 25

<210> SEQ ID NO 436
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 436

gcugcugucu ucuugcuau aauaa 25

<210> SEQ ID NO 437
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 437

cugcugucuu cuugcuau auaau 25

<210> SEQ ID NO 438
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 438

ugcugucuuc uugcuau aaua 25

<210> SEQ ID NO 439
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 439

gcugucuucu ugcuaugaau aaugu 25

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<212> TYPE: RNA
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<400> SEQUENCE: 440

cugucuucu gcuaugaau auguc 25

<210> SEQ ID NO 441
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 441

ugucuucuug cuaugaaaua uguca 25

<210> SEQ ID NO 442

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 442

gucuucuugc uaugaaauau gucaa 25

<210> SEQ ID NO 443

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 443

ucuucuugcu augaaauaug ucaau 25

<210> SEQ ID NO 444

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 444

cuucuugcua ugaauaauug caauc 25

<210> SEQ ID NO 445

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 445

uucuugcuau gaauaauguc aauc 25

<210> SEQ ID NO 446

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 446

ucuugcuau gaaauauguca auccg 25

<210> SEQ ID NO 447

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 447

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cuugcuauga auaaugucaa uccga 25

<210> SEQ ID NO 448
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 448

uugcuaugaa uaaugucaau ccgac 25

<210> SEQ ID NO 449
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 449

ugcuaugaau aaugucaauc cgacc 25

<210> SEQ ID NO 450
<211> LENGTH: 25
<212> TYPE: RNA
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<400> SEQUENCE: 450

gcuaugaaua augucaaucc gaccu 25

<210> SEQ ID NO 451
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 451

cuaugaauaa ugucaauccg accug 25

<210> SEQ ID NO 452
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 452

uaugaauau gucaauccga ccuga 25

<210> SEQ ID NO 453
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 453

augaauaaug ucaauccgac cugag 25

<210> SEQ ID NO 454

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<211> LENGTH: 25
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<400> SEQUENCE: 454

ugaauaaugu caauccgacc ugagc 25

<210> SEQ ID NO 455
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 455

gaauaauguc aauccgaccu gagcu 25

<210> SEQ ID NO 456
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 456

aaauaauguca auccgaccug agcuu 25

<210> SEQ ID NO 457
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 457

auaaauguca uccgaccuga gcuuu 25

<210> SEQ ID NO 458
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 458

uaaugucaau ccgaccugag cuuug 25

<210> SEQ ID NO 459
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 459

aaugucaauc cgaccugagc uuugu 25

<210> SEQ ID NO 460
<211> LENGTH: 25
<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 460

augucaaaucc gaccugagcu uguuu 25

<210> SEQ ID NO 461

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 461

ugucaaauccg accugagcuu uguug 25

<210> SEQ ID NO 462

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 462

gucaaauccga ccugagcuuu guugu 25

<210> SEQ ID NO 463

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 463

ucaaauccgac cugagcuuug uguua 25

<210> SEQ ID NO 464

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 464

caaauccgacc ugagcuuugu uguag 25

<210> SEQ ID NO 465

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 465

aaauccgaccu gagcuuuguu guaga 25

<210> SEQ ID NO 466

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 466

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auccgaccug agcuuuguug uagac 25

<210> SEQ ID NO 467
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 467

uccgaccuga gcuuuguugu agacu 25

<210> SEQ ID NO 468
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 468

ccgaccugag cuuuguugua gacua 25

<210> SEQ ID NO 469
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 469

cgaccugagc uuuguuguag 20

<210> SEQ ID NO 470
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 470

cgaccugagc uuuguuguag acuaa 25

<210> SEQ ID NO 471
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 471

gaccugagcu uuguuguaga cuauc 25

<210> SEQ ID NO 472
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 472

accugagcuu uguuguagac uauca 25

<210> SEQ ID NO 473

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<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 473

ccugagcuuu guuguagacu auc 23

<210> SEQ ID NO 474
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 474

cauuuuugac cuacaugugg 20

<210> SEQ ID NO 475
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 475

uuugaccuac auguggaaag 20

<210> SEQ ID NO 476
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 476

uacauuuuug accuacaugu ggaaag 26

<210> SEQ ID NO 477
<211> LENGTH: 17
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 477

ggucuccuua ccuauga 17

<210> SEQ ID NO 478
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 478

ucuuaccuau gacuauggau gaga 24

<210> SEQ ID NO 479
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 479

auuuuugacc uacauaggaa ag 22

<210> SEQ ID NO 480

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 480

uacgaguuga uugucggacc cag 23

<210> SEQ ID NO 481

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 481

guggucuccu uaccuaugac ugug 25

<210> SEQ ID NO 482

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 482

ugucucagua aucuucuac cuau 24

<210> SEQ ID NO 483

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 483

ugcauguucc agucguugug ugg 23

<210> SEQ ID NO 484

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 484

cacuaaucca gucaaaauagg ucug 25

<210> SEQ ID NO 485

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 485

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auuuaccaac cuucaggauc gagua 25

<210> SEQ ID NO 486
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 486

ggccuaaaac acauacacau a 21

<210> SEQ ID NO 487
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 487

gauagguggu aucaacaucu guaa 24

<210> SEQ ID NO 488
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 488

gauagguggu aucaacaucu g 21

<210> SEQ ID NO 489
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 489

cuuccuggau ggcugaau 19

<210> SEQ ID NO 490
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 490

uguuguuguu uaugcuauu 20

<210> SEQ ID NO 491
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 491

guacauuaag auggacuuc 19

<210> SEQ ID NO 492

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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 492

cuguugcagu aaucuaugag 20

<210> SEQ ID NO 493
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 493

ugcaguaaac uaugaguuuc 20

<210> SEQ ID NO 494
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 494

gagucuucua ggagccuu 18

<210> SEQ ID NO 495
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 495

ugccauuguu ucaucagcuc uuu 23

<210> SEQ ID NO 496
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 496

uccuguagga cauuggcagu 20

<210> SEQ ID NO 497
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 497

cuuggagucu ucuaggagcc 20

<210> SEQ ID NO 498
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 498

ccaauuugug aauguuuucu uuugaacauc

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<210> SEQ ID NO 499

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 499

cccduuuugu gaauguuuuc uuuu

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<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 500

gaaaauugug cauuuaccca uuuu

24

<210> SEQ ID NO 501

<211> LENGTH: 22

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 501

uugugcauuu acccauuuug ug

22

<210> SEQ ID NO 502

<211> LENGTH: 24

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 503

aggacuuacu ugcuuuguuu

20

<210> SEQ ID NO 504

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 504

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cuugaaauua ggagauucau cug 23

<210> SEQ ID NO 505
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 505

caucuucuga uaaauuuuccu guu 23

<210> SEQ ID NO 506
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<212> TYPE: RNA
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ccauuacagu ugucuguguu 20

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<212> TYPE: RNA
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ugacagccug ugaaaucugu gag 23

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uaaucugccu cuucuuuugg 20

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<212> TYPE: RNA
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<220> FEATURE:
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cagcaguagu ugucaucugc 20

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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

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gccugagcug aucugcuggc aucuugc 27

<210> SEQ ID NO 511

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<223> OTHER INFORMATION: oligonucleotide

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ucugcuggca ucuugc 16

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gucugcaucc aggaacaugg guc 23

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uacuuacugu cuguagcucu uucu 24

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cugcauccag gaacaugggu cc 22

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 517

guugaagauc ugauagccgg uuga

24

<210> SEQ ID NO 518

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<212> TYPE: RNA

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<220> FEATURE:

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<400> SEQUENCE: 518

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<400> SEQUENCE: 519

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18

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<212> TYPE: RNA

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21

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 521

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 522

caauuuuucc cacucaguau u

21

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<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

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uugaaguucc uggagucuu 19

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<400> SEQUENCE: 524

uccucaggag gcagcucuaa au 22

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uggcucucuc ccaggg 16

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gagauggcuc ucucccaggg acccugg 27

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
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<400> SEQUENCE: 529

ugggaugguc ccagcaaguu guuug 25

<210> SEQ ID NO 530

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<400> SEQUENCE: 530

guagagcucu gucauuuugg g 21

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<400> SEQUENCE: 531

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<400> SEQUENCE: 532

gccauacgua cguaucauaa acauuc 26

<210> SEQ ID NO 533
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 533

ucugcaggau auccaugggc ugguc 25

<210> SEQ ID NO 534
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 534

gauccucccu guucgucucc uauuaug 27

<210> SEQ ID NO 535
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 535

ugcuuuagac uccuguaccu gaua 24

<210> SEQ ID NO 536
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<212> TYPE: RNA
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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 536

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18

<210> SEQ ID NO 537

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<212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 537

ggacaggccu uuauguucgu gcugc

25

<210> SEQ ID NO 538

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 538

ccuuuauugu cgugcugcu

19

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<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 539

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<212> TYPE: RNA

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<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (5)..(5)

<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 540

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<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (6)..(6)

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 541

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<223> OTHER INFORMATION: I

<220> FEATURE:

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 542

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<212> TYPE: RNA

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<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 543

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<210> SEQ ID NO 544

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<212> TYPE: RNA

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<223> OTHER INFORMATION: I

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 544

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<212> TYPE: RNA

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<223> OTHER INFORMATION: oligonucleotide

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<222> LOCATION: (1)..(1)

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<223> OTHER INFORMATION: I
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<400> SEQUENCE: 545

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<400> SEQUENCE: 546

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<223> OTHER INFORMATION: I
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 547

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<223> OTHER INFORMATION: I
<220> FEATURE:
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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 548

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<220> FEATURE:

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<223> OTHER INFORMATION: oligonucleotide
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 549

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<212> TYPE: RNA
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<223> OTHER INFORMATION: I
<220> FEATURE:
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<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 550

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<210> SEQ ID NO 551
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 551

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<210> SEQ ID NO 552
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide
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<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: I
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 552

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<210> SEQ ID NO 553

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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: I
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 553

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<223> OTHER INFORMATION: I
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<212> TYPE: RNA
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 555

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<210> SEQ ID NO 556
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<212> TYPE: RNA
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<223> OTHER INFORMATION: I
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 556

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ucaaggaaga uggcnuuucu

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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 557

uuugcencug cccaugcca uccug

25

<210> SEQ ID NO 558
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 558

uuugccgcun cccaugcca uccug

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<210> SEQ ID NO 559
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide
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<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 559

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<210> SEQ ID NO 560
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<212> TYPE: RNA
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<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: I
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<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 560

uuunccgcug cccaugcca uccug 25

<210> SEQ ID NO 561

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<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

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<222> LOCATION: (25)..(25)

<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (25)..(25)

<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 561

uuugccgcug cccaugcca uccun 25

<210> SEQ ID NO 562

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<220> FEATURE:

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<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (1)..(1)

<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 562

nuugccgcug cccaugcca uccug 25

<210> SEQ ID NO 563

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

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<222> LOCATION: (2)..(2)

<223> OTHER INFORMATION: I

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (2)..(2)

<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 563

unugccgcug cccaugcca uccug 25

<210> SEQ ID NO 564

<211> LENGTH: 25

<212> TYPE: RNA

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: oligonucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (3)..(3)

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<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 564

uungccgcug cccaugcca uccug

25

<210> SEQ ID NO 565
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide
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<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 565

uuugccgcng cccaugcca uccug

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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide
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<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 566

uuugccgcug cccanugcca uccug

25

<210> SEQ ID NO 567
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: I
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 567

uuugccgcug cccaugccn uccug

25

<210> SEQ ID NO 568
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<212> TYPE: RNA
<213> ORGANISM: Artificial
<220> FEATURE:

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<223> OTHER INFORMATION: oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: I
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<223> OTHER INFORMATION: n is a, c, g, or u
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<223> OTHER INFORMATION: I
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<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 568

uuuncncug cccaugcca uccug

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<210> SEQ ID NO 569
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<212> TYPE: RNA
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: oligonucleotide
<220> FEATURE:
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<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: I
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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 569

uuugccgug cccaangcca uccug

25

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<220> FEATURE:
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<400> SEQUENCE: 570

uuugccgug cccaugcca nccug

25

<210> SEQ ID NO 571
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<400> SEQUENCE: 571

uuugcgcug cccaugcca ucnng 25

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<223> OTHER INFORMATION: I

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<400> SEQUENCE: 573

ucagcuucun uuagccacug 20

<210> SEQ ID NO 574

<211> LENGTH: 20

<212> TYPE: RNA

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<223> OTHER INFORMATION: I

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<223> OTHER INFORMATION: n is a, c, g, or u

<400> SEQUENCE: 574

ucagcuucug uanccacug 20

<210> SEQ ID NO 575

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<220> FEATURE:

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<223> OTHER INFORMATION: I
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<221> NAME/KEY: misc_feature
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ucancuucug uuagccacug

20

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<400> SEQUENCE: 576

ucagcuucug uuagccacun

20

<210> SEQ ID NO 577
<211> LENGTH: 153
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 577

Met Gly Lys Ile Ser Ser Leu Pro Thr Gln Leu Phe Lys Cys Cys Phe
1 5 10 15

Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu
20 25 30

Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala
35 40 45

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
50 55 60

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
65 70 75 80

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
85 90 95

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
100 105 110

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
115 120 125

Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly
130 135 140

Ser Ala Gly Asn Lys Asn Tyr Arg Met
145 150

1. An isolated oligonucleotide comprising a sequence which is complementary to at least part of a dystrophin pre-mRNA exon or at least part of a non-exon region of a dystrophin pre-mRNA said part being a contiguous stretch comprising at least 8 nucleotides, wherein said oligonucleotide comprises one or both of an inosine nucleotide and a nucleotide containing a base able to form a wobble base pair with a complementary base to which it is paired.

2. An isolated oligonucleotide according to claim 1, wherein the contiguous stretch comprises between 13 and 50 nucleotides, of RNA of an exon of a dystrophin pre-mRNA.

3. An isolated oligonucleotide according to claim 2, wherein said exon comprises exon 51, 45, 53, 44, 46, 52, 50, 43, 6, 7, 8, 55, 2, 11, 17, 19, 21, 57, 59, 62, 63, 65, 66, 69, and/or 75.

4. (canceled)

5. An isolated oligonucleotide according to claim 1, wherein the oligonucleotide comprises a first part and a second part, wherein said first part comprises least 8, consecutive nucleotides that are complementary to a first exon and wherein said second part comprises at least 8 consecutive nucleotides that are complementary to a second exon in said dystrophin pre-mRNA.

6. An isolated oligonucleotide according to claim 5, wherein said first and said second exon are separated in said dystrophin pre-mRNA by at least one exon to which said oligonucleotide is not complementary.

7. An oligonucleotide according to claim 5, wherein said first and said second exon are contiguous in said dystrophin pre-mRNA.

8. (canceled)

9. (canceled)

10. (canceled)

11. A composition comprising at least two distinct oligonucleotides as defined in claim 1.

12. A composition according to claim 11, wherein each said distinct oligonucleotide is dosed, independently, in an amount between 0.5 mg/kg and 10 mg/kg, inclusive.

13. A composition according to claim 11 in combination with one or more of:

- (a) an adjunct compound for reducing inflammation, preferably for reducing muscle tissue inflammation,
- (b) an adjunct compound for improving muscle fiber function, integrity and/or survival, and
- (c) a compound exhibiting readthrough activity.

14. (canceled)

15. A method for alleviating one or more symptom(s) of Duchenne Muscular Dystrophy or Becker Muscular Dystrophy in an individual, the method comprising administering to said individual a composition as defined in claim 11.

16. An isolated oligonucleotide according to claim 2 wherein said contiguous stretch comprises between 14 and 25 nucleotides of RNA of an exon of a dystrophin pre-mRNA.

17. An isolated oligonucleotide according to claim 1, wherein the oligonucleotide comprises RNA.

18. An isolated oligonucleotide according to claim 17, wherein said RNA comprises a modified ribonucleotide.

19. An isolated oligonucleotide according to claim 18, wherein said modified ribonucleotide is a 2'-O-methyl modified ribose (RNA).

20. An isolated oligonucleotide according to claim 1, comprising a modified deoxyribose (DNA) base.

21. An isolated oligonucleotide according to claim 1, wherein said oligonucleotide comprises a peptide nucleic acid, a locked nucleic acid, a morpholino phosphorodiamidate, or a combination thereof.

22. An isolated oligonucleotide according to claim 21, comprising a morpholino phosphorodiamidate.

23. An isolated oligonucleotide according to claim 5, wherein said first part and said second part, independently, comprise between 16 and 80 consecutive nucleotides, inclusive.

24. The composition of claim 11, admixed with a pharmaceutically acceptable carrier, adjuvant, diluent and/or excipient.

25. The composition of claim 13, wherein said adjunct composition for reducing inflammation reduces tissue inflammation.

26. The method of claim 15, wherein the composition administered provides the individual with a functional dystrophin protein.

27. The method of claim 15, wherein the composition administered decreases the production of an aberrant dystrophin protein.

28. The method of claim 15, wherein the composition administered increases the production of a functional or a more functional dystrophin protein.

29. The method of claim 15, wherein the composition administered alleviates one or more symptom(s).

* * * * *