MODULATION OF GLUCAGON RECEPTOR EXPRESSION

Inventors: Sanjay Bhanot, Carlsbad, CA (US);
          Susan M. Freier, San Diego, CA (US);
          Kenneth W. Dobie, Del Mar, CA (US);
          Robert McKay, Poway, CA (US)

Correspondence Address:
ISIS PHARMACEUTICALS INC
1896 RUTHERFORD RD.
CARLSBAD, CA 92008 (US)

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Compounds, compositions and methods are provided for modulating the expression of glucagon receptor. The compositions comprise oligonucleotides, targeted to nucleic acid encoding glucagon receptor. Methods of using these compounds for modulation of glucagon receptor expression and for diagnosis and treatment of disease associated with expression of glucagon receptor are provided.
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SEQUENCE LISTING

[0001] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled B10L0007USD3SEQ.txt, created on Apr. 5, 2007 which is 208 Kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention provides compositions and methods for modulating the expression of glucagon receptor. In particular, this invention relates to compounds, particularly oligonucleotide compounds, which, in preferred embodiments, hybridize with nucleic acid molecules encoding glucagon receptor. Such compounds are shown herein to modulate the expression of glucagon receptor.

BACKGROUND OF THE INVENTION

[0003] The maintenance of normal glycemia is a carefully regulated metabolic event. Glucagon, the 29-amino acid peptide responsible for maintaining blood glucose levels in the postabsorptive state, increases glucose release from the liver by activating hepatic glycoegenolysis, glycoegenogenesis, stimulating lipolysis in adipose tissue, and stimulating insulin secretion. During high blood glucose levels, insulin reverses the glucagon-mediated enhancement of glycogenolysis and glycoegenogenesis. In patients with diabetes, insulin is either not available or not fully effective. While treatment for diabetes has traditionally focused on increasing insulin levels, antagonism of glucagon function has been considered as an alternative therapy. As glucagon exerts its physiological effects by signaling through the glucagon receptor, the glucagon receptor has been proposed as a potential therapeutic target for diabetes (Madsen et al., Curr. Pharm. Des., 1999, 5, 683-691).

[0004] Glucagon receptor is belongs to the superfamily of G-protein-coupled receptors having seven transmembrane domains. It is also a member of the smaller sub-family of homologous receptors which bind peptides that are structurally similar to glucagon. The gene encoding human glucagon receptor was cloned in 1994 and analysis of the genomic sequence revealed multiple introns and an 82% identity to the rat glucagon receptor gene (Lok et al., Gene, 1994, 140, 203-209; MacNeil et al., Biochem. Biophys. Res. Commun., 1994, 198, 328-334). Cloning of the rat glucagon receptor gene also led to the description of multiple alternative splice variants (Maget et al., FEBS Lett., 1994, 351, 271-275). Disclosed and claimed in U.S. Pat. No. 5,776,725 is an isolated nucleic acid sequence encoding a human or rat glucagon receptor (Kindsvogel et al., 1998). The human glucagon receptor gene is localized to chromosome 17q25 (Menzel et al., Genomics, 1994, 20, 327-328). A missense mutation of Gly to Ser at codon 40 in the glucagon receptor gene leads to a 3-fold lower affinity for glucagon (Fujisawa et al., Diabetologia, 1995, 38, 983-985) and this mutation has been linked to several disease states, including non-insulin-dependent diabetes mellitus (Fujisawa et al., Diabetes, 1995, 38, 983-985), hypertension (Chambers and Morris, Nat. Genet., 1996, 12, 122), and central adiposity (Stani et al., Obes. Res., 2001, 9, 722-726).

[0005] Inhibiting glucagon function by antagonizing the glucagon receptor has been proposed as a therapeutic target for diabetes. Currently, there are no known therapeutic agents which effectively inhibit the synthesis of glucagon receptor and to date, investigative strategies aimed at modulating glucagon receptor function have involved the use of antibodies, peptidyl antagonists, and small molecules. In addition, targeted disruption of the glucagon receptor gene in mice has shown that, despite a total absence of glucagon receptors and elevated plasma glucagon levels, the mice maintain near-normal glycemia and lipidemia (Parker et al., Biochem. Biophys. Res. Commun., 2002, 290, 839-843). Patent application WO 02/45494 (Allen et al.) discloses transgenic mice expressing mutations in a glucagon receptor gene. Also claimed are agonists or antagonists of glucagon receptor, agents that modulate the function, expression or activity of a glucagon receptor gene, methods of identifying such agents, methods of ameliorating conditions associated with impaired glucose tolerance, methods of identifying agents that affect obesity, weight gain, diabetes, methods of treating obesity or diabetic conditions, and phenotypic data associated with a transgenic mouse comprising a mutation in a glucagon receptor gene.

[0006] A glucagon-neutralizing monoclonal antibody has been described that antagonizes glucagon-stimulated signal transduction in part by binding to the glucagon binding site of the glucagon receptor (Bugly et al., Horm. Metab. Res., 1996, 28, 215-219). An antibody which specifically binds to the amino acid sequence of a glucagon receptor has been disclosed and claimed in U.S. Pat. No. 5,770,445 (Kindsvogel et al., 1998).

[0007] Several peptidyl antagonists of glucagon receptor have been reported in the art. Six glucagon analogs with N-terminal modifications were designed to have a higher affinity than glucagon for the glucagon receptor (Zechel et al., Int. J. Pept. Protein Res., 1991, 38, 131-138). Two somatostatin analogs have been reported to be inhibitors of glucagon secretion (Rosowski and Coy, Biochem. Biophys. Res. Commun., 1994, 205, 341-346).


[0009] There remains a long felt need for additional agents capable of effective inhibition of glucagon receptor function. Antisense technology is an effective means for reducing the expression of specific gene products and has proven to be uniquely useful in a number of therapeutic, diagnostic, and
research applications. The present invention provides compositions and methods for modulating glucagon receptor expression.

SUMMARY OF THE INVENTION

[0010] The present invention is directed to compounds, especially nucleic acid and nucleic acid-like oligomers, which are targeted to a nucleic acid encoding glucagon receptor, and which modulate the expression of glucagon receptor. Pharmaceutical and other compositions comprising the compounds of the invention are also provided. Further provided are methods of screening for modulators of glucagon receptor and methods of modulating the expression of glucagon receptor in cells, tissues or animals comprising contacting said cells, tissues or animals with one or more of the compounds or compositions of the invention. Methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with expression of glucagon receptor are also set forth herein. Such methods comprise administering a therapeutically or prophylactically effective amount of one or more of the compounds or compositions of the invention to the person in need of treatment.

DETAILED DESCRIPTION OF THE INVENTION

A. Overview of the Invention

[0011] The present invention employs compounds, preferably oligonucleotides and similar species for use in modulating the function or effect of nucleic acid molecules encoding glucagon receptor. This is accomplished by providing oligonucleotides which specifically hybridize with one or more nucleic acid molecules encoding glucagon receptor. As used herein, the terms “target nucleic acid” and “nucleic acid molecule encoding glucagon receptor” have been used for convenience to encompass DNA encoding glucagon receptor, RNA (including pre-mRNA and mRNA or portions thereof) transcribed from such DNA, and also cDNA derived from such RNA. The hybridization of a compound of this invention with its target nucleic acid is generally referred to as “antisense”. Consequently, the preferred mechanism believed to be included in the practice of some preferred embodiments of the invention is referred to herein as “antisense inhibition.” Such antisense inhibition is typically based upon hydrogen bonding-based hybridization of oligonucleotide strands or segments such that at least one strand or segment is cleaved, degraded, or otherwise rendered inoperable. In this regard, it is presently preferred to target specific nucleic acid molecules and their functions for such antisense inhibition.

[0012] The functions of DNA to be interfered with can include replication and transcription. Replication and transcription, for example, can be from an endogenous cellular template, a vector, a plasmid construct or otherwise. The functions of RNA to be interfered with can include functions such as translocation of the RNA to a site of protein translation, translocation of the RNA to sites within the cell which are distant from the site of RNA synthesis, translation of protein from the RNA, splicing of the RNA to yield one or more RNA species, and catalytic activity or complex formation involving the RNA which may be engaged in or facilitated by the RNA. One preferred result of such interference with target nucleic acid function is modulation of the expression of glucagon receptor. In the context of the present invention, “modulation” and “modulation of expression” mean either an increase (stimulation) or a decrease (inhibition) in the amount or levels of a nucleic acid molecule encoding the gene, e.g., DNA or RNA. Inhibition is often the preferred form of modulation of expression and mRNA is often a preferred target nucleic acid.

[0013] In the context of this invention, “hybridization” means the pairing of complementary strands of oligomeric compounds. In the present invention, the preferred mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases (nucleobases) of the strands of oligomeric compounds. For example, adenine and thymine are complementary nucleobases which pair through the formation of hydrogen bonds. Hybridization can occur under varying circumstances.

[0014] An antisense compound is specifically hybridizable when binding of the compound to the target nucleic acid interferes with the normal function of the target nucleic acid to cause a loss of activity, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target nucleic acid sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and under conditions in which assays are performed in the case of in vitro assays.

[0015] In the present invention the phrase “stringent hybridization conditions” or “stringent conditions” refers to conditions under which a compound of the invention will hybridize to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances and in the context of this invention, “stringent conditions” under which oligomeric compounds hybridize to a target sequence are determined by the nature and composition of the oligomeric compounds and the assays in which they are being investigated.

[0016] “Complementary,” as used herein, refers to the capacity for precise pairing between two nucleobases of an oligomeric compound. For example, if a nucleobase at a certain position of an oligonucleotide (an oligomeric compound), is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, said target nucleic acid being a DNA, RNA, or oligonucleotide molecule, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be a complementary position. The oligonucleotide and the further DNA, RNA, or oligonucleotide molecule are complementary to each other when a sufficient number of complementary positions in each molecule are occupied by nucleobases which can hydrogen bond with each other. Thus, “specifically hybridizable” and “complementary” are terms which are used to indicate a sufficient degree of precise pairing or complementarity over a sufficient number of nucleobases such that stable and specific binding occurs between the oligonucleotide and a target nucleic acid.

[0017] It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable.
Moreover, an oligonucleotide may hybridize over one or more segments such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure or hairpin structure).

It is preferred that the antisense compounds of the present invention comprise at least 70% sequence complementarity to a target region within the target nucleic acid, more preferably that they comprise 90% sequence complementarity and even more preferably comprise 95% sequence complementarity to the target region within the target nucleic acid sequence to which they are targeted. For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having 4 (four) noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul et al., J. Mol. Biol., 1990, 215, 403-410; Zhang and Madden, Genome Res., 1997, 17, 649-656).

B. Compounds of the Invention

According to the present invention, compounds include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, external guide sequence (EGS) oligonucleotides, alternate splicers, primers, probes, and other oligomeric compounds which hybridize to at least a portion of the target nucleic acid. As such, these compounds may be introduced in the form of single-stranded, double-stranded, circular or hairpin oligomeric compounds and may contain structural elements such as internal or terminal bulges or loops. Once introduced to a system, the compounds of the invention may elicit the action of one or more enzymes or structural proteins to effect modification of the target nucleic acid.

One non-limiting example of such an enzyme is Rnase H, a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are “DNA-like” elicit Rnase H. Activation of Rnase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. Similar roles have been postulated for other ribonucleases such as those in the RNase III and ribonuclease L family of enzymes.

While the preferred form of antisense compound is a single-stranded antisense oligonucleotide, in many species the introduction of double-stranded structures, such as double-stranded RNA (dsRNA) molecules, has been shown to induce potent and specific antisense-mediated reduction of the function of a gene or its associated gene products. This phenomenon occurs in both plants and animals and is believed to have an evolutionary connection to viral defense and transposon silencing.

The first evidence that dsRNA could lead to gene silencing in animals came in 1995 from work in the nematode, Caenorhabditis elegans (Guo and Kempehus, Cell, 1995, 81, 611-620).

Montgomery et al. have shown that the primary interference effects of dsRNA are posttranscriptional (Montgomery et al., Proc. Natl. Acad. Sci. USA, 1998, 95, 15502-15507). The posttranscriptional antisense mechanism defined in Caenorhabditis elegans resulting from exposure to double-stranded RNA (dsRNA) has since been designated RNA interference (RNAi). This term has been generalized to mean antisense-mediated gene silencing involving the introduction of dsRNA leading to the sequence-specific reduction of endogenous targeted mRNA levels (Fire et al., Nature, 1998, 391, 806-811). Recently, it has been shown that it is, in fact, the single-stranded RNA oligomers of antisense polarity of the dsRNAs which are the potent inducers of RNAi (Tijsterman et al., Science, 2002, 295, 694-697).

In the context of this invention, the term “oligomeric compound” refers to a polymer or oligomer comprising a plurality of monomeric units. In the context of this invention, the term “oligonucleotide” refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or mimetics, chimers, analogs and homologs thereof. This term includes oligonucleotides composed of naturally occurring nucleobases, sugars and covalent intranucleoside (backbone) linkages as well as oligonucleotides having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for a target nucleic acid and increased stability in the presence of nucleases.

While oligonucleotides are a preferred form of the compounds of this invention, the present invention comprehends other families of compounds as well, including but not limited to oligonucleotide analogs and mimetics such as those described herein.

The compounds in accordance with this invention preferably comprise from about 8 to about 80 nucleobases (i.e. from about 8 to about 80 linked nucleosides). One ordinary skill in the art will appreciate that the invention embodies compounds of 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, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 nucleobases in length.

In one preferred embodiment, the compounds of the invention are 12 to 50 nucleobases in length. One having ordinary skill in the art will appreciate that this embodies compounds of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleobases in length.

In another preferred embodiment, the compounds of the invention are 15 to 30 nucleobases in length. One having ordinary skill in the art will appreciate that this embodies compounds of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length.
Particularly preferred compounds are oligonucleotides from about 12 to about 50 nucleobases, even more preferably those comprising from about 15 to about 30 nucleobases.

Antisense compounds 8-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative antisense compounds are considered to be suitable antisense compounds as well.

Exemplary preferred antisense compounds include oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 5'-terminus of one of the illustrative preferred antisense compounds (the remaining nucleobases being a consecutive stretch of the same oligonucleotide beginning immediately upstream of the 5'-terminus of the antisense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 8 to about 80 nucleobases). Similarly preferred antisense compounds are represented by oligonucleotide sequences that comprise at least the 8 consecutive nucleobases from the 3'-terminus of one of the illustrative preferred antisense compounds (the remaining nucleobases being a consecutive stretch of the same oligonucleotide beginning immediately downstream of the 3'-terminus of the antisense compound which is specifically hybridizable to the target nucleic acid and continuing until the oligonucleotide contains about 8 to about 80 nucleobases). One having skill in the art armed with the preferred antisense compounds illustrated herein will be able, without undue experimentation, to identify further preferred antisense compounds.

C. Targets of the Invention

“Targeting” an antisense compound to a particular nucleic acid molecule, in the context of this invention, can be a multistep process. The process usually begins with the identification of a target nucleic acid whose function is to be modulated. This target nucleic acid may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. In the present invention, the target nucleic acid encodes glucagon receptor.

The targeting process usually also includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense interaction to occur such that the desired effect, e.g., modulation of expression, will result. Within the context of the present invention, the term “region” is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic. Within regions of target nucleic acids are segments. “Segments” are defined as smaller or sub-portions of regions within a target nucleic acid. “Sites,” as used in the present invention, are defined as positions within a target nucleic acid.

Since, as is known in the art, the translation initiation codon is typically 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is also referred to as the “AUG codon,” the “start codon” or the “AUG start codon”. A minority of genes have a translation initiation codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and 5'-AUA, 5'-ACG and 5'-CUG have been shown to function in vivo. Thus, the terms “translation initiation codon” and “start codon” can encompass many codon sequences, even though the initiator amino acid in each instance is typically methionine (in eukaryotes) or formylmethionine (in prokaryotes). It is also known in the art that eukaryotic and prokaryotic genes may have two or more alternative start codons, any one of which may be preferentially utilized for translation initiation in a particular cell type or tissue, or under a particular set of conditions. In the context of the invention, “start codon” and “translation initiation codon” refer to the codon or codons that are used in vivo to initiate translation of a mRNA transcribed from a gene encoding glucagon receptor, regardless of the sequence(s) of such codons. It is also known in the art that a translation termination codon (or “stop codon”) of a gene may have one of three sequences, i.e., 5'-UAA, 5'-UAG and 5'-UGA (the corresponding DNA sequences are 5'-TAA, 5'-TAG and 5'-TGA, respectively).

The terms “start codon region” and “translation initiation codon region” refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation codon. Similarly, the terms “stop codon region” and “translation termination codon region” refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation termination codon. Consequently, the “start codon region” (or “translation initiation codon region”) and the “stop codon region” (or “translation termination codon region”) are all regions which may be targeted effectively with the antisense compounds of the present invention.

The open reading frame (ORF) or “coding region,” which is known in the art to refer to the region between the translation initiation codon and the translation termination codon, is also a region which may be targeted effectively. Within the context of the present invention, a preferred region is the intragenic region encompassing the translation initiation or termination codon of the open reading frame (ORF) of a gene.

Other target regions include the 5' untranslated region (5'UTR), known in the art to refer to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA (or corresponding nucleotides on the gene), and the 3' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA (or corresponding nucleotides on the gene). The 5' cap site of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap site. It is also preferred to target the 5' cap region.

Although some eukaryotic mRNA transcripts are directly translated, many contain one or more regions, known as “introns,” which are excised from a transcript before it is translated. The remaining (and therefore trans-
lated) regions are known as “exons” and are spliced together to form a continuous mRNA sequence. Targeting splice sites, i.e., intron-exon junctions or exon-intron junctions, may also be particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular splice product is implicated in disease. Aberrant fusion junctions due to rearrangements or deletions are also preferred target sites. mRNA transcripts produced via the process of splicing of two (or more) mRNAs from different gene sources are known as “fusion transcripts”. It is also known that introns can be effectively targeted using antisense compounds targeted to, for example, DNA or pre-mRNA.

It is also known in the art that alternative RNA transcripts can be produced from the same genomic region of DNA. These alternative transcripts are generally known as “variants”. More specifically, “pre-mRNA variants” are transcripts produced from the same genomic DNA that differ from other transcripts produced from the same genomic DNA in either their start or stop position and contain both intronic and exonic sequence.

Upon excision of one or more exon or intron regions, or portions thereof during splicing, pre-mRNA variants produce smaller “miRNA variants”. Consequently, miRNA variants are processed pre-mRNA variants and each unique pre-mRNA variant must always produce a unique miRNA variant as a result of splicing. These miRNA variants are also known as “alternative splice variants”. If no splicing of the pre-mRNA variant occurs then the pre-mRNA variant is identical to the miRNA variant.

It is also known in the art that variants can be produced through the use of alternative signals to start or stop transcription and that pre-mRNAs and miRNAs can possess more that one start codon or stop codon. Variants that originate from a pre-mRNA or miRNA that use alternative start codons are known as “alternative start variants” of that pre-mRNA or miRNA. Those transcripts that use an alternative stop codon are known as “alternative stop variants” of that pre-mRNA or miRNA. One specific type of alternative stop variant is the “polyA variant” in which the multiple transcripts produced result from the alternative selection of one of the “polyA stop signals” by the transcription machinery, thereby producing transcripts that terminate at unique polyA sites. Within the context of the invention, the types of variants described herein are also preferred target nucleic acids.

The locations on the target nucleic acid to which the preferred antisense compounds hybridize are hereinbelow referred to as “preferred target segments.” As used herein the term “preferred target segment” is defined as at least an 8-nucleobase portion of a target region to which an active antisense compound is targeted. While not wishing to be bound by theory, it is presently believed that these target segments represent portions of the target nucleic acid which are accessible for hybridization.

While the specific sequences of certain preferred target segments are set forth herein, one of skill in the art will recognize that these serve to illustrate and describe particular embodiments within the scope of the present invention. Additional preferred target segments may be identified by one having ordinary skill.

Target segments 8-80 nucleobases in length comprising a stretch of at least eight (8) consecutive nucleobases selected from within the illustrative preferred target segments are considered to be suitable for targeting as well.

Target segments can include DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 5’-terminus of one of the illustrative preferred target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5’- terminus of the target segment and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). Similarly preferred target segments are represented by DNA or RNA sequences that comprise at least the 8 consecutive nucleobases from the 3’-terminus of one of the illustrative preferred target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3’-terminus of the target segment and continuing until the DNA or RNA contains about 8 to about 80 nucleobases). One having skill in the art armed with the preferred target segments illustrated herein will be able, without undue experimentation, to identify further preferred target segments.

Once one or more target regions, segments or sites have been identified, antisense compounds are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently well and with sufficient specificity, to give the desired effect.

D. Screening and Target Validation

In a further embodiment, the “preferred target segments” identified herein may be employed in a screen for additional compounds that modulate the expression of glucagon receptor. “Modulators” are those compounds that decrease or increase the expression of a nucleic acid molecule encoding glucagon receptor and which comprise at least an 8-nucleobase portion which is complementary to a preferred target segment. The screening method comprises the steps of contacting a preferred target segment of a nucleic acid molecule encoding glucagon receptor with one or more candidate modulators, and selecting for one or more candidate modulators which decrease or increase the expression of a nucleic acid molecule encoding glucagon receptor. Once it is shown that the candidate modulator or modulators are capable of modulating (e.g., either decreasing or increasing) the expression of a nucleic acid molecule encoding glucagon receptor, the modulator may then be employed in further investigative studies of the function of glucagon receptor, or for use as a research, diagnostic, or therapeutic agent in accordance with the present invention.

The preferred target segments of the present invention may also be combined with their respective complementary antisense compounds of the present invention to form stabilized double-stranded (duplexed) oligonucleotides.

Such double stranded oligonucleotide moieties have been shown in the art to modulate target expression and regulate translation as well as RNA processing via an antisense mechanism. Moreover, the double-stranded moieties may be subject to chemical modifications (Fire et al., Nature, 1998, 391, 806-811; Timmons and Fire, Nature 1998, 395, 854; Timmons et al., Gene, 2001, 263, 103-112; Tabara et al., Science, 1998, 282, 430-431; Montgomery et al., Proc. Natl. Acad. Sci. USA, 1998, 95, 15502-15507;
The compounds of the present invention can also be applied in the areas of drug discovery and target validation. The present invention comprehends the use of the compounds and preferred target segments identified herein in drug discovery efforts to elucidate relationships that exist between glucagon receptor and a disease state, phenotype, or condition. These methods include detecting or modulating glucagon receptor comprising contacting a sample, tissue, cell, or organism with the compounds of the present invention, measuring the nucleic acid or protein level of glucagon receptor and/or a related phenotype or chemical endpoint at some time after treatment, and optionally comparing the measured value to a non-treated sample or sample treated with a further compound of the invention. These methods can also be performed in parallel or in combination with other experiments to determine the function of unknown genes for the process of target validation or to determine the validity of a particular gene product as a target for treatment or prevention of a particular disease, condition, or phenotype.

E. Kits, Research Reagents, Diagnostics, and Therapeutics

The compounds of the present invention can be utilized for diagnostics, therapeutics (including prophylaxis) and as research reagents and kits. Furthermore, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes or to distinguish between functions of various members of a biological pathway.

For use in kits and diagnostics, the compounds of the present invention, either alone or in combination with other compounds or therapeutics, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of a portion or the entire complement of genes expressed within cells and tissues.

As one nonlimiting example, expression patterns within cells or tissues treated with one or more antisense compounds are compared to control cells or tissues not treated with antisense compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.


The compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding glucagon receptor. For example, oligonucleotides that are shown to hybridize with such efficiency and under such conditions as disclosed herein as to be effective glucagon receptor inhibitors will also be effective primers or probes under conditions favoring gene amplification or detection, respectively. These primers and probes are useful in methods requiring the specific detection of nucleic acid molecules encoding glucagon receptor and in the amplification of said nucleic acid molecules for detection or for use in further studies of glucagon receptor. Hybridization of the antisense oligonucleotides, particularly the primers and probes, of the invention with a nucleic acid encoding glucagon receptor can be detected by means known in the art. Such means may include conjugation of an enzyme to the oligonucleotide, radiolabelling of the oligonucleotide or any other suitable detection means. Kits using such detection means for detecting the level of glucagon receptor in a sample may also be prepared.

The specificity and sensitivity of antisense is also harnessed by those of skill in the art for therapeutic uses. Antisense compounds have been employed as therapeutic moieties in the treatment of disease states in animals, including humans. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that antisense compounds can be useful therapeutic modalities that can be configured to be useful in treatment regimes for the treatment of cells, tissues and animals, especially humans.

For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of glucagon receptor is treated by administering antisense compounds in accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to an animal a therapeutically effective amount of a glucagon receptor inhibitor. The glucagon receptor inhibitors of the present invention effectively inhibit the activity of the glucagon receptor protein or inhibit the expression of the glucagon receptor protein. In one embodiment, the activity or expression of glucagon receptor in an animal is inhibited by about 10%. Preferably, the activity or expression of glucagon receptor in an animal is inhibited by about 30%. More preferably, the activity or expression of glucagon receptor in an animal is inhibited by 50% or more. Because
the compounds herein are inhibitors of glucagon receptor, they are believed to be useful in lowering blood glucose, for example, and in treating conditions associated with glucagon receptor activity, such as high blood glucose and other metabolic conditions such as diabetes (including Type 2 diabetes), obesity, and insulin resistance.

[0058] The reduction of the expression of glucagon receptor may be measured, for example, in blood, plasma, serum, adipose tissue, liver or any other body fluid, tissue or organ of the animal.

[0059] Preferably, the cells contained within said fluids, tissues or organs being analyzed contain a nucleic acid molecule encoding glucagon receptor protein and/or the glucagon receptor protein itself.

[0060] The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of a compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the compounds and methods of the invention may also be useful prophylactically.

F. Modifications

[0061] As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to either the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, the phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. In turn, the respective ends of this linear polymeric compound can be further joined to form a circular compound, however, linear compounds are generally preferred. In addition, linear compounds may have internal nucleobase complementarity and may therefore fold in a manner as to produce a fully or partially double-stranded compound. Within oligonucleotides, the phosphate groups are commonly referred to as forming the internucleoside backbone of the oligonucleotide. The normal linkage or backbone of RNA and DNA is a 3' to 5' phosphodiester linkage.

Modified Internucleoside Linkages (Backbones)

[0062] Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

[0063] Preferred modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphorothriesters, aminophosphorothriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramide and aminooalkylphosphoramidates, thionophosphoramidates, thioalkylphosphonates, thioalkylphosphorothioesters, selenophosphates and boronophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be acidic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included.

[0064] Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,908; 4,469,863; 4,476,301; 5,023,243; 5,177,186; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, certain of which are commonly owned with this application, and each of which is herein incorporated by reference.

[0065] Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed from the sugar portion of a nucleoside): siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacethyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneiminio and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH2 component parts.

[0066] Representative United States patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, certain of which are commonly owned with this application, and each of which is herein incorporated by reference.

Modified Sugar and Internucleoside Linkages-Mimetics

[0067] In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage (i.e. the backbone), of the nucleotide units are replaced with novel groups. The nucleobase units are maintained for hybridization with an appropriate target nucleic acid. One such compound, an oligonucleotide mimic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or
indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., *Science*, 1991, 254, 1497-1500.

**[0068]** Preferred embodiments of the invention are oligonucleotides with phosphorothioate backbones. Also preferred are oligonucleosides with heteroatom backbones, and in particular —CH$_2$—N—O—CH$_2$—, —CH$_2$—N(CH$_3$)$_2$—O—CH$_3$—[known as a methylene (methylimino) or MMI backbone], —CH$_2$—N—O(N(CH$_3$)$_2$)—CH$_2$—, —CH$_2$—N(CH$_3$)$_2$—N(CH$_3$)$_2$—CH$_2$—, and —O—N(CH$_3$)$_2$—CH$_2$—CH$_2$—[wherein the native phosphodiester backbone is represented as —O—P—O—CH$_2$—] of the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are oligonucleotides having morpholino backbone structures of the above referenced U.S. Pat. No. 5,034,506.

Modified Sugars

**[0069]** Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O- S- or N-alkyl; O- S- or N-alkenyl; O- S- or N-alknyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C$_1$ to C$_{10}$ alkyl or C$_2$ to C$_{10}$ alkenyl and alkynyl. Particularly preferred are O(2'CH$_3$)$_2$N$_m$CH$_2$, O(2'CH$_3$)$_2$OCH$_3$, O(2'CH$_3$)$_2$NH$_2$, O(2'CH$_3$)$_2$CH$_3$, O(2'CH$_2$)$_2$ONH$_2$, and O(2'CH$_3$)$_2$ON(2'CH$_2$)$_2$O, where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following at the 2' position: C$_1$ to C$_{10}$ lower alkyl, substituted lower alkyl, alkynyl, alkenyl, alkylk, unalkyl, O-alkaryl or O- aralkyl, SH, SCHR, OCN, CN, CN, OCN, SO$_2$CH$_3$, ONO$_2$, NO$_2$, NH$_2$, heterocyclicalkyl, heteroalkylaryl, aminobenzylaminobenzyl, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, for a group improving the pharmacokinetic properties of oligonucleotide, or a group improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O—CH$_2$CH$_2$OCH$_3$, also known as 2'-O(2-methoxy ethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxalkyl group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a O(CH$_2$)$_2$ON(CH$_3$)$_2$ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminooxyethoxy (also known in the art as 2'-O(dimethylamino ethoxy-ethyl or 2'-DMAEE), i.e., 2'-O—CH$_2$—O—CH$_2$—N(CH$_3$)$_2$), also described in examples hereinbelow.

**[0070]** Other preferred modifications include 2'-methoxy (2'-O—CH$_3$), 2'-aminoproxy (2'-OCH$_2$CH$_2$NH$_2$), 2'-allyl (2'-CH$_2$—CH=CH$_2$), 2'-O-allyl (2'-O—CH$_2$—CH$_2$—CH=CH$_2$), and 2'-fluoro (2'-F). The 2'-modification may be in the arabinof (up) position or ribo (down) position. A preferred 2'-arabinof modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2' to 5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

**[0071]** A further preferred modification of the sugar includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring, thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene (—CH$_2$—), group bridging the 2' oxygen atom and the 4' carbon atom where n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

Natural and Modified Nucleobases

**[0072]** Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, “unmodified” or “natural” nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-amino adenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiouracil and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (—C=C—CH$_3$) uracil and cytosine and other alkyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenosines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino adenine, 8-azaguanine and 8-aza adenine, 7-deaza-adenine and 7-deaza guanine and 3-deazaguanine and 3-deaza guanine. Further modified nucleobases include triazine pyrimidines such as phenoazine cytidine (1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)1H-pyrimido [5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridino diethyl cytidine (H-pyridino[3',2',3:4,5]pyrrole[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deaza guanosine, 2-aminopyridine and 2-pyridine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, and those disclosed in International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S. T. and Leblon, B., ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the compounds of the invention. These include 5-substituted
pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 2-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions.

[0073] Representative United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. Nos. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,677; 5,645,985; 5,830,653; 5,763,588; 6,005,096; and 5,681,941, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference, and U.S. Pat. No. 5,750,692, which is commonly owned with the instant application and also herein incorporated by reference.

Conjugates

[0074] Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesteryl, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluorescein, rhodamines, coumarin, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, the entire disclosure of which are incorporated herein by reference. Conjugate moieties include but are not limited to lipid moieties such as a cholesteryl moiety, oleic acid, a thiourea, e.g., hexyl-S-tritylthiol, a thiocolesterol, an aliphatic chain, e.g., dodecanol or undecyl residues, a phospholipid, e.g., dihexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycerol-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmitoyl moiety, or an octadecylamine or hexylamino-carbonyl-oxycarbonyl moiety. Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+) pranoprofen, caprofen, dansylcysteine, 2,3,5-triiodo-benzoic acid, fluordeacetyl, folic acid, a benzothiadiazide, chlorothiazide, a diuretic, indo-methicin, a b-bitururate, a cephalosporin, a sulfon drug, an antibiotic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) which is incorporated herein by reference in its entirety.

[0075] Representative United States patents that teach the preparation of such oligonucleotide conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,252,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,141,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923, 5,599,928 and 5,688,941, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

Chimeric Compounds

[0076] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide.

[0077] The present invention also includes antisense compounds which are chimeric compounds. “Chimeric” antisense compounds or “chimeras,” in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, increased stability and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide-mediated inhibition of gene expression. The cleavage of RNA:RNA hybrids can, in like fashion, be accomplished through the actions of endoribonucleases, such as RNAsel, which cleaves both cellular and viral RNA. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

[0078] Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,056; 5,652,355; 5,652,356; and 5,700,922,
certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

Salts

[0079] The antisense compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. The term “pharmaceutically acceptable salts” refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. For oligonucleotides, preferred examples of pharmaceutically acceptable salts and their uses are further described in U.S. Pat. Nos. 6,287,860, which is incorporated herein in its entirety. Sodium salts are especially suitable salts of the compounds of the present invention.

G. Formulations

[0080] The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor-targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption-assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,035,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,334,259; 5,543,152; 5,536,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

[0081] The present invention also includes pharmaceutical compositions and formulations which include the antisense compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer, intratracheal, intranasal, epidural and transdermal), oral or parenteral. Parenteral administration includes intravenous, intramuscular, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2' O-methoxyethyl modification are believed to be particularly useful for oral administration. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.

[0082] The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0083] The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

[0084] Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, foams and liposome-containing formulations. The pharmaceutical compositions and formulations of the present invention may comprise one or more penetration enhancers, carriers, excipients or other active or inactive ingredients.

[0085] Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Microemulsions are included as an embodiment of the present invention. Emulsions and their uses are well known in the art and are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0086] Formulations of the present invention include liposomal formulations. As used in the present invention, the term “liposome” means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers. Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior that contains the composition to be delivered. Cationic liposomes are positively charged liposomes which are believed to interact with negatively charged DNA molecules to form a stable complex. Liposomes that are pH-sensitive or negatively-charged are believed to entrap DNA rather than complex with it. Both cationic and noncationic liposomes have been used to deliver DNA to cells.

[0087] Liposomes also include “sterically stabilized” liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome comprises one or more glycolipid or is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. Liposomes and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0088] The pharmaceutical formulations and compositions of the present invention may also include surfactants.
The use of surfactants in drug products, formulations and in emulsions is well known in the art. Surfactants and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0089] In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly oligonucleotides. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Penetration enhancers and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety.

[0090] One of skill in the art will recognize that formulations are routinely designed according to their intended use, i.e. route of administration.

[0091] Preferred formulations for topical administration include those in which the oligonucleotides of the invention are admixed with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Preferred lipids and liposomes include neutral (e.g. dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline) negative (e.g. dimyristoylphosphatidyl glycerol DMG) and cationic (e.g. dioleoyltrimethylammoniumpropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA).

[0092] For topical or other administration, oligonucleotides of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, oligonucleotides may be complexed to lipids, in particular to cationic lipids. Preferred fatty acids and esters, pharmaceutically acceptable salts thereof, and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Topical formulations are described in detail in U.S. patent application Ser. No. 09/315,298 filed on May 20, 1999, which is incorporated herein by reference in its entirety.

[0093] Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticles, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. Preferred oral formulations are those in which oligonucleotides of the invention are administered in conjunction with one or more penetration enhancers surfactants and chelators. Preferred surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Preferred bile acids/salts and fatty acids and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Also preferred are combinations of penetration enhancers, for example, fatty acids/salts in combination with bile acids/salts. A particularly preferred combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. Oligonucleotides of the invention may be delivered orally, in granular form including sprayed dried particles, or complexes to form micro or nanoparticles. Oligonucleotide complexing agents and their uses are further described in U.S. Pat. No. 6,287,860, which is incorporated herein in its entirety. Oral formulations for oligonucleotides and their preparation are described in detail in U.S. application Ser. Nos. 09/108,673 (filed Jul. 1, 1998), 09/315,298 (filed May 20, 1999) and 10/071,822, filed Feb. 8, 2002, each of which is incorporated herein by reference in its entirety.

[0094] Compositions and formulations for parenteral, intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

[0095] Certain embodiments of the invention provide pharmaceutical compositions containing one or more oligomeric compounds and one or more other pharmaceutical agents which function by a non-antisense mechanism. Examples of such pharmaceutical agents include but are not limited to cancer chemotherapeutic drugs, anti-inflammatory drugs, anti-viral drugs, and compounds for treatment of metabolic diseases such as diabetes, high blood sugar or obesity, or cardiovascular conditions such as elevated blood cholesterol or blood pressure. Combinations of antisense compounds and other non-antisense drugs are also within the scope of this invention. Two or more combined compounds may be used together or sequentially. When used with the compounds of the invention, such pharmaceutical agents may be used individually (e.g., rosiglitazone and oligonucleotide), sequentially (e.g., 5-fluorouracil and oligonucleotide for a period of time followed by methotrexate and oligonucleotide), or in combination with one or more other treatments (e.g., 5-fluorouracil, methotrexate and oligonucleotide, or 5-fluorouracil, radiotherapy and oligonucleotide).

[0096] In another related embodiment, compositions of the invention may contain one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional antisense compounds targeted to a second nucleic acid target. Alternatively, compositions of the invention may contain two or more antisense compounds targeted to different regions of the same nucleic acid target. Numerous examples of antisense compounds are known in the art. Two or more combined compounds may be used together or sequentially.

H. Dosing

[0097] The formulation of therapeutic compositions and their subsequent administration (dosing) is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50} found to be effective in vitro and in vivo animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art
can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the oligonucleotide is administered in maintenance doses, ranging from 0.01 to 100 g per kg of body weight, once or more daily, to once every 20 years.

**[0098]** While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same.

**EXAMPLES**

**Example 1**

Synthesis of Nucleoside Phosphoramidites

**[0099]** The following compounds, including amidites and their intermediates were prepared as described in U.S. Pat. No. 6,426,220 and published PCT WO 02/36743: 5'-O-Dimethoxytrityl-thymidine intermediate for 5-methyl dC amidite, 5'-O-Dimethoxytrityl-2'-deoxy-5-methylcytidine intermediate for 5-methyl dC amidite, 5'-O-Dimethoxytrityl-2'-deoxy-N4-benzoyl-5-methylcytidine penultimate intermediate for 5-methyl dC amidite, 5'-O-(4,4'-(Dimethoxytritylphenethyl)-2'-deoxy-N4'-benzoyl-5-methylytidin-3'-O-yl)-2'-cyanoethyl-N,N-diisopropyl phosphoramidite (5'-methyl dC amidite), 2'-Fluoro(deoxyadenosine, 2'-Fluoro(deoxyguanosine, 2'-Fluoro(uridine, 2'-Fluoro(exoxytidine, 2'-O-(2-Methoxy(ethyl) modified amidites, 2'-O-(2-Methoxyethyl) 5-methyluridine intermediate, 5'-O-DMT-2'-O-(2-methoxyethyl)-5-methyluridine penultimate intermediate, 5'-O-(4,4'-(Dimethoxy(phenethyl)-2'-O-(2-methoxyethyl)-5-methyluridin-3'-O-yl)-2'-cyanoethyl-N,N-diisopropyl phosphoramidite (MOE T amidite, 5'-O-Dimethoxytrityl-2'-O-(2-methoxyethyl)-5-methylcytidine intermediate, 5'-O-Dimethoxytrityl-2'-O-(2-methoxyethyl)-N4'-benzoyl-5-methylcytidine penultimate intermediate, 5'-O-(4,4'-(Dimethoxytritylphenethyl)-2'-O-(2-methoxyethyl)-N4'-benzoyl-5-methylcytidin-3'-O-yl)-2'-cyanoethyl-N,N-diisopropylphosphoramidite (MOE 5-Me-C amidite, 5'-O-(4,4'-(Dimethoxytritylphenethyl)-2'-O-(2-methoxyethyl)-N4'-benzoyladenosin-3'-O-yl)-2'-cyanoethyl-N,N-diisopropylphosphoramidite (MOE A amidite, 5'-O-(4,4'-(Dimethoxytritylphenethyl)-2'-O-(2-methoxyethyl)-N4'-isobutrylguanosin-5'-O-yl)-2'-cyanoethyl-N,N-diisopropylphosphoramidite (MOE G amidite, 2'-O-(Aminooxyethyl) nucleoside amidites and 2'-O-(dimethylaminooxyethyl) nucleoside amidites, 2'-O-(Dimethylaminooxyethyl) nucleoside amidites, 5'-O-t-BuButyldiphenylsilyl-O2'-2'-anhydro-5-methyluridine, 5'-O-t-BuButyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine, 2'-O-[2-phthalimidoxoyethyl]-t-BuButyldiphenylsilyl-5-methyluridine, 5'-O-t-BuButyldiphenylsilyl-2'-O-[2-formamidooxyethyl]-5-methyluridine, 5'-O-t-BuButyldiphenylsilyl-2'-O-[2-formamidooxyethyl]-5-methyluridine, 5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine, 2'-O-(dimethylaminooxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine, 5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine-3'-O-(2-cyanoethyl)-N,N-diisopropyl phosphoramidite, 2'-O-(Aminooxyethyl) nucleoside amidites, N2-isobutryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-O-[2-cyanoethyl]-N,N-diisopropylphosphoramidite, 2'-dimethylaminoethoxyethoxy (2'-DMEOE) nucleoside amidites, 2'-O-[2-N,N-dimethylaminooxyethyl]-5-methyl uridine, 5'-O-dimethoxytrityl-2'-O-[2-N,N-dimethylaminooxyethyl]-5-methyl uridine and 5'-O-Dimethoxytrityl-2'-O-[2-N,N-dimethylaminooxyethyl]-5-methyl uridine-3'-O-(2-cyanoethyl)-N,N-diisopropylphosphoramidite.

**Example 2**

Oligonucleotide and Oligonucleoside Synthesis

**[0100]** The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

Oligonucleotides: Unsubstituted and substituted phosphodiester (P=O) oligonucleotides are synthesized on an automated DNA synthesizer (Applied Biosystems model 394) using standard phosphoramidite chemistry with oxidation by iodine.

**[0101]** Phosphorothioates (P=S) are synthesized similar to phosphodiester oligonucleotides with the following exceptions: thiation was effected by utilizing a 10% w/v solution of 3,1-H1,2-benzodithiole-3-one 1,1-dioxide in acetonitrile for the oxidation of the phosphate linkages. The thiation reaction step time was increased to 180 sec and preceded by the normal capping step. After cleavage from the CPG column and deblocking in concentrated ammonium hydroxide at 55° C. (12-16 hr), the oligonucleotides were recovered by precipitating with 3 volumes of ethanol from a 1 M NH4Ac solution. Phosphinate oligonucleotides are prepared as described in U.S. Pat. No. 5,508,270, herein incorporated by reference.

**[0102]** Alkyl phosphonate oligonucleotides are prepared as described in U.S. Pat. No. 4,469,863, herein incorporated by reference.

**[0103]** 3'-Deoxy-3'-methylen phosphonate oligonucleotides are prepared as described in U.S. Pat. Nos. 5,610,289 or 5,625,050, herein incorporated by reference.

**[0104]** Phosphoramide oligonucleotides are prepared as described in U.S. Pat. No. 5,256,775 or U.S. Pat. No. 5,366,878, herein incorporated by reference.


**[0106]** 3'-Deoxy-3'-amino phosphoramide oligonucleotides are prepared as described in U.S. Pat. No. 5,476,925, herein incorporated by reference.

**[0107]** Phosphorothioester oligonucleotides are prepared as described in U.S. Pat. No. 5,023,243, herein incorporated by reference.
Borano phosphate oligonucleotides are prepared as described in U.S. Pat. Nos. 5,130,302 and 5,177,198, both herein incorporated by reference.

Oligonucleosides: Methylenevinylimino linked oligonucleosides, also identified as MMI linked oligonucleosides, methylenevinyliminohydrino linked oligonucleosides, also identified as MDH linked oligonucleosides, and methyleneacarbomylamino linked oligonucleosides, also identified as amide-3 linked oligonucleosides, and methyleneaminocarbonyl linked oligonucleosides, also identified as amide-4 linked oligonucleosides, as well as mixed backbone compounds having, for instance, alternating MMI and P=O or P=S linkages are prepared as described in U.S. Pat. Nos. 5,378,825, 5,386,023, 5,489,677, 5,602,240 and 5,610,289, all of which are herein incorporated by reference.

Formacetal and thioformacetal linked oligonucleosides are prepared as described in U.S. Pat. Nos. 5,264,562 and 5,264,564, herein incorporated by reference.

Ethylene oxide linked oligonucleosides are prepared as described in U.S. Pat. No. 5,223,618, herein incorporated by reference.

### Example 3

#### RNA Synthesis

In general, RNA synthesis chemistry is based on the selective incorporation of various protecting groups at strategic intermolecular reactions. Although one of ordinary skill in the art will understand the use of protecting groups in organic synthesis, a useful class of protecting groups includes silyl ethers. In particular bulky silyl ethers are used to protect the 3'-hydroxyl in combination with an acyl-labile orthoester protecting group on the 2'-hydroxyl. This set of protecting groups is then used with standard solid-phase synthesis technology. It is important to first remove the acid labile orthoester protecting group after all other synthetic steps. Moreover, the early use of the silyl protecting groups during synthesis ensures facile removal when desired, without undesired deprotection of 2'-hydroxyl.

Following this procedure for the sequential protection of the 3'-hydroxyl in combination with protection of the 2'-hydroxyl by protecting groups that are differentially removed and are differentially chemically labile, RNA oligonucleotides were synthesized.

RNA oligonucleotides are synthesized in a stepwise fashion. Each nucleotide is added sequentially (3'-to 5'-direction) to a solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are added, coupling the second base onto the 5'-end of the first nucleoside. The support is washed and any unreacted 5'-hydroxyl groups are capped with acetic anhydride to yield 5'-acetyl moieties. The linkage is then oxidized to the more stable and ultimately desired P(V) linkage. At the end of the nucleotide addition cycle, the 5'-silyl group is cleaved with fluoride. The cycle is repeated for each subsequent nucleotide.

Following synthesis, the methyl protecting groups on the phosphates are cleaved in 30 minutes utilizing 1 M disodium-2-carbamoyl-2-ethylenedioxy-1,1-dithiolate trihydrate (S$_2$N$_2$) in DMF. The deprotection solution is washed from the solid support-bound oligonucleotide using water. The support is then treated with 40% methanolamine in water for 10 minutes at 55 °C. This releases the RNA oligonucleotides into solution, deprotects the exocyclic amines, and modifies the 2'-groups. The oligonucleotides can be analyzed by anion-exchange HPLC at this stage.

The 2'-orthoester groups are the last protecting groups to be removed. The ethylene glycol monooctadecyl orthoester protecting group developed by Dharmacon Research, Inc. (Lafayette, Colo.), is one example of a useful orthoester protecting group which has the following important properties. It is stable to the conditions of nucleoside phosphoramidite synthesis and oligonucleotide synthesis. However, after oligonucleotide synthesis the oligonucleotide is treated with methanolamine which not only cleaves the oligonucleotide from the solid support but also removes the acetyl groups from the orthoesters. The resulting 2-ethoxy hydroxyl substituents on the orthoester are less electron withdrawing than the acetylated precursor. As a result, the modified orthoester becomes more labile to acid-catalyzed hydrolysis. Specifically, the rate of cleavage is approximately 10 times faster after the acetyl groups are removed. Therefore, this orthoester possesses sufficient stability in order to be compatible with oligonucleotide synthesis and yet, when subsequently modified, permits deprotection to be carried out under relatively mild aqueous conditions compatible with the final RNA oligonucleotide product.


RNA antisense compounds (RNA oligonucleotides) of the present invention can be synthesized by the methods herein or purchased from Dharmacon Research, Inc. (Lafayette, Colo.). Once synthesized, complementary RNA antisense compounds can then be annealed by methods known in the art to form double stranded (duplexed) antisense compounds. For example, duplexes can be formed by combining 30 μl of each of the complementary strands of RNA oligonucleotides (50 nM RNA oligonucleotide solution) and 15 μl of 5x annealing buffer (100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, 2 mM magnesium acetate) followed by heating for 1 minute at 90 °C, then 1
hour at 37°C. The resulting duplexed antisense compounds can be used in kits, assays, screens, or other methods to investigate the role of a target nucleic acid.

Example 4

Synthesis of Chimeric Oligonucleotides

Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the “gap” segment of linked nucleosides is positioned between 5’ and 3’“wing” segments of linked nucleosides and a second “open end” type wherein the “gap” segment is located at either the 3’ or the 5’ terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as “gapmers” or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as “hemimers” or “wingmers”.

[2’-O-Me]–[2’-deoxy]–[2’-O-Me] Chimeric Phosphorothioate Oligonucleotides

Chimeric oligonucleotides having 2’-O-alkyl phosphorothioate and 2’-deoxy phosphorothioate oligonucleotide segments are synthesized using an Applied Biosystems automated DNA synthesizer Model 394, as above. Oligonucleotides are synthesized using the automated synthesizer and 2’-deoxy-5’-dimethoxytrityl-3’-O-phosphoramidite for the DNA portion and 5’-dimethoxytrityl-2’-O-methyl-3’-O-phosphoramidite for 5’ and 3’ wings. The standard synthesis cycle is modified by incorporating coupling steps with increased reaction times for the 5’-dimethoxytrityl-2’-O-methyl-3’-O-phosphoramidite. The fully protected oligonucleotide is cleaved from the support and deprotected in concentrated ammonia (NH₄OH) for 12-16 hr at 55°C. The deprotected oligo is then recovered by an appropriate method (precipitation, column chromatography, vacuum reduced in vacuo and analyzed spectrophotometrically for yield and for purity by capillary electrophoresis and by mass spectrometry.

[2’-O-(2-Methoxyethyl)]–[2’-deoxy]–[2’-O-(Methoxyethyl)] Chimeric Phosphorothioate Oligonucleotides

Chimeric phosphorothioate oligonucleotides were prepared as per the procedure above for the 2’-O-methyl chimeric oligonucleotide, with the substitution of 2’-O-(methoxyethyl) amidites for the 2’-O-methyl amidites.

Example 5

Design and Screening of Duplexed Antisense Compounds Targeting Glucagon Receptor

In accordance with the present invention, a series of nucleic acid duplexes comprising the antisense compounds of the present invention and their complements can be designed to target glucagon receptor. The nucleobase sequence of the antisense strand of the duplex comprises at least an 8-nucleobase portion of an oligonucleotide in Table 1. The ends of the strands may be modified by the addition of one or more natural or modified nucleobases to form an overhang. The sense strand of the dsRNA is then designed and synthesized as the complement of the antisense strand and may also contain modifications or additions to either terminus. For example, in one embodiment, both strands of the dsRNA duplex would be complementary over the central nucleobases, each having overhangs at one or both termini.

For example, a duplex comprising an antisense strand having the sequence C CGAGGGGCGGACCG (SEQ ID NO: 824) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

<table>
<thead>
<tr>
<th>ccagagccgagcggagcc</th>
<th>Antisense Strand (SEQ ID NO:825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTgcttcgctgcctgcggc</td>
<td>Complement (SEQ ID NO:826)</td>
</tr>
</tbody>
</table>

In another embodiment, a duplex comprising an antisense strand having the same sequence CGAGGGCGGACCG (SEQ ID NO: 824) may be prepared with blunt ends (no single strand overhang) as shown:

<table>
<thead>
<tr>
<th>ccagagccgagcggagcc</th>
<th>Antisense Strand (SEQ ID NO:824)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gcttcgctgcctgcggc</td>
<td>Complement (SEQ ID NO:827)</td>
</tr>
</tbody>
</table>
The RNA duplex can be unimolecular or biomolecular; i.e., the two strands can be part of a single molecule or may be separate molecules. RNA strands of the duplex can be synthesized by methods disclosed herein or purchased from Dharmacon Research Inc. (Lafayette, Colo.). Once synthesized, the complementary strands are unanneled. The single strands are aliquoted and diluted to a concentration of 50 nM. Once diluted, 30 µl of each strand is combined with 15 µl of a 5X solution of annealing buffer. The final concentration of said buffer is 100 nM potassium acetate, 30 nM HEPES-KOH pH 7.4, and 2 mM magnesium acetate. The final volume is 75 µl. This solution is incubated for 1 minute at 90°C and then centrifuged for 15 seconds. The tube is allowed to sit for 1 hour at 37°C at which time the dsRNA duplexes are used in experimentation. The final concentration of the dsRNA duplex is 20 nM. This solution can be stored frozen (-20°C) and freeze-thawed up to 5 times. Once prepared, the duplexed antisense compounds are evaluated for their ability to modulate glucagon receptor expression.

When cells reached 80% confluency, they are treated with duplexed antisense compounds of the invention. For cells grown in 96-well plates, wells are washed once with 200 µl OPTI-MEM-1 reduced-serum medium (Gibco BRL) and then treated with 130 µl of OPTI-MEM-1 containing 12 µg/ml LIPOFECTIN (Gibco BRL) and the desired duplex antisense compound at a final concentration of 200 nM. After 5 hours of treatment, the medium is replaced with fresh medium. Cells are harvested 16 hours after treatment, at which time RNA is isolated and target reduction measured by RT-PCR.

Oligonucleotide Isolation

After cleavage from the controlled pore glass solid support and deblocking in concentrated ammonium hydroxide at 55°C for 12-16 hours, the oligonucleotides or oligonucleosides are recovered by precipitation out of 1 M NH₄OH with ≥3 volumes of ethanol. Synthesized oligonucleotides are analyzed by electrospray mass spectroscopy (molecular weight determination) and by capillary gel electrophoresis and judged to be at least 70% full length material. The relative amounts of phosphorothioate and phosphodiester linkages obtained in the synthesis is determined by the ratio of correct molecular weight relative to the -16 amu product (±324/±48). For some studies oligonucleotides are purified by HPLC, as described by Chiang et al., J. Biol. Chem. 1991, 266, 18162-18171. Results obtained with HPLC-purified material are similar to those obtained with non-HPLC purified material.

Oligonucleotide Synthesis—96 Well Plate Format

Oligonucleotides are synthesized via solid phase P(III) phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a 96-well format. Phosphodiester internucleotide linkages are afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages are generated by sulfuration utilizing 3,4-H-1,2 benzodithiole-3-one, 1,1 dioxiide (Beaucage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyl-diso-propyl phosphoramidites are purchased from commercial vendors (e.g. PE-Applied Biosystems, Foster City, Calif., or Pharmacia, Piscataway, N.J.). Non-standard nucleosides are synthesized as per standard or patented methods. They are utilized as base protected beta-cyanoethyldisopropyl phosphoramidites.

Oligonucleotides are cleaved from support and deprotected with concentrated NH₄OH at elevated temperature (55-60°C) for 12-16 hours and the released product then dried in vacuo. The dried product is then re-suspended in sterile water to afford a master plate from which all analytical and test plate samples are then diluted utilizing robotic pipettors.

Example 8

[0131] Oligonucleotide Analysis—96-Well Plate Format

The concentration of oligonucleotide in each well is assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products is evaluated by capillary electrophoresis (CE) in either the 96-well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™ 5000, ABL 270). Base and backbone composition is confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy. All assay test plates are diluted from the master plate using single and multi-channel robotic pipettors. Plates are judged to be acceptable if at least 85% of the compounds on the plate are at least 85% full length.

Example 9

Cell Culture and Oligonucleotide Treatment

The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. This can be routinely determined using, for example, PCR or Northern blot analysis. The following cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily determined by methods routine in the art, for example Northern blot analysis, ribonuclease protection assays, or RT-PCR.

T-24 Cells:

The human transitional cell bladder carcinoma cell line T-24 is obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). T-24 cells are routinely cultured in complete McCoy's 5A basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per ml, and streptomycin 100 micrograms per ml (Invitrogen Corporation, Carlsbad, Calif.). Cells are routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells are seeded into 96-well plates (Falcon-Primaria #353872) at a density of 7000 cells/well for use in RT-PCR analysis.

For Northern blotting or other analysis, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.
A549 cells:

[0136] The human lung carcinoma cell line A549 is obtained from the American Type Culture Collection (ATCC) (Manassas, Va.). A549 cells are routinely cultured in DMEM basal media (Invitrogen Corporation, Carlsbad, Calif.) supplemented with 10% fetal calf serum (Invitrogen Corporation, Carlsbad, Calif.), penicillin 100 units per ml., and streptomycin 100 micrograms per ml. (Invitrogen Corporation, Carlsbad, Calif.). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence.

NIIDF cells:

[0137] Human neonatal dermal fibroblast (NIIDF) are obtained from the Clonetics Corporation (Walkersville, Md.). NIIDFs are routinely maintained in Fibroblast Growth Medium (Clonetics Corporation, Walkersville, Md.) supplemented as recommended by the supplier. Cells are maintained for up to 10 passages as recommended by the supplier.

HEK Cells:

[0138] Human embryonic kidney cells (HEK) are obtained from the Clonetics Corporation (Walkersville, Md.). HEKs are routinely maintained in Culture Medium (Clonetics Corporation, Walkersville, Md.) formulated as recommended by the supplier. Cells are routinely maintained for up to 10 passages as recommended by the supplier.

HepG2 cells:

[0139] The human hepatoblastoma cell line HepG2 is obtained from the American Type Culture Collection (Manassas, Va.). HepG2 cells are routinely cultured in Eagle’s MEM supplemented with 10% fetal calf serum, non-essential amino acids, and 1 mM sodium pyruvate (Gibco/Life Technologies, Gaithersburg, Md.). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence. Cells are seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

[0140] For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

Primary Mouse Hepatocytes

[0141] Primary mouse hepatocytes are prepared from CD-1 mice purchased from Charles River Labs. Primary mouse hepatocytes are routinely cultured in Hepatocyte Attachment Media (Gibco) supplemented with 10% Fetal Bovine Serum (Gibco/Life Technologies, Gaithersburg, Md.), 250 nM dexamethasone (Sigma), 10 nM bovine insulin (Sigma). Cells are seeded into well plates (Falcon-Primaria #3872) at a density of 10000 cells/well for use in RT-PCR analysis.

[0142] For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

Treatment with Antisense Compounds:

[0143] When cells reached 65-75% confluency, they are treated with oligonucleotide. For cells grown in 96-well plates, wells are washed once with 100 μL OPTI-MEM™-1 reduced-serum medium (Invitrogen Corporation, Carlsbad, Calif.) and then treated with 130 μL of OPTI-MEM™-1 containing 3.75 μg/ml. LIPOFECTINT™ (Invitrogen Corporation, Carlsbad, Calif.) and the desired concentration of oligonucleotide. Cells are treated and data are obtained in triplicate. After 4-7 hours of treatment at 37° C, the medium is replaced with fresh medium. Cells are harvested 16-24 hours after oligonucleotide treatment.

[0144] The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations. For human cells the positive control oligonucleotide is selected from either ISIS 13920 (TCCGAT-CATGCTTCTCATGGG, SEQ ID NO: 1) which is targeted to human H-ras, or ISIS 18078, (GTGCCCGCGACCGAAAATC, SEQ ID NO: 2) which is targeted to human Jun-N-terminal kinase-2 (JNK2). Both controls are 2’-O-methoxethyl gapmers (2’-O-methoxyethyls shown in bold) with a phosphorothioate backbone. For mouse or rat cells the positive control oligonucleotide is ISIS 15770, ATGCATTCTGCCCTCCAGGA, SEQ ID NO: 3, a 2’-O-methoxyethyl gapmer (2’-O-methoxyethyls shown in bold) with a phosphorothioate backbone which is targeted to both mouse and rat c-raf. The concentration of positive control oligonucleotide that results in 80% inhibition of c-H-ras (for ISIS 13920), JNK2 (for ISIS 18078) or c-raf (for ISIS 15770) mRNA is then utilized as the screening concentration for new oligonucleotides in subsequent experiments for that cell line. If 80% inhibition is not achieved, the lowest concentration of positive control oligonucleotide that results in 60% inhibition of c-H-ras, JNK2 or c-raf mRNA is then utilized as the oligonucleotide screening concentration in subsequent experiments for that cell line. If 60% inhibition is not achieved, that particular cell line is deemed as unsuitable for oligonucleotide transfection experiments. The concentrations of antisense oligonucleotides used herein are from 50 nM to 300 nM.

Example 10

Analysis of Oligonucleotide Inhibition of Glucagon Receptor Expression

[0145] Antisense modulation of glucagon receptor expression can be assayed in a variety of ways known in the art. For example, glucagon receptor mRNA levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or real-time PCR (RT-PCR). Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. The preferred method of RNA analysis of the present invention is the use of total cellular RNA as described in other examples herein. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Real-time quantitative (PCR) can be conveniently accomplished using the commercially available ABI PRISM™ 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, Calif. and used according to manufacturer’s instructions.

[0146] Protein levels of glucagon receptor can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA) or fluo-
rescence-activated cell sorting (FACS). Antibodies directed to glucagon receptor can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, Mich.), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art.

Example 11
Design of Phenotypic Assays and in Vivo Studies for the use of Glucagon Receptor Inhibitors

Phenotypic Assays

Once glucagon receptor inhibitors have been identified by the methods disclosed herein, the compounds are further investigated in one or more phenotypic assays, each having measurable endpoints predictive of efficacy in the treatment of a particular disease state or condition.

Phenotypic assays, kits and reagents for their use are well known to those skilled in the art and are herein used to investigate the role and/or association of glucagon receptor in health and disease. Representative phenotypic assays, which can be purchased from any of several commercial vendors, include those for determining cell viability, cytotoxicity, proliferation or cell survival (Molecular Probes, Eugene, Oreg.; PerkinElmer, Boston, Mass.), protein-based assays including enzymatic assays (Panvera, I.C.C. Madison, Wis.; BD Biosciences, Franklin Lakes, N.J.; Oncogene Research Products, San Diego, Calif.), cell regulation, signal transduction, inflammation, oxidative processes and apoptosis (Assay Designs Inc., Ann Arbor, Mich.), triglyceride accumulation (Sigma-Aldrich, St. Louis, Mo.), angiogenesis assays, tube formation assays, cytokine and hormone assays and metabolic assays (Chemicon International Inc., Temecula, Calif.; Amersham Biosciences, Piscataway, N.J.).

In one non-limiting example, cells determined to be appropriate for a particular phenotypic assay (i.e., MCF-7 cells selected for breast cancer studies; adipocytes for obesity studies) are treated with glucagon receptor inhibitors identified from the in vitro studies as well as control compounds at optimal concentrations which are determined by the methods described above. At the end of the treatment period, treated and untreated cells are analyzed by one or more methods specific for the assay to determine phenotypic outcomes and endpoints.

Phenotypic endpoints include changes in cell morphology over time or treatment dose as well as changes in levels of cellular components such as proteins, lipids, nucleic acids, hormones, saccharides or metals. Measurements of cellular status which include pH, stage of the cell cycle, intake or excretion of biological indicators by the cell, are also endpoints of interest.

Analysis of the genotype of the cell (measurement of the expression of one or more of the genes of the cell) after treatment is also used as an indicator of the efficacy or potency of the glucagon receptor inhibitors. Hallmark genes, or those genes suspected to be associated with a specific disease state, condition, or phenotype, are measured in both treated and untreated cells.

In Vivo Studies

The individual subjects of the in vivo studies described herein are warm-blooded vertebrate animals, which includes humans.

The clinical trial is subjected to rigorous controls to ensure that individuals are not unnecessarily put at risk and that they are fully informed about their role in the study. To account for the psychological effects of receiving treatments, volunteers are randomly given placebo or glucagon receptor inhibitor. Furthermore, to prevent the doctors from being biased in treatments, they may not be informed as to whether the medication they are administering is a glucagon receptor inhibitor or a placebo. Using this randomization approach, each volunteer has the same chance of being given either the new treatment or the placebo.

Volunteers may receive either the glucagon receptor inhibitor or placebo for eight week period with biological parameters associated with the indicated disease state or condition being measured at the beginning (baseline measurements before any treatment), end (after the final treatment), and at regular intervals during the study period. Such measurements may include the levels of nucleic acid molecules encoding glucagon receptor or glucagon receptor protein levels in body fluids, tissues or organs compared to pre-treatment levels. Other measurements may include, but are not limited to, indices of the disease state or condition being treated, body weight, blood pressure, serum titers of pharmacologic indicators of disease or toxicity as well as ADME (absorption, distribution, metabolism and excretion) measurements.

Information recorded for each patient may include age (years), gender, height (cm), family history of disease state or condition (yes/no), motivation rating (some/moderate/great) and number and type of previous treatment regimens for the indicated disease or condition.

Volunteers taking part in this study are healthy adults (age 18 to 65 years) and, typically, roughly an equal number of males and females participate in the study. Volunteers with certain characteristics are equally distributed for placebo and glucagon receptor inhibitor treatment. In general, the volunteers treated with placebo have little or no response to treatment, whereas the volunteers treated with the glucagon receptor inhibitor show positive trends in their disease state or condition index at the conclusion of the study.

One of ordinary skill will know how to conduct an appropriate clinical trial and will recognize that this is just one of many protocols which may be appropriately used.

Example 12
RNA Isolation
Poly(A)+ mRNA Isolation

Poly(A)+ mRNA was isolated according to Miura et al., (Clin. Chem., 1996, 42, 1758-1764). Other methods for poly(A)+ mRNA isolation are routine in the art. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well washed with 200 μL cold PBS. 60 μL lysis buffer (10 mM Tris-HCl, pH 7.6, 1 mM EDTA, 0.5 M NaCl, 0.5% NP-40, 20 mM vanadylribonucleoside complex) was added to each well, the plate was gently agitated and then incubated at room temperature for five minutes. 55 μL of lysate was transferred to Oligo (dT) coated 96-well plates (AGCT Inc., Irvine Calif.). Plates were incubated for 60 minutes at room temperature, washed 3 times with 200 μL of wash buffer (10 mM Tris-HCl pH 7.6,
1 mM EDTA, 0.3 M NaCl). After the final wash, the plate was blotted on paper towels to remove excess wash buffer and then air-dried for 5 minutes. 60 µL of elution buffer (5 mM Tris-HCl pH 7.6), preheated to 70°C, was added to each well, the plate was incubated on a 90°C hot plate for 5 minutes, and the eluate was then transferred to a fresh 96-well plate. Cells grown on 100 mm or other standard plates may be treated similarly, using appropriate volumes of all solutions.

Total RNA Isolation

[0159] Total RNA was isolated using an RNEASY kit and purified buffers purchased from Qiagen Inc. (Valencia, Calif.) following the manufacturer’s recommended procedures. Briefly, for cells grown on 96-well plates, growth medium was removed from the cells and each well washed with 200 µL cold PBS. 150 µL Buffer RLT was added to each well and the plate vigorously agitated for 20 seconds. 150 µL of 70% ethanol was then added to each well and the contents mixed by pipetting three times up and down. The samples were then transferred to the RNEASY 96™ plate well plate attached to a QIACUBE™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum was applied for 1 minute. 500 µL of Buffer RW1 was added to each well of the RNEASY 96™ plate incubated for 15 minutes and the vacuum was again applied for 1 minute. An additional 500 µL of Buffer RW1 was added to each well of the RNEASY 96™ plate and the vacuum was applied for 2 minutes. 1 mL of Buffer RPE was then added to each well of the RNEASY 96™ plate and the vacuum was applied for a period of 90 seconds. The Buffer RPE was then washed and the vacuum was applied for an additional 3 minutes. The plate was then removed from the QIAcube manifold and blotted dry on paper towels. The plate was then reattached to the QIAcube manifold fitted with a collection tube rack containing 2 mL collection tubes. RNA was then eluted by pipetting 140 µL of RNase free water into each well, incubating 1 minute, and then applying the vacuum for 3 minutes.

[0160] The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia, Calif.). Essentially, after lysing the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

Example 13

Real-time Quantitative PCR Analysis of Glucagon Receptor mRNA Levels

[0161] Quantitation of glucagon receptor mRNA levels was accomplished by real-time quantitative PCR using the ABI PRISM™ 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, Calif.) according to manufacturer’s instructions. This is a closed-tube, non-gel-based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., FAM or JOE, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 5’ end of the probe and a quencher dye (e.g., TAMRA, obtained from either PE-Applied Biosystems, Foster City, Calif., Operon Technologies Inc., Alameda, Calif. or Integrated DNA Technologies Inc., Coralville, Iowa) is attached to the 3’ end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3’ quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5’- exonuclease activity of Taq polymerase. During the extension phase of the PCR amplification cycle, cleavage of the probe by Taq polymerase releases the reporter dye from the remainder of the probe (and hence from the quencher moiety) and a sequence-specific fluorescent signal is generated. With each cycle, additional reporter dye molecules are cleaved from their respective probes, and the fluorescence intensity is monitored at regular intervals by laser optics built into the ABI PRISM™ Sequence Detection System. In each assay, a series of parallel reactions containing serial dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after anti-sense oligonucleotide treatment of test samples.

[0162] Prior to quantitative PCR analysis, primer-probe sets specific to the target gene being measured are evaluated for their ability to be “multiplexed” with a GAPDH amplification reaction. In multiplexing, both the target gene and the internal standard gene GAPDH are amplified concurrently in a single sample. In this analysis, mRNA isolated from untreated cells is serially diluted. Each dilution is amplified in the presence of primer-probe sets specific for GAPDH only, target gene only (“single-plexing”), or both (multiplexing). Following PCR amplification, standard curves of GAPDH and target mRNA signal as a function of dilution are generated from both the single-plexed and multiplexed samples. If both the slope and correlation coefficient of the GAPDH and target signals generated from the multiplexed samples fall within 10% of their corresponding values generated from the single-plexed samples, the primer-probe set specific for that target is deemed multiplexable. Other methods of PCR are also known in the art.

[0163] PCR reagents were obtained from Invitrogen Corporation, (Carlsbad, Calif.). RT-PCR reactions were carried out by adding 20 µL PCR cocktail (2.5X PCR buffer minus MgCl₂, 6.6 mM MgCl₂, 375 µM each of dATP, dTTP, dCTP and dGTP, 375 nM each of forward primer and reverse primer, 125 nM of probe, 4 Units RNase inhibitor, 1.25 Units PLATINUM® Taq, 5 Units MuLV reverse transcriptase, and 2.5XROX dye) to 96-well plates containing 30 µL total RNA solution (20-200 ng). The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a 10-minute incubation at 95°C, to activate the PLATINUM® Taq, 40 cycles of a two-step PCR protocol were carried out: 95°C for 15 seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

[0164] Gene target quantities obtained by real time RT-PCR are normalized using either expression levels of GAPDH, a gene whose expression is constant, or by quantifying total RNA using Ribogreen™ (Molecular Probes, Inc. Eugene, Ore.). GAPDH expression is quantified by

[0165] In this assay, 170 µL of RiboGreen™ working reagent (RiboGreen™ reagent diluted 1:50 in 10 mM Tris-HCl, 1 mM EDTA, pH 7.5) is pipetted into a 96-well plate containing 50 µL purified, cellular RNA. The plate is read in a CytoFlor 4000 (PE Applied Biosystems) with excitation at 485 nm and emission at 530 nm.

[0166] Probes to human glucagon receptor were designed to hybridize to a human glucagon receptor sequence, using published sequence information (GenBank accession number NM_000160.1, incorporated herein as SEQ ID NO:4). For human glucagon receptor the PCR primers were:

forward primer: GACACCCCCCGGCAATACC (SEQ ID NO: 5)

reverse primer: CCGGATCTCCGGAACGAA (SEQ ID NO: 6) and the PCR probe was:

FAM-TTGGCACCACAAAGT-TAMRA (SEQ ID NO: 7) where FAM is the fluorescent dye and TAMPA is the quencher dye. For human GAPDH the PCR primers were:

forward primer: GAAGGTGAAGGTCGGAGTC (SEQ ID NO:8)

reverse primer: GAAGATGGTGATGAGATTTC (SEQ ID NO:9) and the PCR probe was: 5' JOE-CAAGCTTTCCCTCCGATCTGAC-3' (SEQ ID NO: 10) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

[0167] Probes and primers to mouse glucagon receptor were designed to hybridize to a mouse glucagon receptor sequence, using published sequence information (GenBank accession number NM_008101.1, incorporated herein as SEQ ID NO: 11). For mouse glucagon receptor the PCR primers were:

forward primer: ATTTCTGGCCCTCTGTACCT (SEQ ID NO:12)

reverse primer: CCGGCCCAACACCTTCTGG (SEQ ID NO: 13) and the PCR probe was: FAM-CCACAAAGTGCAGCACCGCTTAGGT-TAMRA

(SEQ ID NO: 14) where FAM is the fluorescent reporter dye and TAMPA is the quencher dye.

For mouse GAPDH the PCR primers were:

forward primer: GGCAAAATCAACGGCACAGT (SEQ ID NO: 15)

reverse primer: GGGTCTCGCTCTGGAAGAT (SEQ ID NO:16) and the PCR probe was: 5' JOE-AAAGCGCAGAATGGGAGACTTGTGATC-TAMRA 3' (SEQ ID NO: 17) where JOE is the fluorescent reporter dye and TAMRA is the quencher dye.

Northern Blot Analysis of Glucagon Receptor mRNA Levels

[0168] Eighteen hours after antisense treatment, cell monolayers were washed twice with cold PBS and lysed in 1 ml RNAZOl™ (TEL-TEST "B" Inc., Friendswood, Tex.). Total RNA was prepared following manufacturer's recommended protocols. Twenty micrograms of total RNA was fractionated by electrophoresis through 1.2% agarose gels containing 1.1% formaldehyde using a MOPS buffer system (AMRESCO, Inc., Solon, Ohio). RNA was transferred from the gel to HYBOND™ -N+ nylon membranes (Amersham Pharmacia Biotech, Piscataway, N.J.) by overnight capillary transfer using a Northern/Southern Transfer buffer system (TEL-TEST "B" Inc., Friendswood, Tex.). RNA transfer was confirmed by UV visualization. Membranes were fixed by UV cross-linking using a STRATALINKER™ UV Crosslinker 2400 (Stratagene, Inc, La Jolla, Calif.) and then probed using QUICKHYB™ hybridization solution (Stratagene, La Jolla, Calif.) using manufacturer’s recommendations for stringent conditions.

[0169] To detect human glucagon receptor, a human glucagon receptor specific probe was prepared by PCR using the forward primer GACACCCCCCGGCAATACC (SEQ ID NO: 5) and the reverse primer CGGATCTCCGGAACGAA (SEQ ID NO: 6). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0170] To detect mouse glucagon receptor, a mouse glucagon receptor specific probe was prepared by PCR using the forward primer ATTTCTGGCCCTCTGTACCT (SEQ ID NO: 12) and the reverse primer CGGCCCCACACCTTCTGG (SEQ ID NO: 13). To normalize for variations in loading and transfer efficiency membranes were stripped and probed for mouse glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA (Clontech, Palo Alto, Calif.).

[0171] Hybridized membranes were visualized and quantitated using a PHOSPHORIMAGER™ and IMAGEQUANT™ Software V3.3 (Molecular Dynamics, Sunnyvale, Calif.). Data was normalized to GAPDH levels in untreated controls.

Example 15

Antisense Inhibition of Human Glucagon Receptor Expression by Chimeric Phosphorothioate Oligonucleotides having 2'-MOE: Wings and a Deoxy Gap

[0172] In accordance with the present invention, a series of antisense compounds were designed to target different regions of the human glucagon receptor RNA, using published sequences (GenBank accession number NM_000160.1, incorporated herein as SEQ ID NO: 4, a concatenation of three contigs from GenBank accession number AC069004.2, incorporated herein as SEQ ID NO: 18, and GenBank accession number AJ245489.1, incorporated herein as SEQ ID NO: 19). The compounds are shown in Table 1. “Target site” indicates the first (5'-most) nucleotide number on the particular target sequence to which the compound binds. All compounds in Table 1 are chimeric oligonucleotides (“gappers”) 20 nucleotides in length, composed of a central “gap” region consisting of ten 2’-deoxy-nucleotides, which is flanked on both sides (5’ and 3’
directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human glucagon receptor mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which HepG2 cells were treated with the antisense oligonucleotides of the present invention. The positive control for each datapoint is identified in the table by sequence ID number. If present, "N.D." indicates "no data".

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Inhibition of human glucagon receptor mRNA levels by chimeric phosphorothioate oligonucleotides having us/3′/6′-MOE wings and a deoxy gap

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Inhibition of human glucagon receptor mRNA levels by chimeric phosphorothioate oligonucleotides having ur/3/36 2’-MOE wings and a deoxy gap

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Inhibition of human glucagon receptor mRNA levels by chimeric phosphorothioate oligonucleotides having 2′-MOE wings and a deoxy gap.
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**TABLE 1-continued**

Inhibition of human glucagon receptor mRNA levels by chimeric phosphorothioate oligonucleotides having us/3/36 2'-MOE wings and a deoxy gap

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Example 16

Antisense Inhibition of Mouse Glucagon Receptor Expression by Chimeric Phosphorothioate Oligonucleotides having 2'-MOE: Wings and a Deoxy Gap

In accordance with the present invention, a second series of antisense compounds were designed to target different regions of the mouse glucagon receptor RNA, using published sequences (GenBank accession number NM_008101.1, incorporated herein as SEQ ID NO: 11, an mRNA sequence derived from GenBank accession number AF229079.1 with an alternate promoter, incorporated herein as SEQ ID NO: 400, GenBank accession number AF229079.1, incorporated herein as SEQ ID NO: 401, a second mRNA sequence derived from GenBank accession number AF229079.1 with an alternate promoter, incorporated herein as SEQ ID NO: 402, and GenBank accession number AA920726.1, incorporated herein as SEQ ID NO: 403). The compounds are shown in Table 2. “Target site” indicates the first (5’-most) nucleotide number on the particular target nucleic acid to which the compound binds. All compounds in Table 2 are chimeric oligonucleotides (‘gapmers’) 20 nucleotides in length, composed of a central “gap” region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5’ and 3’ directions) by five-nucleotide “wings”. The wings are composed of 2’-methoxyethyl (2’-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on mouse glucagon receptor mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which mouse primary hepatocytes were treated with the antisense oligonucleotides of the present invention. The positive control for each datapoint is identified in the table by sequence ID number. If present, “N.D.” indicates “no data”.

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Inhibition of mouse glucagon receptor mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOR wings and a deoxy gap

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### TABLE 3-continued

Sequence and position of preferred target segments identified in glucagon receptor.

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Sequence and position of preferred target segments identified in glucagon receptor.

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### TABLE 3-continued

Sequence and position of preferred target segments identified in glucagon receptor.

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<p>| Oct. 11, 2007 |</p>
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**TABLE 3-continued**

Sequence and position of preferred target segments identified in glucagon receptor.
### TABLE 3-continued

Sequence and position of preferred target segments identified in glucagon receptor.

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TABLE 3-continued

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| 95513 | 400 | 291 | actcgttcgctgctggcagaccc | 432 | M. musculus | 776 |
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[0176] As these “preferred target segments” have been found by experimentation to be open to, and accessible for, hybridization with the antisense compounds of the present invention, one of skill in the art will recognize or be able to ascertain, using no more than routine experimentation, further embodiments of the invention that encompass other compounds that specifically hybridize to these preferred target segments and consequently inhibit the expression of glucagon receptor.

[0177] According to the present invention, antisense compounds include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, external guide sequence (EGS) oligonucleotides, alternate splicers, primers, probes, and other short oligomeric compounds which hybridize to at least a portion of the target nucleic acid.

Example 18
Effects of Antisense Inhibition of Glucagon Receptor in Mice on Plasma Glucose Levels and Glucagon Receptor mRNA Reduction: Lean Animals, db/db Mice and ob/ob Mice

[0179] In accordance with the present invention, two antisense oligonucleotides targeted to the mouse glucagon receptor, ISIS 148359 (agagcattacgaattgatgagg, SEQ ID NO: 408) and ISIS 180475 (gagagatttctctgattgct, SEQ ID NO: 452), were evaluated for therapeutic efficacy in art-accepted mouse models of obesity and diabetes. Ob/ob mice have mutations in the leptin gene and are leptin-deficient, while db/db mice have mutations in the leptin receptor gene. The two strains exhibit obesity and diabetes strongly resembling Type 2 diabetes in humans. Tsang, S. H., 1998, P & S Medical Review, Vol. 5, No. 1.

[0180] Db/db and ob/ob mice were evaluated over the course of 4 weeks for the effects of ISIS 148359 and ISIS 180475 on serum glucose levels and glucagon receptor mRNA levels, while normoglycemic mice were evaluated for 2 weeks. Control animals received saline treatment (50 mg/kg). The normoglycemic mice were dosed subcutaneously twice a week for 2 weeks with 50 mg/kg of ISIS 148359, ISIS 180475 or saline. The db/db and ob/ob mice were dosed subcutaneously twice a week for 6 weeks with 25 mg/kg of ISIS 148359, ISIS 180475, saline, the positive control oligonucleotide ISIS 116847 (ctctctgcttctttgctctt, SEQ ID NO: 817) or the negative control oligonucleotide ISIS 141923 (ctctctctctctctctctct, SEQ ID NO: 818). The mice were monitored weekly for fed or fasted plasma glucose levels (fasted glucose measured 16 hr after last feeding) and upon termination of the experiment the level of glucagon receptor mRNA in the liver was determined. The data are summarized in Table 4.
These data demonstrate that the antisense oligonucleotides ISIS 148359 and ISIS 180475 targeted to glucagon receptor mRNA are capable of decreasing levels of glucagon receptor mRNA in mouse liver. These data further demonstrate that reduction of glucagon receptor expression is accompanied by a decrease in plasma glucose levels in normoglycemic mice, db/db mice and ob/ob mice. It is important to note that the treated mice become normoglycemic and do not become hypoglycemic. Antisense inhibitors of glucagon receptor are thus believed to be useful therapeutic modalities for treatment of hyperglycemia.

Example 19

Glucagon Receptor Antisense Oligonucleotides Lower Plasma Glucose in ob/ob Diabetic Mice — 4 Week Study

C57Bl/6OlaHsd-Lepr<sup>ob</sup> (ob/ob) male mice were purchased from Harlan (Indianapolis, Ind., USA). Animals were acclimated for one week prior to study initiation. Mice were housed five per cage in polycarbonate cages with filter tops. Animals were maintained on a 12:12 hr light-dark cycle (lights on at 6:00 AM) at 21° C. All animals received de-ionized water ad libitum. ob/ob mice received Purina Diet 5015 ad libitum. Antisense compounds were prepared in normal saline, and the solution was sterilized through a 0.2 μm filter. Animals were dosed with antisense compound solutions or vehicle (saline) twice per week (separated by 3.5 days) via subcutaneous injection. Before the initiation of each study and once weekly during the study, blood was collected by tail clip without anesthesia into EDTA plasma tubes containing trasyloL (Serologicals Proteins, Kankakee, Ill., USA) and dipeptidyl peptidase (DPP)-IV inhibitor (Linco Diagnostic Services, St. Charles, Mo., USA). Food intake and body weights were measured weekly. Plasma levels of glucose and triglycerides were determined on the Hitachi 912 clinical chemistry analyzer (Roche, Indianapolis, Ind., USA).

To test the efficacy of antisense inhibitors of glucagon receptor to treat hyperglycemia, 7-8 week-old ob/ob mice were dosed two times per week with antisense inhibitors of glucagon receptor [ISIS 148359 (SEQ ID NO: 408) or ISIS 180475 (SEQ ID NO: 452)], a generic control oligonucleotide (ISIS 141923; SEQ ID NO: 818) whose sequence does not match any known transcripts in the mouse or rat genomes, a mismatch oligonucleotide (ISIS 298682; GGGATTCTCCGTTTGGACCT; SEQ ID NO: 819) whose sequence is identical to ISIS 180475 except for 7 internal bases, or saline twice a week (every 3.5 days) for 4 weeks. All oligonucleotides were administered at 25 mg/kg. Data are the mean values (±SEM where shown) of 8 mice per treatment group. Plasma glucose levels in all mice were approximately 330-370 mg/dl day zero. Whereas hyperglycemia worsened over time in saline- and control oligonucleotide-treated ob/ob mice, animals treated with glucagon receptor antisense compounds showed a dramatic reduction in plasma glucose. At day 12, plasma glucose levels in ob/ob mice treated with control oligonucleotide (ISIS 141923) and saline were approximately 472 and 425 mg/dl, respectively. Plasma glucose levels in mice treated with antisense oligonucleotides ISIS 148359 and ISIS 180475 were 240 and 180 mg/dl, respectively. At day 27, plasma glucose levels in ob/ob mice treated with control oligonucleotide (ISIS 141923) and saline were approximately 435 and 390 mg/dl, respectively. Plasma glucose levels in mice treated with antisense oligonucleotides ISIS 148359 and ISIS 180475 were 165 and 130 mg/dl, respectively. The latter is in the normal range.

A separate study, also using ob/ob mice (as well as db/db mice, lean mice, ZDF rats and lean rats) was also performed in which animals were also dosed subcutaneously every 3.5 days for a total of 9 doses of glucagon receptor antisense compound ISIS 180475 and one or more controls (unrelated control oligonucleotide ISIS 141923, mismatch

<table>
<thead>
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<th>Measured</th>
<th>mice (time of course of study)</th>
<th>day of treatment</th>
<th>ISIS #</th>
<th>Antisense Oligonucleotides</th>
<th>Controls</th>
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<td></td>
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<td></td>
<td></td>
<td>148359</td>
<td>180475</td>
<td>saline</td>
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<tr>
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<tr>
<td>plasma</td>
<td>db/db mice</td>
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<tr>
<td></td>
<td>(4 weeks)</td>
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<td>(4 weeks)</td>
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<td>mg/dl.</td>
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</table>
control oligonucleotide ISIS 298682, and/or saline). The results of this study are shown in Table 5.

[0185] At the end of the 4-week treatment period, liver glucagon receptor mRNA was measured (normalized to total RNA in the same samples using Ribogreen) and was found to be reduced by 85-95%. Data are mean values of four mice per treatment group (P<0.05 using Student’s t-test).

TABLE 5

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<tr>
<td></td>
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<td>Plasma Glucose (mg/dl)</td>
<td>Plasma Triglycerides (mg/dl)</td>
<td>Plasma Insulin (ng/ml)</td>
<td>Plasma Glucagon (pg/ml)</td>
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<td>Saline</td>
<td>56.5 ± 1.5</td>
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<td>163 ± 25</td>
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<td>129 ± 7</td>
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*P < 0.05.
n.d., not determined

Example 20

Glucagon Receptor Antisense Oligonucleotides Lower Plasma Glucose in db/db Diabetic Mice — 4 Week Study

[0186] C57Bl/KsOla1Isd-Lepob (db/db) and lean (db/+ ) male mice were purchased from Harlan (Indianapolis, Ind., USA). Animals were acclimated for one week prior to study initiation. Mice were housed five per cage in polycarbonate cages with filter tops. Animals were maintained on a 12:12 hr light-dark cycle (lights on at 6:00 AM) at 21°C. All animals received de-ionized water ad libitum. db/db mice received Purina Diet 5008 ad libitum. Antisense compounds were prepared in normal saline, and the solution was sterilized through a 0.2 µm filter. Animals were dosed with antisense compound solutions or saline (vehicle) twice per week (separated by 3.5 days) via subcutaneous injection. Before the initiation of each study and once weekly during the study, blood was collected by tail clip without anesthesia into EDTA plasma tubes containing trasylosl (Serologicals Proteins, Kankakee, Ill., USA) and dipeptidyl peptidase (DPP)-IV inhibitor (Linco Diagnostic Services, St. Charles, Mo., USA). Food intake and body weights were measured weekly. Plasma levels of glucose and triglycerides were determined on the Hitachi 912 clinical chemistry analyzer (Roche, Indianapolis, Ind., USA).

[0187] To test the efficacy of antisense inhibitors of glucagon receptor to treat hyperglycemia, 7-8 week-old db/db mice were dosed two times per week with antisense inhibitors of glucagon receptor [ISIS 148359 (SEQ ID NO: 408) or ISIS 180475 (SEQ ID NO: 452)], a generic control oligonucleotide (ISIS 141923) whose sequence does not match any known transcripts in the mouse or rat genomes, a mismatch oligonucleotide (ISIS 298682; SEQ ID NO: 819) whose sequence is identical to ISIS 180475 except for 7 internal bases, or saline for 4 weeks.

[0188] Glucose lowering efficacy and target reduction in db/db mice undergoing glucagon receptor antisense treatment were similar to those observed in similarly treated ob/ob mice; furthermore, plasma triglycerides were lowered from 412±33 to 121±12 mg/dl following glucagon receptor antisense treatment (Table 5). These results in db/db mice are similar to those reported in preliminary studies testing glucagon receptor antisense compound ISIS 148359 for 3 weeks [Osborne et al., 2003, Diabetes 52, A129 (abstract)].

Example 21

Glucagon Receptor Antisense Oligonucleotides Lower Plasma Glucose in ZDF Rats

[0189] ZDF/GmiCrl-fa/fal (ZDF) male rats were purchased from Charles River Laboratories (Wilmington, Mass., USA). Animals were acclimated for one week prior to study initiation. Rats were housed one per cage in polycarbonate cages with filter tops. Animals were maintained on a 12:12 hr light-dark cycle (lights on at 6:00 AM) at 21°C. All animals received de-ionized water ad libitum. ZDF rats received Purina Diet 5008 ad libitum. Antisense compounds
were prepared in normal saline, and the solution was sterilized through a 0.2 μm filter. Seven-week old animals were dosed with antisense compound solutions or vehicle (saline) twice per week (separated by 3.5 days) via subcutaneous injection, for a total of 9 doses (last treatment on day 28), followed by a washout period of equal duration. Oligonucleotide concentration was 25 mg/kg of either glucagon receptor antisense oligonucleotide ISIS 180475 (SEQ ID NO: 452) or negative control oligonucleotide ISIS 141923 (SEQ ID NO: 815). Before the initiation of each study and once weekly during the study, blood was collected by tail clip without anesthesia into EDTA plasma tubes containing trisylol (Sero logicals Proteins, Kankakee, Ill., USA) and dipeptidyl peptidase (DPP)-IV inhibitor (Lincor Diagnostic Services, St. Charles, Mo., USA). Food intake and body weights were measured weekly. Glucagon receptor mRNA (target) was measured by real-time quantitative RT-PCR from livers of five animals removed from the study at each time point. Rat 36B4 ribosomal phosphoprotein mRNA ("18S RNA") was measured and used to normalize RNA input. Data are the mean values of five rats per treatment group. In overall comparisons during the treatment period, target reduction by glucagon receptor antisense compound ISIS 180475 was significantly different when compared to control oligonucleotide-treated animals (P<0.05 adjusted using the Tukey method). Liver glucagon receptor mRNA decreased dramatically to 50% of controls within 24 hours after the first dose of ISIS 180475 and to 30% of controls 48 hr following the seventh dose.

For non-fasted plasma glucose levels, rats were treated as described above. Data are the mean values of five rats per treatment group. In overall comparisons during the treatment period, glucose lowering by the glucagon receptor antisense compound ISIS 180475 showed significant difference when compared to control oligonucleotide-treated animals. (P<0.05 adjusted using the Tukey method). The drop in plasma glucose paralleled the drop in glucagon receptor mRNA levels; there was a significant drop in plasma glucose within 48 hours after the initial glucagon receptor antisense dose. After 9 doses, the control oligonucleotide (ISIS 141923) treated rats had plasma glucose levels averaging approximately 417 mg/dl and antisense (ISIS 180475) treated rats had plasma glucose levels averaging approximately 143 mg/dl.

During the washout phase, hyperglycemia and glucagon receptor expression in liver began to rebound within 10 days, but even one month after the final dose, efficacy was still observed as plasma glucose and target mRNA levels in washout animals remained below pre-treatment levels. Glucose lowering achieved by the twice per week dosing schedule and the gradual rebound of glucagon receptor mRNA during the washout period are both consistent with the extended half lives of 2-methoxyethoxy modified phosphorothioate oligonucleotides (typically ranging from 9 to 19 days according to published reports).

Non-fasted plasma insulin levels were also determined for rats treated as described above. Data are the mean values of five rats per treatment group. No significant changes were observed during the treatment period; however, individual comparisons between glucagon receptor antisense and control oligonucleotide treated animals on day 38 and 56 (washout period) were significant (P<0.05). Plasma insulin levels declined during the treatment phase in both control oligonucleotide and antisense-treated animals. During the washout phase of the control oligonucleotide treated group, insulin levels continued to decline as hyperglycemia progressed. This result is expected since beta-cell failure typically occurs in ZDF rats between 8 and 12 weeks of age. Interestingly, the mild elevation of glucose in glucagon receptor antisense-treated animals during the washout period resulted in a robust rise in plasma insulin to levels nearly as high as at start of study. This is consistent with evidence of preserved beta-cell function.

Example 22

Glucagon Receptor Antisense Oligonucleotides do not cause Hyperglycemia or Hypoglycemia, in spite of Hyperglycagonemia

In addition to effects on blood glucose, treatment with the antisense inhibitor of glucagon receptor (ISIS 180475; SEQ ID NO: 452) resulted in marked (and reversible) hyperglycagonemia in both normal and diabetic rodents (Table 5). This level of hyperglycagonemia is similar to that observed in glucagon receptor knockout mice (Parker et al., 2002, Biochem Biophys Res Commun. 290, 839-843; Gelling et al., 2003, Proc. Natl. Acad. Sci. U.S.A. 100, 1438-1443). Because of these high levels of serum glucagon, it was important to determine whether the antisense inhibitors of glucagon receptor might induce hyperglycagonemia, particularly as hepatic glucagon receptor levels gradually return to normal following treatment withdrawal. It is therefore significant that at no time during the treatment or washout periods did animals with hyperglycagonemia exhibit hyperglycemia. In fact, glucagon receptor antisense-treated animals showed a moderate decrease in fed plasma glucose at all time points tested.

Example 23

Glucagon Receptor mRNA is Reduced in Islets of Antisense-Treated db/db Mice

Pancreatic islets were isolated from 12-week-old male db/db mice (n=5-6 per treatment group) that had been treated twice per week (every 3.5 days) by subcutaneous injection with saline or glucagon receptor antisense oligonucleotide ISIS 180475 (SEQ ID NO: 452) at 25 mg/kg for a total of 9 doses. Mice were sacrificed by cervical dislocation. The common bile duct was cannulated with a 27-gauge needle and the pancreas was distended with 3 ml of Hank's buffer (Sigma, Taufkirchen, Germany) containing 2% bovine serum albumin (Applichem, Darmstadt, Germany) and 1 mg/ml collagenase (Serva, Heidelberg, Germany). Subsequently, the pancreas was removed and digested in Hank's buffer at 37° C. Islets were purified on a Histopaque-1077™ (Sigma) gradient for 15 min at 750g.
Islets were cultured overnight in RPMI-1640 medium containing 10% FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin (Invitrogen, Karlsruhe, Germany). 200 islets from 3 individuals were pooled to give one sample for RNA extraction. Real-time quantitative RT-PCR was used to profile gene expression. Islet glucagon receptor mRNA levels were decreased by approximately 75% in antisense-treated animals compared to saline-treated controls. It should be noted that, in addition to pharmacologic effect of the antisense compound, a compensatory response to hyper-glucagonemia or the increased alpha-cell populations in treated animals could contribute to the results observed.

Example 24

Glucagon Receptor Antisense Oligonucleotides Decrease the Number of Functional Glucagon Receptors

[0196] To assess whether the reduction in glucagon receptor mRNA correlates with a reduction in functional glucagon receptor number, a homologous competition assay was performed using hepatocyte membranes prepared from mice treated with control or glucagon receptor antisense compounds. 125I-glucagon binding was effectively competed by increasing concentrations of unlabeled glucagon in control membrane samples. 15-20 µg of membrane from control oligonucleotide- or glucagon receptor oligonucleotide (ISIS 180475; SEQ ID NO: 452)-treated db/db mice were incubated with 0.1 nM 125I-glucagon (2000 Ci/mmol, PerkinElmer, Boston, Mass., USA) and the indicated concentrations of unlabeled glucagon (Eli Lilly and Company, Indianapolis, Ind., USA) in buffer containing 50 mM Hapes, 1 mM MgCl2, 5 mM EGTA, 0.005% Tween 20, 0.1% BSA, and EDTA-free protease inhibitor cocktail (Roche). Assays were performed under steady state conditions in the presence of excess labeled ligand on 96-well MultiScreen-HV 0.45 µm filter plates (Millipore, Bedford, Mass., USA). Following incubation for 2 hrs at room temperature, plates were rapidly washed by filtration with ice-cold buffer (20 mM Tris, pH 7.4) and dried for 45 min at 50°C. Following the addition of Optiphase Supermix (PerkinElmer), plates were counted on a Wallac Microbeta scintillation counter. Data analyses were performed using GraphPad Prism software and expressed as mean+/−SEM. Data obtained for samples from animals treated with glucagon receptor oligonucleotide near the limits of detection for the assay and curve-fitting parameters. In order to derive a numerical value for apparent Bmax, the Kd was fixed at the average value (0.69+/−0.2 nM) obtained from the samples from the control antisense-treated animals.

[0197] Functional GCGR expression was found to be decreased approximately 85% by glucagon receptor antisense treatment and is in accord with quantitative RT-PCR results.

Example 25

Antisense Inhibitors of Human and Monkey Glucagon Receptor—Dose Response

[0198] Based on the screen in Example 15 above, a subset of human glucagon receptor antisense oligonucleotides were chosen for further study. Dose-response studies were conducted for ISIS 315166, 310457, 315324, 315278, 315181, 315297, 315163 and 310456 in both human HepG2 cell cultures and in cynomolgus monkey primary hepatocytes. These six compounds are homologous to both human and cynomolgus monkey glucagon receptor nucleic acid targets. The universal control ISIS 29848 (NNNNNNNNNNNNNNNNNN; SEQ ID NO: 820, where N is an equimolar mixture of A, C, G and T, a chimeric 2’ MOE gapmer with a phosphorothiate backbone and with MOEs at positions 1-5 & 16-20) was used as negative control.

[0199] The human hepatoblastoma cell line HepG2 was obtained from the American Type Culture Collection (Manassas, Va.). HepG2 cells are routinely cultured in Eagle’s MEM supplemented with 10% fetal calf serum, non-essential amino acids, and 1 mM sodium pyruvate (Gibco/Life Technologies, Gaithersburg, Md.). Cells are routinely passaged by trypsinization and dilution when they reach 90% confluence.

[0200] Primary cynomolgus monkey hepatocytes were obtained from CellzDirect (Los Angeles) and plated onto collagen-coated 24-well plates (Costar) at a density of 75,000 cells/well. The culturing medium for these hepatocytes was Williams’ E media (Invitrogen) supplemented with 10% FBS (Invitrogen). Cells were allowed to attach overnight and were then treated with oligonucleotide-Lipofectin mixture for 4 hours. The oligonucleotide-Lipofectin mixture was washed off and then cells were incubated in normal medium.

[0201] Cells were treated with oligonucleotide for 20 hours at doses of 1, 5, 10, 25, 50, 100 nM for HepG2 cells and 5, 10, 25, 50, 100 and 200 nM for primary monkey hepatocytes (n=5). RNA was analyzed by RT-PCR to determine percent inhibition of glucagon receptor expression compared to control (ISIS 29848), at each oligonucleotide concentration. The results were plotted to give the IC50, the dose of oligonucleotide which results in 50% reduction of glucagon receptor mRNA levels. Results are shown in Table 6.

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<td>25</td>
<td>20</td>
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Based on these results, three compounds (ISIS 315297, 310457 and 315163) were chosen for study in monkeys.

Example 26

Dose-Ranging Study of Antisense Inhibition of Glucagon Receptor Expression in Cynomolgus Monkeys

[0202] A monkey study was performed at SNBL USA, Ltd., Everett, Wash. Forty mature (6-8 years old) male Macaca fascicularis (purpose-bred cynomolgus monkeys)
weighing approximately 5-10 kg at the initiation of dosing were used. The animals were individually housed in primary climate-controlled enclosures conforming to the Animal Welfare Act. Animals were offered Purina Mills Laboratory Profiled Fiber Plus® Monkey Diet (Animal Specialties, Hubbard, Oreg.). Occasional fresh fruit and vegetable treats were also offered. Fresh drinking water was available to all animals, ad libitum. Before fasting measurements, food was removed from enclosures between 1630 and 1700 on the afternoon before the scheduled blood draw. After the animals were fasted for at least 16 hours, blood samples for plasma analysis were collected BEFORE dosing or feeding. For fasting analysis, approximately 2.3-2.5 mL of blood was drawn from a peripherel vein. Approximately 1.8 to 2.0 mL was be deposited into a K2-EDTA tube containing DPP-IV inhibitor at 10 μL/mL of blood and trasylool at 250 KIU/mL of blood. Approximately 0.5 mL was deposited into a lithium heparin tube. Once the blood had been deposited into the EDTA plus additives tube, it was inverted to mix and placed on ice within 5 minutes. The blood in the lithium heparin tube was also placed on ice within 5 minutes. Blood samples were centrifuged (2000xg, 15 minutes at 4 °C) to obtain plasma within 30 minutes of sample collection. The plasma was frozen at or below -70°C. Samples were shipped on dry ice via overnight courier as described below for subsequent analysis. For non-fasted analysis, the animals were given their AM feeding (between 0830 and 0930) on the day of the blood draw. Ninety minutes after feeding, blood was drawn. The number of biscuits remaining was counted at the time of the blood draw. Samples are prepared and shipped as above.

Monkeys were dosed subcutaneously for 10 weeks with ISIS 315297, ISIS 310457 or ISIS 315163 at three concentrations. In week 1, oligonucleotides were given at 2.0, 5.0 and 20 mg/kg/dose (Day 1, 3 and 5); in week 2 through 10, oligonucleotides were given at 1.0, 2.5 and 10 mg/kg/dose (twice weekly starting at Day 8). The larger dose (6.5 or 60 mg/kg/week, i.e. 3 injections of 2, 5 or 20 mg/kg) was given in week 1 in order to rapidly achieve the desired steady state oligonucleotide concentration. In week 1, compounds were administered 3 times, every other day; for weeks 2-10, compounds were administered twice per week, with at least 2 days between dosings.

Oligonucleotides were given by subcutaneous (SC) injection, using volumes of 0.1-0.5 mL/kg. For each dosing of each animal, the appropriate volume of the relevant ASO solution or of the control vehicle was administered subcutaneously using a syringe and needle (27G). The total volume of the relevant dosing solution or the control solution was calculated on the basis of the animal’s most recent body weight. Multiple injection sites on the upper back (intrascapular region) of each monkey were employed. During acclimation the skin of the upper back was shaved and a clock-like grid (points at 12, 3, 6, and 9 o'clock) was tattooed on each animal. Injection points were a minimum of 5 cm apart. The injection site was rotated so that each site was used for fourth dose, starting with 12 o'clock and rotating clockwise. The needle was inserted away from the dot and angled so that the dose was deposited underneath the dot.

After the 10 week study (approx. 2 days after last dose), animals were euthanized and three 1 to 4 gram samples of liver tissue were removed and individually snap frozen over liquid nitrogen; alternatively, biopsies could be taken from living animals and frozen. Frozen tissues were homogenized in 4M guanidinium isothiocyanate solution and subjected to CsCl centrifugation (150,000g for 16 hr at 18 °C). The supernatant was removed and the RNA pellet was resuspended in water, following which it was applied to RNEASY mini columns (Qiagen, Valencia Calif.). After purification and quantitation, the tissues were subjected to RT-PCR analysis as described in previous examples using the following primers and probe:

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RNA amounts were normalized to 18S RNA levels in the tissue. Results are shown in Table 7, as percent reduction in glucagon receptor mRNA in antisense-treated monkeys compared to saline-treated monkeys.

| Glucagon receptor mRNA reduction in monkey liver after treatment with antisense inhibitors of glucagon receptor - RT-PCR expr 1 |  |
|---|---|---|---|
| ISIS # | SEQ ID NO: | % reduction at 2 mg/kg | % reduction at 5 mg/kg | % reduction at 20 mg/kg |
| 310457 | 184 | 17 | 31 | 64 |
| 315297 | 365 | 2 | 21 | 49 |
| 315163 | 231 | 22 | 18 | 47 |

RNA analysis of the same tissue samples by RT-PCR was repeated independently using the same primer-probe set as above. Results are shown in Table 8 as percent reduction in glucagon receptor mRNA in antisense-treated monkeys compared to saline-treated monkeys.

| Glucagon receptor mRNA reduction in monkey liver after treatment with antisense inhibitors of glucagon receptor - RT-PCR expr 2 |  |
|---|---|---|---|
| ISIS # | SEQ ID NO: | % reduction at 2 mg/kg | % reduction at 5 mg/kg | % reduction at 20 mg/kg |
| 310457 | 184 | 25 | 23 | 63 |
| 315297 | 365 | 18 | 21 | 56 |
| 315163 | 231 | 25 | 29 | 44 |

The results obtained by RT-PCR were confirmed by Northern blot analysis according to standard methods (Example 14). The cDNA probe that was used for northern blots was a 900-base fragment of monkey GCGR generated by RT-PCR from cynomolgus monkey liver. Results are shown in Table 9.
TABLE 9
Glucagon receptor mRNA reduction in monkey liver after treatment with antisense inhibitors of glucagon receptor - Northern blot

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<th>% reduction at 5 mg/kg</th>
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[0209] Blood glucose levels were measured in monkeys after treatment with antisense inhibitors of glucagon receptor. Glucose readings were performed using a drop of blood from the blood samples collected as above and read on a One Touch Profile® (LifeScan Inc., a Johnson and Johnson Company). Because normoglycemic (nondiabetic) monkeys were used in this study, no significant changes in blood glucose levels were expected or observed. At no point did animals become hypoglycemic after antisense treatment.

[0210] Glucagon levels were measured in plasma of fasted monkeys before (baseline) and after treatment for 5 weeks or 10 weeks with antisense inhibitors of glucagon receptor. Monkeys were anesthetized prior to blood collection to avoid artifacts due to stress. Glucagon levels were determined by radioimmunoassay, ELISA and/or Luminex immunoassay by contract laboratory (Linco, St. Charles Mo.). Results are shown in Table 10.

TABLE 10
Fasted glucagon levels in monkey liver after treatment with antisense inhibitors of glucagon receptor

<table>
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<tr>
<th>ISIS #</th>
<th>SEQ ID NO:</th>
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[0211] Glucagon-like peptide 1 (GLP-1) levels were measured in plasma of fasted monkeys before (baseline) and after treatment for 5 weeks or 10 weeks with antisense inhibitors of glucagon receptor. Monkeys were anesthetized prior to blood collection to avoid artifacts due to stress. GLP-1 levels were determined by radioimmunoassay, ELISA and/or Luminex immunoassay by contract laboratory (Linco, St. Charles Mo.). Results are shown in Table 11.

TABLE 11
Fasted GLP-1 levels in monkey liver after treatment with antisense inhibitors of glucagon receptor

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<400> SEQUENCE: 21

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<210> SEQ ID NO 22
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 22
gtctccctc gttasggcgc 20

<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 23
gagtgccgag gtcgagagac 20

<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 24
tgtgtgtgtc ggtctctcgc 20

<210> SEQ ID NO 25
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 25
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<210> SEQ ID NO 26
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 26
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<210> SEQ ID NO 27
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 27
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<400> SEQUENCE: 28
ggacgtcgct tgggcagcta

<210> SEQ ID NO 29
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 29
cagcagga taacttgagta

<210> SEQ ID NO 30
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ggacotgtgg tgggcaggcc

<210> SEQ ID NO 31
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<400> SEQUENCE: 31
aasttcataca aatggagogga

<210> SEQ ID NO 32
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<220> FEATURE:
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<400> SEQUENCE: 32	tctcaasag gaasttcatac

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<400> SEQUENCE: 33	cactttcct caccaggaagt
SEQ ID NO 34
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 34
cactgtcac cgtagagctt

SEQ ID NO 35
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 35
ggtgacactg gtcaagctag

SEQ ID NO 36
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 36
cacaccagct cgtggggag

SEQ ID NO 37
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 37
aagttctgtg gacacacagc

SEQ ID NO 38
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 38
ataccttgctg aagttctgctg

SEQ ID NO 39
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 39
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SEQ ID NO 40
LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 40
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<210> SEQ ID NO 41
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 41
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<210> SEQ ID NO 42
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 42
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<210> SEQ ID NO 43
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 43
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<210> SEQ ID NO 44
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 44
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<210> SEQ ID NO 45
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 45
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<210> SEQ ID NO 46
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
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<211> LENGTH: 20
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 47

ggcaacctct tctggaacct

<210> SEQ ID NO 48
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 48
gaatgtctg tctcctttgg

<210> SEQ ID NO 49
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 49
ccccaggtt ggcaagcgct

<210> SEQ ID NO 50
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 50
agggcttctcttcttcacc

<210> SEQ ID NO 51
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<210> SEQ ID NO 52
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<212> TYPE: DNA
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<400> SEQUENCE: 52
ttctggtgt aggggtcct
<210> SEQ ID NO 53
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 53
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<210> SEQ ID NO 54
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<212> TYPE: DNA
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<400> SEQUENCE: 54
tgagtcgac gccaattttc

<210> SEQ ID NO 55
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 55
tggtgacact gaggctgctg

<210> SEQ ID NO 56
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 56
gccaggtgct gacaatgagg

<210> SEQ ID NO 57
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 57
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<210> SEQ ID NO 58
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 58
gtgccacagc caagcaggtt

<210> SEQ ID NO 59
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 59

cagacaattg accactgccc

<210> SEQ ID NO 60
<211> LENGTH: 20
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 60

ccgccggatc caccgagagc

<210> SEQ ID NO 61
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

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tgatcagat gcgccggagagc

<210> SEQ ID NO 62
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 62
ggagagagat gaaagagttg

<210> SEQ ID NO 63
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 63
cgagattttg ccgagagcaag

<210> SEQ ID NO 64
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 64
tgcstctgcc gtgccgcagcag

<210> SEQ ID NO 65
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 65
acttgtagtc tgtgttggtc

<210> SEQ ID NO 66
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 66
asgtcgaga aagcgctttgac

<210> SEQ ID NO 67
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 67
gcactttttg ccagggcccg

<210> SEQ ID NO 68
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 68
cctcctcctl agcactttttgc

<210> SEQ ID NO 69
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 69
aactgcaag ctcttttgtgg

<210> SEQ ID NO 70
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 70
atgactctg gtgccacca

<210> SEQ ID NO 71
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 71
ctagggagc caccagccaa
<210> SEQ ID NO 72
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 72
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<210> SEQ ID NO 73
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 73
ttccagcagg ttccagaggqg

<210> SEQ ID NO 74
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 74
ttctgcaagg ttgcagcaag

<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 75
ttctgcaqac aggcaactqg

<210> SEQ ID NO 76
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 76
agaaggagcc caatctcgca

<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 77
tgcccacagg acaagcagg

<210> SEQ ID NO 78
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 78

tggactctc tgccacccc

<210> SEQ ID NO: 79
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 79

tggacrcaac tgtccgacac

<210> SEQ ID NO: 80
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 80

acatggacat tgcgcacata

<210> SEQ ID NO: 81
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 81

tttccatgc acatgggagt

<210> SEQ ID NO: 82
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 82

gttgaggac atttccatgc

<210> SEQ ID NO: 83
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 83

cacggtgcc acatggagtc

<210> SEQ ID NO: 84
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 84
agatgtctgc gtttgctagc
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<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 85
tataacttt ttagagagtg
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<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 86	tacaagtgg tctgggctg
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<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 87 agctotgtag ttcagttacc
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<210> SEQ ID NO 88
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 88
gttcagttgcttggctg
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<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 89
cagcaaccgc tgggtacagg
20

<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 90 agaaqgtgtgctggtgaga
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<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 92
cctttgagctcgggcgctg

<210> SEQ ID NO 93
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TYPE: DNA
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SEQUENCE: 173
acggaagtc ctccacgtga

SEQ ID NO: 174
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 174
cacctctcag acggaagtc

SEQ ID NO: 175
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 175
tgacctggt caccgtagag

SEQ ID NO: 176
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 176
tgtgtgcac tcgtcaacgt

SEQ ID NO: 177
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 177
ggtgtgtggt acactggtca

SEQ ID NO: 178
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 178
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gcgtggc\ acctt\tgttt

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acgcaagc tggcccggc

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- `agcccgttgt gtcattgctg` 20
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<210> SEQ ID NO 299
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<210> SEQ ID NO 305
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<210> SEQ ID NO 314
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<210> SEQ ID NO 317
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<400> SEQUENCE: 317
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<210> SEQ ID NO 318
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<400> SEQUENCE: 319
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<212> TYPE: DNA
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<400> SEQUENCE: 328
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<210> SEQ ID NO 338
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<400> SEQUENCE: 338

agagatgtt ggcgggtgta 20

<210> SEQ ID NO 339
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<400> SEQUENCE: 339

gccagtgtg tcaattgctg 20

<210> SEQ ID NO 340
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<212> TYPE: DNA
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<400> SEQUENCE: 340

aagaagttga tcagagatggc 20

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

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<210> SEQ ID NO 342
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<400> SEQUENCE: 342

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<400> SEQUENCE: 343

acacgaacg gtgtgcaact 20

<210> SEQ ID NO 344
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gggcagcag ctcaggttgtg  20

<210> SEQ ID NO 351
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<210> SEQ ID NO 352
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<212> TYPE: DNA
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<210> SEQ ID NO 353
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 353
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<210> SEQ ID NO 354
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<210> SEQ ID NO 355
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<400> SEQUENCE: 355
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<210> SEQ ID NO 356
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<212> TYPE: DNA
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<400> SEQUENCE: 356
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<400> SEQUENCE: 357

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<210> SEQ ID NO 358
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 358

gaacacgaag cgtgttgca 20

<210> SEQ ID NO 359
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<400> SEQUENCE: 359

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<400> SEQUENCE: 360

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<400> SEQUENCE: 361

aggaatactt gttgaaagt 20

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<400> SEQUENCE: 362

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<212> TYPE: DNA
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<400> SEQUENCE: 363

aggsagagc cgagagagag
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<212> TYPE: DNA
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<400> SEQUENCE: 364

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<400> SEQUENCE: 365

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<210> SEQ ID NO: 366
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<400> SEQUENCE: 366

asgcccgtgt tgtcattgct
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<210> SEQ ID NO: 367
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<400> SEQUENCE: 367

atgcctctgg gcaagctagct
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<210> SEQ ID NO: 368
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<400> SEQUENCE: 368

catacctctg gacgctgctgt
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<210> SEQ ID NO: 369
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acctotcasa cggaaagtcc

<210> SEQ ID NO 370
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<400> SEQUENCE: 370
gcatctcttg asacgcagcc

<210> SEQ ID NO 371
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<400> SEQUENCE: 371
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<210> SEQ ID NO 372
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<400> SEQUENCE: 372
cgaaagccc atgtctgtcat

<210> SEQ ID NO 373
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<212> TYPE: DNA
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<400> SEQUENCE: 373
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<210> SEQ ID NO 374
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 374
tgtacggygt cttgacagcc

<210> SEQ ID NO 375
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 375
ggcacacgc agttgtgcag
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<210> SEQ ID NO 376
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 376
tactacacttggaagttgct

<210> SEQ ID NO 377
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 377
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<210> SEQ ID NO 378
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 378
aaccaggaag tocatacactt

<210> SEQ ID NO 379
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 379
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<210> SEQ ID NO 380
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 380
tgtactaga tggccaggaa

<210> SEQ ID NO 381
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 381
agcggtggtg cactttgtgg

<210> SEQ ID NO 382
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<210> SEQ ID NO 383
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 382

GCTGGCCGCGC gCGC gCGC gCGC 20

<210> SEQ ID NO: 383
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 383

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<213> ORGANISM: M. musculus
<220> FEATURE:

<400> SEQUENCE: 402

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<212> TYPE: DNA
<213> ORGANISM: M. musculus
<220> FEATURE:

<400> SEQUENCE: 403

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 404

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<210> SEQ ID NO: 405
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 405

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<210> SEQ ID NO: 405
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 406

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<400> SEQUENCE: 407
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<210> SEQ ID NO 408
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 408
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<210> SEQ ID NO 409
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<400> SEQUENCE: 409
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<210> SEQ ID NO 410
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 410
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<210> SEQ ID NO 411
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 411
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<210> SEQ ID NO 412
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<400> SEQUENCE: 412
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 413

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<210> SEQ ID NO 414
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<400> SEQUENCE: 414

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<210> SEQ ID NO 415
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<400> SEQUENCE: 415

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<210> SEQ ID NO 416
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<212> TYPE: DNA
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<400> SEQUENCE: 416

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<210> SEQ ID NO 417
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<400> SEQUENCE: 417

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<210> SEQ ID NO 418
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<400> SEQUENCE: 418

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aagagcttgc tggagcagcag 20

<210> SEQ ID NO: 420
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<400> SEQUENCE: 420
tagagaacag ccaccaagcag 20

<210> SEQ ID NO: 421
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 421
ggasacagt gaagacgacc 20

<210> SEQ ID NO: 422
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 422
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<210> SEQ ID NO: 423
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 423
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<210> SEQ ID NO: 424
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 424
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<210> SEQ ID NO: 425
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 425
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 426
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<210> SEQ ID NO 427
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 427
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<210> SEQ ID NO 428
<211> LENGTH: 20
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 428
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<210> SEQ ID NO 429
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 429
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<210> SEQ ID NO 430
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 430
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<210> SEQ ID NO 431
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 431
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<210> SEQ ID NO 432
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 432
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<210> TYPE: DNA
<211> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 432

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<210> SEQ ID NO 433
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 433
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<210> SEQ ID NO 434
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 434

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<210> SEQ ID NO 435
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 435
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<210> SEQ ID NO 436
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 436

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<210> SEQ ID NO 437
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 437
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<210> SEQ ID NO 438
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 438
ctctotgagg cccagcagga

<210> SEQ ID NO 439
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 439
acagagccag cctgtgagcc

<210> SEQ ID NO 440
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 440
actgtgggca ctctgaggcc

<210> SEQ ID NO 441
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 441
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<210> SEQ ID NO 442
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 442
atgagctgactgcatgt

<210> SEQ ID NO 443
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 443
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<210> SEQ ID NO 444
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide
<400> SEQUENCE: 444
tcattgctgg tccagcactg
<210> SEQ ID NO 445
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 445

gacaggaata cgcaagatcc

<210> SEQ ID NO 446
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 446
cgcagcttg gcacaagag

<210> SEQ ID NO 447
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 447
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<210> SEQ ID NO 448
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 448
gcatatgca tctgatgggc

<210> SEQ ID NO 449
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 449
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<210> SEQ ID NO 450
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 450
cctggaggg agctgagga
<210> SEQ ID NO 452
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 452

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<210> SEQ ID NO 453
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 453

gagctttgcc ttcctgcacat

<210> SEQ ID NO 454
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 454

tttctctcctg asgagcttttg

<210> SEQ ID NO 455
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 455

gctgaagttt ctcacaggga

<210> SEQ ID NO 456
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 456

tgcttgcact ctaagctgca
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acagocaytc ccactgtgctc

<210> SEQ ID NO 458
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 459
ccttgggag cttcaggtggg

<210> SEQ ID NO 459
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 460
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<210> SEQ ID NO 460
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 461
gcccttttgc gasacacaacc

<210> SEQ ID NO 461
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 462
atctggctct ggtyggctct

<210> SEQ ID NO 462
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 463
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acagctgtgc tgcttctgtg

agacctgtgcc aggtcaggac

gtttctcaat ctcatacaac

aacatacga gttcattagat

ctggaacta ctcagacgtc

ctgggaacca ctcagagttc
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antisense Oligonucleotide

<400> SEQUENCE: 470

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ORGANISM:  H. sapiens
FEATURE:

SEQUENCE:  650
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SEQ ID NO 651
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ORGANISM:  H. sapiens
FEATURE:

SEQUENCE:  651
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SEQ ID NO 652
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ORGANISM:  H. sapiens
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SEQUENCE:  652
caataccacg gccacaacct
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SEQ ID NO 653
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ORGANISM:  H. sapiens
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SEQUENCE:  653
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SEQ ID NO 654
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ORGANISM:  H. sapiens
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SEQUENCE:  654
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SEQ ID NO 655
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SEQUENCE: 664
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SEQ ID NO 665
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TYPE: DNA
ORGANISM: H. sapiens

SEQUENCE: 665
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SEQ ID NO 666
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens

SEQUENCE: 666
cctcgctcc ggtcgatcgc

SEQ ID NO 667
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens

SEQUENCE: 667
gtgccggcgg tgytctgca

SEQ ID NO 668
LENGTH: 20
TYPE: DNA
ORGANISM: H. sapiens

SEQUENCE: 668
gcacacactg ctggcoccg

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gtcaggtgcttaac 20

<210> SEQ ID NO 815


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LENGTH: 20
TYPE: DNA
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FEATURE:

SEQUENCE: 815

tcatgagccc tgggcttgg

SEQ ID NO 816
LENGTH: 20
TYPE: DNA
ORGANISM: M. musculus
FEATURE:

SEQUENCE: 816
cgtgcctctc gcgccctgag

SEQ ID NO 817
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 817
cgtcagccc tctgggtttga

SEQ ID NO 818
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 819
cctttctgta gctttctctc

SEQ ID NO 819
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 819
gcgtttccos gttttgacct

SEQ ID NO 820
LENGTH: 20
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
NAME/KEY: unsure
LOCATION: (i) ...(20)
OTHER INFORMATION: Antisense Oligonucleotide

SEQUENCE: 820

nnnnnnnnnn nnnnnnnnnn

SEQ ID NO 821
LENGTH: 16
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
-continued

400> SEQUENCE: 821
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  cacgagctg gcctcag 18

400> SEQUENCE: 823
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400> SEQUENCE: 824
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400> SEQUENCE: 825
  cgagagccgc agggaccctt 21

400> SEQUENCE: 826
  cgacccguc acgcuucqctt 21

400> SEQUENCE: 827

What is claimed is:

1. A compound comprising 8 to 80 nucleobases targeted to the region comprising nucleotides 951 to 985 of SEQ ID NO: 4.
2. The compound of claim 1 which comprises at least an 8-nucleobase portion of SEQ ID NO: 203, 384, 261, 329, 204, 249, 390, 371, 292, 205, 128, 57.
3. The compound of claim 1 which consists of SEQ ID NO: 203, 384, 261, 329, 204, 249, 390, 371, 292, 205, 128, 57.
4. The compound of claim 1 which is at least 70% complementary to SEQ ID NO: 4.
5. The compound of claim 1 which is at least 80% complementary to SEQ ID NO: 4.
6. The compound of claim 1 which is at least 90% complementary to SEQ ID NO: 4.
7. The compound of claim 1 which is at least 95% complementary to SEQ ID NO: 4.
8. The compound of claim 1 which is 12 to 50 nucleobases in length.
9. The compound of claim 1 which is 15 to 30 nucleobases in length.
10. The compound of claim 1 which is 20 nucleobases in length.
11. The compound of claim 1 comprising an oligonucleotide.
12. The compound of claim 11, wherein the oligonucleotide is DNA.
13. The compound of claim 11, wherein the oligonucleotide is RNA.
14. The compound of claim 11, wherein the oligonucleotide is chimeric.
15. The compound of claim 11, wherein at least a portion of said compound hybridizes with RNA to form an oligonucleotide-RNA duplex.
16. The compound of claim 11, wherein the oligonucleotide is single-stranded.
17. The compound of claim 1 comprising at least one chemical modification.
18. The compound of claim 17 comprising at least one modified internucleoside linkage, sugar moiety, or nucleobase.
19. The compound of claim 17 comprising at least one 2′-O-methoxyethyl sugar moiety.
20. The compound of claim 17 comprising at least one phosphorothiate internucleoside linkage.
21. The compound of claim 17 comprising at least one 5-methylcytosine.
22. The compound of claim 14, wherein every internucleoside linkage is a phosphorothiate linkage, nucleobases 1-5 and 16-20 comprise a 2′-O-methoxyethyl modification and every cytidine residue comprises a 5-methyl modification.
23. The compound of claim 1, wherein the compound is a sodium salt.
24. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutical carrier, diluent or excipient.
25. The composition of claim 24 comprising a colloidal dispersion system.
26. A kit or assay device comprising the compound of claim 1.
27. A method of inhibiting the expression of human glucagon receptor in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that expression of human glucagon receptor is inhibited.
28. A method of treating or delaying the onset of a disease or condition associated with glucagon receptor in a human comprising administering to said human a therapeutically or prophylactically effective amount of the compound of claim 1 so that expression of human glucagon receptor is inhibited.
29. The method of claim 28 wherein the disease or condition is a metabolic disease or condition.
30. The method of claim 29, wherein the disease or condition is diabetes, obesity or hyperglycemia.
31. The method of claim 30 wherein the blood glucose levels are plasma glucose levels.
32. The method of claim 29, wherein the disease or condition is Type 2 diabetes.
33. A method of decreasing blood glucose levels in a human comprising administering to said human the compound of claim 1.
34. The method of claim 31 wherein the blood glucose levels are plasma glucose levels.
35. The method of claim 31 wherein the human has diabetes or is obese.
36. A method of preventing or delaying the onset of an increase in blood glucose levels in a human comprising administering to said human the compound of claim 1.
37. The method of claim 33 wherein the human suffers from diabetes, obesity or insulin resistance.
38. The method of claim 33 wherein the blood glucose levels are plasma glucose levels.

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