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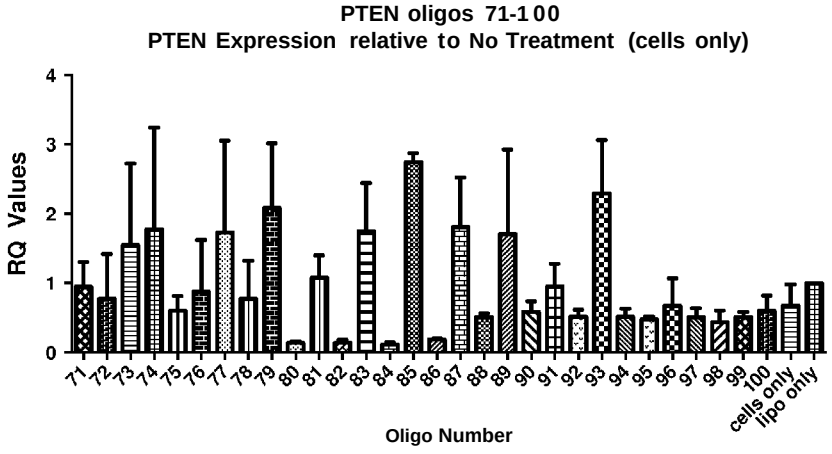

(57) Abstract: Aspects of the invention provide single stranded oligonucleotides for activating or enhancing expression of PTEN. Further aspects provide compositions and kits comprising single stranded oligonucleotides for activating or enhancing expression of PTEN. Methods for modulating expression of PTEN using the single stranded oligonucleotides are also provided. Further aspects of the invention provide methods for selecting a candidate oligonucleotide for activating or enhancing expression of PTEN.

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COMPOSITIONS AND METHODS FOR MODULATING PTEN EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/785,885, entitled "COMPOSITIONS AND METHODS FOR MODULATING PTEN EXPRESSION", filed March 14, 2013 and U.S. Provisional Application No. 61/648,041, entitled "COMPOSITIONS AND METHODS FOR MODULATING PTEN EXPRESSION", filed May 16, 2012, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to oligonucleotide based compositions, as well as methods of using oligonucleotide based compositions for treating disease.

BACKGROUND OF THE INVENTION

Cancer includes a multitude of diseases characterized by uncontrolled growth of cells in an individual, which can ultimately result in morbidity and mortality. In 2008, over 7.6 million people died from cancer worldwide, accounting for approximately 13% of all deaths in the world. Cancer is one of the highest priority public health concerns, with over 12 million cases in the United States alone causing an economic impact of over 225 billion dollars in direct and indirect medical costs.

Phosphatase and tensin homolog (PTEN) is one of the most common tumor suppressors involved in the development of cancer. PTEN controls cell growth and apoptosis, as well as genomic instability, cell migration, and metabolism. Mutations in the PTEN gene cause inactivation of PTEN protein and/or reduction in levels of PTEN protein, resulting in uncontrolled cell growth that leads to cancer. PTEN mutations occur at high frequency in many cancers, making it an important target for cancer treatment.

SUMMARY OF THE INVENTION

Aspects of the invention disclosed herein provide methods and compositions that are useful for upregulating PTEN in cells. In some embodiments, single stranded oligonucleotides are provided that target a PRC2-associated region of a PTEN gene (e.g.,

human PTEN) and thereby cause upregulation of the gene. In some embodiments, single stranded oligonucleotides are provided that target a PRC2-associated region of the gene encoding PTEN. In some embodiments, these single stranded oligonucleotides activate or enhance expression of PTEN by relieving or preventing PRC2 mediated repression of PTEN. Aspects of the invention disclosed herein, provide methods and compositions that are useful for upregulating certain tumor suppressor genes. In some embodiments, the methods and compositions for upregulating PTEN expression disclosed herein provide alternative approaches for treating cancer, such as prostate or breast cancer.

Further aspects of the invention provide methods for selecting oligonucleotides for activating or enhancing expression of PTEN. In some embodiments, methods are provided for selecting a set of oligonucleotides that is enriched in candidates *(e.g.,* compared with a random selection of oligonucleotides) for activating or enhancing expression of PTEN. Accordingly, the methods may be used to establish sets of clinical candidates that are enriched in oligonucleotides that activate or enhance expression of PTEN. Such libraries may be utilized, for example, to identify lead oligonucleotides for developing therapeutics to treat PTEN. Furthermore, in some embodiments, oligonucleotide chemistries are provided that are useful for controlling the pharmacokinetics, biodistribution, bioavailability and/or efficacy of the single stranded oligonucleotides for activating expression of PTEN.

According to some aspects of the invention single stranded oligonucleotides are provided that have a region of complementarity that is complementarty with *(e.g.,* at least 8 consecutive nucleotides of) a PRC2-associated region of a PTEN gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1 or 2. In some embodiments, the oligonucleotide has at least one of the following features: a) a sequence that is 5'X-Y-Z, in which X is any nucleotide and in which X is at the 5' end of the oligonucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length; b) a sequence that does not comprise three or more consecutive guanosine nucleotides; c) a sequence that has less than a threshold level of sequence identity with every sequence of nucleotides, of equivalent length to the second nucleotide sequence, that are between 50 kilobases upstream of a 5'-end of an off-target gene and 50 kilobases downstream of a 3'-end of the off-target gene; d) a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single

stranded loops; and e) a sequence that has greater than 60% G-C content. In some embodiments, the single stranded oligonucleotide has at least two of features a), b), c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has at least three of features a), b), c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has at least four of features a), b), c), d), and e), each independently selected. In some embodiments, the single stranded oligonucleotide has each of features a), b), c), d), and e). In certain embodiments, the oligonucleotide has the sequence 5'X-Y-Z, in which the oligonucleotide is 8-50 nucleotides in length.

According to some aspects of the invention, single stranded oligonucleotides are provided that have a sequence X-Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed sequence of a human microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length, in which the single stranded oligonucleotide is complementary with a PRC2-associated region of a PTEN gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1 or 2. In some aspects of the invention, single stranded oligonucleotides are provided that have a sequence 5'-X-Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed sequence of a human microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length, in which the single stranded oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of a PTEN gene, e.g., a PRC2-associated region of the nucleotide sequence set forth as SEQ ID NO: 1 or 2. In some embodiments, Y is a sequence selected from Table 1. In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 5 to 148.

In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 89025, or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 89025, in which the 5' end of the nucleotide sequence provided is the 5' end of the oligonucleotide. In some embodiments, the region of complementarity *(e.g.,* the at least 8 consecutive nucleotides) is also present within the nucleotide sequence set forth as SEQ ID NO: 3 or 4.

In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 89025. In some embodiments, the

single stranded oligonucleotide comprises a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 89025.

In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 5 to 118. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 63340, 89008 to 89021, or 89024 to 89025 or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 149 to 63340, 89008 to 89021, or 89024 to 89025, wherein the 5' end of the nucleotide sequence provided in any one of SEQ ID NOS: 149 to 63340, 89008 to 89021, or 89024 to 89025 is the 5' end of the oligonucleotide. In some embodiments, the at least 8 consecutive nucleotides are also present within the nucleotide sequence set forth as SEQ ID NO: 3.

In some embodiments, the PRC2-associated region is a sequence listed in any one of SEQ ID NOS: 119 to 148. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 63196 to 89007 or 89020 to 89025 or a fragment thereof that is at least 8 nucleotides. In some embodiments, the single stranded oligonucleotide comprises a nucleotide sequence as set forth in any one of SEQ ID NOS: 63196 to 89007 or 89020 to 89025, wherein the 5' end of the nucleotide sequence provided in any one of SEQ ID NOS: 63196 to 89007 or 89020 to 89025 is the 5' end of the oligonucleotide. In some embodiments, the at least 8 consecutive nucleotides are present within the nucleotide sequence set forth as SEQ ID NO: 4.

In some embodiments, a single stranded oligonucleotide comprises a nucleotide sequence as set forth in Table 4. In some embodiments, the single stranded oligonucleotide comprises a fragment of at least 8 nucleotides of a nucleotide sequence as set forth in Table 4. In some embodiments, a single stranded oligonucleotide consists of a nucleotide sequence as set forth in Table 4.

In some embodiments, the single stranded oligonucleotide does not comprise three or more consecutive guanosine nucleotides. In some embodiments, the single stranded oligonucleotide does not comprise four or more consecutive guanosine nucleotides.

In some embodiments, the single stranded oligonucleotide is 8 to 30 nucleotides in length. In some embodiments, the single stranded oligonucleotide is up to 50 nucleotides in

length. In some embodiments, the single stranded oligonucleotide is 8 to 10 nucleotides in length and all but 1, 2, or 3 of the nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides.

In some embodiments, the single stranded oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of a PTEN gene, e.g., a PRC2-associated region of a nucleotide sequence set forth as SEQ ID NO: 1 or 2, in which the nucleotide sequence of the single stranded oligonucleotide comprises one or more of a nucleotide sequence selected from the group consisting of

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

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

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

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

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

(f) XXXXXX, XxXXXXX, XXxXXXX, XXXxXXX, XXXXxXX, XXXXXxX and XXXXXXx, wherein "X" denotes a nucleotide analogue, (X) denotes an optional nucleotide analogue, and "x" denotes a DNA or RNA nucleotide unit.In some embodiments, at least one nucleotide of the oligonucleotide is a nucleotide analogue. In some embodiments, the at least one nucleotide analogue results in an increase in Tm of the oligonucleotide in a range of 1 to 5 °C compared with an oligonucleotide that does not have the at least one nucleotide analogue.

In some embodiments, at least one nucleotide of the oligonucleotide comprises a 2' O-methyl. In some embodiments, each nucleotide of the oligonucleotide comprises a 2' O-methyl. In some embodiments, the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, or at least one bridged nucleotide. In some embodiments, the

bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide. In some embodiments, each nucleotide of the oligonucleotide is a LNA nucleotide.

In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-0-methyl nucleotides. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and ENA nucleotide analogues. In some embodiments, the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and LNA nucleotides. In some embodiments, the 5' nucleotide of the oligonucleotide is a deoxyribonucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise alternating LNA nucleotides and 2'-0-methyl nucleotides. In some embodiments, the 5' nucleotide of the oligonucleotide is a LNA nucleotide. In some embodiments, the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one LNA nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides.

In some embodiments, the single stranded oligonucleotide comprises modified internucleotide linkages *(e.g.,* phosphorothioate internucleotide linkages or other linkages) between at least two, at least three, at least four, at least five or more nucleotides. In some embodiments, the single stranded oligonucleotide comprises modified internucleotide linkages *(e.g.,* phosphorothioate internucleotide linkages or other linkages) between between all nucleotides.

In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group. In some embodiments, the nucleotide at the 3' position of the oligonucleotide has a 3' thiophosphate. In some embodiments, the single stranded oligonucleotide has a biotin moiety or other moiety conjugated to its 5' or 3' nucleotide. In some embodiments, the single stranded oligonucleotide has cholesterol, Vitamin A, folate, sigma receptor ligands, aptamers, peptides, such as CPP, hydrophobic molecules, such as lipids, ASGPR or dynamic polyconjugates and variants thereof at its 5' or 3' end.

According to some aspects of the invention compositions are provided that comprise any of the oligonucleotides disclosed herein, and a carrier. In some embodiments, compositions are provided that comprise any of the oligonucleotides in a buffered solution. In some embodiments, the oligonucleotide is conjugated to the carrier. In some embodiments, the carrier is a peptide. In some embodiments, the carrier is a steroid. According to some

aspects of the invention pharmaceutical compositions are provided that comprise any of the oligonucleotides disclosed herein, and a pharmaceutically acceptable carrier.

According to other aspects of the invention, kits are provided that comprise a container housing any of the compositions disclosed herein.

According to some aspects of the invention, methods of increasing expression of PTEN in a cell are provided. In some embodiments, the methods involve delivering any one or more of the single stranded oligonucleotides disclosed herein into the cell. In some embodiments, delivery of the single stranded oligonucleotide into the cell results in a level of expression of PTEN that is greater *(e.g.,* at least 50% greater) than a level of expression of PTEN in a control cell that does not comprise the single stranded oligonucleotide.

According to some aspects of the invention, methods of increasing levels of PTEN in a subject are provided. According to some aspects of the invention, methods of treating a condition *(e.g.,* cancer) associated with decreased levels of PTEN in a subject are provided. In some embodiments, the methods involve administering any one or more of the single stranded oligonucleotides disclosed herein to the subject.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a graph depecting the level of PTEN expression in HepG2 cells treated with oligos relative to cells receiving no oligos. The PTEN expression was measured by pRTPCR for oligos named PTEN-41 to PTEN-70 as set forth in Table 4. The oligo concentration was 30 nM and the time of the experiment was 48 hours. The housekeeping gene used for the qRTPCR control was PPIB.

FIG. 2 is a graph depecting the level of PTEN expression in HepG2 cells treated with oligos relative to cells receiving no oligos. The PTEN expression was measured by pRTPCR for oligos named PTEN-71 to PTEN-100 as set forth in Table 4. The oligo concentration was 30 nM and the time of the experiment was 48 hours. The housekeeping gene used for the qRTPCR control was PPIB.

BRIEF DESCRIPTION OF TABLES

Table 1: Hexamers that are not seed sequences of human miRNAs

Table 2: Oligonucleotide sequences made for testing in the lab. RQ (column 3) and RQ SE (column 4) shows the activity of the oligo relative to a control well (usually carrier

alone) and the standard error or the triplicate replicates of the experiment. [oligo] is shown in nanomolar for in vitro experiments and in milligrams per kilogram of body weight for in vivo experiments. The sequence of each oligonucleotide, including any modified nucleotides, is shown in Table 4.

Table 3: A listing of oligonucleotide modifications

Table 4: Formatted oligonucleotide sequences made for testing showing nucleotide modifications. The table shows the sequence of the modified nucleotides, where InaX represents an LNA nucleotide with 3' phosphorothioate linkage, omeX is a 2'-**0**-methyl nucleotide, dX is a deoxy nucleotide. An s at the end of a nucleotide code indicates that the nucleotide had a 3' phosphorothioate linkage. The "-Sup" at the end of the sequence marks the fact that the 3' end lacks either a phosphate or thiophosphate on the 3' linkage. The Formatted Sequence column shows the sequence of the oligonucleotide, including modified nucleotides, for the oligonucleotides tested in Table 2.

Table 5: Cell lines

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

Aspects of the invention provided herein relate to the discovery of polycomb repressive complex 2 (PRC2)-interacting RNAs. Polycomb repressive complex 2 (PRC2) is a histone methyltransferase and a known epigenetic regulator involved in silencing of genomic regions through methylation of histone H3. Among other functions, PRC2 interacts with long noncoding RNAs (IncRNAs), such as RepA, Xist, and Tsix, to catalyze trimethylation of histone H3-lysine27. PRC2 contains four subunits, Eed, Suzl2, RbAp48, and Ezh2. Aspects of the invention relate to the recognition that single stranded oligonucleotides that bind to PRC2-associated regions of RNAs *(e.g.,* IncRNAs) that are expressed from within a genomic region that encompasses or that is in functional proximity to the PTEN gene can induce or enhance expression of PTEN. In some embodiments, this upregulation is believed to result from inhibition of PRC2 mediated repression of PTEN.

As used herein, the term "PRC2-associated region" refers to a region of a nucleic acid that comprises or encodes a sequence of nucleotides that interact directly or indirectly with a component of PRC2. A PRC2-associated region may be present in a RNA *(e.g.,* a long non-coding RNA (IncRNA)) that that interacts with a PRC2. A PRC2-associated region may be

present in a DNA that encodes an RNA that interacts with PRC2. In some cases, the PRC2-associated region is equivalently referred to as a PRC2-interacting region.

In some embodiments, a PRC2-associated region is a region of an RNA that crosslinks to a component of PRC2 in response to *in situ* ultraviolet irradiation of a cell that expresses the RNA, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that immunoprecipitates with an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that immunoprecipitates with an antibody that binds specifically to SUZ12, EED, EZH2 or RBBP4 (which as noted above are components of PRC2), or a region of genomic DNA that encodes that RNA region.

In some embodiments, a PRC2-associated region is a region of an RNA that is protected from nucleases *(e.g.,* RNases) in an RNA-immunoprecipitation assay that employs an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that protected RNA region. In some embodiments, a PRC2-associated region is a region of an RNA that is protected from nucleases *(e.g.,* RNases) in an RNA-immunoprecipitation assay that employs an antibody that targets SUZ12, EED, EZH2 or RBBP4, or a region of genomic DNA that encodes that protected RNA region.

In some embodiments, a PRC2-associated region is a region of an RNA within which occur a relatively high frequency of sequence reads in a sequencing reaction of products of an RNA-immunoprecipitation assay that employs an antibody that targets a component of PRC2, or a region of genomic DNA that encodes that RNA region. In some embodiments, a PRC2-associated region is a region of an RNA within which occur a relatively high frequency of sequence reads in a sequencing reaction of products of an RNA-immunoprecipitation assay that employs an antibody that binds specifically to SUZ12, EED, EZH2 or RBBP4, or a region of genomic DNA that encodes that protected RNA region. In such embodiments, the PRC2-associated region may be referred to as a "peak."

In some embodiments, a PRC2-associated region comprises a sequence of 40 to 60 nucleotides that interact with PRC2 complex. In some embodiments, a PRC2-associated region comprises a sequence of 40 to 60 nucleotides that encode an RNA that interacts with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of up to 5kb in length that comprises a sequence *(e.g.,* of 40 to 60 nucleotides) that interacts with

PRC2. In some embodiments, a PRC2-associated region comprises a sequence of up to 5kb in length within which an RNA is encoded that has a sequence *(e.g.*, of 40 to 60 nucleotides) that is known to interact with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of about 4kb in length that comprise a sequence *(e.g.*, of 40 to 60 nucleotides) that interacts with PRC2. In some embodiments, a PRC2-associated region comprises a sequence of about 4kb in length within which an RNA is encoded that includes a sequence *(e.g.*, of 40 to 60 nucleotides) that is known to interact with PRC2. In some embodiments, a PRC2-associated region has a sequence as set forth in any one of SEQ ID NOS: 5 to 148.

In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region in a genomic region that encompasses or that is in proximity to the PTEN gene. In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region that has a sequence as set forth in any one of SEQ ID NOS: 5 to 148. In some embodiments, single stranded oligonucleotides are provided that specifically bind to, or are complementary to, a PRC2-associated region that has a sequence as set forth in any one of SEQ ID NOS: 5 to 148 combined with up to 2kb, up to 5kb, or up to lOkb of flanking sequences from a corresponding genomic region to which these SEQ IDs map (e.g., in a human genome). In some embodiments, single stranded oligonucleotides have a sequence as set forth in any one of SEQ ID NOS: 149 to 89025. In some embodiments, single stranded oligonucleotides have a sequence as set forth in Table 4.

Without being bound by a theory of invention, these oligonucleotides are able to interfere with the binding of and function of PRC2, by preventing recruitment of PRC2 to a specific chromosomal locus. For example, a single administration of single stranded oligonucleotides designed to specifically bind a PRC2-associated region IncRNA can stably displace not only the IncRNA, but also the PRC2 that binds to the IncRNA, from binding chromatin. After displacement, the full complement of PRC2 is not recovered for up to 24 hours. Further, IncRNA can recruit PRC2 in a cis fashion, repressing gene expression at or near the specific chromosomal locus from which the IncRNA was transcribed.

Methods of modulating gene expression are provided, in some embodiments, that may be carried out *in vitro, ex vivo,* or *in vivo.* It is understood that any reference to uses of compounds throughout the description contemplates use of the compound in preparation of a

pharmaceutical composition or medicament for use in the treatment of condition *(e.g.,* cancer) associated with decreased levels or activity of PTEN. Thus, as one nonlimiting example, this aspect of the invention includes use of such single stranded oligonucleotides in the preparation of a medicament for use in the treatment of disease, wherein the treatment involves upregulating expression of PTEN.

In further aspects of the invention, methods are provided for selecting a candidate oligonucleotide for activating expression of PTEN. The methods generally involve selecting as a candidate oligonucleotide, a single stranded oligonucleotide comprising a nucleotide sequence that is complementary to a PRC2-associated region *(e.g.,* a nucleotide sequence as set forth in any one of SEQ ID NOS: 5 to 148). In some embodiments, sets of oligonucleotides may be selected that are enriched *(e.g.,* compared with a random selection of oligonucleotides) in oligonucleotides that activate expression of PTEN.

Single Stranded Oligonucleotides for Modulating Expression of PTEN

In one aspect of the invention, single stranded oligonucleotides complementary to the PRC2-associated regions are provided for modulating expression of PTEN in a cell. In some embodiments, expression of PTEN is upregulated or increased. In some embodiments, single stranded oligonucleotides complementary to these PRC2-associated regions inhibit the interaction of PRC2 with long RNA transcripts such that gene expression is upregulated or increased. In some embodiments, single stranded oligonucleotides complementary to these PRC2-associated regions inhibit the interaction of PRC2 with long RNA transcripts, resulting in reduced methylation of histone H3 and reduced gene inactivation, such that gene expression is upregulated or increased. In some embodiments, this interaction may be disrupted or inhibited due to a change in the structure of the long RNA that prevents or reduces binding to PRC2. The oligonucleotide may be selected using any of the methods disclosed herein for selecting a candidate oligonucleotide for activating expression of PTEN.

The single stranded oligonucleotide may comprise a region of complementarity that is complementary with a PRC2-associated region of a nucleotide sequence set forth in any one of SEQ ID NOS: 1 to 4. The region of complementarity of the single stranded oligonucleotide may be complementary with at least 6, *e.g.,* at least 7, at least 8, at least 9, at least 10, at least 15 or more consecutive nucleotides of the PRC2-associated region.

The PRC2-associated region may map to a position in a chromosome between 50 kilobases upstream of a 5'-end of the PTEN gene and 50 kilobases downstream of a 3'-end of the PTEN gene. The PRC2-associated region may map to a position in a chromosome between 25 kilobases upstream of a 5'-end of the PTEN gene and 25 kilobases downstream of a 3'-end of the PTEN gene. The PRC2-associated region may map to a position in a chromosome between 12 kilobases upstream of a 5'-end of the PTEN gene and 12 kilobases downstream of a 3'-end of the PTEN gene. The PRC2-associated region may map to a position in a chromosome between 5 kilobases upstream of a 5'-end of the PTEN gene and 5 kilobases downstream of a 3'-end of the PTEN gene.

The genomic position of the selected PRC2-associated region relative to the PTEN gene may vary. For example, the PRC2-associated region may be upstream of the 5' end of the PTEN gene. The PRC2-associated region may be downstream of the 3' end of the PTEN gene. The PRC2-associated region may be within an intron of the PTEN gene. The PRC2-associated region may be within an exon of the PTEN gene. The PRC2-associated region may traverse an intron-exon junction, a 5'-UTR-exon junction or a 3'-UTR-exon junction of the PTEN gene.

The single stranded oligonucleotide may comprise a sequence having the formula X-Y-Z, in which X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of varying length. In some embodiments X is the 5' nucleotide of the oligonucleotide. In some embodiments, when X is anchored at the 5' end of the oligonucleotide, the oligonucleotide does not have any nucleotides or nucleotide analogs linked 5' to X. In some embodiments, other compounds such as peptides or sterols may be linked at the 5' end in this embodiment as long as they are not nucleotides or nucleotide analogs. In some embodiments, the single stranded oligonucleotide has a sequence 5'X-Y-Z and is 8-50 nucleotides in length. Oligonucleotides that have these sequence characteristics are predicted to avoid the miRNA pathway. Therefore, in some embodiments, oligonucleotides having these sequence characteristics are unlikely to have an unintended consequence of functioning in a cell as a miRNA molecule. The Y sequence may be a nucleotide sequence of 6 nucleotides in length set forth in Table 1.

The single stranded oligonucleotide may have a sequence that does not contain guanosine nucleotide stretches *(e.g.,* 3 or more, 4 or more, 5 or more, 6 or more consecutive

guanosine nucleotides). In some embodiments, oligonucleotides having guanosine nucleotide stretches have increased non-specific binding and/or off-target effects, compared with oligonucleotides that do not have guanosine nucleotide stretches.

The single stranded oligonucleotide may have a sequence that has less than a threshold level of sequence identity with every sequence of nucleotides, of equivalent length, that map to a genomic position encompassing or in proximity to an off-target gene. For example, an oligonucleotide may be designed to ensure that it does not have a sequence that maps to genomic positions encompassing or in proximity with all known genes *(e.g.,* all known protein coding genes) other than PTEN. In a similar embodiment, an oligonucleotide may be designed to ensure that it does not have a sequence that maps to any other known PRC2-associated region, particularly PRC2-associated regions that are functionally related to any other known gene *(e.g.,* any other known protein coding gene). In either case, the oligonucleotide is expected to have a reduced likelihood of having off-target effects. The threshold level of sequence identity may be 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99% or 100% sequence identity.

The single stranded oligonucleotide may have a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single stranded loops. In has been discovered that, in some embodiments, oligonucleotides that are complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising one or more single stranded loops *(e.g.,* at least two single stranded loops) have a greater likelihood of being active *(e.g.,* of being capable of activating or enhancing expression of a target gene) than a randomly selected oligonucleotide. In some cases, the secondary structure may comprise a double stranded stem between the at least two single stranded loops. Accordingly, the region of complementarity between the oligonucleotide and the PRC2-associated region may be at a location of the PRC2 associated region that encodes at least a portion of at least one of the loops. In some cases, the region of complementarity between the oligonucleotide and the PRC2-associated region may be at a location of the PRC2-associated region that encodes at least a portion of at least two of the loops. In some cases, the region of complementarity between the oligonucleotide and the PRC2-associated region may be at a location of the PRC2 associated region that encodes at least a portion of the double stranded stem. In some embodiments, a PRC2-associated region *(e.g.,* of an IncRNA) is identified *(e.g.,* using RIP-

Seq methodology or information derived therefrom). In some embodiments, the predicted secondary structure RNA *(e.g.*, IncRNA) containing the PRC2-associated region is determined using RNA secondary structure prediction algorithms, *e.g.*, RNAfold, mfold. In some embodiments, oligonucleotides are designed to target a region of the RNA that forms a secondary structure comprising one or more single stranded loop *(e.g.*, at least two single stranded loops) structures which may comprise a double stranded stem between the at least two single stranded loops.

The single stranded oligonucleotide may have a sequence that is has greater than 30% G-C content, greater than 40% G-C content, greater than 50% G-C content, greater than 60% G-C content, greater than 70% G-C content, or greater than 80% G-C content. The single stranded oligonucleotide may have a sequence that has up to 100% G-C content, up to 95% G-C content, up to 90% G-C content, or up to 80% G-C content. In some embodiments in which the oligonucleotide is 8 to 10 nucleotides in length, all but 1, 2, 3, 4, or 5 of the nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides. In some embodiments, the sequence of the PRC2-associated region to which the single stranded oligonucleotide is complementary comprises no more than 3 nucleotides selected from adenine and uracil.

The single stranded oligonucleotide may be complementary to a chromosome of a different species *(e.g.*, a mouse, rat, rabbit, goat, monkey, *etc.)* at a position that encompasses or that is in proximity to that species' homolog of PTEN. The single stranded oligonucleotide may be complementary to a human genomic region encompassing or in proximity to the PTEN gene and also be complementary to a mouse genomic region encompassing or in proximity to the mouse homolog of PTEN. For example, the single stranded oligonucleotide may be complementary to a sequence as set forth in SEQ ID NO: 1 or 2, which is a human genomic region encompassing or in proximity to the PTEN gene, and also be complementary to a sequence as set forth in SEQ ID NO: 3 or 4, which is a mouse genomic region encompassing or in proximity to the mouse homolog of the PTEN gene. Oligonucleotides having these characteristics may be tested *in vivo* or *in vitro* for efficacy in multiple species *(e.g.*, human and mouse). This approach also facilitates development of clinical candidates for treating human disease by selecting a species in which an appropriate animal exists for the disease.

In some embodiments, the region of complementarity of the single stranded oligonucleotide is complementary with at least 8 to 15, 8 to 30, 8 to 40, or 10 to 50, or 5 to 50, or 5 to 40 bases, ***e.g.,*** 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 consecutive nucleotides of a PRC2-associated region. In some embodiments, the region of complementarity is complementary with at least 8 consecutive nucleotides of a PRC2-associated region. In some embodiments the sequence of the single stranded oligonucleotide is based on an RNA sequence that binds to PRC2, or a portion thereof, said portion having a length of from 5 to 40 contiguous base pairs, or about 8 to 40 bases, or about 5 to 15, or about 5 to 30, or about 5 to 40 bases, or about 5 to 50 bases.

Complementary, as the term is used in the art, refers to the capacity for precise pairing between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the same position of PRC2-associated region, then the single stranded nucleotide and PRC2-associated region are considered to be complementary to each other at that position. The single stranded nucleotide and PRC2-associated region are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides that can hydrogen bond with each other through their bases. Thus, "complementary" is a term which is used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the single stranded nucleotide and PRC2-associated region. For example, if a base at one position of a single stranded nucleotide is capable of hydrogen bonding with a base at the corresponding position of a PRC2-associated region, then the bases are considered to be complementary to each other at that position. 100% complementarity is not required.

The single stranded oligonucleotide may be at least 80% complementary to (optionally one of at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% complementary to) the consecutive nucleotides of a PRC2-associated region. In some embodiments the single stranded oligonucleotide may contain 1, 2 or 3 base mismatches compared to the portion of the consecutive nucleotides of a PRC2-associated region. In some embodiments the single stranded oligonucleotide may have up to 3 mismatches over 15 bases, or up to 2 mismatches over 10 bases.

It is understood in the art that a complementary nucleotide sequence need not be 100% complementary to that of its target to be specifically hybridizable. In some embodiments, a complementary nucleic acid sequence for purposes of the present disclosure is specifically hybridizable when binding of the sequence to the target molecule *(e.g.,* IncRNA) interferes with the normal function of the target *(e.g.,* IncRNA) to cause a loss of activity *(e.g.,* inhibiting PRC2-associated repression with consequent up-regulation of gene expression) and there is a sufficient degree of complementarity to avoid non-specific binding of the sequence to non-target sequences under conditions in which avoidance of non-specific binding is desired, *e.g.,* under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the assays are performed under suitable conditions of stringency.

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

In some embodiments, the PRC2-associated region occurs on the same DNA strand as a gene sequence (sense). In some embodiments, the PRC2-associated region occurs on the opposite DNA strand as a gene sequence (anti-sense). Oligonucleotides complementary to a PRC2-associated region can bind either sense or anti-sense sequences. Base pairings may include both canonical Watson-Crick base pairing and non-Watson-Crick base pairing *(e.g.,* Wobble base pairing and Hoogsteen base pairing). It is understood that for complementary base pairings, adenosine-type bases (A) are complementary to thymidine-type bases (T) or uracil-type bases (U), that cytosine-type bases (C) are complementary to guanosine-type bases (G), and that universal bases such as 3-nitropyrrole or 5-nitroindole can hybridize to and are considered complementary to any A, C, U, or T. Inosine (I) has also been considered in the art to be a universal base and is considered complementary to any A, C, U or T.

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

nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a different pyrimidine nucleotide or vice versa. In some embodiments, any one or more thymidine (T) nucleotides (or modified nucleotide thereof) in a sequence provided herein, including a sequence provided in the sequence listing, may be suitably replaced with a uridine (U) nucleotide (or a modified nucleotide thereof) or vice versa.

In some embodiments, GC content of the single stranded oligonucleotide is preferably between about 30-60 %. Contiguous runs of three or more Gs or Cs may not be preferable in some embodiments. Accordingly, in some embodiments, the oligonucleotide does not comprise a stretch of three or more guanosine nucleotides.

In some embodiments, the single stranded oligonucleotide specifically binds to, or is complementary to an RNA that is encoded in a genome (e.g., a human genome) as a single contiguous transcript (e.g., a non-spliced RNA). In some embodiments, the single stranded oligonucleotide specifically binds to, or is complementary to an RNA that is encoded in a genome (e.g., a human genome), in which the distance in the genome between the 5'end of the coding region of the RNA and the 3' end of the coding region of the RNA is less than 1 kb, less than 2 kb, less than 3 kb, less than 4 kb, less than 5 kb, less than 7 kb, less than 8 kb, less than 9 kb, less than 10 kb, or less than 20 kb.

It is to be understood that any oligonucleotide provided herein can be excluded. For example, in some embodiments, an oligonucleotide does not comprise or consist of a sequence as set for in SEQ ID NOs: 89026 to 89028. In some embodiments, a single stranded oligonucleotide is not complementary to SEQ ID NO: 89029. In some embodiments, a single stranded oligonucleotide is not complementary to SEQ ID NO: 89030.

In some embodiments, it has been found that single stranded oligonucleotides disclosed herein may increase expression of mRNA corresponding to the gene by at least about 50% (i.e. 150% of normal or 1.5 fold), or by about 2 fold to about 5 fold. In some embodiments, expression may be increased by at least about 15 fold, 20 fold, 30 fold, 40 fold, 50 fold or 100 fold, or any range between any of the foregoing numbers. It has also been found that increased mRNA expression has been shown to correlate to increased protein expression.

In some or any of the embodiments of the oligonucleotides described herein, or processes for designing or synthesizing them, the oligonucleotides will upregulate gene

expression and may specifically bind or specifically hybridize or be complementary to the PRC2 binding RNA that is transcribed from the same strand as a protein coding reference gene. The oligonucleotide may bind to a region of the PRC2 binding RNA that originates within or overlaps an intron, exon, intron exon junction, 5' UTR, 3' UTR, a translation initiation region, or a translation termination region of a protein coding sense strand of a reference gene (refGene).

In some or any of the embodiments of oligonucleotides described herein, or processes for designing or synthesizing them, the oligonucleotides will upregulate gene expression and may specifically bind or specifically hybridize or be complementary to a PRC2 binding RNA that transcribed from the opposite strand (the antisense strand) of a protein coding reference gene. The oligonucleotide may bind to a region of the PRC2 binding RNA that originates within or overlaps an intron, exon, intron exon junction, 5' UTR, 3' UTR, a translation initiation region, or a translation termination region of a protein coding antisense strand of a reference gene

The oligonucleotides described herein may be modified, *e.g.,* comprise a modified sugar moiety, a modified internucleoside linkage, a modified nucleotide and/or combinations thereof. In addition, the oligonucleotides can exhibit one or more of the following properties: do not induce substantial cleavage or degradation of the target RNA; do not cause substantially complete cleavage or degradation of the target RNA; do not activate the RNAse H pathway; do not activate RISC; do not recruit any Argonaute family protein; are not cleaved by Dicer; do not mediate alternative splicing; are not immune stimulatory; are nuclease resistant; have improved cell uptake compared to unmodified oligonucleotides; are not toxic to cells or mammals; may have improved endosomal exit; do interfere with interaction of IncRNA with PRC2, preferably the Ezh2 subunit but optionally the Suzl2, Eed, RbAp46/48 subunits or accessory factors such as Jarid2; do decrease histone H3 lysine27 methylation and/or do upregulate gene expression.

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

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

Methodfor Selecting Candidate Oligonucleotides for Activating Expression ofPTEN

Methods are provided herein for selecting a candidate oligonucleotide for activating or enhancing expression of PTEN. The target selection methods may generally involve steps for selecting single stranded oligonucleotides having any of the structural and functional characteristics disclosed herein. Typically, the methods involve one or more steps aimed at identifying oligonucleotides that target a PRC2-associated region that is functionally related to PTEN, for example a PRC2-associated region of a IncRNA that regulates expression of PTEN by facilitating *(e.g.,* in a *cis*-regulatory manner) the recruitment of PRC2 to the PTEN gene. Such oligonucleotides are expected to be candidates for activating expression of PTEN because of their ability to hybridize with the PRC2-associated region of a nucleic acid *(e.g.,* a IncRNA). In some embodiments, this hybridization event is understood to disrupt interaction of PRC2 with the nucleic acid *(e.g.,* a IncRNA) and as a result disrupt recruitment of PRC2 and its associated co-repressors *(e.g.,* chromatin remodeling factors) to the PTEN gene locus.

Methods of selecting a candidate oligonucleotide may involve selecting a PRC2-associated region *(e.g.,* a nucleotide sequence as set forth in any one of SEQ ID NOS: 5 to 148) that maps to a chromosomal position encompassing or in proximity to the PTEN gene *(e.g.,* a chromosomal position having a sequence as set forth in any one of SEQ ID NOS: 1 to 4). The PRC2-associated region may map to the strand of the chromosome comprising the sense strand of the PTEN gene, in which case the candidate oligonucleotide is complementary to the sense strand of the PTEN gene *(i.e.,* is antisense to the PTEN gene). Alternatively, the PRC2-associated region may map to the strand of the first chromosome comprising the antisense strand of the PTEN gene, in which case the oligonucleotide is complementary to the antisense strand (the template strand) of the PTEN gene *(i.e.,* is sense to the PTEN gene).

Methods for selecting a set of candidate oligonucleotides that is enriched in oligonucleotides that activate expression of PTEN may involve selecting one or more PRC2-associated regions that map to a chromosomal position that encompasses or that is in proximity to the PTEN gene and selecting a set of oligonucleotides, in which each oligonucleotide in the set comprises a nucleotide sequence that is complementary with the one or more PRC2-associated regions. As used herein, the phrase, "a set of oligonucleotides

that is enriched in oligonucleotides that activate expression of refers to a set of oligonucleotides that has a greater number of oligonucleotides that activate expression of a target gene *(e.g.,* PTEN) compared with a random selection of oligonucleotides of the same physicochemical properties *(e.g.,* the same GC content, T_m, length *etc.)* as the enriched set.

Where the design and/or synthesis of a single stranded oligonucleotide involves design and/or synthesis of a sequence that is complementary to a nucleic acid or PRC2-associated region described by such sequence information, the skilled person is readily able to determine the complementary sequence, *e.g.,* through understanding of Watson Crick base pairing rules which form part of the common general knowledge in the field.

In some embodiments design and/or synthesis of a single stranded oligonucleotide involves manufacture of an oligonucleotide from starting materials by techniques known to those of skill in the art, where the synthesis may be based on a sequence of a PRC2-associated region, or portion thereof.

Methods of design and/or synthesis of a single stranded oligonucleotide may involve one or more of the steps of:

Identifying and/or selecting PRC2-associated region;

Designing a nucleic acid sequence having a desired degree of sequence identity or complementarity to a PRC2-associated region or a portion thereof;

Synthesizing a single stranded oligonucleotide to the designed sequence;

Purifying the synthesized single stranded oligonucleotide; and

Optionally mixing the synthesized single stranded oligonucleotide with at least one pharmaceutically acceptable diluent, carrier or excipient to form a pharmaceutical composition or medicament.

Single stranded oligonucleotides so designed and/or synthesized may be useful in method of modulating gene expression as described herein.

Preferably, single stranded oligonucleotides of the invention are synthesized chemically. Oligonucleotides used to practice this invention can be synthesized *in vitro* by well-known chemical synthesis techniques.

Oligonucleotides of the invention can be stabilized against nucleolytic degradation such as by the incorporation of a modification, *e.g.,* a nucleotide modification. For example, nucleic acid sequences of the invention include a phosphorothioate at least the first, second, or third internucleotide linkage at the 5' or 3' end of the nucleotide sequence. As another

example, the nucleic acid sequence can include a 2'-modified nucleotide, *e.g.,* a 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-0-methyl, 2'-0-methoxyethyl (2'-0-MOE), 2'-0-aminopropyl (2'-0-AP), 2'-0-dimethylaminoethyl (2'-0-DMAOE), 2'-0-dimethylaminopropyl (2'-0-DMAP), 2'-0-dimethylaminoethyloxyethyl (2'-0-DMAEOE), or 2'-0--N-methylacetamido (2'-0--NMA). As another example, the nucleic acid sequence can include at least one 2'-0-methyl-modified nucleotide, and in some embodiments, all of the nucleotides include a 2'-0-methyl modification. In some embodiments, the nucleic acids are "locked," i.e., comprise nucleic acid analogues in which the ribose ring is "locked" by a methylene bridge connecting the 2'-O atom and the 4'-C atom.

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

In some embodiments, the method may further comprise the steps of amplifying the synthesized single stranded oligonucleotide, and/or purifying the single stranded oligonucleotide (or amplified single stranded oligonucleotide), and/or sequencing the single stranded oligonucleotide so obtained.

As such, the process of preparing a single stranded oligonucleotide may be a process that is for use in the manufacture of a pharmaceutical composition or medicament for use in the treatment of disease, optionally wherein the treatment involves modulating expression of a gene associated with a PRC2-associated region.

In the methods described above a PRC2-associated region may be, or have been, identified, or obtained, by a method that involves identifying RNA that binds to PRC2.

Such methods may involve the following steps: providing a sample containing nuclear ribonucleic acids, contacting the sample with an agent that binds specifically to PRC2 or a subunit thereof, allowing complexes to form between the agent and protein in the sample, partitioning the complexes, synthesizing nucleic acid that is complementary to nucleic acid present in the complexes.

Where the single stranded oligonucleotide is based on a PRC2-associated region, or a portion of such a sequence, it may be based on information about that sequence, *e.g.,* sequence information available in written or electronic form, which may include sequence information contained in publicly available scientific publications or sequence databases.

Nucleotide Analogues

In some embodiments, the oligonucleotide may comprise at least one ribonucleotide, at least one deoxyribonucleotide, and/or at least one bridged nucleotide. In some embodiments, the oligonucleotide may comprise a bridged nucleotide, such as a locked nucleic acid (LNA) nucleotide, a constrained ethyl (cEt) nucleotide, or an ethylene bridged nucleic acid (ENA) nucleotide. Examples of such nucleotides are disclosed herein and known in the art. In some embodiments, the oligonucleotide comprises a nucleotide analog disclosed in one of the following United States Patent or Patent Application Publications: US 7,399,845, US 7,741,457, US 8,022,193, US 7,569,686, US 7,335,765, US 7,314,923, US 7,335,765, and US 7,816,333, US 201 10009471, the entire contents of each of which are incorporated herein by reference for all purposes. The oligonucleotide may have one or more 2' O-methyl nucleotides. The oligonucleotide may consist entirely of 2' O-methyl nucleotides.

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

The oligonucleotide may be of up to 50 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30, 2 to 40, 2 to 45, or more nucleotides of the oligonucleotide are nucleotide analogues. The oligonucleotide may be of 8 to 30 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30 nucleotides of the oligonucleotide are nucleotide analogues.
The oligonucleotide may be of 8 to 15 nucleotides in length in which 2 to 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11, 2 to 12, 2 to 13, 2 to 14 nucleotides of the oligonucleotide are nucleotide analogues. Optionally, the oligonucleotides may have every nucleotide except 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides modified.

The oligonucleotide may consist entirely of bridged nucleotides *{e.g.,* LNA nucleotides, cEt nucleotides, ENA nucleotides). The oligonucleotide may comprise

alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and 2'-0-methyl nucleotides. The oligonucleotide may comprise alternating deoxyribonucleotides and ENA nucleotide analogues. The oligonucleotide may comprise alternating deoxyribonucleotides and LNA nucleotides. The oligonucleotide may comprise alternating LNA nucleotides and 2'-0-methyl nucleotides. The oligonucleotide may have a 5' nucleotide that is a bridged nucleotide *(e.g.,* a LNA nucleotide, cEt nucleotide, ENA nucleotide). The oligonucleotide may have a 5' nucleotide that is a deoxyribonucleotide.

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

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

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

In some embodiments, the single stranded oligonucleotides are chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the target) and a region that is a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. Chimeric single stranded oligonucleotides of the invention may be formed as

composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures comprise, but are not limited to, US patent nos. 5,013,830; 5,149,797; 5, 220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, each of which is herein incorporated by reference.

In some embodiments, the single stranded oligonucleotide comprises at least one nucleotide modified at the 2' position of the sugar, most preferably a 2'-0-alkyl, 2'-0-alkyl-0-alkyl or 2'-fluoro-modified nucleotide. In other preferred embodiments, RNA modifications include 2'-fluoro, 2'-amino and 2' O-methyl modifications on the ribose of pyrimidines, abasic residues or an inverted base at the 3' end of the RNA. Such modifications are routinely incorporated into oligonucleotides and these oligonucleotides have been shown to have a higher Tm (i.e., higher target binding affinity) than 2'-deoxyoligonucleotides against a given target.

A number of nucleotide and nucleoside modifications have been shown to make the oligonucleotide into which they are incorporated more resistant to nuclease digestion than the native oligodeoxynucleotide; these modified oligos survive intact for a longer time than unmodified oligonucleotides. Specific examples of modified oligonucleotides include those comprising modified backbones, for example, phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Most preferred are oligonucleotides with phosphorothioate backbones and those with heteroatom backbones, particularly CH_2 -NH-O-CH_2, CH,~N(CH_3)~0~CH_2 (known as a methylene(methylimino) or MMI backbone, CH_2 --0--N (CH_3)-CH_2, CH_2 -N (CH_3)-N (CH_3)-CH_2 and O-N (CH_3)- CH_2 -CH_2 backbones, wherein the native phosphodiester backbone is represented as O- P — O- CH,); amide backbones (see De Mesmaeker et al. Ace. Chem. Res. 1995, 28:366-374); morpholino backbone structures (see Summerton and Weller, U.S. Pat. No. 5,034,506); peptide nucleic acid (PNA) backbone (wherein the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the nucleotides being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone, see Nielsen et al., Science 1991, 254, 1497). Phosphorus-containing linkages include, but are not limited to, phosphorothioates, chiral

phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates comprising 3'alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates comprising 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'; see US patent nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5, 177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455, 233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563, 253; 5,571,799; 5,587,361; and 5,625,050.

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

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

Modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These comprise those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH2 component parts; see US patent nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264, 562; 5, 264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596, 086; 5,602,240; 5,610,289; 5,602,240; 5,608,046;

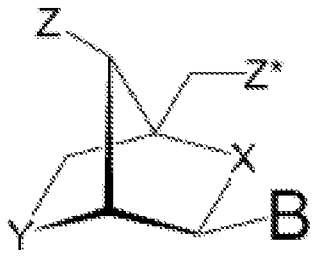
5,610,289; 5,618,704; 5,623, 070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

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

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

Other preferred modifications include ethylene-bridged nucleic acids (ENAs) *(e.g.,* International Patent Publication No. WO 2005/042777, Morita et al., Nucleic Acid Res., Suppl 1:241-242, 2001; Surono et al., Hum. Gene Ther., 15:749-757, 2004; Koizumi, Curr. Opin. Mol. Ther., 8:144-149, 2006 and Horie et al., Nucleic Acids Symp. Ser (Oxf), 49:171-172, 2005; the disclosures of which are incorporated herein by reference in their entireties). Preferred ENAs include, but are not limited to, 2'-0,4'-C-ethylene -bridged nucleic acids.

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



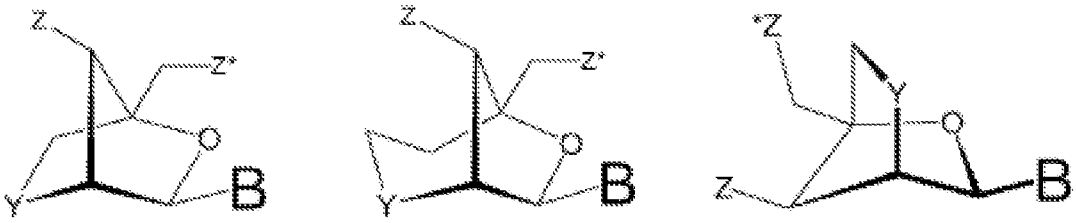
where X and Y are independently selected among the groups -O-,

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

-CH_2-0-, -CH_2-S-, -CH_2-N(H)-, -CH_2-N(R)-, -CH_2-CH_2- or -CH_2-CH- (if part of a double bond),

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

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

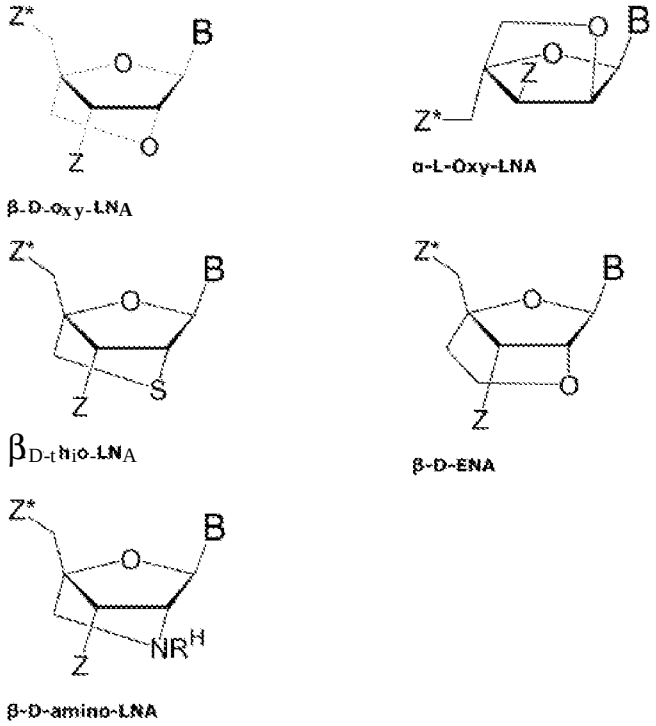


wherein Y is -0-, -S-, -NH-, or N(R^H); Z and Z* are independently selected among an intemucleoside linkage, a terminal group or a protecting group; B constitutes a natural or non-natural nucleotide base moiety, and RH is selected from hydrogen and Ci-4-alkyl.

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

In some embodiments, the LNA used in the oligomer of the invention comprises intemucleoside linkages selected from -0-P(O)$_2$-O-, -0-P(0,S)-0-, -0-P(S)$_2$-O-, -S-P(0)$_2$-0-, -S-P(0,S)-0-, -S-P(S)$_2$-0-, -0-P(O)$_2$-S-, -0-P(0,S)-S-, -S-P(0)$_2$-S-, -0-PO(R^H)-0-, -0-PO(OCH_3)-0-, -0-PO(NR^H)-0-, -0-PO(OCH_2CH_2S-R)-O-, -0-PO(BH_3)-0-, -0-PO(NHR^H)-0-, -0-P(0)$_2$-NR^H-, -NR^H-P(0)$_2$-0-, -NR^H-CO-0-, where R^H is selected from hydrogen and Ci_4-alkyl.

Specifically preferred LNA units are shown in scheme 2:



Scheme 2

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

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

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

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

LNAs are described in additional detail herein.

One or more substituted sugar moieties can also be included, *e.g.,* one of the following at the 2' position: OH, SH, SCH_3, F, OCN, OCH_3 OCH_3, OCH_3 $0(CH_2)n$ CH_3, $0(CH_2)n$ NH_2 or $0(CH_2)n$ CH_3 where n is from 1 to about 10; C I to CIO lower alkyl, alkoxyalkoxy, substituted lower alkyl, alkaryl or aralkyl; CI; Br; CN; CF_3 ; OCF_3; 0-, S-, or N-alkyl; 0-, S-, or N-alkenyl; $SOCH_3$; $S0_2$ CH_3; $ON0_2$; $N0_2$; N_3; NH2; heterocycloalkyl; heterocyclo alkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy [2'-0-$CH_2CH_2OCH_3$, also known as 2'-0-(2-methoxyethyl)] (Martin et al, Helv. Chim. Acta, 1995, 78, 486). Other preferred modifications include 2'-methoxy (2'-0-CH_3), 2'-propoxy (2'-OCH_2 CH_2CH_3) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

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

stability by 0.6-1.2°C. (Sanghvi, in Crooke, and Lebleu, eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and may be used as base substitutions.

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

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

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

Further, nucleobases comprise those disclosed in United States Patent No. 3,687,808, those disclosed in "The Concise Encyclopedia of Polymer Science And Engineering", pages 858-859, Kroschwitz, ed. John Wiley & Sons, 1990;, those disclosed by Englisch et al., Angewandle Chemie, International Edition, 1991, 30, page 613, and those disclosed by Sanghvi, Chapter 15, Antisense Research and Applications," pages 289- 302, Crooke, and Lebleu, eds., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, comprising 2-aminopropyladenine, 5-propynyluracil and 5- propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2<0>C (Sanghvi, et al., eds, "Antisense Research and Applications," CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-0-methoxyethyl sugar modifications. Modified nucleobases are described in US patent nos. 3,687,808, as well as 4,845,205; 5,130,302; 5,134,066; 5,175, 273; 5, 367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,596,091; 5,614,617; 5,750,692, and 5,681,941, each of which is herein incorporated by reference.

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

polyethylene glycol chain (Mancharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-t oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277, 923-937). See also US patent nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552, 538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486, 603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762, 779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082, 830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5, 245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391, 723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5, 565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599, 928 and 5,688,941, each of which is herein incorporated by reference.

These moieties or conjugates can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugate groups include cholesterols, lipids, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve uptake, enhance resistance to degradation, and/or strengthen sequence-specific hybridization with the target nucleic acid. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve uptake, distribution, metabolism or excretion of the compounds of the present invention. Representative conjugate groups are disclosed in International Patent Application No. PCT/US92/09196, filed Oct. 23, 1992, and U.S. Pat. No. 6,287,860, which are incorporated herein by reference. Conjugate moieties include, but are not limited to, lipid moieties such as a cholesterol moiety, cholic acid, a thioether, *e.g.,* hexyl-5-tritylthiol, a thiocholesterol, an aliphatic chain, *e.g.,* dodecandiol or undecyl residues, a phospholipid, *e.g.,* di-hexadecyl-rac- glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxy

cholesterol moiety. See, ***e.g.,*** U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941.

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

In some embodiments, the single stranded oligonucleotide comprises locked nucleic acids (LNA), ENA modified nucleotides, 2'-0-methyl nucleotides, or 2'-fluoro-deoxyribonucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and 2'-0-methyl nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and ENA modified nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating deoxyribonucleotides and locked nucleic acid nucleotides. In some embodiments, the single stranded oligonucleotide comprises alternating locked nucleic acid nucleotides and 2'-0-methyl nucleotides.

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

In some embodiments, the single stranded oligonucleotide comprises phosphorothioate internucleotide linkages. In some embodiments, the single stranded

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

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

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

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

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

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

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

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

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

Methods for Modulating Gene Expression

In one aspect, the invention relates to methods for modulating gene expression in a cell *(e.g.,* a cell for which PTEN levels are reduced) for research purposes *(e.g.,* to study the function of the gene in the cell). In another aspect, the invention relates to methods for modulating gene expression in a cell *(e.g.,* a cell for which PTEN levels are reduced) for gene or epigenetic therapy. The cells can be *in vitro, ex vivo,* or *in vivo (e.g.,* in a subject who has a disease resulting from reduced expression or activity of PTEN. In some embodiments,

methods for modulating gene expression in a cell comprise delivering a single stranded oligonucleotide as described herein. In some embodiments, delivery of the single stranded oligonucleotide to the cell results in a level of expression of gene that is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200% or more greater than a level of expression of gene in a control cell to which the single stranded oligonucleotide has not been delivered. In certain embodiments, delivery of the single stranded oligonucleotide to the cell results in a level of expression of gene that is at least 50% greater than a level of expression of gene in a control cell to which the single stranded oligonucleotide has not been delivered.

In another aspect of the invention, methods comprise administering to a subject *(e.g.* a human) a composition comprising a single stranded oligonucleotide as described herein to increase protein levels in the subject. In some embodiments, the increase in protein levels is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, or more, higher than the amount of a protein in the subject before administering.

As another example, to increase expression of PTEN in a cell, the methods include introducing into the cell a single stranded oligonucleotide that is sufficiently complementary to a PRC2-associated region *(e.g.,* of a long non-coding RNA) that maps to a genomic position encompassing or in proximity to the PTEN gene.

In another aspect of the invention provides methods of treating a condition *(e.g.,* cancer) associated with decreased levels of expression of PTEN in a subject, the method comprising administering a single stranded oligonucleotide as described herein. In some embodiments, the condition is cancer. Examples of cancer include but are not limited to leukemias, lymphomas, myelomas, carcinomas, metastatic carcinomas, sarcomas, adenomas, nervous system cancers and genito-urinary cancers. In some embodiments, the cancer is adult and pediatric acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, anal cancer, cancer of the appendix, astrocytoma, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma, fibrous histiocytoma, brain cancer, brain stem glioma, cerebellar astrocytoma, malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, hypothalamic glioma, breast cancer, male breast cancer, bronchial adenomas, Burkitt lymphoma, carcinoid tumor, carcinoma of unknown origin, central nervous system lymphoma, cerebellar astrocytoma, malignant glioma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colorectal cancer, cutaneous T-

cell lymphoma, endometrial cancer, ependymoma, esophageal cancer, Ewing family tumors, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric cancer, gastrointestinal stromal tumor, extracranial germ cell tumor, extragonadal germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, islet cell tumors, Kaposi sarcoma, kidney cancer, renal cell cancer, laryngeal cancer, lip and oral cavity cancer, small cell lung cancer, non-small cell lung cancer, primary central nervous system lymphoma, Waldenstrom macroglobulinema, malignant fibrous histiocytoma, medulloblastoma, melanoma, Merkel cell carcinoma, malignant mesothelioma, squamous neck cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplasia syndromes, myeloproliferative disorders, chronic myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, oropharyngeal cancer, ovarian cancer, pancreatic cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary cancer, plasma cell neoplasms, pleuropulmonary blastoma, prostate cancer, rectal cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, uterine sarcoma, Sezary syndrome, non-melanoma skin cancer, small intestine cancer, squamous cell carcinoma, squamous neck cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer, trophoblastic tumors, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Wilms tumor. In some embodiments, the cancer is prostate cancer or breast cancer.

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

For therapeutics, an animal, preferably a human, suspected of having cancer, e.g., breast or prostate cancer, is treated by administering single stranded oligonucleotide in

accordance with this invention. For example, in one non-limiting embodiment, the methods comprise the step of administering to the animal in need of treatment, a therapeutically effective amount of a single stranded oligonucleotide as described herein.

Formulation, Delivery, And Dosing

The oligonucleotides described herein can be formulated for administration to a subject for treating a condition *(e.g.,* cancer) associated with decreased levels of PTEN. It should be understood that the formulations, compositions and methods can be practiced with any of the oligonucleotides disclosed herein.

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

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

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

stranded oligonucleotide composition is formulated in a manner that is compatible with the intended method of administration.

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

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

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

In one embodiment, the single stranded oligonucleotide preparation includes at least a second therapeutic agent *(e.g.*, an agent other than an oligonucleotide). For example, *e.g.*, a single stranded oligonucleotide composition for the treatment of a cancer might further comprise a chemotherapeutic agent.

Route of Delivery

A composition that includes a single stranded oligonucleotide can be delivered to a subject by a variety of routes. Exemplary routes include: intravenous, intradermal, topical, rectal, parenteral, anal, intravaginal, intranasal, pulmonary, ocular. The term "therapeutically effective amount" is the amount of oligonucleotide present in the composition that is needed to provide the desired level of PTEN expression in the subject to be treated to give the anticipated physiological response. The term "physiologically effective amount" is that amount delivered to a subject to give the desired palliative or curative effect. The term

"pharmaceutically acceptable carrier" means that the carrier can be administered to a subject with no significant adverse toxicological effects to the subject.

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

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

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

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

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

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

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

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

In oral delivery, compositions can be targeted to a surface of the oral cavity, *e.g.,* to sublingual mucosa which includes the membrane of ventral surface of the tongue and the floor of the mouth or the buccal mucosa which constitutes the lining of the cheek. The

sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many agents. Further, the sublingual mucosa is convenient, acceptable and easily accessible.

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

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

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

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

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

as sorbic acid, EDTA or benzylchronium chloride, and the usual quantities of diluents and/or carriers. The single stranded oligonucleotide can also be administered to the interior of the eye, and can be introduced by a needle or other delivery device which can introduce it to a selected area or structure.

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

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

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

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

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

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

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

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

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

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

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

treated cells are insulated from other cells, *e.g.*, by a semi-permeable porous barrier that prevents the cells from leaving the implant, but enables molecules from the body to reach the cells and molecules produced by the cells to enter the body. In one embodiment, the porous barrier is formed from alginate.

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

Dosage

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

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

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

In one embodiment, a subject is administered an initial dose and one or more maintenance doses of a single stranded oligonucleotide. The maintenance dose or doses are generally lower than the initial dose, *e.g.*, one-half less of the initial dose. A maintenance regimen can include treating the subject with a dose or doses ranging from 0.0001 to 100 mg/kg of body weight per day, *e.g.*, 100, 10, 1, 0.1, 0.01, 0.001, or 0.0001 mg per kg of bodyweight per day. The maintenance doses may be administered no more than once every

1, 5, 10, or 30 days. Further, the treatment regimen may last for a period of time which will vary depending upon the nature of the particular disease, its severity and the overall condition of the patient. In some embodiments the dosage may be delivered no more than once per day, *e.g.,* no more than once per 24, 36, 48, or more hours, *e.g.,* no more than once for every 5 or 8 days. Following treatment, the patient can be monitored for changes in his condition and for alleviation of the symptoms of the disease state. The dosage of the oligonucleotide may either be increased in the event the patient does not respond significantly to current dosage levels, or the dose may be decreased if an alleviation of the symptoms of the disease state is observed, if the disease state has been ablated, or if undesired side-effects are observed.

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

In some embodiments, the oligonucleotide pharmaceutical composition includes a plurality of single stranded oligonucleotide species. In another embodiment, the single stranded oligonucleotide species has sequences that are non-overlapping and non-adjacent to another species with respect to a naturally occurring target sequence *(e.g.,* a PRC2-associated region). In another embodiment, the plurality of single stranded oligonucleotide species is specific for different PRC2-associated regions. In another embodiment, the single stranded oligonucleotide is allele specific.

In some cases, a patient is treated with a single stranded oligonucleotide in conjunction with other therapeutic modalities. For example, a patient being treated for cancer may be administered a single stranded oligonucleotide in conjunction with a chemotherapy.

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

The concentration of the single stranded oligonucleotide composition is an amount sufficient to be effective in treating or preventing a disorder or to regulate a physiological condition in humans. The concentration or amount of single stranded oligonucleotide

administered will depend on the parameters determined for the agent and the method of administration, *e.g.* nasal, buccal, pulmonary. For example, nasal formulations may tend to require much lower concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

Certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a single stranded oligonucleotide can include a single treatment or, preferably, can include a series of treatments. It will also be appreciated that the effective dosage of a single stranded oligonucleotide used for treatment may increase or decrease over the course of a particular treatment. For example, the subject can be monitored after administering a single stranded oligonucleotide composition. Based on information from the monitoring, an additional amount of the single stranded oligonucleotide composition can be administered.

Dosing is dependent on severity and responsiveness of the disease condition to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of disease state is achieved. Optimal dosing schedules can be calculated from measurements of PTEN expression levels 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 compounds, and can generally be estimated based on EC50s found to be effective in in vitro and in vivo animal models. In some embodiments, the animal models include transgenic animals that express a human PTEN. In another embodiment, the composition for testing includes a single stranded oligonucleotide that is complementary, at least in an internal region, to a sequence that is conserved between PTEN in the animal model and the PTEN in a human.

In one embodiment, the administration of the single stranded oligonucleotide composition is parenteral, *e.g.* intravenous *(e.g.,* as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral or ocular. Administration can be provided by the subject or

by another person, *e.g.*, a health care provider. The composition can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

Kits

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

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

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

MATERIALS AND METHODS:

Real Time PCR

RNA was harvested from the cells using Promega SV 96 Total RNA Isolation system or Trizol omitting the DNAse step. In separate pilot experiments, 50 ng of RNA was determined to be sufficient template for the reverse transcriptase reaction. RNA harvested from cells was normalized so that 50ng of RNA was input to each reverse transcription reaction. For the few samples that were too dilute to reach this limit, the maximum input volume was added. Reverse transcriptase reaction was performed using the Superscript II kit and real time PCR performed on cDNA samples using icycler SYBR green chemistry (Biorad). A baseline level of mRNA expression for each target gene was determined through quantitative PCR as outlined above. Baseline levels were also determined for mRNA of various housekeeping genes which are constitutively expressed. A "control" housekeeping gene with approximately the same level of baseline expression as the target gene was chosen for comparison purposes.

Cell Culture

Human hepatocyte Hep3B, human hepatocyte HepG2 cells, mouse hepatoma Hepal-6 cells, and human renal proximal tubule epithelial cells (RPTEC) were cultured using conditions known in the art (see, *e.g.* Current Protocols in Cell Biology). Details of the cell lines used in the experiments described herein are provided in Table 5.

Table 5. Cell lines

Cell line	Source	Species	Gender	Cell Type	Tissue	Status	Culture Conditions
HepG2	ATCC	human	M	hepatocytes	liver	immortalized	Eagle's MEM + 10% FBS
Hepa1-6	ATCC	mouse	N/A	hepatocytes	liver	immortalized	DMEM + 10% FBS
Hep3B	ATCC	human	M	hepatocytes	liver	immortalized	Eagle's MEM + 10% FBS
Hepa 1-6	ATCC	mouse	N/A	hepatocytes	liver	immortalized	DMEM + 10% FBS

Oligonucleotide design

Oligonucleotides were designed within PRC2-interacting regions in order to upregulate PTEN. The sequence and structure of each oligonucleotide is shown in Table 2 or

5. The following table provides a description of the nucleotide analogs, modifications and intranucleotide linkages used for certain oligonucleotides tested and described in Table 2 or 5.

Table 3: Oligonucleotide Modifications

Symbol	Feature Description
bio	5' biotin
dAs	DNA w/3' thiophosphate
dCs	DNA w/3' thiophosphate
dGs	DNA w/3' thiophosphate
dTs	DNA w/3' thiophosphate
dG	DNA
enaAs	ENA w/3' thiophosphate
enaCs	ENA w/3' thiophosphate
enaGs	ENA w/3' thiophosphate
enaTs	ENA w/3' thiophosphate
fluAs	2'-fluoro w/3' thiophosphate
fluCs	2'-fluoro w/3' thiophosphate
fluGs	2'-fluoro w/3' thiophosphate
fluUs	2'-fluoro w/3' thiophosphate
InaAs	LNA w/3' thiophosphate
InaCs	LNA w/3' thiophosphate
InaGs	LNA w/3' thiophosphate
InaTs	LNA w/3' thiophosphate
omeAs	2'-OMe w/3' thiophosphate
omeCs	2'-OMe w/3' thiophosphate
omeGs	2'-OMe w/3' thiophosphate
omeTs	2'-OMe w/3' thiophosphate
InaAs-Sup	LNA w/3' thiophosphate at 3' terminus
InaCs-Sup	LNA w/3' thiophosphate at 3' terminus
InaGs-Sup	LNA w/3' thiophosphate at 3' terminus
InaTs-Sup	LNA w/3' thiophosphate at 3' terminus
InaA-Sup	LNA w/3' OH at 3' terminus
InaC-Sup	LNA w/3' OH at 3' terminus
InaG-Sup	LNA w/3' OH at 3' terminus
InaT-Sup	LNA w/3' OH at 3' terminus
omeA-Sup	2'-OMe w/3' OH at 3' terminus
omeC-Sup	2'-OMe w/3' OH at 3' terminus
omeG-Sup	2'-OMe w/3' OH at 3' terminus
omeU-Sup	2'-OMe w/3' OH at 3' terminus

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

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

Cells were seeded into each well of 24-well plates at a density of 25,000 cells per 500uL and transfections were performed with Lipofectamine and the single stranded oligonucleotides. Control wells contained Lipofectamine alone. At 48 hours post-transfection, approximately 200 uL of cell culture supernatants were stored at -80 C for ELISA. At 48 hours post-transfection, RNA was harvested from the cells and quantitative PCR was carried out as outlined above. The percent induction of target mRNA expression by each oligonucleotide was determined by normalizing mRNA levels in the presence of the oligonucleotide to the mRNA levels in the presence of control (Lipofectamine alone). This was compared side-by-side with the increase in mRNA expression of the "control" housekeeping gene.

RESULTS:

In vitro delivery of single stranded oligonucleotides upregulated PTEN expression

Oligonucleotides were designed as candidates for upregulating PTEN expression. Single stranded oligonucleotides were designed to be complementary to a PRC2-interacting region within a sequence as set forth in SEQ ID NO: 1, 2, 3, or 4. Multiple oligonucleotides were tested in at least duplicate. The sequence and structural features of the oligonucleotides are set forth in Table 4. Briefly, cells were transfected in vitro with each of the oligonucleotides as described above. PTEN expression in cells following treatment was evaluated by qRT-PCR. Oligonucleotides that upregulated PTEN expression were identified. Further details are outlined in Table 2 and FIGs. 1 and 2.

Tables

Table 1: Hexamers that are not seed sequences of human miRNAs

AAAAAA, AAAAAG, AAAACA, AAAAGA, AAAAGC, AAAAGG, AAAAUA, AAACAA, AAACAC, AAACAG, AAACAU, AAACCC, AAACCU, AAACGA, AAACGC, AAACGU, AAACUA, AAACUC, AAACUU, AAAGAU, AAAGCC, AAAGGA, AAAGGG, AAAGUC, AAAUAC, AAAUAU, AAAUCG, AAAUCU, AAAUGC, AAAUGU, AAAUUA, AAAUUG, AACAAC, AACAAG, AACAAU, AACACA, AACACG, AACAGA, AACAGC, AACAGG, AACAUC, AACAUG, AACCAA, AACCAC, AACCAG, AACCAU, AACCCC, AACCCG, AACCGA, AACCGC, AACCGG, AACCUA, AACCUU, AACGAA, AACGAC, AACGAG, AACGAU, AACGCU, AACGGG, AACGGU, AACGUA, AACGUC, AACGUG, AACGUU, AACUAU, AACUCA, AACUCC, AACUCG, AACUGA, AACUGC, AACUGU, AACU UA, AACUUC, AACU UG, AACUUU, AAGAAA, AAGAAG, AAGAAU, AAGACG, AAGAGA, AAGAGC, AAGAGG, AAGAGU, AAGAUU, AAGCAA, AAGCAC, AAGCAG, AAGCAU, AAGCCA, AAGCCC, AAGCCG, AAGCCU, AAGCGA, AAGCGG, AAGCGU, AAGCUA, AAGGAA, AAGGAC, AAGGCU, AAGGGC, AAGGGU, AAGGUU, AAGUAA, AAGUAC, AAGUAU, AAGUCC, AAGUCG, AAGUGA, AAGUGG, AAGUUA, AAGU UU, AAUAAA, AAUAAC, AAUAAG, AAUAAU, AAUACA, AAUACC, AAUACG, AAUAGA, AAUAGC, AAUAGG, AAUAGU, AAUAUC, AAUAU U, AAUCAA, AAUCAU, AAUCCA, AAUCCC, AAUCCG, AAUCGA, AAUCGC, AAUCGU, AAUCUA, AAUCUG, AAUCUU, AAUGAA, AAUGAC, AAUGAG, AAUGAU, AAUGCG, AAUGCU, AAUGGA, AAUGGU, AAUGUA, AAUGUC, AAUGUG, AAUUAA, AAUUAC, AAUUAG, AAU UCC, AAU UCG, AAUUGA, AAUUGG, AAU UGU, AAUUUC, AAU UUG, ACAAAA, ACAAAC, ACAAAG, ACAAAU, ACAACC, ACAACG, ACAACU, ACAAGA, ACAAGC, ACAAGU, ACAAUC, ACAAUG, ACAAUU, ACACAG, ACACCA, ACACCC, ACACCG, ACACCU, ACACGA, ACACGC, ACACGU, ACACUC, ACACUG, ACACUU, ACAGAA, ACAGAC, ACAGCC, ACAGCG, ACAGCU, ACAGGG, ACAGUC, ACAGUG, ACAGU U, ACAUAA, ACAUAC, ACAUCC, ACAUCG, ACAUCU, ACAUGA, ACAUGC, ACAUGU, ACAU UG, ACAU UU, ACCAAA, ACCAAC, ACCAAG, ACCAAU, ACCACC, ACCACG, ACCAGA, ACCAGU, ACCAUA, ACCAUG, ACCAU U, ACCCAA, ACCCAC, ACCCCA, ACCCCG, ACCCGA, ACCCGC, ACCCUA, ACCCUC, ACCCUU, ACCGAA, ACCGAC, ACCGAU, ACCGCA, ACCGCC, ACCGCG, ACCGCU, ACCGGA, ACCGGC, ACCGGU, ACCGUA, ACCGUC, ACCGUG, ACCGUU, ACCUAA, ACCUAC, ACCUAG, ACCUAU, ACCUCA, ACCUCC, ACCUCG, ACCUCU, ACCUGA, ACCUGC, ACCUGU, ACCUUA, ACCUUC, ACCUU U, ACGAAA, ACGAAC, ACGAAG, ACGAAU, ACGACA, ACGACC, ACGACG, ACGACU, ACGAGA, ACGAGC, ACGAGG, ACGAGU, ACGAUA, ACGAUC, ACGAUG, ACGAUU, ACGCAA, ACGCAG, ACGCAU, ACGCCC, ACGCCG, ACGCCU, ACGCGA, ACGCGG, ACGCGU, ACGCUA, ACGCUG, ACGCUU, ACGGAA, ACGGAC, ACGGAG, ACGGAU, ACGGCC, ACGGCG, ACGGCU, ACGGGC, ACGGGG, ACGGGU, ACGGUA, ACGGUC, ACGGUG, ACGGUU, ACGUAA, ACGUAC, ACGUAU, ACGUCC, ACGUCG, ACGUCU, ACGUGA, ACGUGC, ACGUGG, ACGUGU, ACGUUA, ACGU UC, ACGUUG, ACGUU U, ACUAAA, ACUAAG, ACUAAU, ACUACA, ACUACC, ACUACG, ACUACU, ACUAGG, ACUAUC, ACUAUG, ACUAUU, ACUCAU, ACUCCC, ACUCCG, ACUCCU, ACUCGA, ACUCGC, ACUCGG, ACUCUC, ACUCUU, ACUGAG, ACUGAU, ACUGCC, ACUGCG, ACUGCU, ACUGGG, ACUGGU, ACUGUC, ACUUAA, ACU UAC, ACUUAU, ACU UCA, ACUUCC, ACUUCG, ACUUCU, ACUUGA, ACU UGC, ACU UGU, ACUUUA, ACU UUC, ACUU UG, AGAAAA, AGAAAC, AGAAAG, AGAACC, AGAACG, AGAACU, AGAAGC, AGAAGU, AGAAUA, AGAAUC, AGAAUG, AGAAUU, AGACAA, AGACAC, AGACAU, AGACCA, AGACCC, AGACCG, AGACCU, AGACGA, AGACGC, AGACGU, AGACUA, AGACUC, AGACUU, AGAGAC, AGAGAG, AGAGAU, AGAGCC, AGAGCG, AGAGCU, AGAGGC, AGAGGG, AGAGGU, AGAGUA, AGAGUU, AGAUAC, AGAUAG, AGAUAU, AGAUCC, AGAUCG, AGAUCU, AGAUGA, AGAUGC, AGAUGG, AGAU UA,

AGAU UC, AGAUUG, AGAUU U, AGCAAC, AGCACA, AGCACG, AGCACU, AGCAGA, AGCAUA, AGCAUC, AGCAUG, AGCCAA, AGCCAU, AGCCCA, AGCCGA, AGCCGC, AGCCGG, AGCCGU, AGCCUA, AGCCUC, AGCGAA, AGCGAG, AGCGAU, AGCGCA, AGCGCC, AGCGCG, AGCGCU, AGCGGA, AGCGGC, AGCGGU, AGCGUA, AGCGUC, AGCGUG, AGCGUU, AGCUAA, AGCUAC, AGCUAG, AGCUAU, AGCUCA, AGCUCC, AGCUCG, AGCUCU, AGCUGA, AGCUGG, AGCUGU, AGCU UC, AGCUU U, AGGAAU, AGGACC, AGGACG, AGGAGA, AGGAGU, AGGAUA, AGGCAA, AGGCAU, AGGCCG, AGGCGA, AGGCGC, AGGCGG, AGGCUA, AGGCUC, AGGCUU, AGGGAC, AGGGAU, AGGGGA, AGGGGU, AGGGUA, AGGGUG, AGGUAA, AGGUAC, AGGUCA, AGGUCC, AGGUCU, AGGUGA, AGGUGC, AGGUGG, AGGUGU, AGGU UC, AGGUUG, AGUAAA, AGUAAG, AGUAAU, AGUACA, AGUACG, AGUAGC, AGUAGG, AGUAUA, AGUAUC, AGUAUG, AGUAUU, AGUCAA, AGUCAC, AGUCAG, AGUCAU, AGUCCA, AGUCCG, AGUCCU, AGUCGA, AGUCGC, AGUCGG, AGUCGU, AGUCUA, AGUCUC, AGUCUG, AGUCU U, AGUGAA, AGUGAC, AGUGCG, AGUGGG, AGUGUC, AGU UAA, AGU UAC, AGUUAG, AGUUCC, AGU UCG, AGUUGA, AGUUGC, AGUUGU, AGUUUA, AGUUUC, AGUU UG, AGU UUU, AUAAAC, AUAAAU, AUAACA, AUAACC, AUAACG, AUAACU, AUAAGA, AUAAGC, AUAAGG, AUAAGU, AUAAUC, AUAAUG, AUAAUU, AUACAC, AUACAG, AUACAU, AUACCA, AUACCC, AUACCG, AUACGA, AUACGC, AUACGG, AUACGU, AUACUA, AUACUC, AUACUG, AUACUU, AUAGAA, AUAGAC, AUAGAU, AUAGCA, AUAGCG, AUAGCU, AUAGGA, AUAGGU, AUAGUA, AUAGUC, AUAGUG, AUAGUU, AUAUAC, AUAUAG, AUAUCC, AUAUCG, AUAUCU, AUAUGA, AUAUGC, AUAUGG, AUAUGU, AUAUUC, AUAU UG, AUAUU U, AUCAAA, AUCAAC, AUCAAG, AUCAAU, AUCACA, AUCACC, AUCACG, AUCAGC, AUCAGG, AUCCAA, AUCCAU, AUCCCC, AUCCCG, AUCCGA, AUCCGC, AUCCGG, AUCCUA, AUCCUC, AUCCUG, AUCGAA, AUCGAC, AUCGAG, AUCGAU, AUCGCA, AUCGCC, AUCGCG, AUCGCU, AUCGGC, AUCGGG, AUCGGU, AUCGUC, AUCGUG, AUCGU U, AUCUAA, AUCUAC, AUCUAG, AUCUAU, AUCUCC, AUCUCG, AUCUGU, AUCUUG, AUCUU U, AUGAAA, AUGAAC, AUGAAG, AUGAAU, AUGACC, AUGACU, AUGAGG, AUGAGU, AUGAUA, AUGAUC, AUGAU U, AUGCAA, AUGCAG, AUGCCA, AUGCCC, AUGCCG, AUGCGA, AUGCGG, AUGCGU, AUGCUC, AUGCUU, AUGGAC, AUGGCC, AUGGGA, AUGGGC, AUGGGU, AUGGUC, AUGGUG, AUGUAC, AUGUAU, AUGUCA, AUGUCC, AUGUCG, AUGUGU, AUGUUA, AUGUUC, AUUAAA, AUUAAC, AUUAAG, AUUAAU, AUUACA, AUUACC, AUUACG, AUUACU, AUUAGA, AUUAGC, AUUAGG, AUUAGU, AUUAUA, AUUAUC, AUUAUG, AUUCAC, AUUCCA, AUUCCG, AUUCCU, AUUCGA, AUUCGC, AUUCGG, AUUCGU, AUUCUA, AUUCUC, AUUCU U, AUUGAA, AUUGAC, AUUGAU, AUUGCC, AUUGCG, AUUGCU, AUUGGA, AUUGGC, AUUGGG, AUUGGU, AUUGUA, AUUGUC, AUUGUG, AUUGU U, AUUUAA, AUUUAG, AUUUAU, AUU UCC, AUU UCG, AUU UCU, AUUUGA, AUUUGC, AUUUGU, AUUUUA, AUUUUC, AUU UUG, AUU UUU, CAAAAG, CAAACA, CAAACC, CAAACG, CAAACU, CAAAGA, CAAAGG, CAAAUA, CAAAUU, CAACAC, CAACAU, CAACCA, CAACCC, CAACCG, CAACGA, CAACGC, CAACGG, CAACGU, CAACUA, CAACUC, CAACUG, CAACUU, CAAGAA, CAAGAC, CAAGAU, CAAGCA, CAAGCC, CAAGCG, CAAGCU, CAAGGA, CAAGGG, CAAGUC, CAAGUG, CAAGU U, CAAUAA, CAAUAC, CAAUAG, CAAUCC, CAAUCG, CAAUCU, CAAUGA, CAAUGC, CAAUGG, CAAUGU, CAAU UC, CAAU UG, CAAU UU, CACAAU, CACACA, CACACG, CACACU, CACAGA, CACAGC, CACAGG, CACAUA, CACAUC, CACAUU, CACCAA, CACCAC, CACCAU, CACCCA, CACCCC, CACCCG, CACCGA, CACCGC, CACCGG, CACCGU, CACCUA, CACCU U, CACGAA, CACGAC, CACGAG, CACGAU, CACGCA, CACGCC, CACGCU, CACGGA, CACGGC, CACGGG, CACGG U, CACGUA, CACGUC, CACGUG, CACGU U, CACUAA, CACUAG, CACUAU, CACUCA, CACUCG, CACUGA, CACUGC, CACUGG, CACUUA, CACU UC, CACU UU, CAGAAA, CAGAAG, CAGAAU, CAGACC, CAGACG, CAGAGC, CAGAUA, CAGAUC, CAGCCG, CAGCCU, CAGCGA, CAGCGC, CAGCGG, CAGCGU,

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CGGU UA, CGGU UC, CGGUUG, CGGUUU, CGUAAA, CGUAAC, CGUAAG, CGUAAU, CGUACA, CGUACG, CGUACU, CGUAGA, CGUAGC, CGUAGG, CGUAGU, CGUAUA, CGUAUC, CGUAUG, CGUAUU, CGUCAA, CGUCAC, CGUCAG, CGUCAU, CGUCCA, CGUCCC, CGUCCG, CGUCCU, CG UCGA, CGUCGG, CGUCGU, CGUCUA, CGUCUC, CGUCUG, CGUCU U, CGUGAA, CGUGAC, CGUGAG, CGUGAU, CGUGCC, CGUGCG, CGUGCU, CGUGGA, CGUGGG, CGUGGU, CGUGUA, CGUGUG, CGUUAA, CGUUAC, CGU UAG, CGU UAU, CGUUCA, CGUUCC, CGUUCG, CGU UCU, CGUUGA, CGUUGC, CGU UGU, CGU UUA, CGUUUC, CGU U UU, CUAAAA, CUAAAC, CUAAAU, CUAACA, CUAACC, CUAACG, CUAACU, CUAAGA, CUAAGC, CUAAGU, CUAAUA, CUAAUC, CUAAUG, CUACAC, CUACAU, CUACCA, CUACCC, CUACCG, CUACCU, CUACGA, CUACGC, CUACGG, CUACGU, CUACUA, CUACUC, CUACUG, CUAGAA, CUAGAG, CUAGAU, CUAGCA, CUAGCC, CUAGCG, CUAGCU, CUAGGA, CUAGGG, CUAGGU, CUAGUG, CUAGUU, CUAUAA, CUAUAG, CUAUAU, CUAUCA, CUAUCC, CUAUCG, CUAUCU, CUAUGA, CUAUGC, CUAUGG, CUAUGU, CUAUUA, CUAUUG, CUCAAC, CUCAAG, CUCAAU, CUCACC, CUCACG, CUCAGC, CUCAUA, CUCAUC, CUCAUG, CUCAU U, CUCCAC, CUCCCC, CUCCCG, CUCCGA, CUCCGC, CUCCGG, CUCCUA, CUCCUC, CUCCU U, CUCGAA, CUCGAC, CUCGAG, CUCGAU, CUCGCA, CUCGCC, CUCGCG, CUCGGG, CUCGGU, CUCGUA, CUCGUC, CUCGUG, CUCGU U, CUCUAA, CUCUAC, CUCUAU, CUCUCA, CUCUCC, CUCUCU, CUCUGC, CUCUGU, CUCUUA, CUCU UG, CUGAAG, CUGACC, CUGACG, CUGAGC, CUGAUA, CUGAUC, CUGCCG, CUGCCU, CUGCGA, CUGCUA, CUGCUU, CUGGAG, CUGGAU, CUGGCG, CUGGGU, CUGUAC, CUGUCA, CUGUCC, CUGUCG, CUGUGG, CUGUGU, CUGUUA, CUGU UU, CUUAAC, CUUAAG, CU UAAU, CU UACC, CUUACG, CUUAGA, CU UAGC, CU UAGG, CUUAGU, CUUAUA, CU UAUC, CU UAUG, CUUAUU, CU UCAG, CU UCAU, CUUCCA, CUUCCC, CU UCCG, CU UCCU, CUUCGA, CUUCGC, CU UCGG, CUUCGU, CU UCUA, CUUGAC, CUUGAG, CUUGAU, CUUGCA, CUUGCC, CUUGCG, CU UGCU, CUUGGC, CUUGGU, CU UGUU, CUU UAC, CU UUAG, CU UUAU, CUU UCA, CUU UCG, CU UUCU, CUUUGA, CU UUGC, CU UUGU, CU U UUA, CUUU UC, CUU UUG, CUU UUU, GAAAAA, GAAAAG, GAAAAU, GAAACC, GAAACG, GAAAGA, GAAAGC, GAAAGU, GAAAUA, GAAAUC, GAAAUG, GAAAUU, GAACAA, GAACAC, GAACAG, GAACAU, GAACCA, GAACCC, GAACCG, GAACCU, GAACGA, GAACGC, GAACGG, GAACGU, GAACUA, GAACUG, GAACUU, GAAGAC, GAAGAG, GAAGCA, GAAGCG, GAAGCU, GAAGUC, GAAUAA, GAAUAC, GAAUAG, GAAUAU, GAAUCC, GAAUCG, GAAUCU, GAAUGA, GAAUGC, GAAUGU, GAAU UA, GAAU UC, GAAUU U, GACAAA, GACAAG, GACAAU, GACACC, GACAGA, GACAGG, GACAUA, GACAUG, GACAUU, GACCAA, GACCAC, GACCAG, GACCCA, GACCCC, GACCCG, GACCGC, GACCGG, GACCGU, GACCUA, GACCUC, GACCU U, GACGAA, GACGAC, GACGAG, GACGAU, GACGCA, GACGCC, GACGCG, GACGCU, GACGGA, GACGGC, GACGGG, GACGGU, GACGUA, GACGUC, GACGUG, GACGUU, GACUAA, GACUAC, GACUAG, GACUAU, GACUCA, GACUCC, GACUCG, GACUGG, GACUGU, GACUUA, GACUUG, GACUU U, GAGAAU, GAGAGA, GAGAGC, GAGAGG, GAGAUA, GAGAUC, GAGCAA, GAGCAU, GAGCCA, GAGCGA, GAGCGG, GAGCGU, GAGGGU, GAGGUC, GAGGUG, GAGUAA, GAGUAG, GAGUCC, GAGUUC, GAGU UU, GAUAAA, GAUAAC, GAUAAG, GAUAAU, GAUACA, GAUACC, GAUACG, GAUACU, GAUAGA, GAUAGC, GAUAGG, GAUAGU, GAUAUA, GAUCAA, GAUCAC, GAUCAU, GAUCCA, GAUCCC, GAUCCU, GAUCGC, GAUCGG, GAUCGU, GAUCUA, GAUCUG, GAUCU U, GAUGAA, GAUGAC, GAUGAG, GAUGCA, GAUGCC, GAUGCG, GAUGCU, GAUGGC, GAUGGG, GAUGGU, GAUGUG, GAUGUU, GAUUAA, GAUUAC, GAUUAG, GAUUAU, GAUUCA, GAUUCG, GAU UCU, GAUUGA, GAUUGC, GAU UUA, GAU UUC, GAUU UG, GAUUU U, GCAAAC, GCAAAG, GCAAAU, GCAACA, GCAACC, GCAAGC, GCAAGU, GCAAUA, GCAAUC, GCAAUG, GCAAUU, GCACAA, GCACAC, GCACAG, GCACCC, GCACCG, GCACCU, GCACGA, GCACGC, GCACGU, GCACUA, GCACUC, GCACUG, GCACUU, GCAGAU, GCAGCC, GCAGCG, GCAGGC,

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UCGU UU, UCUAAC, UCUAAG, UCUAAU, UCUACA, UCUACC, UCUACG, UCUACU, UCUAGC, UCUAGG, UCUAGU, UCUAUA, UCUAUC, UCUAUG, UCUAUU, UCUCAG, UCUCAU, UCUCCG, UCUCGC, UCUCGG, UCUCGU, UCUCUC, UCUGAA, UCUGAU, UCUGCA, UCUGCG, UCUGCU, UCUGGC, UCUGGU, UCUGUC, UCUGUG, UCUGU U, UCUUAA, UCU UAC, UCUUAG, UCU UAU, UCU UCA, UCUUCC, UCUUCG, UCUUCU, UCU UGC, UCU UGG, UCUUGU, UCUU UA, UCU UUC, UCU UUG, UCU UUU, UGAAAA, UGAAAC, UGAACA, UGAACC, UGAAGG, UGAAUC, UGAAUG, UGACAA, UGACAC, UGACAG, UGACCA, UGACCC, UGACCG, UGACGA, UGACGC, UGACGG, UGACGU, UGACUA, UGACUC, UGACU U, UGAGAG, UGAGAU, UGAGCA, UGAGCC, UGAGCU, UGAGGC, UGAGGU, UGAGUA, UGAGUU, UGAUAC, UGAUAG, UGAUAU, UGAUCA, UGAUCG, UGAUCU, UGAUGA, UGAUGC, UGAUGG, UGAUGU, UGAUUA, UGAU UC, UGAUUG, UGAUU U, UGCAAC, UGCAAG, UGCACA, UGCACG, UGCAGG, UGCAGU, UGCAUC, UGCCCA, UGCCCC, UGCCCG, UGCCGA, UGCCGC, UGCCGG, UGCCGU, UGCCUA, UGCCUC, UGCCUG, UGCCU U, UGCGAA, UGCGAC, UGCGAU, UGCGCC, UGCGCG, UGCGCU, UGCGGC, UGCGGG, UGCGGU, UGCGUA, UGCGUC, UGCGUG, UGCGUU, UGCUAC, UGCUAU, UGCUCC, UGCUCG, UGCUGC, UGCUGG, UGCUGU, UGCUUA, UGCUUU, UGGAAC, UGGAAG, UGGAGC, UGGAUC, UGGAUU, UGGCAA, UGGCAC, UGGCAG, UGGCCG, UGGCCU, UGGCGA, UGGCGC, UGGCGU, UGGCUA, UGGCUC, UGGCUU, UGGGAA, UGGGCA, UGGGCC, UGGGGC, UGGGUC, UGGUAA, UGGUAG, UGGUAU, UGGUCC, UGGUCG, UGGUCU, UGGUGA, UGGUGC, UGGUGG, UGGUGU, UGGU UA, UGGUUG, UGUAAA, UGUAAC, UGUAAG, UGUACC, UGUACG, UGUACU, UGUAGA, UGUAGC, UGUAGU, UGUAUC, UGUAUU, UGUCAA, UGUCAC, UGUCAG, UGUCAU, UGUCCA, UGUCCC, UG UCCG, UGUCGA, UGUCGC, UGUCGG, UGUCGU, UGUCUA, UGUCUC, UGUGAC, UGUGAG, UGUGAU, UGUGCA, UGUGGU, UGUGUA, UGUGUU, UGUUAC, UGUUAG, UGU UAU, UGUUCA, UGUUCC, UGUUCG, UGU UGG, UGUUGU, UGU UUA, UGU UUC, UGU UUG, UGUUU U, UUAAAA, UUAAAC, UUAAAG, UUAAAU, UUAACC, UUAACG, UUAACU, UUAAGU, UUAAUA, UUAAUC, UUAAUG, UUAAU U, UUACAA, UUACAC, UUACAG, UUACAU, UUACCA, UUACCC, UUACCG, UUACCU, UUACGA, UUACGC, UUACGG, UUACGU, UUACUA, UUACUC, UUACUG, UUACUU, UUAGAA, UUAGAC, UUAGCC, UUAGCG, UUAGCU, UUAGGC, UUAGGU, UUAGUA, UUAGUC, UUAGUU, UUAUAA, UUAUAC, UUAUAG, UUAUAU, UUAUCC, UUAUCG, UUAUCU, UUAUGA, UUAUGG, UUAUGU, UUAU UA, UUAUUC, UUAU UG, UUAU UU, UUCAAC, UUCAAU, UUCACA, UUCACC, UUCACG, UUCACU, UUCAGC, UUCAGG, UUCAGU, UUCAUA, UUCAUC, UUCAUG, UUCAUU, UUCCAA, UUCCCA, UUCCCG, UUCCGA, UUCCGU, UUCCU U, UUCGAA, UUCGAC, UUCGAG, UUCGAU, UUCGCA, UUCGCC, UUCGCG, UUCGCU, UUCGGA, UUCGGC, UUCGGG, UUCGGU, UUCGUA, UUCGUC, UUCGUG, UUCGU U, UUCUAC, UUCUAG, UUCUCA, UUCUCG, UUCUGG, UUCU UA, UUCUUU, UUGAAA, UUGAAC, UUGAAG, UUGAAU, UUGACC, UUGACG, UUGACU, UUGAGA, UUGAGC, UUGAGU, UUGAUA, UUGAUC, UUGAUG, UUGAUU, UUGCAA, UUGCAC, UUGCAG, UUGCAU, UUGCCC, UUGCCG, UUGCGA, UUGCGC, UUGCGG, UUGCGU, UUGCUA, UUGCUC, UUGCUG, UUGCUU, UUGGAA, UUGGAG, UUGGCC, UUGGCG, UUGGCU, UUGGGC, UUGGGU, UUGGUA, UUGGUG, UUGUAA, UUGUAC, UUGUCA, UUGUCG, UUGUCU, UUGUGC, UUGUGG, UUGU UA, UUGUUG, UUGUUU, UUUAAA, UUUAAC, UUUAAG, UUUAAU, UUUACA, UUUACC, UUUACG, UUUACU, UUUAGA, UUUAGC, UUUAGG, UUUAGU, UUUAUA, UUUAUC, UUUAUG, UUUAU U, UUUCAU, UUUCCA, UUUCCG, UUUCCU, UUUCGA, UUUCGC, UUUCGG, UUUCGU, UUUCUA, UUUCUC, UUUCUG, UUUCUU, UUUGAA, UUUGAC, UUUGAG, UUUGAU, UUUGCC, UUUGCU, UUUGGA, UUUGGC, UUUGGG, UUUGGU, UUUGUA, UUUGUC, UUUGUU,

UUUUAA, UUUUAG, UUUUAU, UUUUCC, UUUUCG, UUUUCU, UUUUGA, UUUUGC, UUUUGG, UUUUGU, UUUUUA, UUUUUC, UUUUUU

Table 2: Oligonucleotide sequences made for testing in the lab.

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89008	PTEN-01 m02	2.07734157	0.07716663	PTEN	20	HepG2	48	qRTPCR
89009	PTEN-02 m02	1.26854341	0.16243777	PTEN	20	HepG2	48	qRTPCR
89010	PTEN-03 m02	1.30714473	0.33072241	PTEN	20	HepG2	48	qRTPCR
89011	PTEN-04 m02	1.43075199	0.23754811	PTEN	20	HepG2	48	qRTPCR
1531	PTEN-05 m02	2.48295792	0.17894507	PTEN	20	HepG2	48	qRTPCR
2270	PTEN-06 m02	1.95904764	0.07701882	PTEN	20	HepG2	48	qRTPCR
2219	PTEN-07 m02	1.41561727	0.20169914	PTEN	20	HepG2	48	qRTPCR
3435	PTEN-08 m02	2.38066121	0.32688117	PTEN	20	HepG2	48	qRTPCR
3385	PTEN-09 m02	1.77863697	0.51981065	PTEN	20	HepG2	48	qRTPCR
4787	PTEN-10 m02	1.53628756	0.04477097	PTEN	20	HepG2	48	qRTPCR
4757	PTEN-11 m02	2.00722045	0.03907423	PTEN	20	HepG2	48	qRTPCR
24934	PTEN-12 m02	2.87341341	0.22858809	PTEN	20	HepG2	48	qRTPCR
24915	PTEN-13 m02	1.39985102	0.27951483	PTEN	20	HepG2	48	qRTPCR
39332	PTEN-14 m02	1.13225265	0.28233818	PTEN	20	HepG2	48	qRTPCR
39286	PTEN-15 m02	2.06522348	0.52388625	PTEN	20	HepG2	48	qRTPCR
41316	PTEN-16 m02	2.52617646	0.34816317	PTEN	20	HepG2	48	qRTPCR
41283	PTEN-17 m02	0.90722331	0.03658693	PTEN	20	HepG2	48	qRTPCR
89012	PTEN-18 m02	1.68961825	0.22045151	PTEN	20	HepG2	48	qRTPCR
89013	PTEN-19 m02	1.62789613	0.12130118	PTEN	20	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89014	PTEN-20 m02	1.22542567	0.05148674	PTEN	20	HepG2	48	qRTPCR
89015	PTEN-21 m02	2.42492141	0.18846349	PTEN	20	HepG2	48	qRTPCR
51816	PTEN-22 m02	1.42177642	0.32012534	PTEN	20	HepG2	48	qRTPCR
61111	PTEN-23 m02	2.79874813	0.41016463	PTEN	20	HepG2	48	qRTPCR
61047	PTEN-24 m02	1.95805572	0.39009138	PTEN	20	HepG2	48	qRTPCR
89016	PTEN-25 m02	0.70686318	0.0728727	PTEN	20	HepG2	48	qRTPCR
89017	PTEN-26 m02	2.02768836	0.38003317	PTEN	20	HepG2	48	qRTPCR
89018	PTEN-27 m02	4.00051813	0.78898907	PTEN	20	HepG2	48	qRTPCR
89019	PTEN-28 m02	2.60996786	0.27580702	PTEN	20	HepG2	48	qRTPCR
74236	PTEN-29 m02	1.66419883	0.10743023	PTEN	20	HepG2	48	qRTPCR
74236	PTEN-29 m08	0.1455604	0.08859417	PTEN	20	HepG2	48	qRTPCR
89028	GAPDH-01 m08	0.85279659	0.23907675	PTEN	20	HepG2	48	qRTPCR
	Ctrl Un	1.0025582	0.08223117	PTEN	0	HepG2	48	qRTPCR
89020	PTEN-31 m09	0.92246603	0.01811418	PTEN	20	HepG2	48	qRTPCR
76350	PTEN-32 m02	0.59041966	0.0553571	PTEN	20	HepG2	48	qRTPCR
76389	PTEN-33 m08	0.70839633	0.04445999	PTEN	20	HepG2	48	qRTPCR
89021	PTEN-34 m09	0.91015271	0.0100545	PTEN	20	HepG2	48	qRTPCR
89022	PTEN-35 m02	1.67446482	0.03672742	PTEN	20	HepG2	48	qRTPCR
89023	PTEN-36 m08	0.20413836	0.00285569	PTEN	20	HepG2	48	qRTPCR
89024	PTEN-37 m09	0.8558968	0.11695596	PTEN	20	HepG2	48	qRTPCR
80510	PTEN-38 m02	1.27326102	0.06420006	PTEN	20	HepG2	48	qRTPCR
80568	PTEN-39 m08	1.09455124	0.02327048	PTEN	20	HepG2	48	qRTPCR
89025	PTEN-40 m09	1.01353301	0.06007095	PTEN	20	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	Ctrl Lipo	1.00879958	0.02091684	PTEN	0	HepG2	48	qRTPCR
	Ctrl Un	1.00106773	0.03209554	PTEN	0	HepG2	48	qRTPCR
89008	PTEN-01 m02	1.16942963	0.27074957	PTEN	40	HepG2	48	qRTPCR
89009	PTEN-02 m02	0.58364213	0.08602143	PTEN	40	HepG2	48	qRTPCR
89010	PTEN-03 m02	0.57577003	0.1469602	PTEN	40	HepG2	48	qRTPCR
89011	PTEN-04 m02	0.74661135	0.21933073	PTEN	40	HepG2	48	qRTPCR
1531	PTEN-05 m02	1.0956027	0.25635873	PTEN	40	HepG2	48	qRTPCR
2270	PTEN-06 m02	1.24117945	0.06291238	PTEN	40	HepG2	48	qRTPCR
2219	PTEN-07 m02	0.99520541	0.09748897	PTEN	40	HepG2	48	qRTPCR
3435	PTEN-08 m02	1.14301868	0.11760352	PTEN	40	HepG2	48	qRTPCR
3385	PTEN-09 m02	0.79500619	0.0643118	PTEN	40	HepG2	48	qRTPCR
4787	PTEN-10 m02	0.91090948	0.09807166	PTEN	40	HepG2	48	qRTPCR
4757	PTEN-11 m02	1.29538626	0.10511705	PTEN	40	HepG2	48	qRTPCR
24934	PTEN-12 m02	1.5806376	0.1204557	PTEN	40	HepG2	48	qRTPCR
24915	PTEN-13 m02	0.89485268	0.06086845	PTEN	40	HepG2	48	qRTPCR
39332	PTEN-14 m02	0.53139911	0.04823343	PTEN	40	HepG2	48	qRTPCR
39286	PTEN-15 m02	1.1093499	0.16465839	PTEN	40	HepG2	48	qRTPCR
41316	PTEN-16 m02	1.66867704	0.22298241	PTEN	40	HepG2	48	qRTPCR
41283	PTEN-17 m02	0.58678397	0.07173485	PTEN	40	HepG2	48	qRTPCR
89012	PTEN-18 m02	0.89349839	0.10026699	PTEN	40	HepG2	48	qRTPCR
89013	PTEN-19 m02	1.11350447	0.1080962	PTEN	40	HepG2	48	qRTPCR
89014	PTEN-20 m02	0.66291212	0.09468355	PTEN	40	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.62278391	0.5136251	PTEN	40	HepG2	48	qRTPCR
51816	PTEN-22	0.84245363	0.07213382	PTEN	40	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
61111	PTEN-23 m02	1.60469847	0.37430621	PTEN	40	HepG2	48	qRTPCR
61047	PTEN-24 m02	1.31940485	0.50246153	PTEN	40	HepG2	48	qRTPCR
89016	PTEN-25 m02	0.49625983	0.0643317	PTEN	40	HepG2	48	qRTPCR
89017	PTEN-26 m02	2.04149224	0.23998972	PTEN	40	HepG2	48	qRTPCR
89018	PTEN-27 m02	2.87891201	0.42448096	PTEN	40	HepG2	48	qRTPCR
89019	PTEN-28 m02	1.3180416	0.29901882	PTEN	40	HepG2	48	qRTPCR
74236	PTEN-29 m02	0.87647912	0.04578777	PTEN	40	HepG2	48	qRTPCR
74236	PTEN-29 m08	0.32506054	0.08996561	PTEN	40	HepG2	48	qRTPCR
89028	GAPDH-01 m08	0.53336134	0.20011246	PTEN	50	HepG2	48	qRTPCR
	Ctrl Lipo	0.60524214	0.0625741	PTEN	0	HepG2	48	qRTPCR
	Ctrl Un	1.0025582	0.08223117	PTEN	0	HepG2	48	qRTPCR
89020	PTEN-31 m09	0.79191976	0.02979202	PTEN	40	HepG2	48	qRTPCR
76350	PTEN-32 m02	0.54328864	0.00958811	PTEN	40	HepG2	48	qRTPCR
76389	PTEN-33 m08	0.73927941	0.08871459	PTEN	40	HepG2	48	qRTPCR
89021	PTEN-34 m09	0.76155003	0.01629929	PTEN	40	HepG2	48	qRTPCR
89022	PTEN-35 m02	1.52719074	0.05398883	PTEN	40	HepG2	48	qRTPCR
89023	PTEN-36 m08	0.28703011	0.04288889	PTEN	40	HepG2	48	qRTPCR
89024	PTEN-37 m09	0.81216946	0.03832362	PTEN	40	HepG2	48	qRTPCR
80510	PTEN-38 m02	1.17120221	0.07105324	PTEN	40	HepG2	48	qRTPCR
80568	PTEN-39 m08	0.73651641	0.04205119	PTEN	40	HepG2	48	qRTPCR
89025	PTEN-40 m09	0.77040957	0.09600221	PTEN	40	HepG2	48	qRTPCR
	Ctrl Lipo	1.00879958	0.02091684	PTEN	0	HepG2	48	qRTPCR
	Ctrl Un	1.00106773	0.03209554	PTEN	0	HepG2	48	qRTPCR
	Ctrl Un	1.65645803	0.08223117	PTEN	20	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	Ctrl Lipo	1	0.0625741	PTEN	20	HepG2		qRTPCR
89028	GAPDH-01 m08	1.40901721	0.23907675	PTEN	20	HepG2		qRTPCR
89008	PTEN-01 m02	3.43224872	0.07716663	PTEN	20	HepG2		qRTPCR
89009	PTEN-02 m02	2.09592711	0.16243777	PTEN	20	HepG2		qRTPCR
89010	PTEN-03 m02	2.15970541	0.33072241	PTEN	20	HepG2		qRTPCR
89011	PTEN-04 m02	2.3639332	0.23754811	PTEN	20	HepG2		qRTPCR
1531	PTEN-05 m02	4.10242075	0.17894507	PTEN	20	HepG2		qRTPCR
2270	PTEN-06 m02	3.23679979	0.07701882	PTEN	20	HepG2		qRTPCR
2219	PTEN-07 m02	2.33892714	0.20169914	PTEN	20	HepG2		qRTPCR
3435	PTEN-08 m02	3.93340293	0.32688117	PTEN	20	HepG2		qRTPCR
3385	PTEN-09 m02	2.93871964	0.51981065	PTEN	20	HepG2		qRTPCR
4787	PTEN-10 m02	2.53830236	0.04477097	PTEN	20	HepG2		qRTPCR
4757	PTEN-11 m02	3.31639241	0.03907423	PTEN	20	HepG2		qRTPCR
24934	PTEN-12 m02	4.74754352	0.22858809	PTEN	20	HepG2		qRTPCR
24915	PTEN-13 m02	2.31287765	0.27951483	PTEN	20	HepG2		qRTPCR
39332	PTEN-14 m02	1.87074326	0.28233818	PTEN	20	HepG2		qRTPCR
39286	PTEN-15 m02	3.41222685	0.52388625	PTEN	20	HepG2		qRTPCR
41316	PTEN-16 m02	4.17382777	0.34816317	PTEN	20	HepG2		qRTPCR
41283	PTEN-17 m02	1.49894273	0.03658693	PTEN	20	HepG2		qRTPCR
89012	PTEN-18 m02	2.79164014	0.22045151	PTEN	20	HepG2		qRTPCR
89013	PTEN-19 m02	2.68966091	0.12130118	PTEN	20	HepG2		qRTPCR
89014	PTEN-20 m02	2.02468662	0.05148674	PTEN	20	HepG2		qRTPCR
89015	PTEN-21 m02	4.00653101	0.18846349	PTEN	20	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
51816	PTEN-22 m02	2.34910348	0.32012534	PTEN	20	HepG2		qRTPCR
61111	PTEN-23 m02	4.62417922	0.41016463	PTEN	20	HepG2		qRTPCR
61047	PTEN-24 m02	3.23516092	0.39009138	PTEN	20	HepG2		qRTPCR
89016	PTEN-25 m02	1.16790147	0.0728727	PTEN	20	HepG2		qRTPCR
89017	PTEN-26 m02	3.35021013	0.38003317	PTEN	20	HepG2		qRTPCR
89018	PTEN-27 m02	6.60978121	0.78898907	PTEN	20	HepG2		qRTPCR
89019	PTEN-28 m02	4.31227054	0.27580702	PTEN	20	HepG2		qRTPCR
74236	PTEN-29 m02	2.74964136	0.10743023	PTEN	20	HepG2		qRTPCR
74236	PTEN-29 m08	0.24049945	0.08859417	PTEN	20	HepG2		qRTPCR
89020	PTEN-31 m09	0.91441952	0.01811418	PTEN	20	HepG2		qRTPCR
76350	PTEN-32 m02	0.58526953	0.0553571	PTEN	20	HepG2		qRTPCR
76389	PTEN-33 m08	0.70221711	0.04445999	PTEN	20	HepG2		qRTPCR
89021	PTEN-34 m09	0.90221361	0.0100545	PTEN	20	HepG2		qRTPCR
89022	PTEN-35 m02	1.65985875	0.03672742	PTEN	20	HepG2		qRTPCR
89023	PTEN-36 m08	0.2023577	0.00285569	PTEN	20	HepG2		qRTPCR
89024	PTEN-37 m09	0.84843097	0.11695596	PTEN	20	HepG2		qRTPCR
80510	PTEN-38 m02	1.26215458	0.06420006	PTEN	20	HepG2		qRTPCR
80568	PTEN-39 m08	1.08500366	0.02327048	PTEN	20	HepG2		qRTPCR
89025	PTEN-40 m09	1.00469214	0.06007095	PTEN	20	HepG2		qRTPCR
	Ctrl Lipo	1	0.02091684	PTEN	20	HepG2		qRTPCR
	Ctrl Un	0.99233559	0.03209554	PTEN	20	HepG2		qRTPCR
	Ctrl Un	1.65645803	0.08223117	PTEN	50	HepG2		qRTPCR
	Ctrl Lipo	1	0.0625741	PTEN	50	HepG2		qRTPCR
89028	GAPDH-01 m08	0.88123629	0.20011246	PTEN	50	HepG2		qRTPCR
89008	PTEN-01	1.93216822	0.27074957	PTEN	50	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
89009	PTEN-02 m02	0.96431179	0.08602143	PTEN	50	HepG2		qRTPCR
89010	PTEN-03 m02	0.95130526	0.1469602	PTEN	50	HepG2		qRTPCR
89011	PTEN-04 m02	1.23357463	0.21933073	PTEN	50	HepG2		qRTPCR
1531	PTEN-05 m02	1.81018905	0.25635873	PTEN	50	HepG2		qRTPCR
2270	PTEN-06 m02	2.05071551	0.06291238	PTEN	50	HepG2		qRTPCR
2219	PTEN-07 m02	1.64430951	0.09748897	PTEN	50	HepG2		qRTPCR
3435	PTEN-08 m02	1.88853122	0.11760352	PTEN	50	HepG2		qRTPCR
3385	PTEN-09 m02	1.3135341	0.0643118	PTEN	50	HepG2		qRTPCR
4787	PTEN-10 m02	1.50503314	0.09807166	PTEN	50	HepG2		qRTPCR
4757	PTEN-11 m02	2.14027771	0.10511705	PTEN	50	HepG2		qRTPCR
24934	PTEN-12 m02	2.61157889	0.1204557	PTEN	50	HepG2		qRTPCR
24915	PTEN-13 m02	1.47850359	0.06086845	PTEN	50	HepG2		qRTPCR
39332	PTEN-14 m02	0.87799423	0.04823343	PTEN	50	HepG2		qRTPCR
39286	PTEN-15 m02	1.83290261	0.16465839	PTEN	50	HepG2		qRTPCR
41316	PTEN-16 m02	2.7570404	0.22298241	PTEN	50	HepG2		qRTPCR
41283	PTEN-17 m02	0.96950283	0.07173485	PTEN	50	HepG2		qRTPCR
89012	PTEN-18 m02	1.476266	0.10026699	PTEN	50	HepG2		qRTPCR
89013	PTEN-19 m02	1.83976692	0.1080962	PTEN	50	HepG2		qRTPCR
89014	PTEN-20 m02	1.09528414	0.09468355	PTEN	50	HepG2		qRTPCR
89015	PTEN-21 m02	2.68121434	0.5136251	PTEN	50	HepG2		qRTPCR
51816	PTEN-22 m02	1.39192824	0.07213382	PTEN	50	HepG2		qRTPCR
61111	PTEN-23 m02	2.65133301	0.37430621	PTEN	50	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
61047	PTEN-24 m02	2.17996196	0.50246153	PTEN	50	HepG2		qRTPCR
89016	PTEN-25 m02	0.81993601	0.0643317	PTEN	50	HepG2		qRTPCR
89017	PTEN-26 m02	3.37301735	0.23998972	PTEN	50	HepG2		qRTPCR
89018	PTEN-27 m02	4.75662849	0.42448096	PTEN	50	HepG2		qRTPCR
89019	PTEN-28 m02	2.17770957	0.29901882	PTEN	50	HepG2		qRTPCR
74236	PTEN-29 m02	1.44814622	0.04578777	PTEN	50	HepG2		qRTPCR
74236	PTEN-29 m08	0.53707519	0.08996561	PTEN	50	HepG2		qRTPCR
89020	PTEN-31 m09	0.78501198	0.02979202	PTEN	50	HepG2		qRTPCR
76350	PTEN-32 m02	0.53854963	0.00958811	PTEN	50	HepG2		qRTPCR
76389	PTEN-33 m08	0.7328308	0.08871459	PTEN	50	HepG2		qRTPCR
89021	PTEN-34 m09	0.75490717	0.01629929	PTEN	50	HepG2		qRTPCR
89022	PTEN-35 m02	1.51386932	0.05398883	PTEN	50	HepG2		qRTPCR
89023	PTEN-36 m08	0.2845264	0.04288889	PTEN	50	HepG2		qRTPCR
89024	PTEN-37 m09	0.80508505	0.03832362	PTEN	50	HepG2		qRTPCR
80510	PTEN-38 m02	1.16098602	0.07105324	PTEN	50	HepG2		qRTPCR
80568	PTEN-39 m08	0.73009191	0.04205119	PTEN	50	HepG2		qRTPCR
89025	PTEN-40 m09	0.76368942	0.09600221	PTEN	50	HepG2		qRTPCR
	Ctrl Lipo	1	0.02091684	PTEN	50	HepG2		qRTPCR
	Ctrl Un	0.99233559	0.03209554	PTEN	50	HepG2		qRTPCR
	Ctrl Un	1	0.04964277	PTEN	20	HepG2		qRTPCR
	Ctrl Lipo	0.60369776	0	PTEN	20	HepG2		qRTPCR
89028	GAPDH-01 m08	0.85062053	0.1443301	PTEN	20	HepG2		qRTPCR
89008	PTEN-01 m02	2.07204086	0.04658532	PTEN	20	HepG2		qRTPCR
89009	PTEN-02 m02	1.2653065	0.09806331	PTEN	20	HepG2		qRTPCR
89010	PTEN-03	1.30380932	0.19965638	PTEN	20	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
89011	PTEN-04 m02	1.42710117	0.14340726	PTEN	20	HepG2		qRTPCR
1531	PTEN-05 m02	2.47662221	0.10802874	PTEN	20	HepG2		qRTPCR
2270	PTEN-06 m02	1.95404878	0.04649609	PTEN	20	HepG2		qRTPCR
2219	PTEN-07 m02	1.41200508	0.12176532	PTEN	20	HepG2		qRTPCR
3435	PTEN-08 m02	2.37458653	0.19733743	PTEN	20	HepG2		qRTPCR
3385	PTEN-09 m02	1.77409846	0.31380852	PTEN	20	HepG2		qRTPCR
4787	PTEN-10 m02	1.53236745	0.02702814	PTEN	20	HepG2		qRTPCR
4757	PTEN-11 m02	2.00209867	0.02358903	PTEN	20	HepG2		qRTPCR
24934	PTEN-12 m02	2.86608139	0.13799812	PTEN	20	HepG2		qRTPCR
24915	PTEN-13 m02	1.39627906	0.16874248	PTEN	20	HepG2		qRTPCR
39332	PTEN-14 m02	1.12936351	0.17044692	PTEN	20	HepG2		qRTPCR
39286	PTEN-15 m02	2.0599537	0.31626896	PTEN	20	HepG2		qRTPCR
41316	PTEN-16 m02	2.51973047	0.21018532	PTEN	20	HepG2		qRTPCR
41283	PTEN-17 m02	0.90490837	0.02208745	PTEN	20	HepG2		qRTPCR
89012	PTEN-18 m02	1.6853069	0.13308608	PTEN	20	HepG2		qRTPCR
89013	PTEN-19 m02	1.62374227	0.07322925	PTEN	20	HepG2		qRTPCR
89014	PTEN-20 m02	1.22229878	0.03108243	PTEN	20	HepG2		qRTPCR
89015	PTEN-21 m02	2.4187338	0.11377499	PTEN	20	HepG2		qRTPCR
51816	PTEN-22 m02	1.41814851	0.19325895	PTEN	20	HepG2		qRTPCR
61111	PTEN-23 m02	2.79160664	0.24761547	PTEN	20	HepG2		qRTPCR
61047	PTEN-24 m02	1.9530594	0.23549729	PTEN	20	HepG2		qRTPCR
89016	PTEN-25 m02	0.7050595	0.04399309	PTEN	20	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89017	PTEN-26 m02	2.02251435	0.22942517	PTEN	20	HepG2		qRTPCR
89018	PTEN-27 m02	3.99031011	0.47631093	PTEN	20	HepG2		qRTPCR
89019	PTEN-28 m02	2.60330806	0.16650408	PTEN	20	HepG2		qRTPCR
74236	PTEN-29 m02	1.65995233	0.06485539	PTEN	20	HepG2		qRTPCR
74236	PTEN-29 m08	0.14518898	0.0534841	PTEN	20	HepG2		qRTPCR
89020	PTEN-31 m09	0.92148213	0.01825408	PTEN	20	HepG2		qRTPCR
76350	PTEN-32 m02	0.58978992	0.05578465	PTEN	20	HepG2		qRTPCR
76389	PTEN-33 m08	0.70764076	0.04480338	PTEN	20	HepG2		qRTPCR
89021	PTEN-34 m09	0.90918195	0.01013216	PTEN	20	HepG2		qRTPCR
89022	PTEN-35 m02	1.67267884	0.03701109	PTEN	20	HepG2		qRTPCR
89023	PTEN-36 m08	0.20392063	0.00287774	PTEN	20	HepG2		qRTPCR
89024	PTEN-37 m09	0.85498391	0.11785929	PTEN	20	HepG2		qRTPCR
80510	PTEN-38 m02	1.27190297	0.06469592	PTEN	20	HepG2		qRTPCR
80568	PTEN-39 m08	1.0933838	0.02345021	PTEN	20	HepG2		qRTPCR
89025	PTEN-40 m09	1.01245199	0.06053492	PTEN	20	HepG2		qRTPCR
	Ctrl Lipo	1.00772361	0.02107839	PTEN	20	HepG2		qRTPCR
	Ctrl Un	1	0.03234343	PTEN	20	HepG2		qRTPCR
	Ctrl Un	1	0.04964277	PTEN	20	HepG2		qRTPCR
	Ctrl Lipo	0.60369776	0.03777585	PTEN	20	HepG2		qRTPCR
89028	GAPDH-01 m08	0.53200038	0.12080745	PTEN	20	HepG2		qRTPCR
89008	PTEN-01 m02	1.16644562	0	PTEN	50	HepG2		qRTPCR
89009	PTEN-02 m02	0.58215287	0.05193094	PTEN	50	HepG2		qRTPCR
89010	PTEN-03 m02	0.57430085	0.08871955	PTEN	50	HepG2		qRTPCR
89011	PTEN-04 m02	0.74470624	0.13240947	PTEN	50	HepG2		qRTPCR
1531	PTEN-05	1.09280707	0.15476319	PTEN	50	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
2270	PTEN-06 m02	1.23801236	0.03798006	PTEN	50	HepG2		qRTPCR
2219	PTEN-07 m02	0.99266597	0.05885387	PTEN	50	HepG2		qRTPCR
3435	PTEN-08 m02	1.14010207	0.07099698	PTEN	50	HepG2		qRTPCR
3385	PTEN-09 m02	0.79297759	0.03882489	PTEN	50	HepG2		qRTPCR
4787	PTEN-10 m02	0.90858514	0.05920564	PTEN	50	HepG2		qRTPCR
4757	PTEN-11 m02	1.29208086	0.06345893	PTEN	50	HepG2		qRTPCR
24934	PTEN-12 m02	1.57660432	0.07271884	PTEN	50	HepG2		qRTPCR
24915	PTEN-13 m02	0.89256931	0.03674615	PTEN	50	HepG2		qRTPCR
39332	PTEN-14 m02	0.53004315	0.02911841	PTEN	50	HepG2		qRTPCR
39286	PTEN-15 m02	1.1065192	0.0994039	PTEN	50	HepG2		qRTPCR
41316	PTEN-16 m02	1.66441911	0.13461398	PTEN	50	HepG2		qRTPCR
41283	PTEN-17 m02	0.58528669	0.04330617	PTEN	50	HepG2		qRTPCR
89012	PTEN-18 m02	0.89121847	0.06053096	PTEN	50	HepG2		qRTPCR
89013	PTEN-19 m02	1.11066317	0.06525743	PTEN	50	HepG2		qRTPCR
89014	PTEN-20 m02	0.66122058	0.05716025	PTEN	50	HepG2		qRTPCR
89015	PTEN-21 m02	1.61864309	0.31007432	PTEN	50	HepG2		qRTPCR
51816	PTEN-22 m02	0.84030396	0.04354703	PTEN	50	HepG2		qRTPCR
61111	PTEN-23 m02	1.6006038	0.22596782	PTEN	50	HepG2		qRTPCR
61047	PTEN-24 m02	1.31603815	0.3033349	PTEN	50	HepG2		qRTPCR
89016	PTEN-25 m02	0.49499353	0.03883691	PTEN	50	HepG2		qRTPCR
89017	PTEN-26 m02	2.03628302	0.14488126	PTEN	50	HepG2		qRTPCR
89018	PTEN-27 m02	2.87156596	0.25625821	PTEN	50	HepG2		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89019	PTEN-28 m02	1.31467839	0.18051699	PTEN	50	HepG2		qRTPCR
74236	PTEN-29 m02	0.87424263	0.02764197	PTEN	50	HepG2		qRTPCR
74236	PTEN-29 m08	0.32423109	0.05431204	PTEN	50	HepG2		qRTPCR
89020	PTEN-31 m09	0.7910751	0.03002212	PTEN	50	HepG2		qRTPCR
76350	PTEN-32 m02	0.54270918	0.00966216	PTEN	50	HepG2		qRTPCR
76389	PTEN-33 m08	0.7384909	0.08939978	PTEN	50	HepG2		qRTPCR
89021	PTEN-34 m09	0.76073777	0.01642518	PTEN	50	HepG2		qRTPCR
89022	PTEN-35 m02	1.52556185	0.05440582	PTEN	50	HepG2		qRTPCR
89023	PTEN-36 m08	0.28672397	0.04322014	PTEN	50	HepG2		qRTPCR
89024	PTEN-37 m09	0.81130321	0.03861962	PTEN	50	HepG2		qRTPCR
80510	PTEN-38 m02	1.16995302	0.07160203	PTEN	50	HepG2		qRTPCR
80568	PTEN-39 m08	0.73573085	0.04237598	PTEN	50	HepG2		qRTPCR
89025	PTEN-40 m09	0.76958786	0.0967437	PTEN	50	HepG2		qRTPCR
	Ctrl Lipo	1.00772361	0.02107839	PTEN	50	HepG2		qRTPCR
	Ctrl Un	1	0.03234343	PTEN	50	HepG2		qRTPCR
89009	PTEN-02 m02	1.0982509	0.1586551	PTEN	30	HepG2	24	qRTPCR
89009	PTEN-02 m02	0.99719324	0.05132647	PTEN	11	HepG2	24	qRTPCR
89009	PTEN-02 m02	0.88589652	0.12645115	PTEN	3	HepG2	24	qRTPCR
89009	PTEN-02 m02	1.2230848	0.06052544	PTEN	1	HepG2	24	qRTPCR
2270	PTEN-06 m02	1.62728701	0.0451605	PTEN	30	HepG2	24	qRTPCR
2270	PTEN-06 m02	1.76720502	0.10294151	PTEN	11	HepG2	24	qRTPCR
2270	PTEN-06 m02	1.21745384	0.06668203	PTEN	3	HepG2	24	qRTPCR
2270	PTEN-06 m02	1.40404264	0.09823707	PTEN	1	HepG2	24	qRTPCR
3435	PTEN-08	1.20540523	0.06145149	PTEN	30	HepG2	24	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
3435	PTEN-08 m02	1.22162236	0.12818637	PTEN	11	HepG2	24	qRTPCR
3435	PTEN-08 m02	1.07655185	0.01829564	PTEN	3	HepG2	24	qRTPCR
3435	PTEN-08 m02	1.22200493	0.03064369	PTEN	1	HepG2	24	qRTPCR
4757	PTEN-11 m02	1.83239021	0.23862574	PTEN	30	HepG2	24	qRTPCR
4757	PTEN-11 m02	1.45452274	0.06069463	PTEN	11	HepG2	24	qRTPCR
4757	PTEN-11 m02	1.11924938	0.11721998	PTEN	3	HepG2	24	qRTPCR
4757	PTEN-11 m02	1.24880457	0.06593657	PTEN	1	HepG2	24	qRTPCR
24934	PTEN-12 m02	2.23991852	0.30124776	PTEN	30	HepG2	24	qRTPCR
24934	PTEN-12 m02	1.50154797	0.15484213	PTEN	10	HepG2	24	qRTPCR
24934	PTEN-12 m02	0.98072498	0.0611128	PTEN	3	HepG2	24	qRTPCR
24934	PTEN-12 m02	0.81034647	0.04567827	PTEN	1	HepG2	24	qRTPCR
39332	PTEN-14 m02	0.99514277	0.07636867	PTEN	30	HepG2	24	qRTPCR
39332	PTEN-14 m02	0.97907289	0.01006397	PTEN	10	HepG2	24	qRTPCR
39332	PTEN-14 m02	0.84459155	0.03335593	PTEN	3	HepG2	24	qRTPCR
39332	PTEN-14 m02	0.88820806	0.02650809	PTEN	1	HepG2	24	qRTPCR
89012	PTEN-18 m02	1.49952932	0.03578299	PTEN	30	HepG2	24	qRTPCR
89012	PTEN-18 m02	1.34422924	0.07018228	PTEN	10	HepG2	24	qRTPCR
89012	PTEN-18 m02	1.00497711	0.01061478	PTEN	3	HepG2	24	qRTPCR
89012	PTEN-18 m02	0.92278419	0.03476822	PTEN	1	HepG2	24	qRTPCR
89014	PTEN-20 m02	1.51345667	0.09728243	PTEN	30	HepG2	24	qRTPCR
89014	PTEN-20 m02	1.3863721	0.04205612	PTEN	10	HepG2	24	qRTPCR
89014	PTEN-20 m02	0.89557657	0.01105855	PTEN	3	HepG2	24	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89014	PTEN-20 m02	0.86194444	0.0364247	PTEN	1	HepG2	24	qRTPCR
89015	PTEN-21 m02	1.30538318	0.16314638	PTEN	30	HepG2	24	qRTPCR
89015	PTEN-21 m02	1.18062371	0.09732135	PTEN	21	HepG2	24	qRTPCR
89015	PTEN-21 m02	0.97040661	0.06963223	PTEN	3	HepG2	24	qRTPCR
89015	PTEN-21 m02	1.0278295	0.03699383	PTEN	1	HepG2	24	qRTPCR
61047	PTEN-24 m02	0.99204407	0.17988926	PTEN	30	HepG2	24	qRTPCR
61047	PTEN-24 m02	1.1180164	0.04440793	PTEN	10	HepG2	24	qRTPCR
61047	PTEN-24 m02	0.99799219	0.02293249	PTEN	3	HepG2	24	qRTPCR
61047	PTEN-24 m02	1.01719516	0.08656623	PTEN	1	HepG2	24	qRTPCR
89017	PTEN-26 m02	1.5379591	0.06571744	PTEN	30	HepG2	24	qRTPCR
89017	PTEN-26 m02	1.26911916	0.08909136	PTEN	26	HepG2	24	qRTPCR
89017	PTEN-26 m02	0.97204718	0.04196938	PTEN	3	HepG2	24	qRTPCR
89017	PTEN-26 m02	1.06410638	0.10576526	PTEN	1	HepG2	24	qRTPCR
74236	PTEN-29 m02	0.82482925	0.13273844	PTEN	30	HepG2	24	qRTPCR
74236	PTEN-29 m02	0.91107691	0.01926194	PTEN	10	HepG2	24	qRTPCR
74236	PTEN-29 m02	0.98053985	0.08594844	PTEN	3	HepG2	24	qRTPCR
74236	PTEN-29 m02	0.9651474	0.03931144	PTEN	1	HepG2	24	qRTPCR
80510	PTEN-38 m02	1.25307314	0.07084655	PTEN	30	HepG2	24	qRTPCR
80510	PTEN-38 m02	1.28169767	0.02097112	PTEN	38	HepG2	24	qRTPCR
80510	PTEN-38 m02	1.00537715	0.04083891	PTEN	3	HepG2	24	qRTPCR
80510	PTEN-38 m02	1.0492189	0.0349326	PTEN	1	HepG2	24	qRTPCR
89026	EPO-24 m02	0.86760378	0.03265872	PTEN	30	HepG2	24	qRTPCR
89026	EPO-24	0.81482346	0.08728095	PTEN	10	HepG2	24	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
89026	EPO-24 m02	1.06392969	0.05303057	PTEN	3	HepG2	24	qRTPCR
89026	EPO-24 m02	0.7805751	0.0305135	PTEN	1	HepG2	24	qRTPCR
89027	EPO-26 m02	1.33551385	0.05349752	PTEN	30	HepG2	24	qRTPCR
89027	EPO-26 m02	1.22390414	0.03938204	PTEN	10	HepG2	24	qRTPCR
89027	EPO-26 m02	1.02694941	0.00480371	PTEN	3	HepG2	24	qRTPCR
89027	EPO-26 m02	1.01459505	0.08741608	PTEN	1	HepG2	24	qRTPCR
	Ctrl Lipo	1.00462922	0.06037335	PTEN	0	HepG2	24	qRTPCR
	Ctrl Un	0.88071848	0.12784742	PTEN	0	HepG2	24	qRTPCR
89009	PTEN-02 m02	1.46477803	0.7474237	PTEN	30	HepG2	48	qRTPCR
89009	PTEN-02 m02	1.01137021	0.16132825	PTEN	11	HepG2	48	qRTPCR
89009	PTEN-02 m02	0.81310277	0.06880307	PTEN	3	HepG2	48	qRTPCR
89009	PTEN-02 m02	0.8486586	0.01849678	PTEN	1	HepG2	48	qRTPCR
2270	PTEN-06 m02	2.85710097	0.35776687	PTEN	30	HepG2	48	qRTPCR
2270	PTEN-06 m02	1.18875887	0.03783696	PTEN	11	HepG2	48	qRTPCR
2270	PTEN-06 m02	0.95449277	0.0583779	PTEN	3	HepG2	48	qRTPCR
2270	PTEN-06 m02	0.96211099	0.04721487	PTEN	1	HepG2	48	qRTPCR
3435	PTEN-08 m02	1.88035523	0.18243256	PTEN	30	HepG2	48	qRTPCR
3435	PTEN-08 m02	1.49020931	0.20520954	PTEN	11	HepG2	48	qRTPCR
3435	PTEN-08 m02	0.85554216	0.00592182	PTEN	3	HepG2	48	qRTPCR
3435	PTEN-08 m02	0.96517098	0.04200204	PTEN	1	HepG2	48	qRTPCR
4757	PTEN-11 m02	3.22705308	0.6903216	PTEN	30	HepG2	48	qRTPCR
4757	PTEN-11 m02	1.42835425	0.02553456	PTEN	11	HepG2	48	qRTPCR
4757	PTEN-11 m02	1.04751998	0.05158269	PTEN	3	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
4757	PTEN-11 m02	0.89693723	0.02115135	PTEN	1	HepG2	48	qRTPCR
24934	PTEN-12 m02	4.13121569	0.35536819	PTEN	30	HepG2	48	qRTPCR
24934	PTEN-12 m02	2.07585312	0.23260644	PTEN	10	HepG2	48	qRTPCR
24934	PTEN-12 m02	0.8531069	0.03670898	PTEN	3	HepG2	48	qRTPCR
24934	PTEN-12 m02	0.97079745	0.04386586	PTEN	1	HepG2	48	qRTPCR
39332	PTEN-14 m02	1.08646801	0.12188481	PTEN	30	HepG2	48	qRTPCR
39332	PTEN-14 m02	0.94777822	0.07122232	PTEN	10	HepG2	48	qRTPCR
39332	PTEN-14 m02	0.87325546	0.01209211	PTEN	3	HepG2	48	qRTPCR
39332	PTEN-14 m02	1.02829335	0.03677628	PTEN	1	HepG2	48	qRTPCR
89012	PTEN-18 m02	1.6596831	0.0716892	PTEN	30	HepG2	48	qRTPCR
89012	PTEN-18 m02	1.11386544	0.0075925	PTEN	10	HepG2	48	qRTPCR
89012	PTEN-18 m02	0.82274509	0.06384491	PTEN	3	HepG2	48	qRTPCR
89012	PTEN-18 m02	0.98683131	0.01512816	PTEN	1	HepG2	48	qRTPCR
89014	PTEN-20 m02	2.12211892	0.09010447	PTEN	30	HepG2	48	qRTPCR
89014	PTEN-20 m02	1.30781117	0.12046862	PTEN	10	HepG2	48	qRTPCR
89014	PTEN-20 m02	0.94736486	0.09664968	PTEN	3	HepG2	48	qRTPCR
89014	PTEN-20 m02	1.10803154	0.14710099	PTEN	1	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.61396358	0.04820963	PTEN	30	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.51129517	0.02945828	PTEN	21	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.16458905	0.0729312	PTEN	3	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.1654895	0.04826152	PTEN	1	HepG2	48	qRTPCR
61047	PTEN-24 m02	1.64326629	0.06246528	PTEN	30	HepG2	48	qRTPCR
61047	PTEN-24	1.85353816	0.09219538	PTEN	10	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
61047	PTEN-24 m02	1.23903878	0.07674058	PTEN	3	HepG2	48	qRTPCR
61047	PTEN-24 m02	1.1174449	0.05886819	PTEN	1	HepG2	48	qRTPCR
89017	PTEN-26 m02	2.01287105	0.141602	PTEN	30	HepG2	48	qRTPCR
89017	PTEN-26 m02	1.61056721	0.04139243	PTEN	26	HepG2	48	qRTPCR
89017	PTEN-26 m02	1.1545886	0.02124798	PTEN	3	HepG2	48	qRTPCR
89017	PTEN-26 m02	0.95517578	0.01388491	PTEN	1	HepG2	48	qRTPCR
74236	PTEN-29 m02	1.03846275	0.02923373	PTEN	30	HepG2	48	qRTPCR
74236	PTEN-29 m02	1.02821907	0.04727622	PTEN	10	HepG2	48	qRTPCR
74236	PTEN-29 m02	0.9190216	0.00144861	PTEN	3	HepG2	48	qRTPCR
74236	PTEN-29 m02	0.92302254	0.03985553	PTEN	1	HepG2	48	qRTPCR
80510	PTEN-38 m02	1.90042475	0.08465078	PTEN	30	HepG2	48	qRTPCR
80510	PTEN-38 m02	1.36286581	0.08694025	PTEN	38	HepG2	48	qRTPCR
80510	PTEN-38 m02	0.9684545	0.0800668	PTEN	3	HepG2	48	qRTPCR
80510	PTEN-38 m02	0.91404889	0.0427886	PTEN	1	HepG2	48	qRTPCR
89026	EPO-24 m02	0.99305557	0.03814135	PTEN	30	HepG2	48	qRTPCR
89026	EPO-24 m02	0.77547435	0.04235052	PTEN	10	HepG2	48	qRTPCR
89026	EPO-24 m02	0.85539995	0.07078874	PTEN	3	HepG2	48	qRTPCR
89026	EPO-24 m02	0.87696025	0.08296927	PTEN	1	HepG2	48	qRTPCR
89027	EPO-26 m02	2.01641558	0.09576255	PTEN	30	HepG2	48	qRTPCR
89027	EPO-26 m02	1.22175384	0.04802197	PTEN	10	HepG2	48	qRTPCR
89027	EPO-26 m02	1.16564668	0.11262306	PTEN	3	HepG2	48	qRTPCR
89027	EPO-26 m02	0.82858321	0.02271264	PTEN	1	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	Ctrl Lipo	1.05767042	0.17116388	PTEN	0	HepG2	48	qRTPCR
	Ctrl Un	0.93915544	0.10892164	PTEN	0	HepG2	48	qRTPCR
89009	PTEN-02 m02	0.97666252	0.1354761	PTEN	30	HepG2	72	qRTPCR
89009	PTEN-02 m02	1.00752547	0.16426145	PTEN	11	HepG2	72	qRTPCR
89009	PTEN-02 m02	0.81755697	0.03379991	PTEN	3	HepG2	72	qRTPCR
89009	PTEN-02 m02	1.06992971	0.1605443	PTEN	1	HepG2	72	qRTPCR
2270	PTEN-06 m02	3.41999891	0.16738836	PTEN	30	HepG2	72	qRTPCR
2270	PTEN-06 m02	1.25174068	0.05649362	PTEN	11	HepG2	72	qRTPCR
2270	PTEN-06 m02	1.00347552	0.04899899	PTEN	3	HepG2	72	qRTPCR
2270	PTEN-06 m02	0.99356033	0.02091453	PTEN	1	HepG2	72	qRTPCR
3435	PTEN-08 m02	1.65432855	0.0909187	PTEN	30	HepG2	72	qRTPCR
3435	PTEN-08 m02	1.22845612	0.07200488	PTEN	11	HepG2	72	qRTPCR
3435	PTEN-08 m02	0.97914285	0.05421504	PTEN	3	HepG2	72	qRTPCR
3435	PTEN-08 m02	1.06312692	0.02153226	PTEN	1	HepG2	72	qRTPCR
4757	PTEN-11 m02	3.97514163	0.49899891	PTEN	30	HepG2	72	qRTPCR
4757	PTEN-11 m02	1.68168717	0.09937693	PTEN	11	HepG2	72	qRTPCR
4757	PTEN-11 m02	1.18447354	0.06462689	PTEN	3	HepG2	72	qRTPCR
4757	PTEN-11 m02	1.07739558	0.02987555	PTEN	1	HepG2	72	qRTPCR
24934	PTEN-12 m02	2.88261149	0.40274864	PTEN	30	HepG2	72	qRTPCR
24934	PTEN-12 m02	1.70370469	0.05618161	PTEN	10	HepG2	72	qRTPCR
24934	PTEN-12 m02	1.08174308	0.04560774	PTEN	3	HepG2	72	qRTPCR
24934	PTEN-12 m02	0.87362133	0.04721127	PTEN	1	HepG2	72	qRTPCR
39332	PTEN-14 m02	1.14988278	0.04895403	PTEN	30	HepG2	72	qRTPCR
39332	PTEN-14	1.17750015	0.08452395	PTEN	10	HepG2	72	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
39332	PTEN-14 m02	1.05618608	0.06979462	PTEN	3	HepG2	72	qRTPCR
39332	PTEN-14 m02	1.06198179	0.06585623	PTEN	1	HepG2	72	qRTPCR
89012	PTEN-18 m02	1.40960515	0.16370331	PTEN	30	HepG2	72	qRTPCR
89012	PTEN-18 m02	1.06542063	0.03893821	PTEN	10	HepG2	72	qRTPCR
89012	PTEN-18 m02	1.02330293	0.05629308	PTEN	3	HepG2	72	qRTPCR
89012	PTEN-18 m02	1.05102676	0.08030083	PTEN	1	HepG2	72	qRTPCR
89014	PTEN-20 m02	1.62119779	0.31040535	PTEN	30	HepG2	72	qRTPCR
89014	PTEN-20 m02	1.35467513	0.04732026	PTEN	10	HepG2	72	qRTPCR
89014	PTEN-20 m02	1.08378636	0.03666093	PTEN	3	HepG2	72	qRTPCR
89014	PTEN-20 m02	0.98424969	0.01637807	PTEN	1	HepG2	72	qRTPCR
89015	PTEN-21 m02	1.46213006	0.00991718	PTEN	30	HepG2	72	qRTPCR
89015	PTEN-21 m02	1.47920213	0.11756689	PTEN	21	HepG2	72	qRTPCR
89015	PTEN-21 m02	0.87291673	0.01686106	PTEN	3	HepG2	72	qRTPCR
89015	PTEN-21 m02	0.93910066	0.02767981	PTEN	1	HepG2	72	qRTPCR
61047	PTEN-24 m02	1.80684086	0.06078274	PTEN	30	HepG2	72	qRTPCR
61047	PTEN-24 m02	1.49732935	0.02362927	PTEN	10	HepG2	72	qRTPCR
61047	PTEN-24 m02	0.86393564	0.20666007	PTEN	3	HepG2	72	qRTPCR
61047	PTEN-24 m02	1.01127543	0.0107217	PTEN	1	HepG2	72	qRTPCR
89017	PTEN-26 m02	2.68896605	0.15483944	PTEN	30	HepG2	72	qRTPCR
89017	PTEN-26 m02	1.93845847	0.0784448	PTEN	26	HepG2	72	qRTPCR
89017	PTEN-26 m02	1.08283373	0.0689543	PTEN	3	HepG2	72	qRTPCR
89017	PTEN-26 m02	0.91349945	0.03111099	PTEN	1	HepG2	72	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
74236	PTEN-29 m02	1.49261841	0.05640001	PTEN	30	HepG2	72	qRTPCR
74236	PTEN-29 m02	1.20535844	0.09496339	PTEN	10	HepG2	72	qRTPCR
74236	PTEN-29 m02	0.8863063	0.03600426	PTEN	3	HepG2	72	qRTPCR
74236	PTEN-29 m02	1.30911877	0.46191081	PTEN	1	HepG2	72	qRTPCR
80510	PTEN-38 m02	4.42807942	0.49064121	PTEN	30	HepG2	72	qRTPCR
80510	PTEN-38 m02	1.54553765	0.03440618	PTEN	38	HepG2	72	qRTPCR
80510	PTEN-38 m02	1.03735148	0.02902325	PTEN	3	HepG2	72	qRTPCR
80510	PTEN-38 m02	2.26315161	1.35763416	PTEN	1	HepG2	72	qRTPCR
89026	EPO-24 m02	1.67875199	0.39539629	PTEN	30	HepG2	72	qRTPCR
89026	EPO-24 m02	0.94781399	0.03075526	PTEN	10	HepG2	72	qRTPCR
89026	EPO-24 m02	0.86477016	0.04224438	PTEN	3	HepG2	72	qRTPCR
89026	EPO-24 m02	0.93871667	0.06867827	PTEN	1	HepG2	72	qRTPCR
89027	EPO-26 m02	3.93004559	0.17623487	PTEN	30	HepG2	72	qRTPCR
89027	EPO-26 m02	3.44769712	1.15554929	PTEN	10	HepG2	72	qRTPCR
89027	EPO-26 m02	1.05783507	0.08519439	PTEN	3	HepG2	72	qRTPCR
89027	EPO-26 m02	0.91829613	0.06244161	PTEN	1	HepG2	72	qRTPCR
	Ctrl Lipo	1.03812723	0.13640407	PTEN	0	HepG2	72	qRTPCR
	Ctrl Un	0.93786818	0.04603847	PTEN	0	HepG2	72	qRTPCR
89009	PTEN-02 m02	1.00192323	0.06384049	PTEN	10	Hepal-6		qRTPCR
2270	PTEN-06 m02	0.98616635	0.0176667	PTEN	10	Hepal-6		qRTPCR
3435	PTEN-08 m02	1.05746468	0.05531259	PTEN	10	Hepal-6		qRTPCR
4757	PTEN-11 m02	1.01204996	0.01092563	PTEN	10	Hepal-6		qRTPCR
24934	PTEN-12 m02	1.07632948	0.04574082	PTEN	10	Hepal-6		qRTPCR
39332	PTEN-14	1.06518352	0.02811564	PTEN	10	Hepal-6		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
89012	PTEN-18 m02	1.01395632	0.04020887	PTEN	10	Hepal-6		qRTPCR
89014	PTEN-20 m02	1.0950544	0.01366641	PTEN	10	Hepal-6		qRTPCR
89015	PTEN-21 m02	1.06581741	0.04496326	PTEN	10	Hepal-6		qRTPCR
61047	PTEN-24 m02	1.12352649	0.022694	PTEN	10	Hepal-6		qRTPCR
89017	PTEN-26 m02	1.14241583	0.0166511	PTEN	10	Hepal-6		qRTPCR
74236	PTEN-29 m02	1.05573041	0.02490786	PTEN	10	Hepal-6		qRTPCR
80510	PTEN-38 m02	1.40021393	0.34360751	PTEN	10	Hepal-6		qRTPCR
89028	GAPDH-01 m08	1.22881095	0.06666012	PTEN	10	Hepal-6		qRTPCR
	Ctrl Lipo	1	0.01959829	PTEN	10	Hepal-6		qRTPCR
	Ctrl Un	1.04030087	0.04129801	PTEN	10	Hepal-6		qRTPCR
89009	PTEN-02 m02	1.14814831	0.03320934	PTEN	30	Hepal-6		qRTPCR
2270	PTEN-06 m02	1.10962206	0.02297176	PTEN	30	Hepal-6		qRTPCR
3435	PTEN-08 m02	1.19030608	0.02929796	PTEN	30	Hepal-6		qRTPCR
4757	PTEN-11 m02	1.24683225	0.02635534	PTEN	30	Hepal-6		qRTPCR
24934	PTEN-12 m02	1.09813989	0.01545405	PTEN	30	Hepal-6		qRTPCR
39332	PTEN-14 m02	1.0326915	0.01490324	PTEN	30	Hepal-6		qRTPCR
89012	PTEN-18 m02	1.2319987	0.03616069	PTEN	30	Hepal-6		qRTPCR
89014	PTEN-20 m02	1.40570267	0.25549233	PTEN	30	Hepal-6		qRTPCR
89015	PTEN-21 m02	1.41997346	0.03262106	PTEN	30	Hepal-6		qRTPCR
61047	PTEN-24 m02	1.41997346	0.03262106	PTEN	30	Hepal-6		qRTPCR
89017	PTEN-26 m02	1.24007256	0.05638453	PTEN	30	Hepal-6		qRTPCR
74236	PTEN-29 m02	1.3398242	0.07400006	PTEN	30	Hepal-6		qRTPCR
80510	PTEN-38 m02	1.22733667	0.03394197	PTEN	30	Hepal-6		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89028	GAPDH-01 m08	1.56542122	0.06355372	PTEN	30	Hepal-6		qRTPCR
	Ctrl Lipo	1	0.01959829	PTEN	30	Hepal-6		qRTPCR
	Ctrl Un	1.04030087	0.04129801	PTEN	30	Hepal-6		qRTPCR
89009	PTEN-02 m02	0.92360342	0.03349449	PTEN	60	Hep3B	48	qRTPCR
89009	PTEN-02 m02	1.04834346	0.07896624	PTEN	30	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.17881248	0.05266207	PTEN	30	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.13241756	0.13049124	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	0.86968245	0.0572627	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.26286894	0.15728533	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.01454439	0.11885369	PTEN	30	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.31376172	0.03431848	PTEN	60	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.38052137	0.10634841	PTEN	30	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.71498482	0.06435312	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	1.27136187	0.07621645	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.71179619	0.17139365	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.39108759	0.09886701	PTEN	30	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.4911762	0.09105287	PTEN	60	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.78085377	0.02210956	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	1.04259626	0.12867428	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.76614857	0.22160492	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.60135694	0.16260323	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	0.99701322	0.06922262	PTEN	60	Hep3B	48	qRTPCR
89014	PTEN-20 m02	1.3725978	0.14495239	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24	1.32337927	0.0951828	PTEN	30	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
74236	PTEN-29 m02	1.30741505	0.0593633	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.43597449	0.02228448	PTEN	60	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.72085864	0.06859071	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.45978871	0.09850196	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.4349891	0.1194869	PTEN	60	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.55835987	0.04645892	PTEN	30	Hep3B	48	qRTPCR
	Ctrl Lipo	1.02542727	0.10278592	PTEN	0	Hep3B	48	qRTPCR
	Ctrl Un	1.01549182	0.04571984	PTEN	0	Hep3B	48	qRTPCR
89008	PTEN-01 m02	0.97978589	0.07413196	PTEN	30	Hep3B	48	qRTPCR
89009	PTEN-02 m02	1.06663909	0.11957983	PTEN	30	Hep3B	48	qRTPCR
89010	PTEN-03 m02	1.4259353	0.12798011	PTEN	30	Hep3B	48	qRTPCR
89011	PTEN-04 m02	1.35604316	0.04210534	PTEN	30	Hep3B	48	qRTPCR
1531	PTEN-05 m02	1.40591605	0.10318003	PTEN	30	Hep3B	48	qRTPCR
2270	PTEN-06 m02	1.28264515	0.10187842	PTEN	30	Hep3B	48	qRTPCR
2219	PTEN-07 m02	1.19295416	0.09040707	PTEN	30	Hep3B	48	qRTPCR
3435	PTEN-08 m02	1.13031934	0.24329104	PTEN	30	Hep3B	48	qRTPCR
3385	PTEN-09 m02	1.17249987	0.31262063	PTEN	30	Hep3B	48	qRTPCR
4787	PTEN-10 m02	1.30534932	0.24048396	PTEN	30	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.16030594	0.15168937	PTEN	30	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.00762685	0.17820605	PTEN	30	Hep3B	48	qRTPCR
24915	PTEN-13 m02	1.05469305	0.03726579	PTEN	30	Hep3B	48	qRTPCR
39332	PTEN-14 m02	1.21390707	0.05560444	PTEN	30	Hep3B	48	qRTPCR
39286	PTEN-15 m02	1.32131413	0.08109832	PTEN	30	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
41316	PTEN-16 m02	1.06944172	0.09841118	PTEN	30	Hep3B	48	qRTPCR
41283	PTEN-17 m02	1.72152287	0.0267616	PTEN	30	Hep3B	48	qRTPCR
89012	PTEN-18 m02	1.29045757	0.12325518	PTEN	30	Hep3B	48	qRTPCR
89013	PTEN-19 m02	1.08112434	0.04754823	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	1.38134312	0.05598906	PTEN	30	Hep3B	48	qRTPCR
89015	PTEN-21 m02	1.67846148	0.13152567	PTEN	30	Hep3B	48	qRTPCR
51816	PTEN-22 m02	1.50369396	0.0657247	PTEN	30	Hep3B	48	qRTPCR
61111	PTEN-23 m02	1.43381392	0.08413907	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.26542716	0.04216795	PTEN	30	Hep3B	48	qRTPCR
89016	PTEN-25 m02	1.44528983	0.00607422	PTEN	30	Hep3B	48	qRTPCR
89017	PTEN-26 m02	1.9061656	0.14732026	PTEN	30	Hep3B	48	qRTPCR
89018	PTEN-27 m02	0.96727622	0.07488091	PTEN	30	Hep3B	48	qRTPCR
89019	PTEN-28 m02	1.26936613	0.02232618	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.1752558	0.07292346	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m08	1.15035798	0.02630625	PTEN	30	Hep3B	48	qRTPCR
	Ctrl Un	1.02306739	0.06109769	PTEN	0	Hep3B	48	qRTPCR
	Ctrl Lipo	1.0003564	0.01898647	PTEN	0	Hep3B	48	qRTPCR
89008	PTEN-01 m02	0.92043686	0.03752159	PTEN	10	Hep3B	48	qRTPCR
89009	PTEN-02 m02	1.21754828	0.10735102	PTEN	10	Hep3B	48	qRTPCR
89010	PTEN-03 m02	1.45133911	0.06747642	PTEN	10	Hep3B	48	qRTPCR
89011	PTEN-04 m02	1.28473538	0.0779697	PTEN	10	Hep3B	48	qRTPCR
1531	PTEN-05 m02	1.49921065	0.0701304	PTEN	10	Hep3B	48	qRTPCR
2270	PTEN-06 m02	1.33980352	0.09599047	PTEN	10	Hep3B	48	qRTPCR
2219	PTEN-07	1.16777521	0.07720115	PTEN	10	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
3435	PTEN-08 m02	1.12689576	0.24130018	PTEN	10	Hep3B	48	qRTPCR
3385	PTEN-09 m02	1.05940742	0.25562672	PTEN	10	Hep3B	48	qRTPCR
4787	PTEN-10 m02	1.22747037	0.20038013	PTEN	10	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.03856807	0.12350597	PTEN	10	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.03006371	0.19607521	PTEN	10	Hep3B	48	qRTPCR
24915	PTEN-13 m02	1.27504716	0.02479226	PTEN	10	Hep3B	48	qRTPCR
39332	PTEN-14 m02	1.24085106	0.04932634	PTEN	10	Hep3B	48	qRTPCR
39286	PTEN-15 m02	1.04257666	0.029586	PTEN	10	Hep3B	48	qRTPCR
41316	PTEN-16 m02	1.68241978	0.07559047	PTEN	10	Hep3B	48	qRTPCR
41283	PTEN-17 m02	1.28249736	0.0267581	PTEN	10	Hep3B	48	qRTPCR
89012	PTEN-18 m02	1.07746042	0.02797078	PTEN	10	Hep3B	48	qRTPCR
89013	PTEN-19 m02	1.45541497	0.10222415	PTEN	10	Hep3B	48	qRTPCR
89014	PTEN-20 m02	1.54825801	0.07879196	PTEN	10	Hep3B	48	qRTPCR
89015	PTEN-21 m02	1.67890365	0.06594263	PTEN	10	Hep3B	48	qRTPCR
51816	PTEN-22 m02	1.54053623	0.18233703	PTEN	10	Hep3B	48	qRTPCR
61111	PTEN-23 m02	1.38494224	0.03292358	PTEN	10	Hep3B	48	qRTPCR
61047	PTEN-24 m02	1.29367045	0.03064696	PTEN	10	Hep3B	48	qRTPCR
89016	PTEN-25 m02	1.26920881	0.04947473	PTEN	10	Hep3B	48	qRTPCR
89017	PTEN-26 m02	1.63378684	0.06378599	PTEN	10	Hep3B	48	qRTPCR
89018	PTEN-27 m02	1.06068076	0.03216688	PTEN	10	Hep3B	48	qRTPCR
89019	PTEN-28 m02	1.28451012	0.07798072	PTEN	10	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.21981924	0.03228177	PTEN	10	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
74236	PTEN-29 m08	1.23666534	0.08419671	PTEN	10	Hep3B	48	qRTPCR
	Ctrl Un	1.04012555	0.05867931	PTEN	0	Hep3B	48	qRTPCR
	Ctrl Lipo	1.00223105	0.04756608	PTEN	0	Hep3B	48	qRTPCR
89008	PTEN-01 m02	1.1137004	0.0931079	PTEN	10	Hepa 1-6	48	qRTPCR
89009	PTEN-02 m02	1.0035978	0.02812044	PTEN	10	Hepa 1-6	48	qRTPCR
89010	PTEN-03 m02	1.05192516	0.0703927	PTEN	10	Hepa 1-6	48	qRTPCR
4787	PTEN-10 m02	1.08530622	0.00902527	PTEN	10	Hepa 1-6	48	qRTPCR
4757	PTEN-11 m02	0.9557331	0.00283882	PTEN	10	Hepa 1-6	48	qRTPCR
24934	PTEN-12 m02	1.08964401	0.04984101	PTEN	10	Hepa 1-6	48	qRTPCR
39286	PTEN-15 m02	0.97259979	0.02440388	PTEN	10	Hepa 1-6	48	qRTPCR
41316	PTEN-16 m02	1.0365827	0.04750994	PTEN	10	Hepa 1-6	48	qRTPCR
89012	PTEN-18 m02	0.85087168	0.0025735	PTEN	10	Hepa 1-6	48	qRTPCR
89014	PTEN-20 m02	0.93102279	0.05061869	PTEN	10	Hepa 1-6	48	qRTPCR
89015	PTEN-21 m02	1.16902374	0.0429716	PTEN	10	Hepa 1-6	48	qRTPCR
89017	PTEN-26 m02	1.0293176	0.0184284	PTEN	10	Hepa 1-6	48	qRTPCR
	Ctrl Un	0.84552636	0.01109569	PTEN	0	Hepa 1-6	48	qRTPCR
	Ctrl Lipo	1.01139402	0.10962385	PTEN	0	Hepa 1-6	48	qRTPCR
89008	PTEN-01 m02	1.37435346	0.02323858	PTEN	30	Hepa 1-6	48	qRTPCR
89009	PTEN-02 m02	1.12987697	0.03603001	PTEN	30	Hepa 1-6	48	qRTPCR
89010	PTEN-03 m02	1.28804849	0.05734154	PTEN	30	Hepa 1-6	48	qRTPCR
4787	PTEN-10 m02	1.30510831	0.08103648	PTEN	30	Hepa 1-6	48	qRTPCR
4757	PTEN-11 m02	1.12166013	0.05363097	PTEN	30	Hepa 1-6	48	qRTPCR
24934	PTEN-12 m02	1.33108042	0.07811614	PTEN	30	Hepa 1-6	48	qRTPCR
39286	PTEN-15	1.01185682	0.00189352	PTEN	30	Hepa 1-	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02					6		
41316	PTEN-16 m02	1.16866925	0.02809223	PTEN	30	Hepa 1-6	48	qRTPCR
89012	PTEN-18 m02	0.89133594	0.03029202	PTEN	30	Hepa 1-6	48	qRTPCR
89014	PTEN-20 m02	1.03423232	0.0202734	PTEN	30	Hepa 1-6	48	qRTPCR
89015	PTEN-21 m02	1.29714156	0.02402855	PTEN	30	Hepa 1-6	48	qRTPCR
89017	PTEN-26 m02	1.15902681	0.05021543	PTEN	30	Hepa 1-6	48	qRTPCR
	Ctrl Un	0.84552636	0.01109569	PTEN	0	Hepa 1-6	48	qRTPCR
	Ctrl Lipo	1.01139402	0.10962385	PTEN	0	Hepa 1-6	48	qRTPCR
89008	PTEN-01 m02	0.86285661	0.05510382	PTEN	30	Hep3B	48	qRTPCR
89009	PTEN-02 m02	0.72230437	0.04148145	PTEN	30	Hep3B	48	qRTPCR
89010	PTEN-03 m02	0.9712617	0.05943612	PTEN	30	Hep3B	48	qRTPCR
89011	PTEN-04 m02	1.63103	0.16131455	PTEN	30	Hep3B	48	qRTPCR
1531	PTEN-05 m02	12.5867884	3.69478325	PTEN	30	Hep3B	48	qRTPCR
2270	PTEN-06 m02	14.7667628	3.39064883	PTEN	30	Hep3B	48	qRTPCR
2219	PTEN-07 m02	1.40708516	2.59883266	PTEN	30	Hep3B	48	qRTPCR
3435	PTEN-08 m02	0.9471562	1.60845526	PTEN	30	Hep3B	48	qRTPCR
3385	PTEN-09 m02	0.81907938	1.36136205	PTEN	30	Hep3B	48	qRTPCR
4787	PTEN-10 m02	0.89187466	2.26205371	PTEN	30	Hep3B	48	qRTPCR
4757	PTEN-11 m02	2.31852915	1.96994502	PTEN	30	Hep3B	48	qRTPCR
24934	PTEN-12 m02	17.3869845	13.4332744	PTEN	30	Hep3B	48	qRTPCR
24915	PTEN-13 m02	0.61071708	0.05126922	PTEN	30	Hep3B	48	qRTPCR
39332	PTEN-14 m02	0.85673537	0.18563565	PTEN	30	Hep3B	48	qRTPCR
39286	PTEN-15 m02	1.27622982	0.18613699	PTEN	30	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
41316	PTEN-16 m02	3.58483495	1.44558974	PTEN	30	Hep3B	48	qRTPCR
41283	PTEN-17 m02	10.9556451	1.18019211	PTEN	30	Hep3B	48	qRTPCR
89012	PTEN-18 m02	9.36666671	6.85482901	PTEN	30	Hep3B	48	qRTPCR
89013	PTEN-19 m02	0.83633443	0.05438837	PTEN	30	Hep3B	48	qRTPCR
89014	PTEN-20 m02	0.88713052	0.0783516	PTEN	30	Hep3B	48	qRTPCR
89015	PTEN-21 m02	1.40307095	0.04531143	PTEN	30	Hep3B	48	qRTPCR
51816	PTEN-22 m02	3.43364668	0.7915353	PTEN	30	Hep3B	48	qRTPCR
61111	PTEN-23 m02	17.7646203	6.94603845	PTEN	30	Hep3B	48	qRTPCR
61047	PTEN-24 m02	6.28877419	1.5223077	PTEN	30	Hep3B	48	qRTPCR
89016	PTEN-25 m02	1.8032164	1.06260753	PTEN	30	Hep3B	48	qRTPCR
89017	PTEN-26 m02	1.43011915	0.10624378	PTEN	30	Hep3B	48	qRTPCR
89018	PTEN-27 m02	1.58157067	0.10623726	PTEN	30	Hep3B	48	qRTPCR
89019	PTEN-28 m02	2.08807696	0.30247562	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m02	8.31569114	3.41551951	PTEN	30	Hep3B	48	qRTPCR
74236	PTEN-29 m08	9.18788254	3.57067981	PTEN	30	Hep3B	48	qRTPCR
89024	PTEN-37 m09	0.33231411	0.03482309	PTEN	30	Hep3B	48	qRTPCR
80510	PTEN-38 m02	0.13553843	0.1252565	PTEN	30	Hep3B	48	qRTPCR
80568	PTEN-39 m08	0.53521351	0.21978072	PTEN	30	Hep3B	48	qRTPCR
89025	PTEN-40 m09	0.37926266	0.14463753	PTEN	30	Hep3B	48	qRTPCR
	Ctrl Un	1.14804388	0.21533079	PTEN	0	Hep3B	48	qRTPCR
	Ctrl Lipo	1.03719306	0.19807141	PTEN	0	Hep3B	48	qRTPCR
89008	PTEN-01 m02	2.05245662	0.20849317	PTEN	10	Hep3B	48	qRTPCR
89009	PTEN-02 m02	4.6327993	0.60451206	PTEN	10	Hep3B	48	qRTPCR
89010	PTEN-03	5.43854888	1.15640189	PTEN	10	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
89011	PTEN-04 m02	3.17966472	0.47379274	PTEN	10	Hep3B	48	qRTPCR
1531	PTEN-05 m02	3.5266118	1.66486019	PTEN	10	Hep3B	48	qRTPCR
2270	PTEN-06 m02	1.35115222	0.06218687	PTEN	10	Hep3B	48	qRTPCR
2219	PTEN-07 m02	1.60557273	0.24378354	PTEN	10	Hep3B	48	qRTPCR
3435	PTEN-08 m02	3.10947058	0.70732608	PTEN	10	Hep3B	48	qRTPCR
3385	PTEN-09 m02	3.03871076	0.22498395	PTEN	10	Hep3B	48	qRTPCR
4787	PTEN-10 m02	2.2479158	0.37901219	PTEN	10	Hep3B	48	qRTPCR
4757	PTEN-11 m02	1.21883105	0.07976438	PTEN	10	Hep3B	48	qRTPCR
24934	PTEN-12 m02	1.14115249	0.02730918	PTEN	10	Hep3B	48	qRTPCR
24915	PTEN-13 m02	1.69100252	0.99325225	PTEN	10	Hep3B	48	qRTPCR
39332	PTEN-14 m02	3.36385824	1.36800003	PTEN	10	Hep3B	48	qRTPCR
39286	PTEN-15 m02	2.84179964	0.74559864	PTEN	10	Hep3B	48	qRTPCR
41316	PTEN-16 m02	1.88684418	0.03985459	PTEN	10	Hep3B	48	qRTPCR
41283	PTEN-17 m02	1.01964017	0.0972503	PTEN	10	Hep3B	48	qRTPCR
89012	PTEN-18 m02	0.59801882	0.08785774	PTEN	10	Hep3B	48	qRTPCR
89013	PTEN-19 m02	4.02083263	0.66361002	PTEN	10	Hep3B	48	qRTPCR
89014	PTEN-20 m02	3.9185628	0.52870307	PTEN	10	Hep3B	48	qRTPCR
89015	PTEN-21 m02	4.12632285	1.01483873	PTEN	10	Hep3B	48	qRTPCR
51816	PTEN-22 m02	1.51460652	0.21316211	PTEN	10	Hep3B	48	qRTPCR
61111	PTEN-23 m02	1.30255321	0.03915479	PTEN	10	Hep3B	48	qRTPCR
61047	PTEN-24 m02	0.82458263	0.0788691	PTEN	10	Hep3B	48	qRTPCR
89016	PTEN-25 m02	1.56039569	0.31056364	PTEN	10	Hep3B	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89017	PTEN-26 m02	4.76968333	0.46855982	PTEN	10	Hep3B	48	qRTPCR
89018	PTEN-27 m02	2.74961402	0.24086949	PTEN	10	Hep3B	48	qRTPCR
89019	PTEN-28 m02	2.44340558	0.19230037	PTEN	10	Hep3B	48	qRTPCR
74236	PTEN-29 m02	1.27433857	0.13289234	PTEN	10	Hep3B	48	qRTPCR
74236	PTEN-29 m08	0.13776815	0.00417678	PTEN	10	Hep3B	48	qRTPCR
89020	PTEN-31 m09	0.20004166	0.39065427	PTEN	10	Hep3B	48	qRTPCR
76350	PTEN-32 m02	0.1361327	0.24521716	PTEN	10	Hep3B	48	qRTPCR
76389	PTEN-33 m08	0.48342976	0.01192756	PTEN	10	Hep3B	48	qRTPCR
89021	PTEN-34 m09	1.08759613	0.10351	PTEN	10	Hep3B	48	qRTPCR
89022	PTEN-35 m02	0.28097529	0.05874989	PTEN	10	Hep3B	48	qRTPCR
89023	PTEN-36 m08	0.48746008	0.10270125	PTEN	10	Hep3B	48	qRTPCR
89024	PTEN-37 m09	0.46050347	0.23685356	PTEN	10	Hep3B	48	qRTPCR
80510	PTEN-38 m02	0.2342252	0.24522214	PTEN	10	Hep3B	48	qRTPCR
80568	PTEN-39 m08	0.48046262	0.06091974	PTEN	10	Hep3B	48	qRTPCR
89025	PTEN-40 m09	1.27629494	0.38069875	PTEN	10	Hep3B	48	qRTPCR
	Ctrl Un	0.80860729	0.15650089	PTEN	0	Hep3B	48	qRTPCR
	Ctrl Lipo	1.00514358	0.0697499	PTEN	0	Hep3B	48	qRTPCR
89008	PTEN-01 m02	0.83191514	0.05510382	PTEN	30	Hep3B		qRTPCR
89009	PTEN-02 m02	0.69640301	0.04148145	PTEN	30	Hep3B		qRTPCR
89010	PTEN-03 m02	0.9364329	0.05943612	PTEN	30	Hep3B		qRTPCR
89011	PTEN-04 m02	1.57254234	0.16131455	PTEN	30	Hep3B		qRTPCR
1531	PTEN-05 m02	12.1354345	3.69478325	PTEN	30	Hep3B		qRTPCR
2270	PTEN-06 m02	14.2372365	3.39064883	PTEN	30	Hep3B		qRTPCR
2219	PTEN-07	4.11965478	2.59883266	PTEN	30	Hep3B		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
3435	PTEN-08 m02	2.66792238	1.60845526	PTEN	30	Hep3B		qRTPCR
3385	PTEN-09 m02	2.2817098	1.36136205	PTEN	30	Hep3B		qRTPCR
4787	PTEN-10 m02	3.14656477	2.26205371	PTEN	30	Hep3B		qRTPCR
4757	PTEN-11 m02	4.57983826	1.96994502	PTEN	30	Hep3B		qRTPCR
24934	PTEN-12 m02	19.458362	13.4332744	PTEN	30	Hep3B		qRTPCR
24915	PTEN-13 m02	0.58881717	0.05126922	PTEN	30	Hep3B		qRTPCR
39332	PTEN-14 m02	0.82601341	0.18563565	PTEN	30	Hep3B		qRTPCR
39286	PTEN-15 m02	1.23046506	0.18613699	PTEN	30	Hep3B		qRTPCR
41316	PTEN-16 m02	3.45628514	1.44558974	PTEN	30	Hep3B		qRTPCR
41283	PTEN-17 m02	10.562783	1.18019211	PTEN	30	Hep3B		qRTPCR
89012	PTEN-18 m02	9.03078425	6.85482901	PTEN	30	Hep3B		qRTPCR
89013	PTEN-19 m02	0.80634403	0.05438837	PTEN	30	Hep3B		qRTPCR
89014	PTEN-20 m02	0.8553186	0.0783516	PTEN	30	Hep3B		qRTPCR
89015	PTEN-21 m02	1.35275775	0.04531143	PTEN	30	Hep3B		qRTPCR
51816	PTEN-22 m02	3.31051838	0.7915353	PTEN	30	Hep3B		qRTPCR
61111	PTEN-23 m02	17.1275928	6.94603845	PTEN	30	Hep3B		qRTPCR
61047	PTEN-24 m02	6.06326291	1.5223077	PTEN	30	Hep3B		qRTPCR
89016	PTEN-25 m02	1.73855426	1.06260753	PTEN	30	Hep3B		qRTPCR
89017	PTEN-26 m02	1.37883603	0.10624378	PTEN	30	Hep3B		qRTPCR
89018	PTEN-27 m02	1.52485659	0.10623726	PTEN	30	Hep3B		qRTPCR
89019	PTEN-28 m02	2.0131999	0.30247562	PTEN	30	Hep3B		qRTPCR
74236	PTEN-29 m02	8.01749596	3.41551951	PTEN	30	Hep3B		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
74236	PTEN-29 m08	8.85841116	3.57067981	PTEN	30	Hep3B		qRTPCR
89020	PTEN-31 m09	0	0	PTEN	30	Hep3B		qRTPCR
76350	PTEN-32 m02	0	0	PTEN	30	Hep3B		qRTPCR
76389	PTEN-33 m08	0	0	PTEN	30	Hep3B		qRTPCR
89021	PTEN-34 m09	0	0	PTEN	30	Hep3B		qRTPCR
89022	PTEN-35 m02	0	0	PTEN	30	Hep3B		qRTPCR
89023	PTEN-36 m08	0	0	PTEN	30	Hep3B		qRTPCR
89024	PTEN-37 m09	1.22567385	0.03482309	PTEN	30	Hep3B		qRTPCR
80510	PTEN-38 m02	1.01471094	0.1252565	PTEN	30	Hep3B		qRTPCR
80568	PTEN-39 m08	1.17109414	0.21978072	PTEN	30	Hep3B		qRTPCR
89025	PTEN-40 m09	0.90144206	0.14463753	PTEN	30	Hep3B		qRTPCR
	Ctrl Un	1.10687578	0.21533079	PTEN	30	Hep3B		qRTPCR
	Ctrl Lipo	1	0.19807141	PTEN	30	Hep3B		qRTPCR
89008	PTEN-01 m02	2.04195366	0.20849317	PTEN	10	Hep3B		qRTPCR
89009	PTEN-02 m02	4.60909206	0.60451206	PTEN	10	Hep3B		qRTPCR
89010	PTEN-03 m02	5.41071841	1.15640189	PTEN	10	Hep3B		qRTPCR
89011	PTEN-04 m02	3.16339355	0.47379274	PTEN	10	Hep3B		qRTPCR
1531	PTEN-05 m02	3.50856521	1.66486019	PTEN	10	Hep3B		qRTPCR
2270	PTEN-06 m02	1.34423802	0.06218687	PTEN	10	Hep3B		qRTPCR
2219	PTEN-07 m02	1.5973566	0.24378354	PTEN	10	Hep3B		qRTPCR
3435	PTEN-08 m02	3.09355861	0.70732608	PTEN	10	Hep3B		qRTPCR
3385	PTEN-09 m02	3.02316088	0.22498395	PTEN	10	Hep3B		qRTPCR
4787	PTEN-10 m02	2.23641263	0.37901219	PTEN	10	Hep3B		qRTPCR
4757	PTEN-11	1.21259398	0.07976438	PTEN	10	Hep3B		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
24934	PTEN-12 m02	1.13531291	0.02730918	PTEN	10	Hep3B		qRTPCR
24915	PTEN-13 m02	1.68234922	0.99325225	PTEN	10	Hep3B		qRTPCR
39332	PTEN-14 m02	3.3466445	1.36800003	PTEN	10	Hep3B		qRTPCR
39286	PTEN-15 m02	2.82725741	0.74559864	PTEN	10	Hep3B		qRTPCR
41316	PTEN-16 m02	1.8771887	0.03985459	PTEN	10	Hep3B		qRTPCR
41283	PTEN-17 m02	1.01442241	0.0972503	PTEN	10	Hep3B		qRTPCR
89012	PTEN-18 m02	0.5949586	0.08785774	PTEN	10	Hep3B		qRTPCR
89013	PTEN-19 m02	4.00025698	0.66361002	PTEN	10	Hep3B		qRTPCR
89014	PTEN-20 m02	3.89851049	0.52870307	PTEN	10	Hep3B		qRTPCR
89015	PTEN-21 m02	4.10520738	1.01483873	PTEN	10	Hep3B		qRTPCR
51816	PTEN-22 m02	1.50685588	0.21316211	PTEN	10	Hep3B		qRTPCR
61111	PTEN-23 m02	1.29588771	0.03915479	PTEN	10	Hep3B		qRTPCR
61047	PTEN-24 m02	0.82036303	0.0788691	PTEN	10	Hep3B		qRTPCR
89016	PTEN-25 m02	1.55241073	0.31056364	PTEN	10	Hep3B		qRTPCR
89017	PTEN-26 m02	4.74527562	0.46855982	PTEN	10	Hep3B		qRTPCR
89018	PTEN-27 m02	2.73554353	0.24086949	PTEN	10	Hep3B		qRTPCR
89019	PTEN-28 m02	2.43090204	0.19230037	PTEN	10	Hep3B		qRTPCR
74236	PTEN-29 m02	1.26781745	0.13289234	PTEN	10	Hep3B		qRTPCR
74236	PTEN-29 m08	0.13706315	0.00417678	PTEN	10	Hep3B		qRTPCR
89020	PTEN-31 m09	0.78869629	0.39065427	PTEN	10	Hep3B		qRTPCR
76350	PTEN-32 m02	1.51073942	0.24521716	PTEN	10	Hep3B		qRTPCR
76389	PTEN-33 m08	1.05861374	0.01192756	PTEN	10	Hep3B		qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
89021	PTEN-34 m09	1.04312863	0.10351	PTEN	10	Hep3B		qRTPCR
89022	PTEN-35 m02	0.90159995	0.05874989	PTEN	10	Hep3B		qRTPCR
89023	PTEN-36 m08	0.85954822	0.10270125	PTEN	10	Hep3B		qRTPCR
89024	PTEN-37 m09	0.80725368	0.23685356	PTEN	10	Hep3B		qRTPCR
80510	PTEN-38 m02	1.16628729	0.24522214	PTEN	10	Hep3B		qRTPCR
80568	PTEN-39 m08	0.85281606	0.06091974	PTEN	10	Hep3B		qRTPCR
89025	PTEN-40 m09	1.27583985	0.38069875	PTEN	10	Hep3B		qRTPCR
	Ctrl Un	0.80446944	0.15650089	PTEN	10	Hep3B		qRTPCR
	Ctrl Lipo	1	0.0697499	PTEN	10	Hep3B		qRTPCR
89008	PTEN-01 m02	2.46858917	0.03063719	PTEN	30	HepG2	48	qRTPCR
89009	PTEN-02 m02	1.65266096	0.27154944	PTEN	30	HepG2	48	qRTPCR
89010	PTEN-03 m02	1.56078139	0.21101366	PTEN	30	HepG2	48	qRTPCR
89011	PTEN-04 m02	0.65616195	0.18926703	PTEN	30	HepG2	48	qRTPCR
1531	PTEN-05 m02	0.48099904	0.04632197	PTEN	30	HepG2	48	qRTPCR
2270	PTEN-06 m02	0.7909963	0.03270627	PTEN	30	HepG2	48	qRTPCR
2219	PTEN-07 m02	0.53872046	0.14632694	PTEN	30	HepG2	48	qRTPCR
3435	PTEN-08 m02	0.41128342	0.097757	PTEN	30	HepG2	48	qRTPCR
3385	PTEN-09 m02	0.60687582	0.17145346	PTEN	30	HepG2	48	qRTPCR
4787	PTEN-10 m02	0.57459175	0.03798783	PTEN	30	HepG2	48	qRTPCR
4757	PTEN-11 m02	0.90944845	0.09497654	PTEN	30	HepG2	48	qRTPCR
24934	PTEN-12 m02	0.35748511	0.02782391	PTEN	30	HepG2	48	qRTPCR
24915	PTEN-13 m02	0.80041903	0.20317037	PTEN	30	HepG2	48	qRTPCR
39332	PTEN-14 m02	0.73925238	0.19461962	PTEN	30	HepG2	48	qRTPCR
39286	PTEN-15	1.51050395	0.12769327	PTEN	30	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
	m02							
41316	PTEN-16 m02	1.05322562	0.02781351	PTEN	30	HepG2	48	qRTPCR
41283	PTEN-17 m02	1.10492008	0.2491756	PTEN	30	HepG2	48	qRTPCR
89012	PTEN-18 m02	1.02218885	0.10992679	PTEN	30	HepG2	48	qRTPCR
89013	PTEN-19 m02	1.32111033	0.08784151	PTEN	30	HepG2	48	qRTPCR
89014	PTEN-20 m02	0.20726178	0.03784299	PTEN	30	HepG2	48	qRTPCR
89015	PTEN-21 m02	1.16846444	0.18912677	PTEN	30	HepG2	48	qRTPCR
51816	PTEN-22 m02	0.93229274	0.05224198	PTEN	30	HepG2	48	qRTPCR
61111	PTEN-23 m02	1.21504563	0.27766444	PTEN	30	HepG2	48	qRTPCR
61047	PTEN-24 m02	0.41141525	0.05099622	PTEN	30	HepG2	48	qRTPCR
89016	PTEN-25 m02	1.18189558	0.17039788	PTEN	30	HepG2	48	qRTPCR
89017	PTEN-26 m02	0.91690612	0.04448978	PTEN	30	HepG2	48	qRTPCR
89018	PTEN-27 m02	1.05014538	0.11896204	PTEN	30	HepG2	48	qRTPCR
89019	PTEN-28 m02	0.23938043	0.05714057	PTEN	30	HepG2	48	qRTPCR
74236	PTEN-29 m02	0.83974164	0.13173022	PTEN	30	HepG2	48	qRTPCR
74236	PTEN-29 m08	1.11834626	0.1477032	PTEN	30	HepG2	48	qRTPCR
89020	PTEN-31 m09	0.47919683	0.10224302	PTEN	30	HepG2	48	qRTPCR
76350	PTEN-32 m02	0.57689657	0.07699519	PTEN	30	HepG2	48	qRTPCR
76389	PTEN-33 m08	0.57802595	0.22410403	PTEN	30	HepG2	48	qRTPCR
89021	PTEN-34 m09	1.14567902	0.38024147	PTEN	30	HepG2	48	qRTPCR
89022	PTEN-35 m02	0.41306284	0.28507158	PTEN	30	HepG2	48	qRTPCR
89023	PTEN-36 m08	0.09621871	0.05518511	PTEN	30	HepG2	48	qRTPCR
89024	PTEN-37 m09	0.57614296	0.12911061	PTEN	30	HepG2	48	qRTPCR

SeqID	Oligo Name	Avg RQ	Avg RQ SE	Target	[oligo]	cell line	Time (hr)	Assay Type
80510	PTEN-38 m02	0.09621871	0.05518511	PTEN	30	HepG2	48	qRTPCR
80568	PTEN-39 m08	2.22228207	1.70473932	PTEN	30	HepG2	48	qRTPCR
89025	PTEN-40 m09	0.0972852	0.02874248	PTEN	30	HepG2	48	qRTPCR
	Ctrl Un	1.0245258	0.16493375	PTEN	0	HepG2	48	qRTPCR
	Ctrl Lipo	0.20387263	0.03098558	PTEN	0	HepG2	48	qRTPCR

Table 4: Formatted oligonucleotide sequences made for testing in the lab showing nucleotide modifications.

OligoID	Base Sequence	Formatted Sequence	SeqID
PTEN-01 m02	TCTGGAGCAGA GATA	dTs;lnaCs;dTs;lnaGs;dGs;lnaAs;dGs;lnaCs;dAs;lnaGs;dA s;lnaGs;dAs;lnaTs;dA-Sup	89008
PTEN-02 m02	TCCAAGTACTT CCAT	dTs;lnaCs;dCs;lnaAs;dAs;lnaGs;dTs;lnaAs;dCs;lnaTs;dTs ;lnaCs;dCs;lnaAs;dT-Sup	89009
PTEN-03 m02	TGATTTCCCTTA GGA	dTs;lnaGs;dAs;lnaTs;dTs;lnaTs;dCs;lnaCs;dCs;lnaTs;dTs; lnaAs;dGs;lnaGs;dA-Sup	89010
PTEN-04 m02	TATCTAACGAG ACCT	dTs;lnaAs;dTs;lnaCs;dTs;lnaAs;dAs;lnaCs;dGs;lnaAs;dG s;lnaAs;dCs;lnaCs;dT-Sup	89011
PTEN-05 m02	TGCACGGTTAG AAAA	dTs;lnaGs;dCs;lnaAs;dCs;lnaGs;dGs;lnaTs;dTs;lnaAs;dG s;lnaAs;dAs;lnaAs;dA-Sup	1531
PTEN-06 m02	TTCTAAGAGAG TGAC	dTs;lnaTs;dCs;lnaTs;dAs;lnaAs;dGs;lnaAs;dGs;lnaAs;dG s;lnaTs;dGs;lnaAs;dC-Sup	2270
PTEN-07 m02	AGGTCAAGTCT AAGT	dAs;lnaGs;dGs;lnaTs;dCs;lnaAs;dAs;lnaGs;dTs;lnaCs;dT s;lnaAs;dAs;lnaGs;dT-Sup	2219
PTEN-08 m02	TGACCACTAAC ˉIIIl	dTs;lnaGs;dAs;lnaCs;dCs;lnaAs;dCs;lnaTs;dAs;lnaAs;dC s;lnaTs;dTs;lnaTs;dT-Sup	3435
PTEN-09 m02	TACACACTGTT AAAA	dTs;lnaAs;dCs;lnaAs;dCs;lnaAs;dCs;lnaTs;dGs;lnaTs;dTs ;lnaAs;dAs;lnaAs;dA-Sup	3385
PTEN-10 m02	TCCAATCACTA CTTT	dTs;lnaCs;dCs;lnaAs;dAs;lnaTs;dCs;lnaAs;dCs;lnaTs;dAs ;lnaCs;dTs;lnaTs;dT-Sup	4787
PTEN-11 m02	CTTTTCACAGG TTAG	dCs;lnaTs;dTs;lnaTs;dTs;lnaCs;dAs;lnaCs;dAs;lnaGs;dGs ;lnaTs;dTs;lnaAs;dG-Sup	4757
PTEN-12 m02	TAAGTTCTTAA AGCA	dTs;lnaAs;dAs;lnaGs;dTs;lnaTs;dCs;lnaTs;dTs;lnaAs;dAs ;lnaAs;dGs;lnaCs;dA-Sup	24934
PTEN-13 m02	GTCACTACACA CAGG	dGs;lnaTs;dCs;lnaAs;dCs;lnaTs;dAs;lnaCs;dAs;lnaCs;dA s;lnaCs;dAs;lnaGs;dG-Sup	24915
PTEN-14 m02	TTATGTACATCT TTC	dTs;lnaTs;dAs;lnaTs;dGs;lnaTs;dAs;lnaCs;dAs;lnaTs;dCs ;lnaTs;dTs;lnaTs;dC-Sup	39332
PTEN-15 m02	ACAGAATACTA CTTT	dAs;lnaCs;dAs;lnaGs;dAs;lnaAs;dTs;lnaAs;dCs;lnaTs;dA s;lnaCs;dTs;lnaTs;dT-Sup	39286

OligoID	Base Sequence	Formatted Sequence	SeqID
PTEN-16 m02	TGATTAGCACA GACC	dTs;lnaGs;dAs;lnaTs;dTs;lnaAs;dGs;lnaCs;dAs;lnaCs;dA s;lnaGs;dAs;lnaCs;dC-Sup	41316
PTEN-17 m02	TCACCTCCACA CTTT	dTs;lnaCs;dAs;lnaCs;dCs;lnaTs;dCs;lnaCs;dAs;lnaCs;dAs ;lnaCs;dTs;lnaTs;dT-Sup	41283
PTEN-18 m02	TCATTTCTTCTG TTG	dTs;lnaCs;dAs;lnaTs;dTs;lnaTs;dCs;lnaTs;dTs;lnaCs;dTs; lnaGs;dTs;lnaTs;dG-Sup	89012
PTEN-19 m02	TATGTAGCTTT GGAA	dTs;lnaAs;dTs;lnaGs;dTs;lnaAs;dGs;lnaCs;dTs;lnaTs;dTs ;lnaGs;dGs;lnaAs;dA-Sup	89013
PTEN-20 m02	GATAGGTACAG CTGT	dGs;lnaAs;dTs;lnaAs;dGs;lnaGs;dTs;lnaAs;dCs;lnaAs;dG s;lnaCs;dTs;lnaGs;dT-Sup	89014
PTEN-21 m02	TAAACAGCAAC ATAA	dTs;lnaAs;dAs;lnaAs;dCs;lnaAs;dGs;lnaCs;dAs;lnaAs;dC s;lnaAs;dTs;lnaAs;dA-Sup	89015
PTEN-22 m02	TTACCCAAAAG TGAA	dTs;lnaTs;dAs;lnaCs;dCs;lnaCs;dAs;lnaAs;dAs;lnaAs;dG s;lnaTs;dGs;lnaAs;dA-Sup	51816
PTEN-23 m02	TGGCATTAGAA AGTA	dTs;lnaGs;dGs;lnaCs;dAs;lnaTs;dTs;lnaAs;dGs;lnaAs;dA s;lnaAs;dGs;lnaTs;dA-Sup	61111
PTEN-24 m02	TGACAGATATA CTAA	dTs;lnaGs;dAs;lnaCs;dAs;lnaGs;dAs;lnaTs;dAs;lnaTs;dA s;lnaCs;dTs;lnaAs;dA-Sup	61047
PTEN-25 m02	TGAATCGGAAG GGTT	dTs;lnaGs;dAs;lnaAs;dTs;lnaCs;dGs;lnaGs;dAs;lnaAs;dG s;lnaGs;dGs;lnaTs;dT-Sup	89016
PTEN-26 m02	TAATATGAGCA GGTG	dTs;lnaAs;dAs;lnaTs;dAs;lnaTs;dGs;lnaAs;dGs;lnaCs;dA s;lnaGs;dGs;lnaTs;dG-Sup	89017
PTEN-27 m02	CTCATCCAATTC ACT	dCs;lnaTs;dCs;lnaAs;dTs;lnaCs;dCs;lnaAs;dAs;lnaTs;dTs ;lnaCs;dAs;lnaCs;dT-Sup	89018
PTEN-28 m02	TCAAGGAAGG ATGGT	dTs;lnaCs;dAs;lnaAs;dGs;lnaGs;dAs;lnaAs;dGs;lnaGs;d As;lnaTs;dGs;lnaGs;dT-Sup	89019
PTEN-29 m02	TAAATCTTGAG ACGG	dTs;lnaAs;dAs;lnaAs;dTs;lnaCs;dTs;lnaTs;dGs;lnaAs;dG s;lnaAs;dCs;lnaGs;dG-Sup	74236
PTEN-29 m08	TAAATCTTGAG ACGG	lnaTs;lnaAs;lnaAs;dAs;dTs;dCs;dTs;dTs;dGs;dAs;dGs;dA s;lnaCs;lnaGs;lnaG-Sup	74236
PTEN-31 m09	AGCCCTGT	lnaAs;lnaGs;lnaCs;lnaCs;lnaCs;lnaTs;lnaGs;lnaT-Sup	89020
PTEN-32 m02	TCCCACACTGA CATA	dTs;lnaCs;dCs;lnaCs;dAs;lnaCs;dAs;lnaCs;dTs;lnaGs;dAs ;lnaCs;dAs;lnaTs;dA-Sup	76350
PTEN-33 m08	TCATTGCTCCTC CTG	lnaTs;lnaCs;lnaAs;dTs;dTs;dGs;dCs;dTs;dCs;dCs;dTs;dC s;lnaCs;lnaTs;lnaG-Sup	76389
PTEN-34 m09	CCAACCAT	lnaCs;lnaCs;lnaAs;lnaAs;lnaCs;lnaCs;lnaAs;lnaT-Sup	89021
PTEN-35 m02	TTGTAGACAGC ATAT	dTs;lnaTs;dGs;lnaTs;dAs;lnaGs;dAs;lnaCs;dAs;lnaGs;dC s;lnaAs;dTs;lnaAs;dT-Sup	89022
PTEN-36 m08	TTCTTATACATT CTG	lnaTs;lnaTs;lnaCs;dTs;dTs;dAs;dTs;dAs;dCs;dAs;dTs;dTs ;lnaCs;lnaTs;lnaG-Sup	89023
PTEN-37 m09	GCCTTTTG	lnaGs;lnaCs;lnaCs;lnaTs;lnaTs;lnaTs;lnaTs;lnaG-Sup	89024
PTEN-38 m02	TAAGTGGTACA AATT	dTs;lnaAs;dAs;lnaGs;dTs;lnaGs;dGs;lnaTs;dAs;lnaCs;dA s;lnaAs;dAs;lnaTs;dT-Sup	80510

OligoID	Base Sequence	Formatted Sequence	SeqID
PTEN-39 m08	GAAAAGACTGC TATT	lnaGs;lnaAs;lnaAs;dAs;dAs;dGs;dAs;dCs;dTs;dGs;dCs;dTs;lnaAs;lnaTs;lnaT-Sup	80568
PTEN-40 m09	CTGTTCAA	lnaCs;lnaTs;lnaGs;lnaTs;lnaTs;lnaCs;lnaAs;lnaA-Sup	89025
PTEN-41 mOl	AGAACGCCTTA TAAG	lnaAs;omeGs;lnaAs;omeAs;lnaCs;omeGs;lnaCs;omeCs;lnaTs;omeUs;lnaAs;omeUs;lnaAs;omeAs;lnaG-Sup	2905
PTEN-42 mOl	AAGAACGCCTT ATAA	lnaAs;omeAs;lnaGs;omeAs;lnaAs;omeCs;lnaGs;omeCs;lnaCs;omeUs;lnaTs;omeAs;lnaTs;omeAs;lnaA-Sup	2906
PTEN-43 mOl	GTAAGAACGCC TTAT	lnaGs;omeUs;lnaAs;omeAs;lnaGs;omeAs;lnaAs;omeCs;lnaGs;omeCs;lnaCs;omeUs;lnaTs;omeAs;lnaT-Sup	2908
PTEN-44 mOl	AGTAAGAACGC CTTA	lnaAs;omeGs;lnaTs;omeAs;lnaAs;omeGs;lnaAs;omeAs;lnaCs;omeGs;lnaCs;omeCs;lnaTs;omeUs;lnaA-Sup	2909
PTEN-45 mOl	TAGTAAGAACG CCTT	lnaTs;omeAs;lnaGs;omeUs;lnaAs;omeAs;lnaGs;omeAs;lnaAs;omeCs;lnaGs;omeCs;lnaCs;omeUs;lnaT-Sup	2910
PTEN-46 mOl	CTAGTAAGAAC GCCT	lnaCs;omeUs;lnaAs;omeGs;lnaTs;omeAs;lnaAs;omeGs;lnaAs;omeAs;lnaCs;omeGs;lnaCs;omeCs;lnaT-Sup	2911
PTEN-47 mOl	TTTGAAGCCCG AAGG	lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeAs;lnaGs;omeCs;lnaCs;omeCs;lnaGs;omeAs;lnaAs;omeGs;lnaG-Sup	3423
PTEN-48 mOl	TTTTGAAGCCC GAAG	lnaTs;omeUs;lnaTs;omeUs;lnaGs;omeAs;lnaAs;omeGs;lnaCs;omeCs;lnaCs;omeGs;lnaAs;omeAs;lnaG-Sup	3424
PTEN-49 mOl	CTTTTGAAGCC CGAA	lnaCs;omeUs;lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeAs;lnaGs;omeCs;lnaCs;omeCs;lnaGs;omeAs;lnaA-Sup	3425
PTEN-50 mOl	TCGATGACCAC TAAC	lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeGs;lnaAs;omeCs;lnaCs;omeAs;lnaCs;omeUs;lnaAs;omeAs;lnaC-Sup	3439
PTEN-51 mOl	TTCGATGACCA CTAA	lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaCs;omeCs;lnaAs;omeCs;lnaTs;omeAs;lnaA-Sup	3440
PTEN-52 mOl	TTTCGATGACC ACTA	lnaTs;omeUs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeGs;lnaAs;omeCs;lnaCs;omeAs;lnaCs;omeUs;lnaA-Sup	3441
PTEN-53 mOl	TTTTCGATGAC CACT	lnaTs;omeUs;lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaCs;omeCs;lnaAs;omeCs;lnaT-Sup	3442
PTEN-54 mOl	CTTTTCGATGA CCAC	lnaCs;omeUs;lnaTs;omeUs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeGs;lnaAs;omeCs;lnaCs;omeAs;lnaC-Sup	3443
PTEN-55 mOl	GCTTTTCGATG ACCA	lnaGs;omeCs;lnaTs;omeUs;lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaCs;omeCs;lnaA-Sup	3444
PTEN-56 mOl	ĪGCĪĪĪLGAĪ GACC	lnaTs;omeGs;lnaCs;omeUs;lnaTs;omeUs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeGs;lnaAs;omeCs;lnaC-Sup	3445
PTEN-57 mOl	AĪGCĪĪĪLGA TGAC	lnaAs;omeUs;lnaGs;omeCs;lnaTs;omeUs;lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaC-Sup	3446
PTEN-58 mOl	AAĪGCĪĪĪCG ATGA	lnaAs;omeAs;lnaTs;omeGs;lnaCs;omeUs;lnaTs;omeUs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeGs;lnaA-Sup	3447
PTEN-59 mOl	TTAATGCTTTTC GAT	lnaTs;omeUs;lnaAs;omeAs;lnaTs;omeGs;lnaCs;omeUs;lnaTs;omeUs;lnaTs;omeCs;lnaGs;omeAs;lnaT-Sup	3449
PTEN-60 mOl	ACGCAATATTT GATA	lnaAs;omeCs;lnaGs;omeCs;lnaAs;omeAs;lnaTs;omeAs;lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeUs;lnaA-Sup	4490
PTEN-61 mOl	TGACGCAATAT TTGA	lnaTs;omeGs;lnaAs;omeCs;lnaGs;omeCs;lnaAs;omeAs;lnaTs;omeAs;lnaTs;omeUs;lnaTs;omeGs;lnaA-Sup	4492

OligoID	Base Sequence	Formatted Sequence	SeqID
PTEN-62 mOl	TTTGACGCAAT ATTT	lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeCs;lnaGs;omeCs;lnaAs;omeAs;lnaTs;omeAs;lnaTs;omeUs;lnaT-Sup	4494
PTEN-63 mOl	ATTTGACGCAA TATT	lnaAs;omeUs;lnaTs;omeUs;lnaGs;omeAs;lnaCs;omeGs;lnaCs;omeAs;lnaAs;omeUs;lnaAs;omeUs;lnaT-Sup	4495
PTEN-64 mOl	CATTTGACGCA ATAT	lnaCs;omeAs;lnaTs;omeUs;lnaTs;omeGs;lnaAs;omeCs;lnaGs;omeCs;lnaAs;omeAs;lnaTs;omeAs;lnaT-Sup	4496
PTEN-65 mOl	TCAATTTTCCTC GGA	lnaTs;omeCs;lnaAs;omeAs;lnaTs;omeUs;lnaTs;omeUs;lnaCs;omeCs;lnaTs;omeCs;lnaGs;omeGs;lnaA-Sup	4845
PTEN-66 mOl	CTCAATTTTCCT CGG	lnaCs;omeUs;lnaCs;omeAs;lnaAs;omeUs;lnaTs;omeUs;lnaTs;omeCs;lnaCs;omeUs;lnaCs;omeGs;lnaG-Sup	4846
PTEN-67 mOl	CAACGGTTTCT ACAG	lnaCs;omeAs;lnaAs;omeCs;lnaGs;omeGs;lnaTs;omeUs;lnaTs;omeCs;lnaTs;omeAs;lnaCs;omeAs;lnaG-Sup	6111
PTEN-68 mOl	CCAACGGTTTC TACA	lnaCs;omeCs;lnaAs;omeAs;lnaCs;omeGs;lnaGs;omeUs;lnaTs;omeUs;lnaCs;omeUs;lnaAs;omeCs;lnaA-Sup	6112
PTEN-69 mOl	CCCAACGGTTT CTAC	lnaCs;omeCs;lnaCs;omeAs;lnaAs;omeCs;lnaGs;omeGs;lnaTs;omeUs;lnaTs;omeCs;lnaTs;omeAs;lnaC-Sup	6113
PTEN-70 mOl	TTAACCCAACG GTTT	lnaTs;omeUs;lnaAs;omeAs;lnaCs;omeCs;lnaCs;omeAs;lnaAs;omeCs;lnaGs;omeGs;lnaTs;omeUs;lnaT-Sup	6117
PTEN-71 mOl	TTTAACCCAAC GGTT	lnaTs;omeUs;lnaTs;omeAs;lnaAs;omeCs;lnaCs;omeCs;lnaAs;omeAs;lnaCs;omeGs;lnaGs;omeUs;lnaT-Sup	6118
PTEN-72 mOl	GTTTAACCCAA CGGT	lnaGs;omeUs;lnaTs;omeUs;lnaAs;omeAs;lnaCs;omeCs;lnaCs;omeAs;lnaAs;omeCs;lnaGs;omeGs;lnaT-Sup	6119
PTEN-73 mOl	TTCGCTGCCAT ATTC	lnaTs;omeUs;lnaCs;omeGs;lnaCs;omeUs;lnaGs;omeCs;lnaCs;omeAs;lnaTs;omeAs;lnaTs;omeUs;lnaC-Sup	24440
PTEN-74 mOl	ATTCGCTGCCA TATT	lnaAs;omeUs;lnaTs;omeCs;lnaGs;omeCs;lnaTs;omeGs;lnaCs;omeCs;lnaAs;omeUs;lnaAs;omeUs;lnaT-Sup	24441
PTEN-75 mOl	AATTCGCTGCC ATAT	lnaAs;omeAs;lnaTs;omeUs;lnaCs;omeGs;lnaCs;omeUs;lnaGs;omeCs;lnaCs;omeAs;lnaTs;omeAs;lnaT-Sup	24442
PTEN-76 mOl	GAATTCGCTGC CATA	lnaGs;omeAs;lnaAs;omeUs;lnaTs;omeCs;lnaGs;omeCs;lnaTs;omeGs;lnaCs;omeCs;lnaAs;omeUs;lnaA-Sup	24443
PTEN-77 mOl	TGATAGTCTAA CCCT	lnaTs;omeGs;lnaAs;omeUs;lnaAs;omeGs;lnaTs;omeCs;lnaTs;omeAs;lnaAs;omeCs;lnaCs;omeCs;lnaT-Sup	24778
PTEN-78 mOl	CCTTCGATTTCC ATT	lnaCs;omeCs;lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaTs;omeUs;lnaCs;omeCs;lnaAs;omeUs;lnaT-Sup	24818
PTEN-79 mOl	GTCCTTCGATTT CCA	lnaGs;omeUs;lnaCs;omeCs;lnaTs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaTs;omeUs;lnaCs;omeCs;lnaA-Sup	24820
PTEN-80 mOl	TTCATCAGTAT GCGC	lnaTs;omeUs;lnaCs;omeAs;lnaTs;omeCs;lnaAs;omeGs;lnaTs;omeAs;lnaTs;omeGs;lnaCs;omeGs;lnaC-Sup	33629
PTEN-81 mOl	GCTATCGATTT CTTG	lnaGs;omeCs;lnaTs;omeAs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeUs;lnaTs;omeCs;lnaTs;omeUs;lnaG-Sup	51896
PTEN-82 mOl	TGCTATCGATT TCTT	lnaTs;omeGs;lnaCs;omeUs;lnaAs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaTs;omeUs;lnaCs;omeUs;lnaT-Sup	51897
PTEN-83 mOl	ATGCTATCGAT TTCT	lnaAs;omeUs;lnaGs;omeCs;lnaTs;omeAs;lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeUs;lnaTs;omeCs;lnaT-Sup	51898
PTEN-84 mOl	AATGCTATCGA TTTC	lnaAs;omeAs;lnaTs;omeGs;lnaCs;omeUs;lnaAs;omeUs;lnaCs;omeGs;lnaAs;omeUs;lnaTs;omeUs;lnaC-Sup	51899

OligoID	Base Sequence	Formatted Sequence	SeqID
PTEN-85 mOl	AAATGCTATCG ATTT	lnaAs;omeAs;lnaAs;omeUs;lnaGs;omeCs;lnaTs;omeAs; lnaTs;omeCs;lnaGs;omeAs;lnaTs;omeUs;lnaT-Sup	51900
PTEN-86 mOl	GCAAATGCTAT CGAT	lnaGs;omeCs;lnaAs;omeAs;lnaAs;omeUs;lnaGs;omeCs; lnaTs;omeAs;lnaTs;omeCs;lnaGs;omeAs;lnaT-Sup	51902
PTEN-87 mOl	TGCAAATGCTA TCGA	lnaTs;omeGs;lnaCs;omeAs;lnaAs;omeAs;lnaTs;omeGs;l naCs;omeUs;lnaAs;omeUs;lnaCs;omeGs;lnaA-Sup	51903
PTEN-88 mOl	CACGCTCTATA CTGC	lnaCs;omeAs;lnaCs;omeGs;lnaCs;omeUs;lnaCs;omeUs; lnaAs;omeUs;lnaAs;omeCs;lnaTs;omeGs;lnaC-Sup	51915
PTEN-89 mOl	GCACGCTCTAT ACTG	lnaGs;omeCs;lnaAs;omeCs;lnaGs;omeCs;lnaTs;omeCs;l naTs;omeAs;lnaTs;omeAs;lnaCs;omeUs;lnaG-Sup	51916
PTEN-90 mOl	CTGCACGCTCT ATAC	lnaCs;omeUs;lnaGs;omeCs;lnaAs;omeCs;lnaGs;omeCs; lnaTs;omeCs;lnaTs;omeAs;lnaTs;omeAs;lnaC-Sup	51918
PTEN-91 mOl	ATTATCTGCAC GCTC	lnaAs;omeUs;lnaTs;omeAs;lnaTs;omeCs;lnaTs;omeGs;l naCs;omeAs;lnaCs;omeGs;lnaCs;omeUs;lnaC-Sup	51923
PTEN-92 mOl	CATTATCTGCA CGCT	lnaCs;omeAs;lnaTs;omeUs;lnaAs;omeUs;lnaCs;omeUs; lnaGs;omeCs;lnaAs;omeCs;lnaGs;omeCs;lnaT-Sup	51924
PTEN-93 mOl	TCATTATCTGC ACGC	lnaTs;omeCs;lnaAs;omeUs;lnaTs;omeAs;lnaTs;omeCs;l naTs;omeGs;lnaCs;omeAs;lnaCs;omeGs;lnaC-Sup	51925
PTEN-94 mOl	CTTGCACCCTA GCGC	lnaCs;omeUs;lnaTs;omeGs;lnaCs;omeAs;lnaCs;omeCs;l naCs;omeUs;lnaAs;omeGs;lnaCs;omeGs;lnaC-Sup	81225
PTEN-95 mOl	CACCCTAGCGC ATAC	lnaCs;omeAs;lnaCs;omeCs;lnaCs;omeUs;lnaAs;omeGs;l naCs;omeGs;lnaCs;omeAs;lnaTs;omeAs;lnaC-Sup	81229
PTEN-96 mOl	CCCTAGCGCAT ACTG	lnaCs;omeCs;lnaCs;omeUs;lnaAs;omeGs;lnaCs;omeGs; lnaCs;omeAs;lnaTs;omeAs;lnaCs;omeUs;lnaG-Sup	81231
PTEN-97 mOl	CCTAGCGCATA CTGA	lnaCs;omeCs;lnaTs;omeAs;lnaGs;omeCs;lnaGs;omeCs;l naAs;omeUs;lnaAs;omeCs;lnaTs;omeGs;lnaA-Sup	81232
PTEN-98 mOl	CTAGCGCATAC TGAT	lnaCs;omeUs;lnaAs;omeGs;lnaCs;omeGs;lnaCs;omeAs; lnaTs;omeAs;lnaCs;omeUs;lnaGs;omeAs;lnaT-Sup	81233
PTEN-99 mOl	TAGCGCATACT GATG	lnaTs;omeAs;lnaGs;omeCs;lnaGs;omeCs;lnaAs;omeUs; lnaAs;omeCs;lnaTs;omeGs;lnaAs;omeUs;lnaG-Sup	81234
PTEN-100 mOl	GCGCATACTGA TGAA	lnaGs;omeCs;lnaGs;omeCs;lnaAs;omeUs;lnaAs;omeCs; lnaTs;omeGs;lnaAs;omeUs;lnaGs;omeAs;lnaA-Sup	81236
EPO-24 m02	TGCACAGGTCC CGCC	dTs;lnaGs;dCs;lnaAs;dCs;lnaAs;dGs;lnaGs;dTs;lnaCs;dC s;lnaCs;dGs;lnaCs;dC-Sup	89026
EPO-26 m02	TTTCCCGCTGA AGCA	dTs;lnaTs;dTs;lnaCs;dCs;lnaCs;dGs;lnaCs;dTs;lnaGs;dAs ;lnaAs;dGs;lnaCs;dA-Sup	89027
GAPDH-01 m08	TTGTCATACCA GGAA	lnaTs;lnaTs;lnaGs;dTs;dCs;dAs;dTs;dAs;dCs;dCs;dAs;dG s;lnaGs;lnaAs;lnaA-Sup	89028

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID	Chrom	Gene	Chr. Start	Chr. End	Strand
1	chrlO	PTEN	89611194	89740532	+
2	chrlO	PTEN	89611194	89740532	-

SEQID	Chrom	Gene	Chr. Start	Chr. End	Strand
3	chrl9	Pten	32820066	32912650	+
4	chrl9	Pten	32820066	32912650	-
5	chrlO	PTEN	89624228	89624270	+
6	chrlO	PTEN	89624833	89624878	+
7	chrlO	PTEN	89624926	89624970	+
8	chrlO	PTEN	89625394	89625442	+
9	chrlO	PTEN	89625544	89625602	+
10	chrlO	PTEN	89625817	89625863	+
11	chrlO	PTEN	89625913	89625938	+
12	chrlO	PTEN	89625981	89626027	+
13	chrlO	PTEN	89626204	89626244	+
14	chrlO	PTEN	89626597	89626641	+
15	chrlO	PTEN	89626724	89626775	+
16	chrlO	PTEN	89626875	89626911	+
17	chrlO	PTEN	89627125	89627169	+
18	chrlO	PTEN	89628194	89628243	+
19	chrlO	PTEN	89630898	89630936	+
20	chrlO	PTEN	89633768	89633831	+
21	chrlO	PTEN	89637731	89637778	+
22	chrlO	PTEN	89655949	89655994	+
23	chrlO	PTEN	89685417	89685446	+
24	chrlO	PTEN	89686532	89686579	+
25	chrlO	PTEN	89686846	89686893	+
26	chrlO	PTEN	89690160	89690213	+
27	chrlO	PTEN	89691658	89691701	+
28	chrlO	PTEN	89692927	89692973	+
29	chrlO	PTEN	89693941	89693990	+
30	chrlO	PTEN	89695260	89695313	+
31	chrlO	PTEN	89695827	89695873	+
32	chrlO	PTEN	89697310	89697355	+
33	chrlO	PTEN	89698069	89698110	+
34	chrlO	PTEN	89698500	89698543	+
35	chrlO	PTEN	89698790	89698828	+
36	chrlO	PTEN	89699611	89699656	+
37	chrlO	PTEN	89700446	89700493	+
38	chrlO	PTEN	89700876	89700919	+
39	chrlO	PTEN	89701325	89701377	+
40	chrlO	PTEN	89701617	89701717	+
41	chrlO	PTEN	89701764	89701818	+

SEQID	Chrom	Gene	Chr. Start	Chr. End	Strand
42	chr10	PTEN	89701915	89701962	+
43	chr10	PTEN	89712065	89712111	+
44	chr10	PTEN	89712351	89712402	+
45	chr10	PTEN	89712411	89712510	+
46	chr10	PTEN	89714201	89714228	+
47	chr10	PTEN	89717191	89717238	+
48	chr10	PTEN	89720717	89720765	+
49	chr10	PTEN	89723393	89723443	+
50	chr10	PTEN	89725518	89725564	+
51	chr10	PTEN	89725617	89725658	+
52	chr10	PTEN	89725819	89725865	+
53	chr10	PTEN	89726333	89726368	+
54	chr10	PTEN	89726640	89726709	+
55	chr10	PTEN	89727525	89727567	+
56	chr10	PTEN	89727527	89727569	+
57	chr10	PTEN	89728125	89728171	+
58	chr10	PTEN	89728126	89728170	+
59	chr10	PTEN	89728128	89728172	+
60	chr10	PTEN	89730064	89730112	+
61	chr10	PTEN	89730269	89730384	+
62	chr10	PTEN	89622228	89626270	+
63	chr10	PTEN	89622833	89626878	+
64	chr10	PTEN	89622926	89626970	+
65	chr10	PTEN	89623394	89627442	+
66	chr10	PTEN	89623544	89627602	+
67	chr10	PTEN	89623817	89627863	+
68	chr10	PTEN	89623913	89627938	+
69	chr10	PTEN	89623981	89628027	+
70	chr10	PTEN	89624204	89628244	+
71	chr10	PTEN	89624597	89628641	+
72	chr10	PTEN	89624724	89628775	+
73	chr10	PTEN	89624875	89628911	+
74	chr10	PTEN	89625125	89629169	+
75	chr10	PTEN	89626194	89630243	+
76	chr10	PTEN	89628898	89632936	+
77	chr10	PTEN	89631768	89635831	+
78	chr10	PTEN	89635731	89639778	+
79	chr10	PTEN	89653949	89657994	+
80	chr10	PTEN	89683417	89687446	+

SEQID	Chrom	Gene	Chr. Start	Chr. End	Strand
81	chr10	PTEN	89684532	89688579	+
82	chr10	PTEN	89684846	89688893	+
83	chr10	PTEN	89688160	89692213	+
84	chr10	PTEN	89689658	89693701	+
85	chr10	PTEN	89690927	89694973	+
86	chr10	PTEN	89691941	89695990	+
87	chr10	PTEN	89693260	89697313	+
88	chr10	PTEN	89693827	89697873	+
89	chr10	PTEN	89695310	89699355	+
90	chr10	PTEN	89696069	89700110	+
91	chr10	PTEN	89696500	89700543	+
92	chr10	PTEN	89696790	89700828	+
93	chr10	PTEN	89697611	89701656	+
94	chr10	PTEN	89698446	89702493	+
95	chr10	PTEN	89698876	89702919	+
96	chr10	PTEN	89699325	89703377	+
97	chr10	PTEN	89699617	89703717	+
98	chr10	PTEN	89699764	89703818	+
99	chr10	PTEN	89699915	89703962	+
100	chr10	PTEN	89710065	89714111	+
101	chr10	PTEN	89710351	89714402	+
102	chr10	PTEN	89710411	89714510	+
103	chr10	PTEN	89712201	89716228	+
104	chr10	PTEN	89715191	89719238	+
105	chr10	PTEN	89718717	89722765	+
106	chr10	PTEN	89721393	89725443	+
107	chr10	PTEN	89723518	89727564	+
108	chr10	PTEN	89723617	89727658	+
109	chr10	PTEN	89723819	89727865	+
110	chr10	PTEN	89724333	89728368	+
111	chr10	PTEN	89724640	89728709	+
112	chr10	PTEN	89725525	89729567	+
113	chr10	PTEN	89725527	89729569	+
114	chr10	PTEN	89726125	89730171	+
115	chr10	PTEN	89726126	89730170	+
116	chr10	PTEN	89726128	89730172	+
117	chr10	PTEN	89728064	89732112	+
118	chr10	PTEN	89728269	89732384	+
119	chr10	PTEN	89623576	89623622	-

SEQID	Chrom	Gene	Chr. Start	Chr. End	Strand
120	chrlO	PTEN	89623906	89623956	.
121	chrlO	PTEN	89624031	89624073	.
122	chrlO	PTEN	89624202	89624247	.
123	chrlO	PTEN	89624760	89624805	.
124	chrlO	PTEN	89625073	89625113	.
125	chrlO	PTEN	89628887	89628953	.
126	chrlO	PTEN	89665539	89665573	.
127	chrlO	PTEN	89692964	89693006	.
128	chrlO	PTEN	89695528	89695586	.
129	chrlO	PTEN	89695765	89695876	.
130	chrlO	PTEN	89695889	89695911	.
131	chrlO	PTEN	89697361	89697418	.
132	chrlO	PTEN	89697767	89697812	.
133	chrlO	PTEN	89721856	89721896	.
134	chrlO	PTEN	89621576	89625622	.
135	chrlO	PTEN	89621906	89625956	.
136	chrlO	PTEN	89622031	89626073	.
137	chrlO	PTEN	89622202	89626247	.
138	chrlO	PTEN	89622760	89626805	.
139	chrlO	PTEN	89623073	89627113	.
140	chrlO	PTEN	89626887	89630953	.
141	chrlO	PTEN	89663539	89667573	.
142	chrlO	PTEN	89690964	89695006	.
143	chrlO	PTEN	89693528	89697586	.
144	chrlO	PTEN	89693765	89697876	.
145	chrlO	PTEN	89693889	89697911	.
146	chrlO	PTEN	89695361	89699418	.
147	chrlO	PTEN	89695767	89699812	.
148	chrlO	PTEN	89719856	89723896	.

Single Strand Oligonucleotides (Antisense Strand of Target Gene)

SeqID range: 149-63340, 89008-89021, 89024-89025

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The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described

herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

CLAIMS

What is claimed is:

1. A single stranded oligonucleotide having a sequence 5'-X-Y-Z, wherein X is any nucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a seed sequence of a human microRNA, and Z is a nucleotide sequence of 1-23 nucleotides in length, wherein the single stranded oligonucleotide is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of a PTEN gene.

2. The single stranded oligonucleotide of claim 1, wherein the oligonucleotide does not comprise three or more consecutive guanosine nucleotides.

3. The single stranded oligonucleotide of claim 1 or 2, wherein the oligonucleotide does not comprise four or more consecutive guanosine nucleotides.

4. The single stranded oligonucleotide of any one of claims 1 to 3, wherein the oligonucleotide is 8 to 30 nucleotides in length.

5. The single stranded oligonucleotide of any one of claims 1 to 3, wherein the oligonucleotide is 8 to 10 nucleotides in length and all but 1, 2, or 3 of the nucleotides of the complementary sequence of the PRC2-associated region are cytosine or guanosine nucleotides.

6. The single stranded oligonucleotide of any one of claims 1 to 5, wherein at least one nucleotide of the oligonucleotide is a nucleotide analogue.

7. The single stranded oligonucleotide of claim 6, wherein the at least one nucleotide analogue results in an increase in Tm of the oligonucleotide in a range of 1 to 5 °C compared with an oligonucleotide that does not have the at least one nucleotide analogue.

8. The single stranded oligonucleotide of any one of claims 1 to 7, wherein at least one nucleotide of the oligonucleotide comprises a 2' O-methyl.

9. The single stranded oligonucleotide of any one of claims 1 to 8, wherein each nucleotide of the oligonucleotide comprises a 2' O-methyl.

10. The single stranded oligonucleotide of any one of claims 1 to 8, wherein the oligonucleotide comprises at least one ribonucleotide, at least one deoxyribonucleotide, or at least one bridged nucleotide.

11. The single strand oligonucleotide of claim 10, wherein the bridged nucleotide is a LNA nucleotide, a cEt nucleotide or a ENA modified nucleotide.

12. The single stranded oligonucleotide of any one of claims 1 to 6, wherein each nucleotide of the oligonucleotide is a LNA nucleotide.

13. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-fluoro-deoxyribonucleotides.

14. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and 2'-0-methyl nucleotides.

15. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and ENA nucleotide analogues.

16. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating deoxyribonucleotides and LNA nucleotides.

17. The single stranded oligonucleotide of any one of claims 13 to 16, wherein the 5' nucleotide of the oligonucleotide is a deoxyribonucleotide.

18. The single stranded oligonucleotide of any one of claims 1 to 6, wherein the nucleotides of the oligonucleotide comprise alternating LNA nucleotides and 2'-O-methyl nucleotides.

19. The single stranded oligonucleotide of claim 18, wherein the 5' nucleotide of the oligonucleotide is a LNA nucleotide.

20. The single stranded oligonucleotide of any one of claims 1 to 8, wherein the nucleotides of the oligonucleotide comprise deoxyribonucleotides flanked by at least one LNA nucleotide on each of the 5' and 3' ends of the deoxyribonucleotides.

21. The single stranded oligonucleotide of any one of claims 1 to 20, further comprising phosphorothioate internucleotide linkages between at least two nucleotides.

22. The single stranded oligonucleotide of claim 21, further comprising phosphorothioate internucleotide linkages between all nucleotides.

23. The single stranded oligonucleotide of any one of claims 1 to 22, wherein the nucleotide at the 3' position of the oligonucleotide has a 3' hydroxyl group.

24. The single stranded oligonucleotide of any one of claims 1 to 22, wherein the nucleotide at the 3' position of the oligonucleotide has a 3' thiophosphate.

25. The single stranded oligonucleotide of any one of claims 1 to 24, further comprising a biotin moiety conjugated to the 5' nucleotide.

26. A single stranded oligonucleotide comprising a region of complementarity that is complementary with at least 8 consecutive nucleotides of a PRC2-associated region of a PTEN gene, wherein the oligonucleotide has at least one of:

a) a sequence that is 5'X-Y-Z, wherein X is any nucleotide and wherein X is anchored at the 5' end of the oligonucleotide, Y is a nucleotide sequence of 6 nucleotides in length that is not a human seed sequence of a microRNA, and Z is a nucleotide sequence of 1 to 23 nucleotides in length;

b) a sequence that does not comprise three or more consecutive guanosine nucleotides;

c) a sequence that has less than a threshold level of sequence identity with every sequence of nucleotides, of equivalent length to the second nucleotide sequence, that are between 50 kilobases upstream of a 5'-end of an off-target gene and 50 kilobases downstream of a 3'-end of the off-target gene;

d) a sequence that is complementary to a PRC2-associated region that encodes an RNA that forms a secondary structure comprising at least two single stranded loops; and/or

e) a sequence that has greater than 60% G-C content.

27. The single stranded oligonucleotide of claim 26, wherein the oligonucleotide has the sequence 5'X-Y-Z and wherein the oligonucleotide is 8-50 nucleotides in length.

28. A composition comprising a single stranded oligonucleotide of any one of claims 1 to 27 and a carrier.

29. A composition comprising a single stranded oligonucleotide of any one of claims 1 to 27 in a buffered solution.

30. A composition of claim 28, wherein the oligonucleotide is conjugated to the carrier.

31. The composition of claim 30, wherein the carrier is a peptide.

32. The composition of claim 30, wherein the carrier is a steroid.

33. A pharmaceutical composition comprising a composition of any one of claims 28 to 32 and a pharmaceutically acceptable carrier.

34. A kit comprising a container housing the composition of any one of claims 28 to 33.

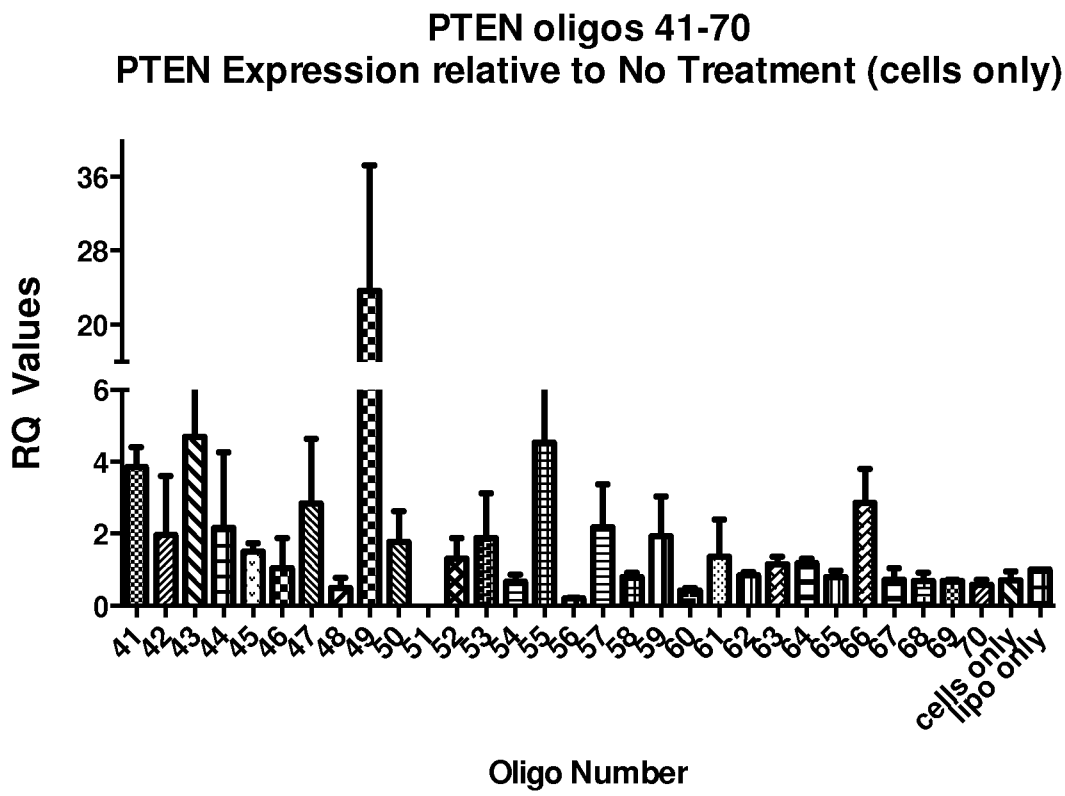
35. A method of increasing expression of a PTEN gene in a cell, the method comprising delivering the single stranded oligonucleotide of any one of claims 1 to 27 into the cell.

36. The method of claim CI, wherein delivery of the single stranded oligonucleotide into the cell results in a level of expression of a PTEN gene that is at least 50% greater than a level of expression of the PTEN gene in a control cell that does not comprise the single stranded oligonucleotide.

37. A method increasing levels of a PTEN gene in a subject, the method comprising administering the single stranded oligonucleotide of any one of claims 1 to 27 to the subject.

38. A method of treating a condition associated with decreased levels of a PTEN gene in a subject, the method comprising administering the single stranded oligonucleotide of any one of claims 1 to 27 to the subject.

39. The method of claim 38, wherein the condition is cancer.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PTEN Expression relative to No Treatment (cells only)
RQ Values
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28
20
6
4
2
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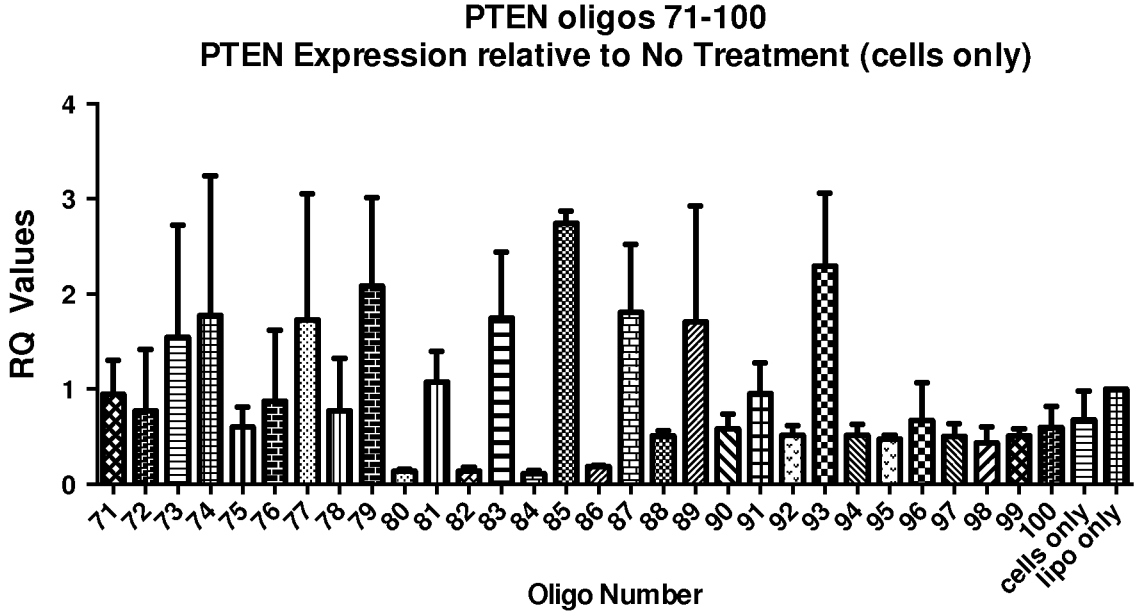
cells only
lipo only
Oligo Number

FIG. 1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PTEN Expression relative to No Treatment (cells only)
RQ Values
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3
2
1
0
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cells only
lipo only
Oligo Number

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041389

A. CLASSIFICATION OF SUBJECT MATTER

C12N 15/ll(2006.01)i, C07H 21/00(2006.01)i, C12N 15/63(2006.01)i, A61K 31/7088(2006.01)i, A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N 15/1 1; A61K 39/395; C12N 5/00; NotA vai/lable; A61K 31/366; A61P 35/00; A61K 48/00; A61K 31/5377; C07H 21/00; C12N 15/63; A61K 31/7088

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: enhancing, activating PTEN expression, single stranded oligonucleotide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category'*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010-0286141 Al (DURDEN, DONALD L. et al.) 11 November 2010 See abstract; claims 94-98.	1-3,26-27
A	US 2011-0150868 Al (YU, DIHUA. et al.) 23 June 2011 See abstract; claims 1-2 and 6-9.	1-3,26-27
A	WO 2005-089169 A2 (EXELIXIS, INC.) 29 September 2005 See abstract; claims 1 and 20.	1-3,26-27
A	US 2004-0002153 Al (MONIA, BRETT P. et al.) 1 January 2004 See abstract; claims 1 and 31.	1-3,26-27

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2013 (29.07.2013)	**29 July 2013 (29.07.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041389

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of itemlc of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of :

a. a sequence listing filed or furnished

☐ on paper

☒ in electronic form

b. time of filing or furnishing

☐ contained in the international application as filed

☒ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041389

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons::

1. ☒ Claims Nos.: 37-39
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 37-39 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☒ Claims Nos.: 7,1 1,19,22,30-32,36,39
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 7,1 1,19,22,30-32 and 39 are unclear since they refer to claims which are not searchable due to not being drafted in accordance with the second and third sentence of Rule 6.4(a).
Claim 36 is unclear. Because reference claim has not been worded in claim 36.

3. ☒ Claims Nos.: 4-6,8-10,12-18,20-21,23-25,28-29,33-35,37-38
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/041389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0286141 Al	11/11/2010	AU 2001-513701 A	11/12/2001
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