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(54) **METHOD AND REAGENT FOR THE TREATMENT OF ASTHMA AND ALLERGIC CONDITIONS**

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(57) **ABSTRACT**

The present invention relates to nucleic acid molecules, including antisense, enzymatic nucleic acid molecules, and RNA interference molecules, such as hammerhead ribozymes, DNAzymes, allozymes, siRNA, decoys and antisense, which modulate the expression of prostaglandin D2 (PTGDS), prostaglandin D2 receptor (PTGDR), and adenosine receptor genes.

Figure 1: Examples of Nuclease Stable Ribozyme Motifs

Figure 2: 2'-O-Me substituted Amberzyme Enzymatic Nucleic Acid Motif

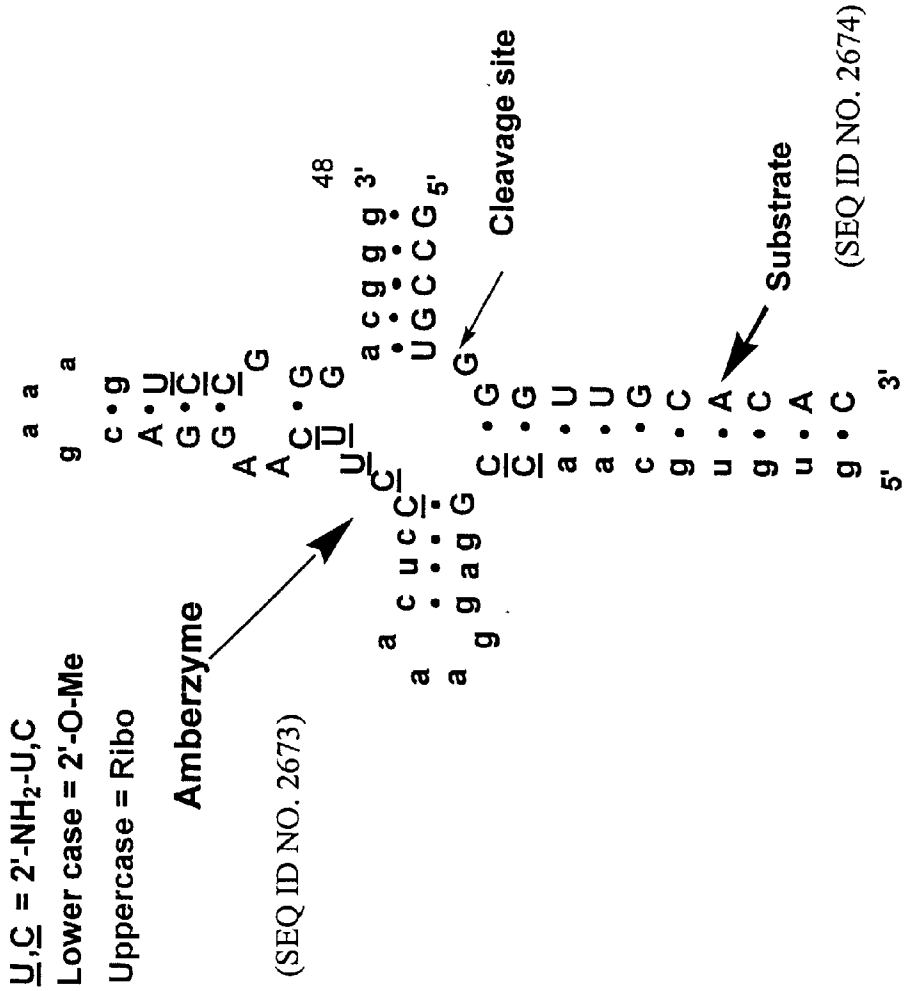
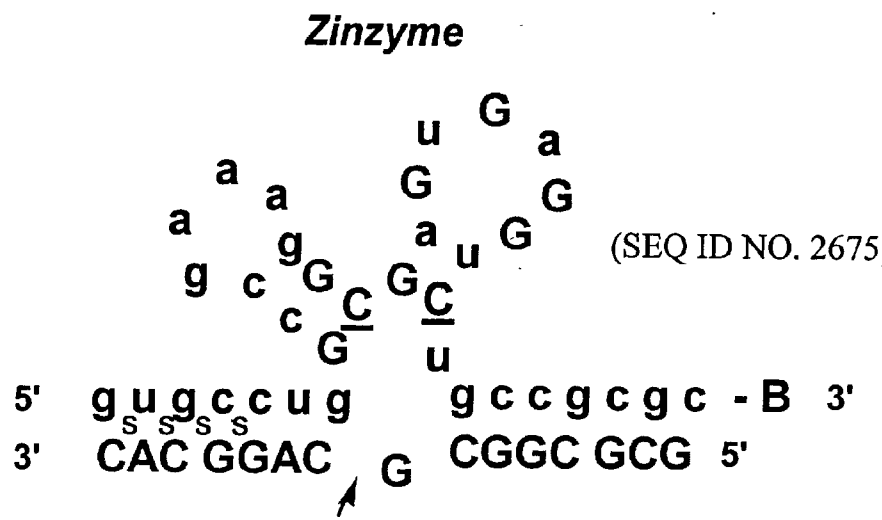


Figure 3: Stabilized Zinzyme Ribozyme Motif



(SEQ ID NO. 2675)

(SEQ ID NO. 2676)

Legend

Uppercase: indicates natural ribo residues

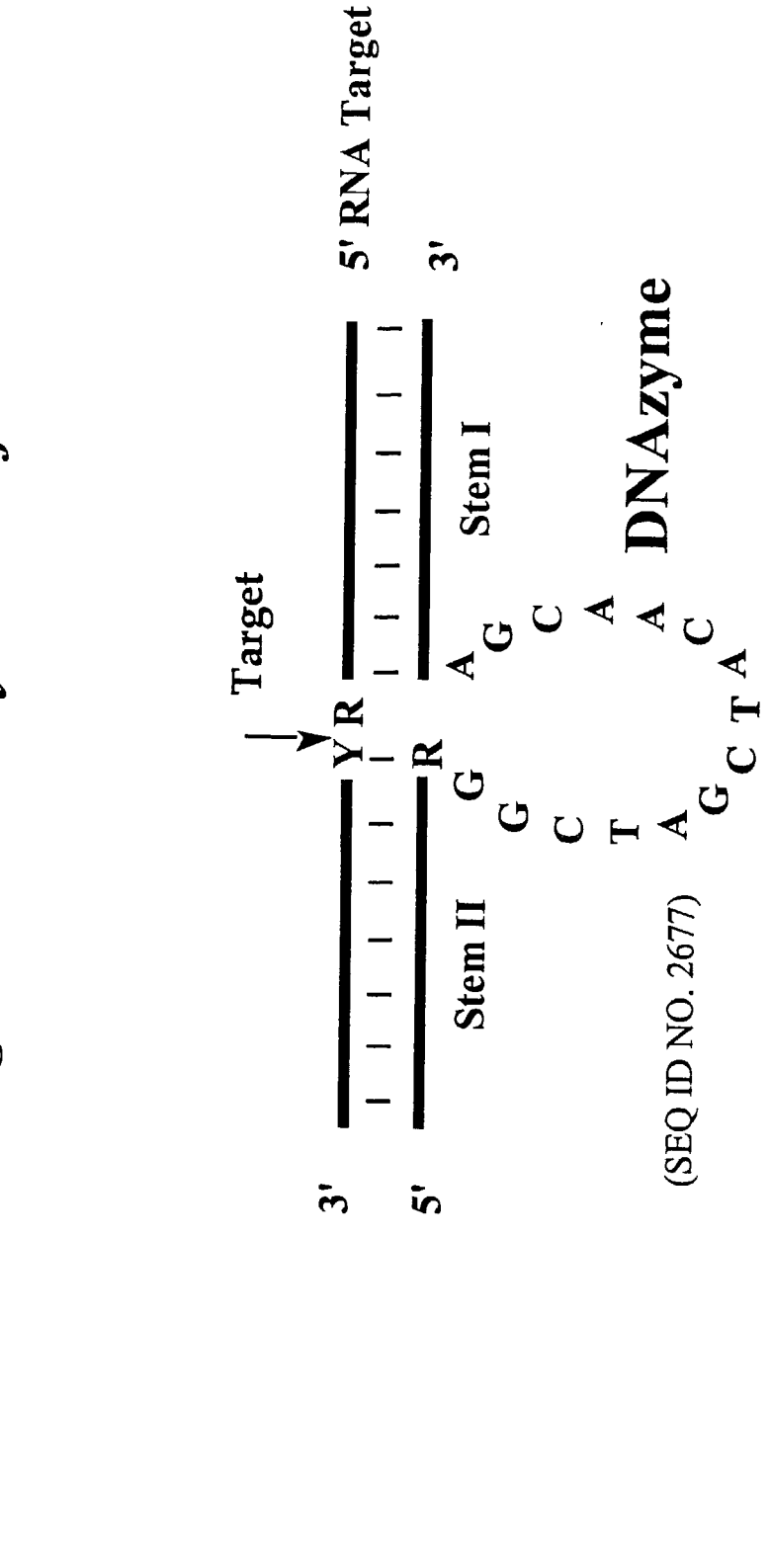
C : indicates 2'-deoxy-2'-amino Cytidine

Lowercase: 2'-O-methyl

S: phosphorothioate/phosphorodithioate linkage

B: 3'-3' abasic moiety

Figure 4: DNAzyme Motif



METHOD AND REAGENT FOR THE TREATMENT OF ASTHMA AND ALLERGIC CONDITIONS

PRIORITY

[0001] This application claims the benefit of U.S. Application Ser. No. 60/315,315, filed on Aug. 28, 2001, which is herein incorporated by reference in its entirity.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to therapeutic compositions and methods for the treatment or diagnosis of diseases or conditions related to allergic response. Specifically, the invention provides compositions and methods for the treatment of diseases or conditions related to levels of factors involved in allergic conditions such as asthma, for example prostaglandin D2 receptor (PTGDR), prostaglandin D2 synthetase (PTGDS) and adenosine A1 receptor (ADORA1). The discussion is provided only for understanding of the invention that follows. This summary is not an admission that any of the work described below is prior art to the claimed invention.

[0003] Asthma is a chronic inflammatory disorder of the lungs characterized by airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. T-lymphocytes that produce TH2 cytokines and cosinophilic leukocytes infiltrate the airways. In the airway and in bronchial alveolar lavage (BAL) fluid of individuals with asthma, high concentrations of TH2 cytokines, interleukin-4 (IL-4), IL-5, and IL-13, are present along with increased levels of adenosine. In contrast to normal individuals, asthmatics respond to adenosine challenge with marked airway obstruction. Upon allergen challenge, mast cells are activated by cross-linked IgE-allergen complexes. Large amounts of prostaglandin D2 (PGD2), the major cyclooxygenase product of arachidonic acid are released. PGD2 is generated from PGH2 via the activity of prostaglandin D2 synthetase (PTGDS). PGD2 receptors and adenosine A1 receptors are present in the lungs and airway along with various other tissues in response to allergic stimuli (Howarth, 1997, *Allergy,* 52, 12).

[0004] The significance of PGD2 as a mediator of allergic asthma has been established with the development of mice deficient in the PGD2 receptor (DP). DP is a heterotrimeric GTP-binding protein-coupled, rhodopsin-type receptor specific for PGD2 (Hirata et al., 1994, *PNAS USA.,* 91, 11192). These mice fail to develop airway hyperreactivity and have greatly reduced eosinophil infiltration and cytokine accumulation in response to allergens. Upon allergen challenge mice deficient in the prostaglandin D2 (PGD2) receptor (DP) did not develop airway hyperactivity. Cytokine, lymphocyte and eosinophil accumulation in the lungs were greatly reduced (Matsuoka et al., 2000, *Science,* 287, 2013). The DP −/− mice exhibited no behavioral, anatomic, or histological abnormalities. Primary immune response is not affected by DP disruption.

[0005] Asthma affects more than 100 million people worldwide and more than 17 million Americans (5% of the population). Since 1980 the incidence has more than doubled and deaths have tripled (5,000 deaths in 1995). Annual asthma-related healthcare costs in the US alone were estimated to exceed $14.5 billion in 2000. Current therapies such as inhalant anti-inflammatories and bronchodilators can be used to treat symptoms, however, these therapies do not prevent or cure asthma.

[0006] Sandberg et al., 2001, *Prog. Respir. Res.,* 31, 370-373, describes ribozyme therapy for asthma and COPD.

[0007] Sullivan et al., International U.S. Pat. No. 5,616,488, describes ribozymes targeting interleukin-5 for treatment and diagnosis of asthma and other inflammatory disorders.

[0008] Stinchcomb et al, International PCT Publication No. WO 95/23225, describes ribozymes and methods for inhibiting the expression of disease related genes including genes associated with asthma.

[0009] Nyce, International PCT Publication Nos. WO 00/62736, WO 00/09525, WO 99/13886, WO 98/23294, WO 96/40266 and U.S. Pat. No. 6,025,339 describe specific antisense oligonucleotides targeting certain mRNAs encoding particular adenosine receptors.

SUMMARY OF THE INVENTION

[0010] The invention features novel nucleic acid-based molecules, for example, enzymatic nucleic acid molecules, allozymes, antisense nucleic acids, 2-5A antisense chimeras, triplex forming oligonucleotides, decoy RNA, dsRNA, siRNA, aptamers, and antisense nucleic acids containing RNA cleaving chemical groups, and methods to modulate gene expression, for example, genes encoding prostaglandin D2 receptor (PTGDR), prostaglandin D2 synthetase (PTGDS), and adenosine receptors (AR) such as adenosine receptor A1, A2a, A2b, and A3. In particular, the instant invention features nucleic-acid based molecules and methods to modulate the expression of PTGDR, PTGDS, and adenosine A1 receptor (ADORA1).

[0011] In one embodiment, the invention features one or more nucleic acid-based molecules and methods that independently or in combination modulate the expression of gene(s) encoding prostaglandin D2 receptors (PTGDR), prostaglandin D2 synthetase (PTGDS) and adenosine receptors such as ADORA1. Specifically, the present invention features nucleic acid molecules that modulate the expression of prostaglandin D2 receptor (PTGDR) gene, for example Genbank Accession Nos. U31332 and U31099, prostaglandin D2 synthetase (PTGDS) gene, for example Genbank Accession No. NM_000954, and Adenosine A1 receptor (ADORA1), for example Genbank Accession No. NM_000674.

[0012] The description below of the various aspects and embodiments is provided with reference to the exemplary prostaglandin D2 receptor (PTGDR), prostaglandin D2 synthetase (PTGDS), and adenosine A1 receptor (ADORA1). However, the various aspects and embodiments are also directed to other genes that express prostaglandin proteins and other receptors involved in allergic reactions. Those additional genes can be analyzed for target sites using the methods described for PTGDS, PTGDR, and ADORA1. Thus, the inhibition and the effects of such inhibition of the other genes can be performed as described herein.

[0013] In another embodiment, the invention features an enzymatic nucleic acid molecule comprising a sequence selected from the group consisting of SEQ ID NOs: 228-454, 831-1206, 1438-1668, 1715-2057, and 2247-2666. In yet another embodiment, the invention features an enzymatic nucleic acid molecule comprising at least one binding arm wherein one or more of said binding arms comprises a

sequence complementary to a sequence selected from the group consisting of SEQ ID NOs: 1-227, 455-830, 1207-1437, 1669-1714, and 2058-2246.

[0014] In one embodiment, the invention features an antisense nucleic acid molecule comprising a sequence complementary to a sequence selected from the group consisting of SEQ ID NOs: 1-227, 455-830, 1207-1437, 1669-1714, and 2058-2246.

[0015] In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing RNA cleaving chemical groups of the invention is adapted to treat asthma.

[0016] In one embodiment, an enzymatic nucleic acid molecule of the invention has an endonuclease activity to cleave RNA encoded by a PTGDS and/or PTGDR gene.

[0017] In another embodiment, an enzymatic nucleic acid molecule of the invention is in a hammerhead, Inozyme, Zinzyme, DNAzyme, Amberzyme, or G-cleaver configuration.

[0018] In another embodiment, an enzymatic nucleic acid molecule of the invention having a hammerhead configuration comprises a sequence complementary to a sequence having SEQ ID NOs: 1-227. In yet another embodiment, an enzymatic nucleic acid molecule of invention having a hammerhead configuration comprises a sequence having SEQ ID NOs: 228-454.

[0019] In another embodiment, an enzymatic nucleic acid molecule of the invention having an Inozyme configuration comprises a sequence complementary to a sequence having SEQ ID NOs: 455-830. In yet another embodiment, an enzymatic nucleic acid molecule of invention having an Inozyme configuration comprises a sequence having SEQ ID NOs: 831-1206.

[0020] In another embodiment, an enzymatic nucleic acid molecule of the invention having a Zinzyme configuration comprises a sequence complementary to a sequence having SEQ ID NOs: 1207-1437. In yet another embodiment, an enzymatic nucleic acid molecule of invention having a Zinzyme configuration comprises a sequence having SEQ ID NOs: 1438-1668.

[0021] In another embodiment, an enzymatic nucleic acid molecule of the invention having a DNAzyme configuration comprises a sequence complementary to a sequence having SEQ ID NOs: 1, 13, 55, 69, 74, 104, 112, 120, 123, 128, 131, 138, 147, 154, 157, 158, 169, 188, 192, 208, 221, 463, 475, 489, 505, 527, 541, 552, 554, 561, 563, 572, 591, 601, 605, 627, 637, 645, 652, 653, 661, 668, 669, 670, 676, 692, 699, 706, 719, 725, 732, 737, 741, 747, 763, 774, 782, 800, 805, 807, 816, 818, 823, 827, 828, 1207-1437, and 1669-1714. In yet another embodiment, an enzymatic nucleic acid molecule of invention having a DNAzyme configuration comprises a sequence having SEQ ID NOs: 1715-2057.

[0022] In another embodiment, an enzymatic nucleic acid molecule of the invention having an Amberzyme configuration comprises a sequence complementary to a sequence having SEQ ID NOs: 1207-1437, and 2058-2246. In yet another embodiment, an enzymatic nucleic acid molecule of invention having an Amberzyme configuration comprises a sequence having SEQ ID NOs: 2247-2666.

[0023] In one embodiment, an enzymatic nucleic acid molecule of the invention comprises between 8 and 100 bases complementary to the RNA of PTGDS, ADORA1 and/or PTGDR gene. In another embodiment, an enzymatic nucleic acid molecule of the invention comprises between 14 and 24 bases complementary to a RNA molecule of a PTGDS or PTGDR gene.

[0024] In one embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing RNA cleaving chemical groups of the invention is chemically synthesized.

[0025] In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing RNA cleaving chemical groups of the invention comprises at least one 2'-sugar modification.

[0026] In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing RNA cleaving chemical groups of the invention comprises at least one nucleic acid base modification.

[0027] In another embodiment, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acids containing RNA cleaving chemical groups of the invention comprises at least one phosphate backbone modification.

[0028] In one embodiment, the invention features a mammalian cell, for example a human cell, including the enzymatic nucleic acid molecule of the invention.

[0029] In another embodiment, the invention features a method of reducing PTGDS, ADORA1 and/or PTGDR expression or activity in a cell, comprising contacting the cell with an enzymatic nucleic acid molecule of the invention, under conditions suitable for the reduction.

[0030] In another embodiment, the invention features a method of reducing PTGDS, ADORA1 and/or PTGDR expression or activity in a cell, comprising the step of contacting the cell with an antisense nucleic acid molecule of the invention under conditions suitable for the reduction.

[0031] In yet another embodiment, the invention features a method of treatment of a patient having a condition associated with the level of PTGDS, ADORA1 and/or PTGDR, comprising contacting cells of the patient with an enzymatic nucleic acid molecule of the invention, under conditions suitable for the treatment.

[0032] In one embodiment, the invention features a method of treatment of a patient having a condition associated with the level of PTGDS, ADORA1 and/or PTGDR, comprising contacting cells of the patient with an antisense nucleic acid molecule of the invention, under conditions suitable for the treatment.

[0033] In another embodiment, a method of treatment of a patient having a condition associated with the level of PTGDS, ADORA1 and/or PTGDR is featured, wherein the method further comprises the use of one or more drug therapies under conditions suitable for the treatment.

[0034] For example, in one embodiment, the invention features a method for treatment of asthma, allergic rhinitis, or atopic dermatitis under conditions suitable for the treatment.

[0035] In another embodiment, the invention features a method of cleaving a RNA molecule of PTGDS, ADORA1 and/or PTGDR gene comprising contacting an enzymatic nucleic acid molecule of the invention with a RNA molecule of a PTGDS, ADORA1 and/or PTGDR gene under conditions suitable for the cleavage, for example, wherein the cleavage is carried out in the presence of a divalent cation, such as Mg^{2+}.

[0036] In one embodiment, an enzymatic nucleic acid molecule of the invention comprises a cap structure, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative, wherein the cap structure is at the 5'-end, or 3'-end, or both the 5'-end and the 3'-end of the enzymatic nucleic acid molecule.

[0037] In another embodiment, an antisense nucleic acid molecule of the invention comprises a cap structure, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative, wherein the cap structure is at the 5'-end, or 3'-end, or both the 5'-end and the 3'-end of the antisense nucleic acid molecule.

[0038] In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one enzymatic nucleic acid molecule of the invention, in a manner which allows expression of the nucleic acid molecule.

[0039] In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

[0040] In yet another embodiment, the expression vector of the invention further comprises a sequence for an antisense nucleic acid molecule complementary to a RNA molecule of a PTGDS, ADORA1 and/or PTGDR gene.

[0041] In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more enzymatic nucleic acid molecules, which can be the same or different.

[0042] In another embodiment, the invention features a method for treatment of asthma, allergic rhinitis, or atopic dermatitis, comprising administering to a patient an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing RNA cleaving chemical groups of the invention, under conditions suitable for the treatment, including administering to the patient one or more other therapies, for example, inhalant anti-inflammatories, bronchodilators, adenosine inhibitors and adenosine A1 receptor inhibitors.

[0043] In one embodiment, the method of treatment features an enzymatic nucleic acid molecule or antisense nucleic acid molecule of the invention comprises at least five ribose residues, at least ten 2'-O-methyl modifications, and a 3'-end modification, such as a 3'-3' inverted abasic moiety. In another embodiment, an enzymatic nucleic acid molecule or antisense nucleic acid molecule of the invention further comprises phosphorothioate linkages on at least three of the 5' terminal nucleotides.

[0044] In another embodiment, the invention features a method of administering to a mammal, for example a human, an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing RNA cleaving chemical groups of the invention, comprising contacting the mammal with the nucleic acid molecule under conditions suitable for the administration, for example, in the presence of a delivery reagent such as a lipid, cationic lipid, phospholipid, or liposome.

[0045] In yet another embodiment, the invention features a method of administering to a mammal an enzymatic nucleic acid molecule, antisense nucleic acid molecule, 2-5A antisense chimera, triplex forming oligonucleotide, decoy RNA, dsRNA, siRNA, aptamer, or antisense nucleic acid containing RNA cleaving chemical groups of the invention in conjunction with a therapeutic agent, comprising contacting the mammal, for example a human, with the nucleic acid molecule and the therapeutic agent under conditions suitable for the administration.

[0046] In one embodiment, the invention features the use of an enzymatic nucleic acid molecule, which can be in a hammerhead, NCH, G-cleaver, Amberzyme, Zinzyme, and/or DNAzyme motif, to down-regulate the expression of a PTGDS, an ADORA1 and/or a PTGDR gene.

[0047] By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, such as PTGDS, ADORA1 and/or PTGDR proteins or PTGDS, ADORA1 and/or PTGDR subunit(s), is reduced below that observed in the absence of the nucleic acid molecules of the invention. In one embodiment, inhibition, down-regulation or reduction with an enzymatic nucleic acid molecule is below that level observed in the presence of an enzymatically inactive or attenuated molecule that is able to bind to the same site on the target RNA molecule, but is unable to cleave that RNA molecule. In another embodiment, inhibition, down-regulation, or reduction with antisense oligonucleotides is below that level observed in the presence of, for example, an oligonucleotide with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of PTGDS, ADORA1 and/or PTGDR with a nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

[0048] By "up-regulate" is meant that the expression of a gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins, protein subunits, or activity of one or more proteins or protein subunits, such as PTGDS, ADORA1 and/or PTGDR proteins or PTGDS, ADORA1 and/or PTGDR subunits, is greater than that observed in the absence of the nucleic acid molecules of the invention. For example, the expression of a gene, such as

PTGDS, ADORA1 and/or PTGDR gene, can be increased in order to treat, prevent, ameliorate, or modulate a pathological condition caused or exacerbated by an absence or low level of gene expression.

[0049] By "modulate" is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more protein subunits, or activity of one or more protein subunits is up-regulated or down-regulated, such that the expression, level, or activity is greater than or less than that observed in the absence of a nucleic acid molecule of the invention.

[0050] By "enzymatic nucleic acid molecule" it is meant a nucleic acid molecule that has complementarity in a substrate binding region to a specified gene target, and also has an enzymatic activity that is active to specifically cleave target a RNA molecule. That is, the enzymatic nucleic acid molecule is able to intermolecularly cleave a RNA molecule and thereby inactivate a target RNA molecule. These complementary regions allow sufficient hybridization of an enzymatic nucleic acid molecule to a target RNA molecule and thus permit cleavage. One hundred percent complementarity is preferred, but complementarity as low as 50-75% can also be useful in this invention (see for example Werner and Uhlenbeck, 1995, *Nucleic Acids Research,* 23, 2092-2096; Hammann et al., 1999, *Antisense and Nucleic Acid Drug Dev.,* 9, 25-31). The nucleic acids can be modified at the base, sugar, and/or phosphate groups. The term enzymatic nucleic acid is used interchangeably with phrases such as ribozymes, catalytic RNA, enzymatic RNA, catalytic DNA, aptazyme or aptamer-binding ribozyme, regulatable ribozyme, catalytic oligonucleotides, nucleozyme, DNAzyme, RNA enzyme, endoribonuclease, endonuclease, minizyme, leadzyme, oligozyme or DNA enzyme. All of these terminologies describe nucleic acid molecules with enzymatic activity. The specific enzymatic nucleic acid molecules described in the instant application are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site that is complementary to one or more of the target nucleic acid regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart a nucleic acid cleaving and/or ligation activity to the molecule (Cech et al, U.S. Pat. No. 4,987,071; Cech et al., 1988, 260 *JAMA* 3030).

[0051] By "nucleic acid molecule" as used herein is meant a molecule having nucleotides.

[0052] The nucleic acid can be single, double, or multiple stranded and can comprise modified or unmodified nucleotides or non-nucleotides or various mixtures and combinations thereof.

[0053] By "enzymatic portion" or "catalytic domain" is meant that portion/region of the enzymatic nucleic acid molecule essential for cleavage of a nucleic acid substrate (for example see FIGS. **1-4**).

[0054] By "substrate binding arm" or "substrate binding domain" is meant that portion/region of a enzymatic nucleic acid that is able to interact, for example via complementarity (i.e., able to base-pair with), with a portion of its substrate. Such complementarity can be 100%, but can be less if desired. For example, as few as 10 bases out of 14 can be base-paired (see for example Werner and Uhlenbeck, 1995, *Nucleic Acids Research,* 23, 2092-2096; Hammann et al, 1999, *Antisense and Nucleic Acid Drug Dev.,* 9, 25-31). Examples of such arms are shown generally in FIGS. **1-4**. That is, these arms contain sequences within a enzymatic nucleic acid that are intended to bring enzymatic nucleic acid and target RNA together through complementary base-pairing interactions. The enzymatic nucleic acid of the invention can have binding arms that are contiguous or non-contiguous and can be of varying lengths. The length of the binding arm(s) can be greater than or equal to four nucleotides and of sufficient length to stably interact with a target RNA; in one embodiment they can be 12-100 nucleotides; in another embodiment they can be 14-24 nucleotides long (see for example Werner and Uhlenbeck, supra; Hamman et al., supra; Hampel et al., EP0360257; Berzal-Herranze et al., 1993, *EMBO J.,* 12, 2567-73) or between 8 and 14 nucleotides long. If two binding arms are chosen, the design is such that the length of the binding arms are symmetrical (i.e., each of the binding arms is of the same length; e.g., four and four, five and five nucleotides, or six and six nucleotides, or seven and seven nucleotides long) or asymmetrical (i.e., the binding arms are of different length; e.g., three and five, six and three nucleotides; three and six nucleotides long; four and five nucleotides long; four and six nucleotides long; four and seven nucleotides long; and the like).

[0055] By "Inozyme" or "NCH" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described as NCH Rz in **FIG. 1**. Inozymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet NCH/, where N is a nucleotide, C is cytidine and H is adenosine, uridine or cytidine, and / represents the cleavage site. H is used interchangeably with X. Inozymes can also possess endonuclease activity to cleave RNA substrates having a cleavage triplet NCN/, where N is a nucleotide, C is cytidine, and / represents the cleavage site. "I" in **FIG. 1** represents an Inosine nucleotide, including a ribo-Inosine or xylo-Inosine nucleoside.

[0056] By "G-cleaver" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described as G-cleaver Rz in **FIG. 1**. G-cleavers possess endonuclease activity to cleave RNA substrates having a cleavage triplet NYN/, where N is a nucleotide, Y is uridine or cytidine and/represents the cleavage site. G-cleavers can be chemically modified as is generally shown in **FIG. 1**.

[0057] By "amberzyme" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **FIG. 2**. Amberzymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet NG/N, where N is a nucleotide, G is guanosine, and/represents the cleavage site. Amberzymes can be chemically modified to increase nuclease stability through substitutions as are generally shown in **FIG. 2**. In addition, differing nucleoside and/or non-nucleoside linkers can be used to substitute the 5'-gaaa-3' loops shown in the figure. Amberzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

[0058] By "zinzyme" motif or configuration is meant, an enzymatic nucleic acid molecule comprising a motif as is generally described in **FIG. 3**. Zinzymes possess endonuclease activity to cleave RNA substrates having a cleavage triplet including but not limited to YG/Y, where Y is uridine or cytidine, and G is guanosine and/represents the cleavage site.

[0059] Zinzymes can be chemically modified to increase nuclease stability through substitutions as are generally shown in **FIG. 3**, including substituting 2'-O-methyl guanosine nucleotides for guanosine nucleotides. In addition, differing nucleotide and/or non-nucleotide linkers can be used to substitute the 5'-gaaa-2' loop shown in the figure. Zinzymes represent a non-limiting example of an enzymatic nucleic acid molecule that does not require a ribonucleotide (2'-OH) group within its own nucleic acid sequence for activity.

[0060] By 'DNAzyme' is meant, an enzymatic nucleic acid molecule that does not require the presence of a 2'-OH group within its own nucleic acid sequence for activity. In particular embodiments the enzymatic nucleic acid molecule can have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. DNAzymes can be synthesized chemically or expressed endogenously in vivo, by means of a single stranded DNA vector or equivalent thereof. An example of a DNAzyme is shown in **FIG. 4** and is generally reviewed in Usman et al., U.S. Pat. No. 6,159,714; Chartrand et al., 1995, *NAR* 23, 4092; Breaker et al., 1995, *Chem. Bio.* 2, 655; Santoro et al., 1997, *PNAS* 94, 4262; Breaker, 1999, *Nature Biotechnology,* 17, 422-423; and Santoro et. al., 2000, *J. Am. Chem. Soc.,* 122, 2433-39. The "10-23" DNAzyme motif is one particular type of DNAzyme that was evolved using in vitro selection (see Santoro et al., supra). Additional DNAzyme motifs can be selected for using techniques similar to those described in these references, and hence, are within the scope of the present invention.

[0061] By "sufficient length" is meant an oligonucleotide of greater than or equal to 3 nucleotides that is of a length great enough to provide the intended function under the expected condition. For example, for binding arms of enzymatic nucleic acid "sufficient length" means that the binding arm sequence is long enough to provide stable binding to a target site under the expected binding conditions. The binding arms are not so long as to prevent useful turnover of the nucleic acid molecule.

[0062] By "stably interact" is meant interaction of the oligonucleotides with target nucleic acid (e.g., by forming hydrogen bonds with complementary nucleotides in the target under physiological conditions) that is sufficient to the intended purpose (e.g., cleavage of target RNA by an enzyme).

[0063] By "equivalent" RNA to PTGDS is meant to include RNA molecules having homology (partial or complete) to RNA molecules encoding PTGDS proteins or encoding proteins with similar function as PTGDS proteins in various organisms, including human, rodent, primate, rabbit, pig, plants, protozoans, fungi, and other microorganisms and parasites. The equivalent RNA sequence can also include in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

[0064] By "equivalent" RNA to PTGDR is meant to include RNA molecules having homology (partial or complete) to RNA molecules encoding PTGDR proteins or encoding proteins with similar function as PTGDR proteins in various organisms, including human, rodent, primate, rabbit, pig, plants, protozoans, fungi, and other microorganisms and parasites. The equivalent RNA sequence can also include in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

[0065] By "equivalent" RNA to ADORA1 is meant to include RNA molecules having homology (partial or complete) to RNA molecule encoding ADORA1 proteins or encoding proteins with similar function as ADORA1 proteins in various organisms, including human, rodent, primate, rabbit, pig, plants, protozoans, fungi, and other microorganisms and parasites. The equivalent RNA sequence can also include in addition to the coding region, regions such as 5'-untranslated region, 3'-untranslated region, introns, intron-exon junction and the like.

[0066] By "homology" is meant the nucleotide sequence of two or more nucleic acid molecules is partially or completely identical.

[0067] By "antisense nucleic acid", it is meant a non-enzymatic nucleic acid molecule that binds to target RNA by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm et al., 1993 *Nature* 365, 566) interactions and alters the activity of the target RNA (for a review, see Stein and Cheng, 1993 *Science* 261, 1004 and Woolf et al., U.S. Pat. No. 5,849,902). Typically, antisense molecules are complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule can bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule can bind such that the antisense molecule forms a loop. Thus, the antisense molecule can be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule can be complementary to a target sequence or both. For a review of current antisense strategies, see Schmajuk et al., 1999, *J. Biol. Chem.,* 274, 21783-21789, Delihas et al., 1997, *Nature,* 15, 751-753, Stein et al., 1997, *Antisense N. A. Drug Dev.,* 7, 151, Crooke, 2000, *Methods Enzymol.,* 313, 3-45; Crooke, 1998, *Biotech. Genet. Eng. Rev.,* 15, 121-157, Crooke, 1997, *Ad. Pharmacol.,* 40, 1-49. In addition, antisense DNA can be used to target RNA by means of DNA-RNA interactions, thereby activating RNase H, which digests the target RNA in the duplex. The antisense oligonucleotides can comprise one or more RNAse H activating region, which is capable of activating RNAse H cleavage of a target RNA. Antisense DNA can be synthesized chemically or expressed via the use of a single stranded DNA expression vector or equivalent thereof.

[0068] By "RNase H activating region" is meant a region (generally greater than or equal to 4-25 nucleotides in length, and in one embodiment from 5-11 nucleotides in length) of a nucleic acid molecule capable of binding to a target RNA to form a non-covalent complex that is recognized by cellular RNase H enzyme (see for example Arrow et al., U.S. Pat. No. 5,849,902; Arrow et al., U.S. Pat. No. 5,989,912). The RNase H enzyme binds to the nucleic acid

molecule-target RNA complex and cleaves the target RNA sequence. The RNase H activating region comprises, for example, phosphodiester, phosphorothioate (at least four of the nucleotides are phosphorothiote substitutions; and in another embodiment, 4-11 of the nucleotides are phosphorothiote substitutions); phosphorodithioate, 5'-thiophosphate, or methylphosphonate backbone chemistry or a combination thereof. In addition to one or more backbone chemistries described above, the RNase H activating region can also comprise a variety of sugar chemistries. For example, the RNase H activating region can comprise deoxyribose, arabino, fluoroarabino or a combination thereof, nucleotide sugar chemistry. Those skilled in the art will recognize that the foregoing are non-limiting examples and that any combination of phosphate, sugar and base chemistry of a nucleic acid that supports the activity of RNase H enzyme is within the scope of the definition of the RNase H activating region and the instant invention.

[0069] By "2-5A antisense chimera" is meant an antisense oligonucleotide containing a 5'-phosphorylated 2'-5'-linked adenylate residue. These chimeras bind to target RNA in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which, in turn, cleaves the target RNA (Torrence et al., 1993 *Proc. Natl. Acad. Sci. USA* 90, 1300; Silverman et al., 2000, *Methods Enzymol.,* 313, 522-533; Player and Torrence, 1998, *Pharmacol. Ther.,* 78, 55-113).

[0070] By "triplex forming oligonucleotides" is meant an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Formation of such triple helix structure has been shown to inhibit transcription of the targeted gene (Duval-Valentin et al., 1992 *Proc. Natl. Acad. Sci. USA* 89, 504; Fox, 2000, *Curr. Med. Chem.,* 7, 17-37; Praseuth et. al., 2000, *Biochim. Biophys. Acta,* 1489, 181-206).

[0071] By "gene" it is meant a nucleic acid that encodes an RNA, for example, nucleic acid sequences including but not limited to structural genes encoding a polypeptide.

[0072] "Complementarity" refers to the ability of a nucleic acid to form hydrogen bond(s) with another RNA molecule by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its target or complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., enzymatic nucleic acid cleavage, antisense or triple helix inhibition. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner et al., 1987, *CSHSymp. Quant. Biol.* LII pp.123-133; Frier et al., 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner et al., 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, 10 out of 10 being 50%, 60%, 70%, 80%, 90%, and 100% complementary). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

[0073] By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" or "2'-OH" is meant a nucleotide with a hydroxyl group at the 2' position of a β-D-ribo-furanose moiety.

[0074] By "decoy RNA" is meant an RNA molecule or aptamer that is designed to preferentially bind to a predetermined ligand. Such binding can result in the inhibition or activation of a target molecule. The decoy RNA or aptamer can compete with a naturally occurring binding target for the binding of a specific ligand. For example, it has been shown that over-expression of HIV trans-activation response (TAR) RNA can act as a "decoy" and efficiently binds HIV tat protein, thereby preventing it from binding to TAR sequences encoded in the HIV RNA (Sullenger et al., 1990, Cell, 63, 601-608). This is but a specific example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art, see for example Gold et al., 1995, *Annu. Rev. Biochem.,* 64, 763; Brody and Gold, 2000, *J. Biotechnol.,* 74, 5; Sun, 2000, *Curr. Opin. Mol. Ther.,* 2, 100; Kusser, 2000, *J. Biotechnol.,* 74, 27; Hermann and Patel, 2000, *Science,* 287, 820; and Jayasena, 1999, *Clinical Chemistry,* 45, 1628. Similarly, a decoy RNA can be designed to bind to a D2 receptor and block the binding of PTGDS or a decoy RNA can be designed to bind to PTGDS and prevent interaction with the D2 receptor.

[0075] The term "double stranded RNA" or "dsRNA" as used herein refers to a double stranded RNA molecule capable of RNA interference, including short interfering RNA "siRNA" (see, e.g., Bass, 2001, *Nature,* 411, 428-429; Elbashir et al., 2001, *Nature,* 411, 494-498).

[0076] The term "allozyme" as used herein refers to an allosteric enzymatic nucleic acid molecule, see, e.g., George et al., U.S. Pat. Nos. 5,834,186 and 5,741,679, Shih et al., U.S. Pat. No. 5,589,332, Nathan et al., U.S. Pat. No. 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker et al., International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger et al., International PCT publication No. WO 99/29842. The term "2-5A chimera" as used herein refers to an oligonucleotide containing a 5'-phosphorylated 2'-5'-linked adenylate residue. These chimeras bind to target RNA in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which, in turn, cleaves the target RNA (Torrence et al., 1993 *Proc. Natl. Acad. Sci. USA* 90, 1300; Silverman et al., 2000, *Methods Enzymol.,* 313, 522-533; Player and Torrence, 1998, *Pharmacol. Ther.,* 78, 55-113).

[0077] The term "triplex forming oligonucleotides" as used herein refers to an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Formation of such triple helix structure has been shown to inhibit transcription of the targeted gene (Duval-Valentin et al., 1992 *Proc. Natl. Acad. Sci. USA* 89, 504; Fox, 2000, *Curr. Med. Chem.,* 7, 17-37; Praseuth et. al., 2000, *Biochim. Biophys. Acta,* 1489, 181-206).

[0078] Several varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in trans (and thus can cleave other RNA molecules) under physiological conditions. Table I summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid that is held in close proximity to an enzymatic portion of the molecule that acts

to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor of gene expression, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme.

[0079] The enzymatic nucleic acid molecule that cleave the specified sites in PTGDS, ADORA1 and PTGDR-specific RNAs represent a novel therapeutic approach to treat a variety of allergic diseases or conditions, including but not limited to asthma, allergic rhinitis, atopic dermatitis, and/or other allergic or inflammatory diseases and conditions which respond to the modulation of PTGDS, ADORA1 and/or PTGDR expression.

[0080] In one embodiment of the inventions described herein, the enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but can also be formed in the motif of a hepatitis delta virus, group I intron, group II intron or RNase P RNA (in association with an RNA guide sequence), Neurospora VS RNA, DNAzymes, NCH cleaving motifs, or G-cleavers. Examples of such hammerhead motifs are described by Dreyfus, supra, Rossi et al., 1992, *AIDS Research and Human Retroviruses* 8, 183; of hairpin motifs by Hampel et al., EP0360257, Hampel and Tritz, 1989 *Biochemistry* 28, 4929, Feldstein et al., 1989, *Gene* 82, 53, Haseloff and Gerlach, 1989, *Gene,* 82, 43, and Hampel et al., 1990 *Nucleic Acids Res.* 18, 299; Chowrira & McSwiggen, U.S. Pat. No. 5,631,359; of the hepatitis delta virus motif is described by Perrotta and Been, 1992 *Biochemistry* 31, 16; of the RNase P motif by Guerrier-Takada et al., 1983 *Cell* 35, 849; Forster and Altman, 1990, *Science* 249, 783; Li and Altman, 1996, *Nucleic Acids Res.* 24, 835; *Neurospora* VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990 *Cell* 61, 685-696; Saville and Collins, 1991 *Proc. Natl. Acad. Sci. USA* 88, 8826-8830; Collins and Olive, 1993 *Biochemistry* 32, 2795-2799; Guo and Collins, 1995, *EMBO. J* 14, 363); Group II introns are described by Griffin et al., 1995, *Chem. Biol.* 2, 761; Michels and Pyle, 1995, *Biochemistry* 34, 2965; Pyle et al., International PCT Publication No. WO 96/22689; of the Group I intron by Cech et al., U.S. Pat. No. 4,987,071 and of DNAzymes by Usman et al., International PCT Publication No. WO 95/11304; Chartrand et al., 1995, *NAR* 23, 4092; Breaker et al., 1995, *Chem. Bio.* 2, 655; Santoro et al., 1997, *PNAS* 94, 4262, and Beigelman et al., International PCT publication No. WO 99/55857. NCH cleaving motifs are described in Ludwig & Sproat, International PCT Publication No. WO 98/58058; and G-cleavers are described in Kore et al., 1998, *Nucleic Acids Research* 26, 4116-4120 and Eckstein et al., International PCT Publication No. WO 99/16871. Additional motifs such as the Aptazyme (Breaker et al., WO 98/43993), Amberzyme (Class I motif; **FIG. 2**; Beigelman et al., U.S. Ser. No. 09/301,511) and Zinzyme (**FIG. 3**) (Beigelman et al., U.S. Ser. No. 09/301,511), all included by reference herein including drawings, can also be used in the present invention. These specific motifs or configurations are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule (Cech et al., U.S. Pat. No. 4,987,071).

[0081] In one embodiment of the present invention, a nucleic acid molecule of the instant invention can be between 12 and 100 nucleotides in length. Exemplary enzymatic nucleic acid molecules of the invention are shown in Table III-VII. For example, enzymatic nucleic acid molecules of the invention can be between 15 and 50 nucleotides in length, and in another embodiment between 25 and 40 nucleotides in length, e.g., 34, 36, or 38 nucleotides in length (for example see Jarvis et al., 1996, *J. Biol. Chem.,* 271, 29107-29112). Exemplary DNAzymes of the invention are can between 15 and 40 nucleotides in length, and in one embodiment, between 25 and 35 nucleotides in length, e.g., 29, 30, 31, or 32 nucleotides in length (see, e.g., Santoro et al., 1998, *Biochemistry,* 37, 13330-13342; Chartrand et al., 1995, Nucleic Acids Research, 23, 4092-4096). Exemplary antisense molecules of the invention can be between 15 and 75 nucleotides in length, and in one embodiment between 20 and 35 nucleotides in length, e.g., 25, 26, 27, or 28 nucleotides in length (see for example Woolf et al., 1992, *PNAS.,* 89, 7305-7309; Milner et al., 1997, *Nature Biotechnology,* 15, 537-541). Exemplary triplex forming oligonucleotide molecules of the invention are between 10 and 40 nucleotides in length, and in one embodiment are between 12 and 25 nucleotides in length, e.g., 18, 19, 20, or 21 nucleotides in length (see for example Maher et al., 1990, *Biochemistry,* 29, 8820-8826; Strobel and Dervan, 1990, *Science,* 249, 73-75). Those skilled in the art will recognize that all that is required is for the nucleic acid molecule to be of length and conformation sufficient and suitable for the nucleic acid molecule to catalyze a reaction contemplated herein. The length of the nucleic acid molecules of the instant invention are not limiting within the general limits stated.

[0082] In one embodiment, a nucleic acid molecule that modulates, for example, down-regulates, PTGDS replication or expression comprises between 8 and 100 bases complementary to a RNA molecule of PTGDS. In another embodiment, a nucleic acid molecule that modulates PTGDS replication or expression comprises between 14 and 24 bases complementary to a RNA molecule of PTGDS.

[0083] In another embodiment, a nucleic acid molecule that modulates, for example, down-regulates, PTGDR replication or expression comprises between 8 and 100 bases complementary to a RNA molecule of PTGDR. In another embodiment, a nucleic acid molecule that modulates PTGDR replication or expression comprises between 14 and 24 bases complementary to a RNA molecule of PTGDR.

[0084] In another embodiment, a nucleic acid molecule that modulates, for example, down-regulates, ADORA1 replication or expression comprises between 8 and 100 bases complementary to a RNA molecule of ADORA1. In another embodiment, a nucleic acid molecule that modulates

ADORA1 replication or expression comprises between 14 and 24 bases complementary to a RNA molecule of ADORA1.

[0085] The invention provides a method for producing a class of nucleic acid-based gene modulating agents that exhibit a high degree of specificity for the RNA of a desired target. For example, the enzymatic nucleic acid molecule is can be targeted to a highly conserved sequence region of target RNAs encoding PTGDS, ADORA1 and/or PTGDR (e.g., PTGDS, ADORA1 and/or PTGDR genes) such that specific treatment of a disease or condition can be provided with either one or several nucleic acid molecules of the invention. Such nucleic acid molecules can be delivered exogenously to specific tissue or cellular targets as required. Alternatively, the nucleic acid molecules (e.g., ribozymes and antisense) can be expressed from DNA and/or RNA vectors that are delivered to specific cells.

[0086] As used in herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism. The cell can, for example, be in vitro, e.g., in cell culture, or present in a multicellular organism, including, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell may be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell).

[0087] By "PTGDR proteins" is meant, a protein receptor or a mutant protein or peptide derivative thereof, having prostaglandin D2 receptor activity, for example, having the ability to bind prostaglandin D2 and/or having GTP-binding protein coupled activity.

[0088] By "PTGDS proteins" is meant, a prostaglandin synthetase protein or a mutant protein or peptide derivative thereof, having prostaglandin D2 synthetase activity, for example, having the ability to convert PGH2 to PGD2.

[0089] By "highly conserved sequence region" is meant, a nucleotide sequence of one or more regions in a target gene does not vary significantly from one generation to the other or from one biological system to the other.

[0090] Nucleic acid-based inhibitors of PTGDS, ADORA1 and PTGDR expression are useful for the prevention and/or treatment of allergic diseases or conditions, including but not limited to asthma, allergic rhinitis, atopic dermatitis, and any other diseases or conditions that are related to or will respond to the levels of PTGDS, ADORA1 and/or PTGDR in a cell or tissue, alone or in combination with other therapies. The reduction of PTGDS, ADORA1 and/or PTGDR expression (specifically PTGDS, ADORA1 and/or PTGDR gene RNA levels) and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

[0091] The nucleic acid-based inhibitors of the invention can be added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues, for example by pulmonary delivery of an aerosol formulation with an inhaler or nebulizer. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through inhalation, injection or infusion pump, with or without their incorporation in biopolymers. In preferred embodiments, the enzymatic nucleic acid inhibitors comprise sequences that are complementary to the substrate sequences in Tables III to VII. Examples of such enzymatic nucleic acid molecules also are shown in Tables III to VII. Examples of such enzymatic nucleic acid molecules consist essentially of sequences defined in these tables.

[0092] In another embodiment, the invention features antisense nucleic acid molecules and 2-5A chimera including sequences complementary to the substrate sequences shown in Tables III to VII. Such nucleic acid molecules can include sequences as shown for the binding arms of the enzymatic nucleic acid molecules in Tables III to VII. Similarly, triplex molecules can be provided targeted to the corresponding DNA target regions, and containing the DNA equivalent of a target sequence or a sequence complementary to the specified target (substrate) sequence. Typically, antisense molecules are complementary to a target sequence along a single contiguous sequence of the antisense molecule. However, in certain embodiments, an antisense molecule can bind to substrate such that the substrate molecule forms a loop, and/or an antisense molecule can bind such that the antisense molecule forms a loop. Thus, the antisense molecule can be complementary to two (or even more) non-contiguous substrate sequences or two (or even more) non-contiguous sequence portions of an antisense molecule can be complementary to a target sequence or both.

[0093] By "consists essentially of" is meant that the active nucleic acid molecule of the invention, for example, an enzymatic nucleic acid molecule, contains an enzymatic center or core equivalent to those in the examples, and binding arms able to bind RNA such that cleavage at the target site occurs. Other sequences can be present that do not interfere with such cleavage. Thus, a core region can, for example, include one or more loop, stem-loop structure, or linker which does not prevent enzymatic activity. Thus, the underlined regions in the sequences in Tables III and IV can be such a loop, stem-loop, nucleotide linker, and/or non-nucleotide linker and can be represented generally as sequence "X". For example, a core sequence for a hammerhead enzymatic nucleic acid can comprise a conserved sequence, such as 5'-CUGAUGAG-3' and 5'-CGAA-3' connected by "X", where X is 5'-GCCGUUAGGC-3' (SEQ ID NO: 2678), or any other Stem II region known in the art, or a nucleotide and/or non-nucleotide linker. Similarly, for other nucleic acid molecules of the instant invention, such as Inozyme, G-cleaver, amberzyme, zinzyme, DNAzyme, antisense, 2-5A antisense, triplex forming nucleic acid, and decoy nucleic acids, other sequences or non-nucleotide linkers can be present that do not interfere with the function of the nucleic acid molecule.

[0094] Sequence X can be a linker of ≥ 2 nucleotides in length, including 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 26, 30, where the nucleotides can be internally base-paired to form a stem of ≥ 2 base pairs. Alternatively or in addition, sequence X can be a non-nucleotide linker. In yet another embodiment, the nucleotide linker X can be a nucleic acid aptamer, such as an ATP aptamer, HIV Rev aptamer (RRE), HIV Tat aptamer (TAR) and others (for a review see Gold et al., 1995, *Annu. Rev. Biochem.,* 64, 763; and Szostak & Ellington, 1993, in *The RNA World*, ed. Gesteland and Atkins, pp. 511, CSH Laboratory Press). A "nucleic acid aptamer" as used herein is meant to indicate a nucleic acid sequence capable of interacting with a ligand. The ligand can be any natural or a synthetic molecule, including but not limited to a resin, metabolites, nucleosides, nucleotides, drugs, toxins,

transition state analogs, peptides, lipids, proteins, amino acids, nucleic acid molecules, hormones, carbohydrates, receptors, cells, viruses, bacteria and others.

[0095] In yet another embodiment, the non-nucleotide linker X is as defined herein. The term "non-nucleotide" as used herein include either abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, or polyhydrocarbon compounds. Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma et al., *Nucleic Acids Res.* 1993, 21:2585 and *Biochemistry* 1993, 32:1751; Durand et al., *Nucleic Acids Res.* 1990, 18:6353; McCurdy et al., *Nucleosides & Nucleotides* 1991, 10:287; Jschke et al., *Tetrahedron Lett.* 1993, 34:301; Ono et al., *Biochemistry* 1991, 30:9914; Arnold et al., International Publication No. WO 89/02439; Usman et al., International Publication No. WO 95/06731; Dudycz et al., International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine. Thus, in a preferred embodiment, the invention features an enzymatic nucleic acid molecule having one or more non-nucleotide moieties, and having enzymatic activity to cleave an RNA or DNA molecule.

[0096] In another aspect of the invention, enzymatic nucleic acid molecules or antisense molecules that interact with target RNA molecules and down-regulate PTGDS, ADORA1 and/or PTGDR (e.g., PTGDS, ADORA1 and/or PTGDR gene) activity are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. Enzymatic nucleic acid molecule or antisense expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the enzymatic nucleic acid molecules or antisense can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of enzymatic nucleic acid molecules or antisense. Such vectors can be repeatedly administered as necessary. Once expressed, the enzymatic nucleic acid molecules or antisense bind to the target RNA and down-regulate its function or expression. Delivery of enzymatic nucleic acid molecule or antisense expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell. Antisense DNA can be expressed via the use of a single stranded DNA intracellular expression vector.

[0097] By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

[0098] By "patient" is meant an organism, which is a donor or recipient of explanted cells, or the cells themselves. "Patient" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A patient can be a mammal or mammalian cells. In one embodiment, a patient is a human or human cells.

[0099] By "enhanced enzymatic activity" is meant to include activity measured in cells and/or in vivo where the activity is a reflection of both the catalytic activity and the stability of the nucleic acid molecules of the invention. In this invention, the product of these properties can be increased in vivo compared to an all RNA enzymatic nucleic acid or all DNA enzyme. In some cases, the activity or stability of the nucleic acid molecule can be decreased (i.e., less than ten-fold), but the overall activity of the nucleic acid molecule is enhanced, in vivo.

[0100] The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed above. For example, to treat a disease or condition associated with the levels of PTGDS, ADORA1 and/or PTGDR, the patient can be treated, or other appropriate cells can be treated, as is evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

[0101] In a further embodiment, the described molecules, such as antisense or enzymatic nucleic acid molecules, can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules can be used in combination with one or more known therapeutic agents to treat allergic diseases or conditions, including but not limited to asthma, allergic rhinitis, atopic dermatitis, and/or other allergic or inflammatory diseases and conditions which respond to the modulation of PTGDS, ADORA1 and/or PTGDR expression.

[0102] In another embodiment, the invention features nucleic acid-based inhibitors (e.g., enzymatic nucleic acid molecules (e.g., ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups) and methods for their use to down regulate or inhibit the expression of genes (e.g., PTGDS, ADORA1 and/or PTGDR) capable of progression and/or maintenance allergic diseases or conditions, including but not limited to asthma, allergic rhinitis, atopic dermatitis, and/or other allergic or inflammatory diseases and conditions which respond to the modulation of PTGDS, ADORA1 and/or PTGDR expression.

[0103] By "comprising" is meant including, but not limited to, whatever follows the word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of". Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present.

[0104] Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0105] **FIG. 1** shows examples of chemically stabilized ribozyme motifs. HH Rz, represents hammerhead ribozyme

motif (Usman et al., 1996, *Curr. Op. Struct. Bio.,* 1, 527); NCH Rz represents the NCH ribozyme motif (Ludwig & Sproat, International PCT Publication No. WO 98/58058); G-Cleaver, represents G-cleaver ribozyme motif (Kore et al., 1998, *Nucleic Acids Research* 26, 4116-4120, Eckstein et al., International PCT publication No. WO 99/16871). N or n, represent independently a nucleotide that can be same or different and have complementarity to each other; rI, represents ribo-Inosine nucleotide; arrow indicates the site of cleavage within the target. Position 4 of the HH Rz and the NCH Rz is shown as having 2'-C-allyl modification, but those skilled in the art will recognize that this position can be modified with other modifications well known in the art, so long as such modifications do not significantly inhibit the activity of the ribozyme.

[**0106**] **FIG. 2** shows an example of the Amberzyme ribozyme motif that is chemically stabilized (see for example Beigelman et al., International PCT publication No. WO 99/55857).

[**0107**] **FIG. 3** shows an example of the Zinzyme A ribozyme motif that is chemically stabilized (see for example Beigelman et al., Beigelman et al., International PCT publication No. WO 99/55857).

[**0108**] **FIG. 4** shows an example of a specific DNAzyme motif, commonly referred to as the "10-23 motif", as described by Santoro et al., 1997, *PNAS,* 94, 4262.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[**0109**] Nucleic Acid Molecules and Mechanism of Action

[**0110**] Antisense: Antisense molecules can be modified or unmodified RNA, DNA, or mixed polymer oligonucleotides and primarily function by specifically binding to matching sequences resulting in inhibition of peptide synthesis (Wu-Pong, Nov 1994, *BioPharm,* 20-33). The antisense oligonucleotide binds to target RNA by Watson Crick base-pairing and blocks gene expression by preventing ribosomal translation of the bound sequences either by steric blocking or by activating RNase H enzyme. Antisense molecules can also alter protein synthesis by interfering with RNA processing or transport from the nucleus into the cytoplasm (Mukhopadhyay & Roth, 1996, *Crit. Rev. in Oncogenesis* 7, 151-190).

[**0111**] In addition, binding of single stranded DNA to RNA can result in nuclease degradation of the heteroduplex (Wu-Pong, supra; Crooke, supra). To date, the only backbone modified DNA chemistry which act as substrates for RNase H are phosphorothioates, phosphorodithioates, and borontrifluoridates. Recently it has been reported that 2'-arabino and 2'-fluoro arabino-containing oligos can also activate RNase H activity.

[**0112**] A number of antisense molecules have been described that utilize novel configurations of chemically modified nucleotides, secondary structure, and/or RNase H substrate domains (Woolf et al., International PCT Publication No. WO 98/13526; Thompson et al., International PCT Publication No. WO 99/54459; Hartmann et al., U.S. S No. 60/101,174, filed on Sep. 21, 1998) all of these are incorporated by reference herein in their entirety.

[**0113**] In addition, antisense deoxyoligoribonucleotides can be used to target RNA by means of DNA-RNA interactions, thereby activating RNase H, which digests the target RNA in the duplex. Antisense DNA can be expressed via the use of a single stranded DNA intracellular expression vector or equivalents and variations thereof.

[**0114**] Triplex Forming Oligonucleotides (TFO): Single stranded DNA can be designed to bind to genomic DNA in a sequence specific manner. TFOs are comprised of pyrimidine-rich oligonucleotides which bind DNA helices through Hoogsteen Base-pairing (Wu-Pong, supra). The resulting triple helix composed of the DNA sense, DNA antisense, and TFO disrupts RNA synthesis by RNA polymerase. The TFO mechanism can result in gene expression or cell death since binding can be irreversible (Mukhopadhyay & Roth, supra).

[**0115**] 2-5A Antisense Chimera: The 2-5A system is an interferon mediated mechanism for RNA degradation found in higher vertebrates (Mitra et al., 1996, *Proc Nat Acad Sci USA* 93, 6780-6785). Two types of enzymes, 2-5A synthetase and RNase L, are required for RNA cleavage. The 2-5A synthetases require double stranded RNA to form 2'-5' oligoadenylates (2-5A). 2-5A then acts as an allosteric effector for utilizing RNase L, which has the ability to cleave single stranded RNA. The ability to form 2-5A structures with double stranded RNA makes this system particularly useful for inhibition of viral replication.

[**0116**] (2'-5') oligoadenylate structures can be covalently linked to antisense molecules to form chimeric oligonucleotides capable of RNA cleavage (Torrence, supra). These molecules putatively bind and activate a 2-5A dependent RNase, the oligonucleotide/enzyme complex then binds to a target RNA molecule which can then be cleaved by the RNase enzyme.

[**0117**] Enzymatic Nucleic Acid: Several varieties of naturally-occurring enzymatic RNAs are presently known. In addition, several in vitro selection (evolution) strategies (Orgel, 1979, *Proc. R. Soc. London*, B 205, 435) have been used to evolve new nucleic acid catalysts capable of catalyzing cleavage and ligation of phosphodiester linkages (Joyce, 1989, *Gene,* 82, 83-87; Beaudry et al., 1992, *Science* 257, 635-641; Joyce, 1992, *Scientific American* 267, 90-97; Breaker et al., 1994, *TIBTECH* 12, 268; Bartel et al., 1993, *Science* 261:1411-1418; Szostak, 1993, *TIBS* 17, 89-93; Kumar et al., 1995, *FASEB J,* 9, 1183; Breaker, 1996, *Curr. Op. Biotech.,* 7, 442; Santoro et al., 1997, *Proc. Natl. Acad. Sci.,* 94, 4262; Tang et al., 1997, *RNA* 3, 914; Nakamaye & Eckstein, 1994, supra; Long & Uhlenbeck, 1994, supra; Ishizaka et al., 1995, supra; Vaish et al., 1997, *Biochemistry* 36, 6495; all of these are incorporated by reference herein). Each can catalyze a series of reactions including the hydrolysis of phosphodiester bonds in trans (and thus can cleave other RNA molecules) under physiological conditions.

[**0118**] The enzymatic nature of an enzymatic nucleic acid molecule has significant advantages, one advantage being that the concentration of enzymatic nucleic acid molecule necessary to affect a therapeutic treatment is lower. This advantage reflects the ability of the enzymatic nucleic acid molecule to act enzymatically. Thus, a single enzymatic nucleic acid molecule is able to cleave many molecules of target RNA. In addition, the enzymatic nucleic acid molecule is a highly specific inhibitor, with the specificity of inhibition depending not only on the base-pairing mecha-

nism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can be chosen to completely eliminate catalytic activity of a enzymatic nucleic acid molecule.

[0119] Nucleic acid molecules having an endonuclease enzymatic activity are able to repeatedly cleave other separate RNA molecules in a nucleotide base sequence-specific manner. With the proper design, such enzymatic nucleic acid molecules can be targeted to RNA transcripts, and achieve efficient cleavage in vitro (Zaug et al., 324, *Nature* 429 1986; Uhlenbeck, 1987 *Nature* 328, 596; Kim et al., 84 *Proc. Natl. Acad. Sci. USA* 8788, 1987; Dreyfus, 1988, *Einstein Quart. J. Bio. Med.,* 6, 92; Haseloff and Gerlach, 334 *Nature* 585, 1988; Cech, 260 *JAMA* 3030, 1988; and Jefferies et al., 17 *Nucleic Acids Research* 1371, 1989; Santoro et al., 1997 supra).

[0120] Because of their sequence specificity, trans-cleaving enzymatic nucleic acid molecules can be used as therapeutic agents for human disease (Usman & McSwiggen, 1995 *Ann. Rep. Med. Chem.* 30, 285-294; Christoffersen and Marr, 1995 *J. Med. Chem.* 38, 2023-2037). Enzymatic nucleic acid molecules can be designed to cleave specific RNA targets within the background of cellular RNA. Such a cleavage event renders the RNA non-functional and abrogates protein expression from that RNA. In this manner, synthesis of a protein associated with a disease state can be selectively inhibited (Warashina et al., 1999, *Chemistry and Biology,* 6, 237-250).

[0121] Enzymatic nucleic acid molecules of the invention that are allosterically regulated ("allozymes") can be used to down-regulate PTGDS and/or PTGDR expression. These allosteric enzymatic nucleic acids or allozymes (see for example George et al., U.S. Pat. Nos. 5,834,186 and 5,741,679, Shih et al., U.S. Pat. No. 5,589,332, Nathan et al., U.S. Pat. No. 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker et al., International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger et al., International PCT publication No. WO 99/29842) are designed to respond to a signaling agent, for example, mutant PTGDS and/or PTGDR protein, wild-type PTGDS and/or PTGDR protein, mutant PTGDS and/or PTGDR RNA, wild-type PTGDS and/or PTGDR RNA, other proteins and/or RNAs involved in PTGDS or PTGDR signal transduction, compounds, metals, polymers, molecules and/or drugs that are targeted to PTGDS and/or PTGDR expressing cells etc., which in turn modulates the activity of the enzymatic nucleic acid molecule. In response to interaction with a predetermined signaling agent, the allosteric enzymatic nucleic acid molecule's activity is activated or inhibited such that the expression of a particular target is selectively down-regulated. The target can comprise wild-type PTGDS, ADORA1 and/or PTGDR, mutant PTGDS, ADORA1 and/or PTGDR, and/or a predetermined component of the PTGDS, ADORA1 or PTGDR signal transduction pathway. In a specific example, allosteric enzymatic nucleic acid molecules that are activated by interaction with a RNA encoding a PTGDR protein are used as therapeutic agents in vivo. The presence of RNA encoding the PTGDS protein activates the allosteric enzymatic nucleic acid molecule that subsequently cleaves the RNA encoding a PTGDR protein resulting in the inhibition of PTGDR protein expression. In this manner, cells that express both PTGDS and PTGDR protein are selectively targeted.

[0122] In another non-limiting example, an allozyme can be activated by a PTGDS or PTGDR protein, peptide, or mutant polypeptide that causes the allozyme to inhibit the expression of PTGDS or PTGDR gene, by, for example, cleaving RNA encoded by PTGDS or PTGDR gene. In this non-limiting example, the allozyme acts as a decoy to inhibit the function of PTGDS or PTGDR and also inhibit the expression of PTGDS or PTGDR once activated by the PTGDS or PTGDR protein.

[0123] Target Sites

[0124] Targets for useful enzymatic nucleic acid molecules and antisense nucleic acids can be determined as disclosed in Draper et al., WO 93/23569; Sullivan et al, WO 93/23057; Thompson et al., WO 94/02595; Draper et al., WO 95/04818; McSwiggen et al., U.S. Pat. No. 5,525,468, and hereby incorporated by reference herein in totality. Other examples include the following PCT applications, which concern inactivation of expression of disease-related genes: WO 95/23225, WO 95/13380, WO 94/02595, incorporated by reference herein. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Enzymatic nucleic acid molecules and antisense to such targets are designed as described in those applications and synthesized to be tested in vitro and in vivo, as also described. The sequences of human PTGDR RNAs were screened for optimal enzymatic nucleic acid and antisense target sites using a computer-folding algorithm. Antisense, hammerhead, DNAzyme, NCH, amberzyme, zinzyme, or G-Cleaver enzymatic nucleic acid molecule binding/cleavage sites were identified. These sites are shown in Tables III to VII (all sequences are 5' to 3' in the tables; underlined regions can be any sequence "X" or linker X, the actual sequence is not relevant here). The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of enzymatic nucleic acid molecule. While human sequences can be screened and enzymatic nucleic acid molecule and/or antisense thereafter designed, as discussed in Stinchcomb et al., WO 95/23225, mouse targeted enzymatic nucleic acid molecules can be useful to test efficacy of action of the enzymatic nucleic acid molecule and/or antisense prior to testing in humans.

[0125] Antisense, hammerhead, DNAzyme, NCH, amberzyme, zinzyme or G-Cleaver enzymatic nucleic acid molecule binding/cleavage sites were identified. The nucleic acid molecules are individually analyzed by computer folding (Jaeger et al., 1989 *Proc. Natl. Acad. Sci. USA,* 86, 7706) to assess whether the sequences fold into the appropriate secondary structure. Those nucleic acid molecules with unfavorable intramolecular interactions such as between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity.

[0126] Antisense, hammerhead, DNAzyme, NCH, amberzyme, zinzyme or G-Cleaver enzymatic nucleic acid molecule binding/cleavage sites were identified and were designed to anneal to various sites in the RNA target. The binding arms are complementary to the target site sequences described above. The nucleic acid molecules were chemically synthesized. The method of synthesis used follows the

procedure for normal DNA/RNA synthesis as described below and in Usman et al., 1987 *J. Am. Chem. Soc.,* 109, 7845; Scaringe et al., 1990 *Nucleic Acids Res.,* 18, 5433; and Wincott et al., 1995 *Nucleic Acids Res.* 23, 2677-2684; Caruthers et al., 1992, *Methods in Enzymology* 211,3-19.

[0127] Synthesis of Nucleic acid Molecules

[0128] Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small refers to nucleic acid motifs less than about 100 nucleotides in length, and in one embodiment less than about 80 nucleotides in length, and in another embodiment less than about 50 nucleotides in length; e.g., antisense oligonucleotides, hammerhead or the NCH ribozymes) can be used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

[0129] Oligonucleotides (e.g., antisense GeneBlocs) are synthesized using protocols known in the art as described in Caruthers et al., 1992, *Methods in Enzymology* 211, 3-19, Thompson et al., International PCT Publication No. WO 99/54459, Wincott et al., 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott et al., 1997, *Methods Mol. Bio.,* 74, 59, Brennan et al., 1998, *Biotechnol Bioeng.,* 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 sec coupling step for 2'-deoxy nucleotides. Table II outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, Calif.) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M=6.6 μmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μL of 0.25 M=15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μL of 0.11 M=4.4 μmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μL of 0.25 M=10 μmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by calorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% N-methylimidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM 12, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

[0130] Deprotection of the antisense oligonucleotides is performed as follows: the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65° C. for 10 min. After cooling to −20° C., the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H_2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder.

[0131] The method of synthesis used for normal RNA including certain enzymatic nucleic acid molecules follows the procedure as described in Usman et al., 1987, *J. Am. Chem. Soc.,* 109, 7845; Scaringe et al., 1990, *Nucleic Acids Res.,* 18, 5433; and Wincott et al., 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott et al., 1997, *Methods Mol. Bio.,* 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. Table II outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, Calif.) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M=6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M=15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M=13.2 μmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M=30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include; detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% N-methylimidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM 12, 49 mM pyridine, 9% water in THF (PERSEPTIVE™). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide 0.05 M in acetonitrile) is used.

[0132] Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65° C. for 10 min. After cooling to −20° C., the supernatant is removed from the polymer support. The support is washed three times with 1.0

mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 μL of a solution of 1.5 mL N-methylpyrrolidinone, 750 μL TEA and 1 mL TEA.3HF to provide a 1.4 M HF concentration) and heated to 65° C. After 1.5 h, the oligomer is quenched with 1.5 M NH_4HCO_3.

[0133] Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65° C. for 15 min. The vial is brought to r.t. TEA.3HF (0.1 mL) is added and the vial is heated at 65° C. for 15 min. The sample is cooled at −20° C. and then quenched with 1.5 M NH_4HCO_3.

[0134] For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing, the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 min. The cartridge is then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

[0135] Inactive hammerhead ribozymes or binding attenuated control (BAC) oligonucleotides are synthesized by substituting a U for G_5 and a U for A14 (numbering from Hertel, K. J., et al., 1992, *Nucleic Acids Res.*, 20, 3252). Similarly, one or more nucleotide substitutions can be introduced in other enzymatic nucleic acid molecules to inactivate the molecule and such molecules can serve as a negative control.

[0136] The average stepwise coupling yields are typically >98% (Wincott et al., 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96 well format, all that is important is the ratio of chemicals used in the reaction.

[0137] Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example by ligation (Moore et al., 1992, *Science* 256, 9923; Draper et al., International PCT publication No. WO 93/23569; Shabarova et al., 1991, *Nucleic Acids Research* 19, 4247; Bellon et al., 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon et al., 1997, *Bioconjugate Chem.* 8, 204).

[0138] The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman et al., 1994, *Nucleic Acids Symp. Ser.* 31, 163). Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott et al., Supra, the totality of which is hereby incorporated herein by reference) and are resuspended in water.

[0139] The sequences of the nucleic acid molecules, including enzymatic nucleic acid molecules and antisense, that are chemically synthesized, are shown in Tables III-VII. The sequences of the enzymatic nucleic acid constructs that are chemically synthesized are complementary to the Substrate sequences shown in Tables III-VII. Those in the art will recognize that these sequences are representative only of many more such sequences where the enzymatic portion of the enzymatic nucleic acid (all but the binding arms) is altered to affect activity. The enzymatic nucleic acid construct sequences listed in Tables III-VII can be formed of ribonucleotides or other nucleotides or non-nucleotides. Such enzymatic nucleic acid molecules with enzymatic activity are equivalent to the enzymatic nucleic acid molecules described specifically in the Tables.

[0140] Optimizing Activity of the Nucleic Acid Molecule of the Invention.

[0141] Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) that prevent their degradation by serum ribonucleases can increase their potency (see e.g., Eckstein et al., International Publication No. WO 92/07065; Perrault et al., 1990 *Nature* 344, 565; Pieken et al., 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman et al., International Publication No. WO 93/15187; and Rossi et al., International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; and Burgin et al., supra; all of these describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules herein). Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired. (All these publications are hereby incorporated by reference herein).

[0142] There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, TIBS. 17, 34; Usman et al., 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin et al., 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein et al., International Publication PCT No. WO 92/07065; Perrault et al. *Nature*, 1990, 344, 565-568; Pieken et al. *Science*, 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman et al. International Publication PCT No. WO 93/15187; Sproat, U.S. Pat. No. 5,334,711 and Beigelman et al., 1995, *J. Biol. Chem.*, 270, 25702; Beigelman et al., International PCT publication No. WO 97/26270; Beigelman et al., U.S. Pat. No. 5,716,824; Usman et al., U.S. Pat. No. 5,627,053; Woolf et al., International PCT Publication No. WO 98/13526; Thompson et al., U.S. S No. 60/082,404 which was filed on Apr. 20, 1998; Karpeisky et al., 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, Biopolymers (*Nucleic acid Sciences*), 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina et al., 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like

into ribozymes without inhibiting catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the nucleic acid molecules of the instant invention.

[0143] While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorothioate, and/or 5'-methylphosphonate linkages improves stability, too many of these modifications can cause some toxicity. Therefore when designing nucleic acid molecules the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity resulting in increased efficacy and higher specificity of these molecules.

[0144] Nucleic acid molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Thus, in a cell and/or in vivo the activity may not be significantly lowered. Therapeutic nucleic acid molecules delivered exogenously are optimally stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Clearly, nucleic acid molecules must be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of RNA and DNA (Wincott et al., 1995 *Nucleic Acids Res.* 23, 2677; Caruthers et al., 1992, *Methods in Enzymology* 211,3-19 (incorporated by reference herein) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

[0145] In one embodiment, nucleic acid molecules of the invention include one or more G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein modifications result in the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substation within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention can enable both enhanced affinity and specificity to nucleic acid targets.

[0146] Therapeutic nucleic acid molecules (e.g., enzymatic nucleic acid molecules and antisense nucleic acid molecules) delivered exogenously are optimally stable within cells until translation of the target RNA has been inhibited long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. These nucleic acid molecules should be resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

[0147] In another embodiment, the invention features conjugates and/or complexes of nucleic acid molecules targeting PTGDS, PTGDR, and/or adenosine receptors. Compositions and conjugates are used to facilitate delivery of molecules into a biological system, such as cells. The conjugates provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel agents for the delivery of molecules, including but not limited to small molecules, lipids, phospholipids, nucleosides, nucleotides, nucleic acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers. These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker molecules.

[0148] The term "biodegradable nucleic acid linker molecule" as used herein, refers to a nucleic acid molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule. The stability of the biodegradable nucleic acid linker molecule can be modulated by using various combinations of ribonucleotides, deoxyribonucleotides, and chemically modified nucleotides, for example 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino, 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus based linkage, for example a phosphoramidate or phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

[0149] The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

[0150] The term "biologically active molecule" as used herein, refers to compounds or molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siRNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

[0151] The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

[0152] In another embodiment, nucleic acid catalysts having chemical modifications that maintain or enhance enzymatic activity are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acid. Thus, in a cell and/or in vivo the activity of the nucleic acid may not be significantly lowered. As exemplified herein such enzymatic nucleic acids are useful in a cell and/or in vivo even if activity over all is reduced 10 fold (Burgin et al., 1996, *Biochemistry,* 35, 14090). Such enzymatic nucleic acids herein are said to "maintain" the enzymatic activity of an all RNA ribozyme or all DNA DNAzyme.

[0153] In another aspect the nucleic acid molecules comprise a 5' and/or a 3'-cap structure.

[0154] By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see for example Wincott et al., WO 97/26270, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap) or at the 3'-terminus (3'-cap) or can be present on both terminus. In non-limiting examples, the 5'-cap includes inverted abasic residue (moiety), 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety (for more details see Wincott et al., International PCT publication No. WO 97/26270, incorporated by reference herein).

[0155] In another embodiment the 3'-cap includes, for example 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

[0156] By the term "non-nucleotide" is meant any group or compound thatcan be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine.

[0157] An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. The alkyl group can have, for example, 1 to 12 carbons. In one embodiment of the invention, the alkyl group is a lower alkyl of from 1 to 7 carbons. In another embodiment the alkyl group is 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) can be hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino, or SH. The term also includes alkenyl groups which are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. The alkenyl group can have, for example, 1 to 12 carbons. In one embodiment of the invention the alkenyl group can be a lower alkenyl of from 1 to 7 carbons. In another embodiment the alkenyl group can be 1 to 4 carbons. The alkenyl group can be substituted or unsubstituted. When substituted the substituted group(s) can be, for example, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups which have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. The alkynyl group can have, for example, 1 to 12 carbons. In one embodiment of the invention, the alkynyl group is a lower alkynyl of from 1 to 7 carbons. In another embodiment of the invention, the alkynyl group is 1 to 4 carbons. The alkynyl group can be substituted or unsubstituted. When substituted the substituted group(s) can be, for example, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

[0158] Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group which has at least one ring having a conjugated p electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which can be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an —C(O)—NH—R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an —C(O)—OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

[0159] By "nucleotide" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a phosphorylated

sugar. Nucleotides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see for example, Usman and McSwiggen, supra; Eckstein et al., International PCT Publication No. WO 92/07065; Usman et al., International PCT Publication No. WO 93/15187; Uhlman & Peyman, supra all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach et al., 1994, Nucleic Acids Res. 22, 2183. Some of the non-limiting examples of chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, for example, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (e.g., 5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine, wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methyloxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin et al., 1996, Biochemistry, 35, 14090; Uhlman & Peyman, supra). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

[0160] By "nucleoside" is meant a heterocyclic nitrogenous base in N-glycosidic linkage with a sugar. Nucleosides are recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleoside sugar moiety. Nucleosides generally comprise a base and sugar group. The nucleosides can be unmodified or modified at the sugar, and/or base moiety, (also referred to interchangeably as nucleoside analogs, modified nucleosides, non-natural nucleosides, non-standard nucleosides and other; see for example, Usman and McSwiggen, supra; Eckstein et al., International PCT Publication No. WO 92/07065; Usman et al., International PCT Publication No. WO 93/15187; Uhlman & Peyman, supra all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach et al., 1994, Nucleic Acids Res. 22, 2183. Some of the non-limiting examples of chemically modified and other natural nucleic acid bases that can be introduced into nucleic acids include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (e.g., 5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-thiouridine, wybutosine, wybutoxosine, 4-acetylcytidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluridine, beta-D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methyloxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, beta-D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin et al., 1996, Biochemistry, 35, 14090; Uhlman & Peyman, supra). By "modified bases" in this aspect is meant nucleoside bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents; such bases can be used at any position, for example, within the catalytic core of an enzymatic nucleic acid molecule and/or in the substrate-binding regions of the nucleic acid molecule.

[0161] In one embodiment, the invention features modified enzymatic nucleic acid molecules with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker et al., 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39. These references are hereby incorporated by reference herein.

[0162] By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, for example a 3',3'-linked or 5',5'-linked deoxyabasic ribose derivative (for more details see Wincott et al., International PCT publication No. WO 97/26270).

[0163] By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, uracil joined to the 1' carbon of β-D-ribo-furanose.

[0164] By "modified nucleoside" is meant any nucleotide base that contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-O-NH_2, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein et al., U.S. Pat. No. 5,672,695 and Matulic-Adamic et al., WO 98/28317, respectively, which are both incorporated by reference in their entireties.

[0165] Various modifications to nucleic acid (e.g., antisense and ribozyme) structure can be made to enhance the utility of these molecules. For example, such modifications can enhance shelf-life, half-life in vitro, stability, and ease of introduction of such oligonucleotides to the target site,

including e.g., enhancing penetration of cellular membranes and conferring the ability to recognize and bind to targeted cells.

[0166] Use of the nucleic acid-based molecules of the invention can lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple enzymatic nucleic acid molecules targeted to different genes, enzymatic nucleic acid molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acid molecules (including different enzymatic nucleic acid molecule motifs) and/or other chemical or biological molecules). The treatment of patients with nucleic acid molecules can also include combinations of different types of nucleic acid molecules. Therapies can be devised which include a mixture of enzymatic nucleic acid molecules (including different enzymatic nucleic acid molecule motifs), antisense and/or 2-5A chimera molecules to one or more targets to alleviate symptoms of a disease.

[0167] Administration of Nucleic Acid Molecules

[0168] A nucleid acid molecule of the invention can be adapted for use to treat asthma and other related diseases and conditions described herein. For example, a nucleic acid molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar et al., 1992, *Trends Cell Bio.,* 2, 139; and *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995 which are both incorporated herein by reference. Sullivan et al., PCT WO 94/02595, further describes the general methods for delivery of enzymatic RNA molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. The nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer. Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump. Other routes of delivery include, but are not limited to oral (tablet or pill form) and/or intrathecal delivery (Gold, 1997, *Neuroscience,* 76, 1153-1158). Other approaches include the use of various transport and carrier systems, for example though the use of conjugates and biodegradable polymers. For a comprehensive review on drug delivery strategies including CNS delivery, see Ho et al., 1999, *Curr. Opin. Mol. Ther.,* 1, 336-343 and Jain, *Drug Delivery Systems: Technologies and Commercial Opportunities*, Decision Resources, 1998 and Groothuis et al., 1997, *J NeuroVirol.,* 3, 387-400. More detailed descriptions of nucleic acid delivery and administration are provided in Sullivan et al., supra, Draper et al., PCT WO93/23569, Beigelman et al., PCT WO99/05094, and Klimuk et al., PCT WO99/04819 all of which have been incorporated by reference herein.

[0169] The molecules of the instant invention can be used as pharmaceutical agents. Pharmaceutical agents prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, or all of the symptoms) of a disease state in a patient.

[0170] The negatively charged polynucleotides of the invention can be administered (e.g., RNA, DNA or protein) and introduced into a patient by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions; suspensions for injectable administration; and the other compositions known in the art.

[0171] The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, e.g., acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

[0172] A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, e.g., local administration or systemic administration, into a cell or patient, including, for example, a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (i.e., a cell to which the negatively charged polymer is desired to be delivered to). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the composition or formulation from exerting its effect.

[0173] By "local administration" is meant in vivo local absorption or accumulation of drugs in the specific tissue, organ, or compartment of the body. Administration routes that can lead to local absorption include, without limitations: inhalation, direct injection, or dermatological applications.

[0174] By "systemic administration" is meant in vivo systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes which lead to systemic absorption include, without limitations: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes expose the desired compound, e.g., nucleic acids, to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention, for example PEG or phospholipids conjugates, can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A nucleic acid formulation that can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells.

[0175] Both local and systemic administration approaches can be used to administer nucleic acid molecules of the

invention for the treatment of asthma or related conditions. In one embodiment, the nucleic acid molecule or formulation comprising the nucleic acid molecule is administered to a patient with an inhaler or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. In another embodiment, the nucleic acid molecule or formulation comprising the nucleic acid molecule is administered to a patient systemically, for example by intravenous or subcutaneous injection, providing sustained uptake of the nucleic acid molecules into relevant bodily tissues.

[0176] By pharmaceutically acceptable formulation is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: PEG conjugated nucleic acids, phospholipid conjugated nucleic acids, nucleic acids containing lipophilic moieties, phosphorothioates, P-glycoprotein inhibitors (such as Pluronic P85) which can enhance entry of drugs into various tissues, for exaple the CNS (Jolliet-Riant and Tillement, 1999, *Fundam. Clin. Pharmacol.,* 13, 16-26); biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery after implantation (Emerich, DF et al, 1999, *Cell Transplant,* 8, 47-58) Alkermes, Inc. Cambridge, Mass.; and loaded nanoparticles, such as those made of polybutylcyanoacrylate, which can deliver drugs across the blood brain barrier and can alter neuronal uptake mechanisms (*Prog Neuropsychopharmacol Biol Psychiatry,* 23, 941-949, 1999). Other non-limiting examples of delivery strategies, including CNS delivery of the nucleic acid molecules of the instant invention include material described in Boado et al., 1998, *J. Pharm. Sci.,* 87, 1308-1315; Tyler et al., 1999, *FEBS Lett.,* 421, 280-284; Pardridge et al., 1995, *PNAS USA.,* 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.,* 15, 73-107; Aldrian-Herrada et al., 1998, *Nucleic Acids Res.,* 26, 4910-4916; and Tyler et al., 1999, *PNAS USA.,* 96, 7053-7058. All these references are hereby incorporated herein by reference.

[0177] The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). Nucleic acid molecules of the invention can also comprise covalently attached PEG molecules of various molecular weights. These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic et al. *Chem. Rev.* 1995, 95, 2601-2627; Ishiwata et al., *Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic et al., *Science* 1995, 267, 1275-1276; Oku et al., 1995, *Biochim. Biophys. Acta,* 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu et al., *J. Biol. Chem.* 1995, 42, 24864-24870; Choi et al., International PCT Publication No. WO 96/10391; Ansell et al., International PCT Publication No. WO 96/10390; Holland et al., International PCT Publication No. WO 96/10392; all of which are incorporated by reference herein). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen. All of these references are incorporated by reference herein.

[0178] The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A. R. Gennaro edit. 1985) hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

[0179] A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, or all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

[0180] The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0181] Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can

be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

[0182] Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0183] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0184] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0185] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0186] Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[0187] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0188] The nucleic acid molecules of the invention can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0189] Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0190] Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0191] It is understood that the specific dose level for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0192] For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

[0193] The nucleic acid molecules of the present invention can also be administered to a patient in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

[0194] Alternatively, certain of the nucleic acid molecules of the instant invention can be expressed within cells from eukaryotic promoters (e.g., Izant and Weintraub, 1985, *Science,* 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci., USA* 83, 399; Scanlon et al., 1991, *Proc. Natl. Acad. Sci. USA,* 88, 10591-5; Kashani-Sabet et al., 1992, *Antisense Res. Dev.,* 2, 3-15; Dropulic et al., 1992, *J. Virol.,* 66, 1432-41; Weerasinghe et al., 1991, *J. Virol.,* 65, 5531-4; Ojwang et al., 1992, *Proc. Natl. Acad. Sci. USA,* 89, 10802-6; Chen et al., 1992, *Nucleic Acids Res.,* 20, 4581-9; Sarver et al., 1990 *Science,* 247, 1222-1225; Thompson et al., 1995, *Nucleic Acids Res.,* 23, 2259; Good et al., 1997, *Gene Therapy,* 4, 45; all of these references are hereby incorporated in their totalities by reference herein). Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper et al, PCT WO 93/23569, and Sullivan et al., PCT WO 94/02595; Ohkawa et al., 1992, *Nucleic Acids Symp. Ser.,* 27, 15-6; Taira et al., 1991, *Nucleic Acids Res.,* 19, 5125-30; Ventura et al., 1993, *Nucleic Acids Res.,* 21, 3249-55; Chowrira et al., 1994, *J. Biol. Chem.,* 269, 25856; all of these references are hereby incorporated in their totalities by reference herein). Gene therapy approaches specific to the CNS are described by Blesch et al., 2000, *Drug News Perspect.,* 13, 269-280; Peterson et al., 2000, *Cent. Nerv. Syst. Dis.,* 485-508; Peel and Klein, 2000, *J. Neurosci. Methods,* 98, 95-104; Hagihara et al., 2000, *Gene Ther.,* 7, 759-763; and Herrlinger et al., 2000, *Methods Mol. Med.,* 35, 287-312. AAV-mediated delivery of nucleic acid to cells of the nervous system is further described by Kaplitt et al., U.S. Pat. No. 6,180,613.

[0195] In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture et al., 1996, *TIG.,* 12, 510) inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. Ribozyme expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the nucleic acid molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the nucleic acid molecule binds to the target mRNA. Delivery of nucleic acid molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture et al., 1996, *TIG.,* 12, 510).

[0196] In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the nucleic acid molecules of the instant invention is disclosed. The nucleic acid sequence encoding the nucleic acid molecule of the instant invention is operable linked in a manner that allows expression of that nucleic acid molecule.

[0197] In another aspect the invention features an expression vector comprising: a) a transcription initiation region (e.g., eukaryotic pol I, II or III initiation region); b) a transcription termination region (e.g., eukaryotic pol I, II or III termination region); c) a nucleic acid sequence encoding at least one of the nucleic acid catalyst of the instant invention; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner that allows expression and/or delivery of said nucleic acid molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the nucleic acid catalyst of the invention; and/or an intron (intervening sequences).

[0198] Transcription of the nucleic acid molecule sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. USA,* 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.,* 21, 2867-72; Lieber et al., 1993, *Methods Enzymol.,* 217, 47-66; Zhou et al., 1990, *Mol. Cell. Biol.,* 10, 4529-37). All of these references are incorporated by reference herein. Several investigators have demonstrated that nucleic acid molecules, such as ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet et al., 1992, *Antisense Res. Dev.,* 2, 3-15; Ojwang et al., 1992, *Proc. Natl. Acad. Sci. USA,* 89, 10802-6; Chen et al., 1992, *Nucleic Acids Res.,* 20, 4581-9; Yu et al., 1993, *Proc. Natl. Acad. Sci. USA,* 90, 6340-4; L'Huillier et al., 1992, *EMBO J,* 11, 4411-8; Lisziewicz et al., 1993, *Proc. Natl. Acad. Sci. U.S. A,* 90, 8000-4; Thompson et al., 1995, *Nucleic Acids Res.,* 23, 2259; Sullenger & Cech, 1993, *Science,* 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as ribozymes in cells (Thompson et al., supra; Couture and Stinchcomb, 1996, supra; Noonberg et al., 1994, *Nucleic Acid Res.,* 22, 2830; Noonberg et al., U.S. Pat. No. 5,624, 803; Good et al., 1997, *Gene Ther.,* 4, 45; Beigelman et al., International PCT Publication No. WO 96/18736; all of these publications are incorporated by reference herein). The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, supra).

[0199] In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the nucleic acid molecules of the invention, in a manner that allows expression of that nucleic acid mol-

ecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; c) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region and said termination region, in a manner that allows expression and/or delivery of said nucleic acid molecule.

[0200] In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; d) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said open reading frame and said termination region, in a manner that allows expression and/or delivery of said nucleic acid molecule. In yet another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) a nucleic acid sequence encoding at least one said nucleic acid molecule; and wherein said sequence is operably linked to said initiation region, said intron and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

[0201] In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; e) a nucleic acid sequence encoding at least one said nucleic acid molecule, wherein said sequence is operably linked to the 3'-end of said open reading frame; and wherein said sequence is operably linked to said initiation region, said intron, said open reading frame and said termination region, in a manner which allows expression and/or delivery of said nucleic acid molecule.

EXAMPLES

[0202] The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

[0203] The following examples demonstrate the selection and design of Antisense, hammerhead, DNAzyme, NCH, Amberzyme, Zinzyme, or G-Cleaver ribozyme molecules and binding/cleavage sites within PTGDS and/or PTGDR RNA.

Example 1

Identification of Potential Target Sites in Human PTGDS, ADORA1 and PTGDR RNA

[0204] The sequence of human PTGDS, ADORA1 and PTGDR genes are screened for accessible sites using a computer-folding algorithm. Regions of the RNA that do not form secondary folding structures and contained potential enzymatic nucleic acid molecule and/or antisense binding/cleavage sites are identified. The sequences of PTGDR binding/cleavage sites are shown in Tables III-VII.

Example 2

Selection of Enzymatic Nucleic Acid Cleavage Sites in Human PTGDS, ADORA1 and PTGDR RNA

[0205] Enzymatic nucleic acid molecule target sites are chosen by analyzing sequences of Human PTGDS (Genbank accession No: NM 000954), ADORA1 (Genbank accession No: NM_000674) and PTGDR gene (Genbank accession Nos: U31332 and U31099) and prioritizing the sites on the basis of folding. Enzymatic nucleic acid molecules are designed that can bind each target and are individually analyzed by computer folding (Christoffersen et al., 1994 *J. Mol. Struc. Theochem,* 311, 273; Jaeger et al., 1989, *Proc. Natl. Acad. Sci. USA,* 86, 7706) to assess whether the enzymatic nucleic acid molecule sequences fold into the appropriate secondary structure. Those enzymatic nucleic acid molecules with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. As noted below, varying binding arm lengths can be chosen to optimize activity. Generally, at least 4 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Example 3

Chemical Synthesis and Purification of Ribozymes and Antisense for Efficient Cleavage and/or blocking of PTGDS, ADORA1 and PTGDR RNA

[0206] Enzymatic nucleic acid molecules and antisense constructs are designed to anneal to various sites in the RNA message. The binding arms of the enzymatic nucleic acid molecules are complementary to the target site sequences described above, while the antisense constructs are fully complementary to the target site sequences described above. The enzymatic nucleic acid molecules and antisense constructs were chemically synthesized. The method of synthesis used followed the procedure for normal RNA synthesis as described above and in Usman et al., (1987 J. Am. Chem. Soc., 109, 7845), Scaringe et al., (1990 Nucleic Acids Res., 18, 5433) and Wincott et al., supra, and made use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields were typically >98%.

[0207] Enzymatic nucleic acid molecules and antisense constructs are also synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, Methods Enzymol. 180, 51). Enzymatic nucleic acid molecules and antisense constructs are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Wincott et al., supra; the totality of which is hereby incorporated herein by reference) and are resuspended in water. The sequences of the chemically synthesized enzymatic nucleic acid molecules used in this study are shown below in Table III-VII. The sequences of the chemically synthesized antisense constructs used in this study are complementary sequences to the Substrate sequences shown below as in Table III-VII.

Example 4

Enzymatic Nucleic Acid Molecule Cleavage of PTGDS, ADORA1 and PTGDR RNA Target in vitro

[0208] Enzymatic nucleic acid molecules targeted to the human PTGDS, ADORA1 and PTGDR RNA are designed and synthesized as described above. These enzymatic nucleic acid molecules can be tested for cleavage activity in vitro, for example, using the following procedure. The target

sequences and the nucleotide location within the PTGDR RNA are given in Tables III-VII.

[0209] Cleavage Reactions: Full-length or partially full-length, internally-labeled target RNA for enzymatic nucleic acid molecule cleavage assay is prepared by in vitro transcription in the presence of [a-^{32}P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as substrate RNA without further purification. Alternately, substrates are 5'-^{32}P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed by pre-warming a 2×concentration of purified enzymatic nucleic acid molecule in enzymatic nucleic acid molecule cleavage buffer (50 mM Tris-HCl, pH 7.5 at 37° C., 10 mM $MgCl_2$) and the cleavage reaction was initiated by adding the 2×enzymatic nucleic acid molecule mix to an equal volume of substrate RNA (maximum of 1-5 nM) that was also pre-warmed in cleavage buffer. As an initial screen, assays are carried out for 1 hour at 37° C. using a final concentration of either 40 nM or 1 mM enzymatic nucleic acid molecule, i.e., enzymatic nucleic acid molecule excess. The reaction is quenched by the addition of an equal volume of 95% formamide, 20 mM EDTA, 0.05% bromophenol blue and 0.05% xylene cyanol after which the sample is heated to 95° C. for 2 minutes, quick chilled and loaded onto a denaturing polyacrylamide gel. Substrate RNA and the specific RNA cleavage products generated by enzymatic nucleic acid molecule cleavage are visualized on an autoradiograph of the gel. The percentage of cleavage is determined by Phosphor Imager® quantitation of bands representing the intact substrate and the cleavage products.

Example 5

In vivo Models used to Evaluate the Down-Regulation of PTGDS, ADORA1 and PTGDR Gene Expression

[0210] Animal Models

[0211] Evaluating the efficacy of anti-PTGDS, ADORA-1 and/or PTGDR agents in animal models is an important prerequisite to human clinical trials. Matsuoka et al., 2000, *Science,* 287, 2012-2016, describe a useful asthma animal model having generating mice deficient in the PTGDR receptor. Sensitization and aerosol challenge of homozygous (PTGDR−/−) mice with ovalbumin was shown to induce increases in the serum concentration of immunoglobin E (IgE), an allergic mediator that activates mast cells, similar to wild-type mice subjected to the same conditions. The concentration of TH2 cytokines and the degree of lymphocyte lung infiltration in the OVA challenged PTGDR −/− mice was shown to be greatly reduced compared to wild type mice. In addition, the PTGDR −/− mice showed only marginal eosinophil infiltration and failed to develop airway hyperreactivity. Similarly, this model can be used to evaluate mice that are treated with nucleic acid molecules of the invention and can furthermore be used as a positive control in determining the response of mice treated with nucleic acid molecules of the invention by using such factors as airway obstruction, lung capacity, and bronchiolar alveolar lavage (BAL) fluid in the evaluation.

[0212] Cell Culture

[0213] Two human cell lines, NPE cells and NCB-20 cells are known to express PTGDR. Cloned human PTGDR has been expressed in CHO and COS7 cells and used in various studies. These PTGDR expressing lung cell lines can be used in cell culture assays to evaluate nucleic acid molecules of the invention. A primary endpoint in these experiments would be the RT-PCR analysis of PTGDR mRNA expression in PTGDR expressing cells. In addition, ligand binding assays can be developed where binding of PTGDS can be evaluated in response to treatment with nucleic acid molecules of the invention.

[0214] Indications

[0215] The present body of knowledge in PTGDS, ADORA1 and PTGDR research indicates the need for methods to assay PTGDS, ADORA1 and PTGDR activity and for compounds that can regulate PTGDS, ADORA1 and PTGDR expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of PTGDS, ADORA1 and/or PTGDR levels. In addition, the nucleic acid molecules can be used to treat disease state related to PTGDS, ADORA1 and/or PTGDR levels.

[0216] Particular degenerative and disease states that can be associated with PTGDS, ADORA1 and PTGDR levels include, but are not limited to allergic diseases and conditions, including but not limited to asthma, allergic rhinitis, atopic dermatitis, and any other diseases or conditions that are related to or will respond to the levels of PTGDS, ADORA1 and/or PTGDR in a cell or tissue, alone or in combination with other therapies.

[0217] The use of anti-inflammatories, bronchodilators, adenosine inhibitors and adenosine A1 receptor inhibitors are examples of other treatments or therapies can be combined with the nucleic acid molecules of the invention. Those skilled in the art will recognize that other drug compounds and therapies can be similarly be readily combined with the nucleic acid molecules of the instant invention (e.g. enzymatic nucleic acid molecules and antisense molecules) are hence within the scope of the instant invention.

[0218] Diagnostic Uses

[0219] The nucleic acid molecules of this invention (e.g., enzymatic nucleic acid molecules) can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of PTGDS, ADORA1 and/or PTGDR RNA in a cell. The close relationship between enzymatic nucleic acid molecule activity and the structure of the target RNA allows the detection of mutations in any region of the molecule that alters the base-pairing and three-dimensional structure of the target RNA. By using multiple enzymatic nucleic acid molecules described in this invention, one can map nucleotide changes which are important to RNA structure and function in vitro, as well as in cells and tissues. Cleavage of target RNAs with enzymatic nucleic acid molecules can be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments can lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple enzymatic nucleic acid molecules targeted to different genes, enzymatic nucleic acid

molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations of enzymatic nucleic acid molecules and/or other chemical or biological molecules). Other in vitro uses of enzymatic nucleic acid molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with PTGDS, ADORA1 or PTGDR-related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with an enzymatic nucleic acid molecule using standard methodology.

[0220] In a specific example, enzymatic nucleic acid molecules which cleave only wild-type or mutant forms of the target RNA are used for the assay. The first enzymatic nucleic acid molecule is used to identify wild-type RNA present in the sample and the second enzymatic nucleic acid molecule is used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA are cleaved by both enzymatic nucleic acid molecules to demonstrate the relative enzymatic nucleic acid molecule efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis requires two enzymatic nucleic acid molecules, two substrates and one unknown sample which is combined into six reactions. The presence of cleavage products is determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (i.e., PTGDS/PTGDR) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively. The use of enzymatic nucleic acid molecules in diagnostic applications contemplated by the instant invention is described, for example, in George et al., U.S. Pat. Nos. 5,834,186 and 5,741,679, Shih et al., U.S. Pat. No. 5,589,332, Nathan et al., U.S. Pat. No. 5,871,914, Nathan and Ellington, International PCT publication No. WO 00/24931, Breaker et al., International PCT Publication Nos. WO 00/26226 and 98/27104, and Sullenger et al., International PCT publication No. WO 99/29842.

[0221] Additional Uses

[0222] Potential uses of sequence-specific enzymatic nucleic acid molecules of the instant invention can have many of the same applications for the study of RNA that DNA restriction endonucleases have for the study of DNA (Nathans et al., 1975 *Ann. Rev. Biochem.* 44:273). For example, the pattern of restriction fragments can be used to establish sequence relationships between two related RNAs, and large RNAs can be specifically cleaved to fragments of a size more useful for study. The ability to engineer sequence specificity of the enzymatic nucleic acid molecule is ideal for cleavage of RNAs of unknown sequence. Applicant has described the use of nucleic acid molecules to down-regulate gene expression of target genes in bacterial, microbial, fungal, viral, and eukaryotic systems including plant, or mammalian cells.

[0223] All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0224] One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[0225] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0226] The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" can be replaced with either of the other two terms. The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

[0227] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0228] Other embodiments are within the following claims.

TABLE I

Characteristics of naturally occurring ribozymes

Group I Introns

Size: ~150 to >1000 nucleotides.
Requires a U in the target sequence immediately 5' of the cleavage site.
Binds 4–6 nucleotides at the 5'-side of the cleavage site.
Reaction mechanism: attack by the 3'-OH of guanosine to generate cleavage products with 3'-OH and 5'-guanosine.
Additional protein cofactors required in some cases to help folding and maintenance of the active structure.
Over 300 known members of this class. Found as an intervening sequence in Tetrahymena thermophila rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.
Major structural features largely established though phylogenetic comparisons, mutagenesis, and biochemical studies [i,ii].
Complete kinetic framework established for one ribozyme [iii,iv,v,vi].
Studies of ribozyme folding and substrate docking underway [vii,viii,ix].
Chemical modification investigation of important residues well established [x,xi].
The small (4–6 nt) binding site may make this ribozyme too non-specific for targeted RNA cleavage, however, the Tetrahymena group I intron has been used to repair a "defective" β-galactosidase message by the ligation of new β-galactosidase sequences onto the defective message [xii].

RNAse P RNA (M1 RNA)

Size: ~290 to 400 nucleotides.
RNA portion of a ubiquitous ribonucleoprotein enzyme.
Cleaves tRNA precursors to form mature tRNA [xiii].
Reaction mechanism: possible attack by M^{2+}-OH to generate cleavage products with 3'-OH and 5'-phosphate.
RNAse P is found throughout the prokaryotes and eukaryotes. The RNA subunit has been sequenced from bacteria, yeast, rodents, and primates.
Recruitment of endogenous RNAse P for therapeutic applications is possible through hybridization of an External Guide Sequence (EGS) to the target RNA [xiv,xv]
Important phosphate and 2'OH contacts recently identified [xvi,xvii]

Group II Introns

Size: >1000 nucleotides.
Trans cleavage of target RNAs recently demonstrated [xviii,xix].
Sequence requirements not fully determined.
Reaction mechanism: 2'-OH of an internal adenosine generates cleavage products with 3'-OH and a "lariat" RNA containing a 3'–5' and a 2'–5' branch point.
Only natural ribozyme with demonstrated participation in DNA cleavage [xx,xxi] in addition to RNA cleavage and ligation.
Major structural features largely established through phylogenetic comparisons [xxii].
Important 2'OH contacts beginning to be identified [xxiii]
Kinetic framework under development [xxiv]

Neurospora VS RNA

Size: ~144 nucleotides.
Trans cleavage of hairpin target RNAs recently demonstrated [xxv].
Sequence requirements not fully determined.
Reaction mechanism: attack by 2'-OH 5'to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
Binding sites and structural requirements not fully determined.
Only 1 known member of this class. Found in Neurospora VS RNA.

Hammerhead Ribozyme
(see text for references)

Size: ~13 to 40 nucleotides.
Requires the target sequence UH immediately 5' of the cleavage site.
Binds a variable number nucleotides on both sides of the cleavage site.
Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent.
Essential structural features largely defined, including 2 crystal structures [xxvi,xxvii]
Minimal ligation activity demonstrated (for engineering through in vitro selection) [xxviii]
Complete kinetic framework established for two or more ribozymes [xxix].
Chemical modification investigation of important residues well established [xxx].

TABLE I-continued

Characteristics of naturally occurring ribozymes
Hairpin Ribozyme
Size: ~50 nucleotides.
Requires the target sequence GUC immediately 3'of the cleavage site.
Binds 4–6 nucleotides at the 5'-side of the cleavage site and a variable number to the 3'-side of the cleavage site.
Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
3 known members of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus, arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent.
Essential structural features largely defined [xxxi,xxxii,xxxiii,xxxiv]
Ligation activity (in addition to cleavage activity) makes ribozyme amenable to engineering through in vitro selection [xxxv]
Complete kinetic framework established for one ribozyme [xxxvi].
Chemical modification investigation of important residues begun [xxxvii,xxxviii].
Hepatitis Delta Virus (HDV) Ribozyme
Size: ~60 nucleotides.
Trans cleavage of target RNAs demonstrated [xxxix].
Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required. Folded ribozyme contains a pseudoknot structure [xl].
Reaction mechanism: attack by 2'-OH 5' to the scissile bond to generate cleavage products with 2',3'-cyclic phosphate and 5'-OH ends.
Only 2 known members of this class. Found in human HDV.
Circular form of HDV is active and shows increased nuclease stability [xli]

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TABLE I-continued

Characteristics of naturally occurring ribozymes

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[0229]

TABLE II

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
A. 2.5 μmol Synthesis Cycle ABI 394 Instrument					
Phosphoramidites	6.5	163 μL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 μL	45 sec	2.5 min	7.5 min

TABLE II-continued

Acetic Anhydride	100	233 μL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 μL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 μL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 μmol Synthesis Cycle ABI 394 Instrument

Phosphoramidites	15	31 μL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 μL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 μL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 μL	5 sec	5 sec	5 sec
TCA	700	732 μL	10 sec	10 sec	10 sec
Iodine	20.6	244 μL	15 sec	15 sec	15 sec
Beaucage	7.7	232 μL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 μmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents: DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O-methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 μL	60 sec	180 sec	360 sec
S-Ethyl Tetrazole	70/105/210	40/60/120 μL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 μL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 μL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 μL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 μL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 μL	NA	NA	NA

*Wait time does not include contact time during delivery.

[0230]

TABLE III

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
12	UUCUGGCU A UUUUCCUC	1	GAGGAAAA CUGAUGAGGCCGUUAGGCCGAA AGCCAGAA	228
14	CUGGCUAU U UUCCUCCU	2	AGGAGGAA CUGAUGAGGCCGUUAGGCCGAA AUAGCCAG	229
15	UGGCUAUU U UCCUCCUG	3	CAGGAGGA CUGAUGAGGCCGUUAGGCCGAA AAUAGCCA	230
16	GGCUAUUU U CCUCCUGC	4	GCAGGAGG CUGAUGAGGCCGUUAGGCCGAA AAAUAGCC	231
17	GCUAUUUU C CUCCUGCC	5	GGCAGGAG CUGAUGAGGCCGUUAGGCCGAA AAAAUAGC	232
20	AUUUUCCU C CUGCCGUU	6	AACGGCAG CUGAUGAGGCCGUUAGGCCGAA AGGAAAAU	233
28	CCUGCCGU U CCGACUCG	7	CGAGUCGG CUGAUGAGGCCGUUAGGCCGAA ACGGCAGG	234
29	CUGCCGUU C CGACUCGG	8	CCGAGUCG CUGAUGAGGCCGUUAGGCCGAA AACGGCAG	235
35	UUCCGACU C GGCACCAG	9	CUGGUGCC CUGAUGAGGCCGUUAGGCCGAA AGUCGGAA	236
47	ACCAGAGU C UGUCUCUA	10	UAGAGACA CUGAUGAGGCCGUUAGGCCGAA ACUCUGGU	237
51	GAGUCUGU C UCUACUGA	11	UCAGUAGA CUGAUGAGGCCGUUAGGCCGAA ACAGACUC	238
53	GUCUGUCU C UACUGAGA	12	UCUCAGUA CUGAUGAGGCCGUUAGGCCGAA AGACAGAC	239
55	CUGUCUCU A CUGAGAAC	13	GUUCUCAG CUGAUGAGGCCGUUAGGCCGAA AGAGACAG	240
73	CAGCGCGU C AGGGCCGA	14	UCGGCCCU CUGAUGAGGCCGUUAGGCCGAA ACGCGCUG	241

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
85	GCCGAGCU C UUCACUGG	15	CCAGUGAA CUGAUGAGGCCGUUAGGCCGAA AGCUCGGC	242
87	CGAGCUCU U CACUGGCC	16	GGCCAGUG CUGAUGAGGCCGUUAGGCCGAA AGAGCUCG	243
88	GAGCUCUU C ACUGGCCU	17	AGGCCAGU CUGAUGAGGCCGUUAGGCCGAA AAGAGCUC	244
100	GGCCUGCU C CGCGCUCU	18	AGAGCGCG CUGAUGAGGCCGUUAGGCCGAA AGCAGGCC	245
107	UCCGCGCU C UUCAAUGC	19	GCAUUGAA CUGAUGAGGCCGUUAGGCCGAA AGCGCGGA	246
109	CGCGCUCU U CAAUGCCA	20	UGGCAUUG CUGAUGAGGCCGUUAGGCCGAA AGAGCGCG	247
110	GCGCUCUU C AAUGCCAG	21	CUGGCAUU CUGAUGAGGCCGUUAGGCCGAA AAGAGCGC	248
130	CAGGCGCU C ACCCUGCA	22	UGCAGGGU CUGAUGAGGCCGUUAGGCCGAA AGCGCCUG	249
145	CAGAGCGU C CCGCCUCU	23	AGAGGCGG CUGAUGAGGCCGUUAGGCCGAA ACGCUCUG	250
152	UCCCGCCU C UCAAAGAG	24	CUCUUUGA CUGAUGAGGCCGUUAGGCCGAA AGGCGGGA	251
154	CCGCCUCU C AAAGAGGG	25	CCCUCUUU CUGAUGAGGCCGUUAGGCCGAA AGAGGCGG	252
178	CCGCGAGU U UAGAUAGG	26	CCUAUCUA CUGAUGAGGCCGUUAGGCCGAA ACUCGCGG	253
179	CGCGAGUU U AGAUAGGA	27	UCCUAUCU CUGAUGAGGCCGUUAGGCCGAA AACUCGCG	254
180	GCGAGUUU A GAUAGGAG	28	CUCCUAUC CUGAUGAGGCCGUUAGGCCGAA AAACUCGC	255
184	GUUUAGAU A GGAGGUUC	29	GAACCUCC CUGAUGAGGCCGUUAGGCCGAA AUCUAAAC	256
191	UAGGAGGU U CCUGCCGU	30	ACGGCAGG CUGAUGAGGCCGUUAGGCCGAA ACCUCCUA	257
192	AGGAGGUU C CUGCCGUG	31	CACGGCAG CUGAUGAGGCCGUUAGGCCGAA AACCUCCU	258
220	GCCGCCCU C GGAGCUUU	32	AAAGCUCC CUGAUGAGGCCGUUAGGCCGAA AGGGCGGC	259
227	UCGGAGCU U UUUCUGUG	33	CACAGAAA CUGAUGAGGCCGUUAGGCCGAA AGCUCCGA	260
228	CGGAGCUU U UUCUGUGG	34	CCACAGAA CUGAUGAGGCCGUUAGGCCGAA AAGCUCCG	261
229	GGAGCUUU U UCUGUGGC	35	GCCACAGA CUGAUGAGGCCGUUAGGCCGAA AAAGCUCC	262
230	GAGCUUUU U CUGUGGCG	36	CGCCACAG CUGAUGAGGCCGUUAGGCCGAA AAAAGCUC	263
231	AGCUUUUU C UGUGGCGC	37	GCGCCACA CUGAUGAGGCCGUUAGGCCGAA AAAAAGCU	264
244	GCGCAGCU U CUCCGCCC	38	GGGCGGAG CUGAUGAGGCCGUUAGGCCGAA AGCUGCGC	265
245	CGCAGCUU C UCCGCCCG	39	CGGGCGGA CUGAUGAGGCCGUUAGGCCGAA AAGCUGCG	266
247	CAGCUUCU C CGCCCGAG	40	CUCGGGCG CUGAUGAGGCCGUUAGGCCGAA AGAAGCUG	267
280	CGGGGGCU C CUUAGCAC	41	GUGCUAAG CUGAUGAGGCCGUUAGGCCGAA AGCCCCCG	268
283	GGGCUCCU U AGCACCCG	42	CGGGUGCU CUGAUGAGGCCGUUAGGCCGAA AGGAGCCC	269
284	GGCUCCUU A GCACCCGG	43	CCGGGUGC CUGAUGAGGCCGUUAGGCCGAA AAGGAGCC	270
306	GGGGCCCU C GCCCUUCC	44	GGAAGGGC CUGAUGAGGCCGUUAGGCCGAA AGGGCCCC	271
312	CUCGCCCU U CCGCAGCC	45	GGCUGCGG CUGAUGAGGCCGUUAGGCCGAA AGGGCGAG	272
313	UCGCCCUU C CGCAGCCU	46	AGGCUGCG CUGAUGAGGCCGUUAGGCCGAA AAGGGCGA	273
322	CGCAGCCU U CACUCCAG	47	CUGGAGUG CUGAUGAGGCCGUUAGGCCGAA AGGCUGCG	274
323	GCAGCCUU C ACUCCAGC	48	GCUGGAGU CUGAUGAGGCCGUUAGGCCGAA AAGGCUGC	275
327	CCUUCACU C CAGCCCUC	49	GAGGGCUG CUGAUGAGGCCGUUAGGCCCAA AGUGAAGG	276
335	CCAGCCCU C UGCUCCCG	50	CGUGAGCA CUGAUGAGGCCGUUACGCCGAA AGGGCUGG	277

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
340	CCUCUGCU C CCGCACGC	51	GCGUGCGG CUGAUGAGGCCGUUAGGCCGAA AGCAGAGG	278
357	CAUGAAGU C GCCGUUCU	52	AGAACGGC CUGAUGAGGCCGUUAGGCCGAA ACUUCAUG	279
363	GUCGCCGU U CUACCGCU	53	ACCCGUAG CUGAUGAGGCCGUUAGGCCGAA ACGGCGAC	280
364	UCGCCGUU C UACCGCUG	54	CAGCGGUA CUGAUGAGGCCGUUAGGCCGAA AACGCCGA	281
366	GCCGUUCU A CCGCUGCC	55	GGCAGCGG CUGAUGAGGCCGUUAGGCCGAA AGAACGGC	282
387	CACCACCU C UCUCGAAA	56	UUUCCACA CUGAUGAGGCCGUUAGGCCGAA AGGUGGUG	283
405	AGGCAACU C GGCGGUGA	57	UCACCGCC CUGAUGAGGCCGUUAGGCCGAA AGUUGCCU	284
427	GCGGUGCU C UUCAGCAC	58	GUGCUGAA CUGAUGAGGCCGUUAGGCCGAA AGCACCCC	285
429	GGUGCUCU U CAGCACCG	59	CGGUGCUG CUGAUGAGGCCUUUAGGCCGAA AGAGCACC	286
430	GUGCUCUU C AGCACCGG	60	CCGGUGCU CUGAUGAGGCCGUUAGGCCGAA AAGAGCAC	287
442	ACCGGCCU C CUGGGCAA	61	UUGCCCAG CUGAUGAGGCCGUUAGGCCGAA AGGCCGGU	288
480	GGCCCGCU C GGGGCUGG	62	CCAGCCCC CUGAUGAGGCCGUUAGGCCGAA AGCGCGCC	289
498	GUGGUGCU C GCGGCGUC	63	GACGCCGC CUGAUGAGGCCGUUAGGCCGAA AGCACCAC	290
506	CGCGGCGU C CACUGCGC	64	GCGCAGUG CUGAUGAGGCCGUUAGGCCCAA ACGCCGCG	291
525	GCUGCCCU C GGUCUUCU	65	AGAAGACC CUGAUGAGGCCGUUAGGCCGAA AGGGCAGC	292
529	CCCUCGGU C UUCUACAU	66	AUGUAGAA CUGAUGAGGCCGUUAGGCCGAA ACCGAGGG	293
531	CUCGGUCU U CUACAUGC	67	GCAUGUAG CUGAUGAGGCCCUUACGCCGAA AGACCGAG	294
532	UCGGUCUU C UACAUGCU	68	AGCAUGUA CUGAUGAGGCCGUUAGGCCGAA AAGACCGA	295
534	GGUCUUCU A CAUGCUGG	69	CCAGCAUG CUGAUGAGGCCGUUAGCCCGAA AGAAGACC	296
559	CUGACGGU C ACCGACUU	70	AAGUCGGU CUGAUGAGGCCGUUAGGCCGAA ACCGUCAG	297
567	CACCGACU U GCUGGGCA	71	UCCCCAGC CUGAUCAGCCCGUUAGGCCCAA AGUCGGUG	298
583	AAGUGCCU C CUAAGCCC	72	GGGCUUAG CUGAUGAGGCCGUUAGGCCGAA AGGCACUU	299
586	UGCCUCCU A AGCCCGGU	73	ACCGGGCU CUGAUGAGGCCCUUAGGCCGAA ACGAGGCA	300
609	GGCUGCCU A CGCUCAGA	74	UCUGAGCG CUGAUGAGGCCGUUAGGCCGAA AGGCAGCC	301
614	CCUACCCU C AGAACCGG	75	CCGGUUCU CUGAUGAGGCCGUUAGGCCGAA AGCGUAGG	302
626	ACCGGAGU C UGCGGGUG	76	CACCCCCA CUGAUGAGGCCCUUAGGCCGAA ACUCCCCU	303
637	CGCGUGCU U CCGCCCGC	77	GCGGGCGC CUGAUGAGGCCGUUAGGCCGAA AGCACCCG	304
648	GCCCGCAU U GGACAACU	78	AGUUGUCC CUGAUGAGGCCGUUAGGCCGAA AUGCGGGC	305
657	CGACAACU C GUUGUGCC	79	GGCACAAC CUGAUGAGGCCGUUAGGCCGAA AGUUGUCC	306
660	CAACUCGU U GUGCCAAG	80	CUUGGCAC CUGAUGAGGCCGUUAGGCCGAA ACGAGUUG	307
672	CCAAGCCU U CGCCUUCU	81	AGAAGGCG CUGAUGAGGCCGUUAGGCCGAA AGGCUUGG	308
673	CAAGCCUU C GCCUUCUU	82	AAGAAGGC CUGAUGAGGCCGUUAGGCCGAA AAGGCUUG	309
678	CUUCGCCU U CUUCAUGU	83	ACAUGAAG CUGAUGAGGCCGUUAGGCCGAA AGGCGAAG	310
679	UUCGCCUU C UUCAUGUC	84	GACAUGAA CUGAUGAGGCCGUUAGGCCGAA AAGGCGAA	311
681	CGCCUUCU U CAUGUCCU	85	AGGACAUC CUGAUGACCCCGUUAGGCCGAA ACAAGGCC	312

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
682	GCCUUCUU C AUGUCCUU	86	AAGGACAU CUGAUGAGGCCGUUAGGCCGAA AAGAAGGC	313
687	CUUCAUGU C CUUCUUUG	87	CAAAGAAG CUGAUGAGGCCGUUAGGCCGAA ACAUGAAG	314
690	CAUGUCCU U CUUUGGGC	88	GCCCAAAG CUGAUGAGGCCGUUAGGCCGAA AGGACAUG	315
691	AUGUCCUU C UUUGGGCU	89	AGCCCAAA CUGAUGAGGCCGUUAGGCCGAA AAGGACAU	316
693	GUCCUUCU U UGGGCUCU	90	AGAGCCCA CUGAUGAGGCCGUUAGGCCGAA AGAAGGAC	317
694	UCCUUCUU U GGGCUCUC	91	GAGAGCCC CUGAUGAGGCCGUUAGGCCGAA AAGAAGGA	318
700	UUUGGGCU C UCCUCGAC	92	GUCGAGGA CUGAUGAGGCCGUUAGGCCGAA AGCCCAAA	319
702	UGGGCUCU C CUCGACAC	93	GUGUCGAG CUGAUGAGGCCGUUAGGCCGAA AGAGCCCA	320
705	GCUCUCCU C GACACUGC	94	GCAGUGUC CUGAUGAGGCCGUUAGGCCGAA AGGAGAGC	321
718	CUGCAACU C CUGGCCAU	95	AUGGCCAG CUGAUGAGGCCGUUAGGCCGAA AGUUGCAG	322
745	UGCUGGCU C UCCCUAGG	96	CCUAGGGA CUGAUGAGGCCGUUAGGCCGAA AGCCAGCA	323
747	CUGGCUCU C CCUAGGGC	97	GCCCUAGG CUGAUGAGGCCGUUAGGCCGAA AGAGCCAG	324
751	CUCUCCCU A GGGCACCC	98	GGGUGCCC CUGAUGAGGCCGUUAGGCCGAA AGGGAGAG	325
761	GGCACCCU U UCUUCUAC	99	GUAGAAGA CUGAUGAGGCCGUUAGGCCGAA AGGGUGCC	326
762	GCACCCUU U CUUCUACC	100	GGUAGAAG CUGAUGAGGCCGUUAGGCCGAA AAGGGUGC	327
763	CACCCUUU C UUCUACCC	101	CGGUAGAA CUGAUGAGCCCGUUAGGCCGAA AAAGGGUG	328
765	CCCUUUCU U CUACCGAC	102	GUCGGUAG CUGAUGAGGCCGUUAGGCCGAA AGAAAGGG	329
766	CCUUUCUU C UACCGACG	103	CGUCGGUA CUGAUGAGGCCGUUAGGCCGAA AAGAAAGG	330
768	UUUCUUCU A CCGACGGC	104	GCCGUCGG CUCAUGAGGCCUUUAGGCCGAA AGAAGAAA	331
781	CGCCACAU C ACCCUGCG	105	CGCAGGGU CUGAUGAGGCCGUUAGGCCGAA AUGUGCCG	332
825	GAGCGCCU U CUCCCUGG	106	CCAGGGAG CUGAUCAGCCCGUUAGGCCGAA AGGCGCUC	333
826	AGCGCCUU C UCCCUGGC	107	GCCAGGGA CUGAUGAGGCCGUUAGGCCGAA AAGGCGCU	334
828	CGCCUUCU C CCUGGCUU	108	AAGCCACG CUGAUGAGGCCGUUAGGCCGAA AGAAGGCG	335
836	CCCUGGCU U UCUGCGCG	109	CGCGCAGA CUGAUGAGGCCGUUAGGCCGAA AUCCAGGG	336
837	CCUGGCUU U CUGCGCGC	110	GCGCGCAG CUGAUCACGCCGUUAGGCCGAA AAGCCAGG	337
838	CUGGCUUU C UGCGCGCU	111	AGCGCGCA CUGAUGAGGCCGUUAGGCCGAA AAAGCCAG	338
847	UGCGCGCU A CCUUUCAU	112	AUGAAAGC CUCAUGAGGCCGUUACGCCGAA AGCGCGCA	339
851	CGCUACCU U UCAUCGCC	113	GCCCAUGA CUGAUGAGGCCGUUAGGCCGAA AGGUAGCG	340
852	GCUACCUU U CAUGGGCU	114	AGCCCAUG CUGAUGAGGCCGUUAGGCCGAA AAGGUAGC	341
853	CUACCUUU C AUGGGCUU	115	AAGCCCAU CUGAUGAGGCCGUUAGGCCGAA AAAGGUAG	342
861	CAUGGGCU U CGGGAAGU	116	ACUUCCCG CUGAUGAGGCCGUUAGGCCGAA AGCCCAUG	343
862	AUGGGCUU C GGGAAGUU	117	AACUUCCC CUGAUGAGGCCGUUAGGCCGAA AAGCCCAU	344
870	CGGGAAGU U CGUGCAGU	118	ACUGCACG CUGAUGAGGCCGUUAGGCCGAA ACUUCCCG	345
871	GGGAAGUU C GUGCAGUA	119	UACUGCAC CUGAUGAGGCCGUUAGGCCGAA AACUUCCC	346
879	CGUGCAGU A CUGCCCCG	120	CGGGGCAG CUGAUGAGGCCGUUAGGCCGAA ACUGCACG	347

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
900	CUGGUGCU U UAUCCAGA	121	UCUGGAUA CUGAUGAGGCCGUUAGGCCGAA AGCACCAG	348
901	UGGUGCUU U AUCCAGAU	122	AUCUGGAU CUGAUGAGGCCGUUAGGCCGAA AAGCACCA	349
902	GGUGCUUU A UCCAGAUG	123	CAUCUGGA CUGAUGAGGCCGUUAGGCCGAA AAAGCACC	350
904	UGCUUUAU C CAGAUGGU	124	ACCAUCUG CUGAUGAGGCCGUUAGGCCGAA AUAAAGCA	351
913	CAGAUGGU C CACGAGGA	125	UCCUCGUG CUGAUGAGGCCGUUAGGCCGAA ACCAUCUG	352
927	GGAGGGCU C GCUGUCGG	126	CCGACAGC CUGAUGAGGCCGUUAGGCCGAA AGCCCUCC	353
933	CUCGCUGU C GGUGCUGG	127	CCAGCACC CUGAUGAGGCCGUUAGGCCGAA ACAGCGAG	354
945	GCUGGGGU A CUCUGUGC	128	GCACAGAG CUGAUGAGGCCGUUAGGCCGAA ACCCCAGC	355
948	GGGGUACU C UGUGCUCU	129	AGAGCACA CUGAUGAGGCCGUUAGGCCGAA AGUACCCC	356
955	UCUGUGCU C UACUCCAG	130	CUGGAGUA CUGAUGAGGCCGUUAGGCCGAA AGCACAGA	357
957	UGUGCUCU A CUCCAGCC	131	GGCUGGAG CUGAUGAGGCCGUUAGGCCGAA AGAGCACA	358
960	GCUCUACU C CAGCCUCA	132	UGAGGCUG CUGAUGAGGCCGUUAGGCCGAA AGUAGAGC	359
967	UCCAGCCU C AUGGCGCU	133	AGCGCCAU CUGAUGAGGCCGUUAGGCCGAA AGGCUGGA	360
982	CUGCUGGU C CUCGCCAC	134	GUGGOGAG CUGAUGAGGCCGUUAGGCCGAA ACCAGCAG	361
985	CUGGUCCU C GCCACCGU	135	ACGGUGGC CUGAUGAGGCCGUUAGGCCGAA AGGACCAG	362
1006	UGCAACCU C GGCGCCAU	136	AUGGCGCC CUGAUGAGGCCGUUAGGCCGAA AGGUUGCA	363
1024	CGCAACCU C UAUGCGAU	137	AUCGCAUA CUGAUGAGGCCGUUAGGCCGAA AGGUUGCG	364
1026	CAACCUCU A UGCGAUGC	138	GCAUCGCA CUGAUGAGGCCGUUAGGCCGAA AGAGGUUG	365
1062	CCCGCGCU C CUCCACCA	139	UGGUGCAG CUGAUGAGGCCGUUAGGCCGAA AGCGCGGG	366
1110	GGAAGCGU C CCCUCAGC	140	GCUGAGGG CUGAUGAGGCCGUUAGGCCGAA ACGCUUCC	367
1115	CGUCCCCU C AGCCCCUG	141	CAGGGGCU CUGAUGAGGCCGUUAGGCCGAA AGGGGACG	368
1136	AGCUGGAU C ACCUCCUG	142	CAGGAGGU CUGAUGAGGCCGUUAGGCCGAA AUCCAGCU	369
1141	GAUCACCU C CUGCUGCU	143	AGCAGCAG CUGAUGAGGCCGUUAGGCCGAA AGGUGAUC	370
1168	ACCGUGCU C UUCACUAU	144	AUAGUGAA CUGAUGAGGCCGUUAGGCCGAA AGCACGGU	371
1170	CGUGCUCU U CACUAUGU	145	ACAUAGUG CUGAUGAGGCCGUUAGGCCGAA AGAGCACG	372
1171	GUGCUCUU C ACUAUGUG	146	CACAUAGU CUGAUGAGGCCGUUAGGCCGAA AAGAGCAC	373
1175	UCUUCACU A UGUGUUCU	147	AGAACACA CUGAUGAGGCCGUUAGGCCGAA AGUGAAGA	374
1181	CUAUGUGU U CUCUGCCC	148	GGGCAGAG CUGAUGAGGCCGUUAGGCCGAA ACACAUAG	375
1182	UAUGUGUU C UCUGCCCG	149	CGGGCAGA CUGAUGAGGCCGUUAGGCCGAA AACACAUA	376
1184	UGUGUUCU C UGCCCGUA	150	UACGGGCA CUGAUGAGCCCGUUAGGCCGAA AGAACACA	377
1192	CUGCCCGU A AUUUAUCG	151	CGAUAAAU CUGAUGAGGCCGUUAGGCCGAA ACGGGCAC	378
1195	CCCGUAAU U UAUCGCGC	152	GCGCGAUA CUGAUGAGGCCGUUAGGCCGAA AUUACGGG	379
1196	CCGUAAUU U AUCGCGCU	153	AGCGCGAU CUCAUGAGGCCGUUAGGCCGAA AAUUACGG	380
1197	CGUAAUUU A UCGCUCUU	154	AAGCGCGA CUGAUGAGGCCGUUAGGCCGAA AAAUUACG	381
1199	UAAUUUAU C GCGCUUAC	155	GUAAGCGC CUGAUGAGGCCGUUAGGCCGAA AUAAAUUA	

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
1205	AUCGCGCU U ACUAUGGA	156	UCCAUAGU CUGAUGAGGCCGUUAGGCCGAA AGCGCGAU	383
1206	UCGCGCUU A CUAUGGAG	157	CUCCAUAG CUGAUGAGGCCGUUAGGCCGAA AAGCGCGA	384
1209	CGCUUACU A UGGAGCAU	158	AUGCUCCA CUGAUGAGGCCGUUAGGCCGAA AGUAAGCG	385
1218	UGGAGCAU U UAAGGAUG	159	CAUCCUUA CUGAUGAGGCCCUUAGGCCGAA AUGCUCCA	386
1219	GGAGCAUU U AAGGAUGU	160	ACAUCCUU CUGAUGAGGCCGUUAGGCCGAA AAUGCUCC	387
1220	GAGCAUUU A AGGAUGUC	161	GACAUCCU CUGAUGAGGCCGUUAGGCCGAA AAAUGCUC	388
1228	AAGGAUGU C AAGGAGAA	162	UUCUCCUU CUGAUGAGGCCGUUAGGCCGAA ACAUCCUC	389
1248	CAGGACCU C UGAAGAAG	163	CUUCUUCA CUGAUGAGGCCGUUAGGCCGAA AGGUCCUG	390
1267	GAAGACCU C CGAGCCUU	164	AAGGCUCG CUGAUGAGGCCGUUAGGCCGAA AGGUCUUC	391
1275	CCGAGCCU U GCGAUUUC	165	GAAAUCGC CUGAUGAGGCCGUUAGGCCGAA AGGCUCGG	392
1281	CUUGCGAU U UCUAUCUG	166	CAGAUAGA CUGAUGAGGCCGUUAGGCCGAA AUCGCAAG	393
1282	UUGCGAUU U CUAUCUGU	167	ACAGAUAG CUGAUGAGGCCGUUAGGCCGAA AAUCGCAA	394
1283	UGCGAUUU C UAUCUGUG	168	CACAGAUA CUGAUGAGGCCGUUAGGCCGAA AAAUCGCA	395
1285	CGAUUUCU A UCUGUGAU	169	AUCACAGA CUGAUGAGGCCGUUAGGCCGAA AGAAAUCG	396
1287	AUUUCUAU C UGUGAUUU	170	AAAUCACA CUGAUGAGGCCGUUAGGCCGAA AUAGAAAU	397
1294	UCUGUGAU U UCAAUUGU	171	ACAAUUGA CUGAUGAGGCCGUUAGGCCGAA AUCACAGA	398
1295	CUGUGAUU U CAAUUGUG	172	CACAAUUG CUGAUGAGGCCGUUAGGCCGAA AAUCACAG	399
1296	UGUGAUUU C AAUUGUGG	173C	CACAAUU CUGAUGAGGCCGUUAGGCCGAA AAAUCACA	400
1300	AUUUCAAU U GUGGACCC	174	GGGUCCAC CUGAUGAGGCCGUUAGGCCGAA AUUGAAAU	401
1310	UGGACCCU U GGAUUUUU	175	AAAAAUCC CUGAUGAGGCCGUUAGGCCGAA AGGGUCCA	402
1315	CCUUGGAU U UUUAUCAU	176	AUGAUAAA CUGAUGAGGCCGUUAGGCCGAA AUCCAAGG	403
1316	CUUGGAUU U UUAUCAUU	177	AAUGAUAA CUGAUGAGGCCGUUAGGCCGAA AAUCCAAG	404
1317	UUGGAUUU U UAUCAUUU	178	AAAUGAUA CUGAUGAGGCCGUUAGGCCGAA AAAUCCAA	405
1318	UGGAUUUU U AUCAUUUU	179	AAAAUGAU CUGAUGAGGCCGUUAGGCCGAA AAAAUCCA	406
1319	GGAUUUUU A UCAUUUUC	180	GAAAAUGA CUGAUGAGGCCGUUAGGCCGAA AAAAAUCC	407
1321	AUUUUUAU C AUUUUCAG	181	CUGAAAAU CUGAUGAGGCCGUUAGGCCGAA AUAAAAAU	408
1324	UUUAUCAU U UUCAGAUC	182	GAUCUGAA CUGAUGAGGCCGUUAGGCCGAA AUGAUAAA	409
1325	UUAUCAUU U UCAGAUCU	183	AGAUCUGA CUGAUGAGGCCGUUAGGCCGAA AAUGAUAA	410
1326	UAUCAUUU U CAGAUCUC	184	GAGAUCUG CUGAUGAGGCCGUUAGGCCGAA AAAUGAUA	411
1327	AUCAUUUU C AGAUCUCC	185	GGAGAUCU CUGAUGAGGCCGUUAGGCCGAA AAAAUGAU	412
1332	UUUCAGAU C UCCAGUAU	186	AUACUGGA CUGAUGAGGCCGUUAGGCCGAA AUCUGAAA	413
1334	UCAGAUCU C CAGUAUUU	187	AAAUACUG CUGAUGAGGCCGUUAGGCCGAA AGAUCUGA	414
1339	UCUCCAGU A UUUCGGAU	188	AUCCGAAA CUGAUGAGGCCGUUAGGCCGAA ACUGGAGA	415
1341	UCCAGUAU U UCGGAUAU	189	AUAUCCGA CUGAUGAGGCCGUUAGGCCGAA AUACUGGA	416
1342	CCAGUAUU U CGGAUAUU	190	AAUAUCCG CUGAUGAGGCCGUUAGGCCGAA AAUACUGG	417
1343	CAGUAUUU C GGAUAUUU	191	AAAUAUCC CUGAUGAGGCCGUUAGGCCGAA AAAUACUG	418

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
1348	UUUCGGAU A UUUUUUCA	192	UGAAAAAA CUGAUGAGGCCGUUAGGCCGAA AUCCGAAA	419
1350	UCGGAUAU U UUUUCACA	193	UGUGAAAA CUGAUGAGGCCGUUAGGCCGAA AUAUCCGA	420
1351	CGGAUAUU U UUUCACAA	194	UUGUGAAA CUGAUGAGGCCGUUAGGCCGAA AAUAUCCG	421
1352	GGAUAUUU U UUCACAAG	195	CUUGUGAA CUGAUGAGGCCGUUAGGCCGAA AAAUAUCC	422
1353	GAUAUUUU U UCACAAGA	196	UCUUGUGA CUGAUGAGGCCGUUAGGCCGAA AAAAUAUC	423
1354	AUAUUUUU U CACAAGAU	197	AUCUUGUG CUGAUGAGGCCGUUAGGCCGAA AAAAAUAU	424
1355	UAUUUUUU C ACAAGAUU	198	AAUCUUGU CUGAUGAGGCCGUUAGGCCGAA AAAAAAUA	425
1363	CACAAGAU U UUCAUUAG	199	CUAAUGAA CUGAUGAGGCCGUUAGGCCGAA AUCUUGUG	426
1364	ACAAGAUU U UCAUUAGA	200	UCUAAUGA CUGAUGAGGCCGUUAGGCCGAA AAUCUUGU	427
1365	CAAGAUUU U CAUUAGAC	201	GUCUAAUG CUGAUGAGGCCGUUAGGCCGAA AAAUCUUG	428
1366	AAGAUUUU C AUUAGACC	202	CGUCUAAU CUGAUGAGGCCGUUACGCCGAA AAAAUCUU	429
1369	AUUUUCAU U AGACCUCU	203	AGAGGUCU CUGAUGAGGCCGUUAGGCCGAA AUGAAAAU 430	
1370	UUUUCAUU A GACCUCUU	204	AAGAGGUC CUGAUGAGGCCGUUAGGCCGAA AAUGAAAA 431	
1376	UUAGACCU C UUAGGUAC	205	GUACCUAA CUGAUGAGGCCGUUAGGCCGAA AGGUCUAA	432
1378	AGACCUCU U AGGUACAG	206	CUGUACCU CUGAUGAGGCCGUUAGGCCGAA AGAGGUCU	433
1379	GACCUCUU A GGUACAGG	207	CCUGUACC CUGAUGAGGCCGUUAGGCCGAA AAGAGGUC	434
1383	UCUUAGGU A CAGGAGCC	208	GGCUCCUG CUGAUGAGGCCGUUAGGCCGAA ACCUAAGA	435
1403	GCAGCAAU U CCACUAAC	209	GUUAGUGG CUGAUGAGGCCGUUAGGCCGAA AUUGCUGC	436
1404	CAGCAAUU C CACUAACA	210	UGUUAGUG CUGAUGAGGCCGUUAGGCCGAA AAUUGCUG	437
1409	AUUCCACU A ACAUGGAA	211	UUCCAUGU CUGAUGAGGCCGUUAGGCCGAA AGUGGAAU	438
1419	CAUGGAAU C CAGUCUGU	212	ACAGACUG CUGAUGAGGCCGUUAGGCCGAA AUUCCAUG	439
1424	AAUCCAGU C UGUGACAG	213	CUGUCACA CUGAUGAGGCCGUUAGGCCGAA ACUGGAUU	440
1436	GACAGUGU U UUUCACUC	214	GAGUGAAA CUGAUGAGGCCGUUAGGCCGAA ACACUGUC	441
1437	ACAGUGUU U UUCACUCU	215	AGAGUGAA CUGAUGAGGCCGUUAGGCCGAA AACACUGU	442
1438	CAGUGUUU U UCACUCUG	216	CAGAGUGA CUGAUGAGGCCGUUAGGCCGAA AAACACUG	443
1439	AGUGUUUU U CACUCUGU	217	ACAGAGUG CUGAUGAGGCCGUUAGGCCGAA AAAACACU	444
1440	GUGUUUUU C ACUCUGUG	218	CACAGAGU CUGAUGAGGCCGUUAGGCCGAA AAAAACAC	445
1444	UUUUCACU C UGUGGUAA	219	UUACCACA CUGAUGAGGCCGUUAGGCCGAA AGUGAAAA	446
1451	UCUGUGGU A AGCUGAGG	220	CCUCAGCU CUGAUGAGGCCGUUAGGCCGAA ACCACAGA	447
1463	UGAGGAAU A UGUCACAU	221	AUGUGACA CUGAUGAGGCCGUUAGGCCGAA AUUCCUCA	448
1467	GAAUAUGU C ACAUUUUC	222	GAAAAUGU CUGAUGAGGCCGUUAGGCCGAA ACAUAUUC	449
1472	UGUCACAU U UUCAGUCA	223	UGACUGAA CUGAUGAGGCCGUUAGGCCGAA AUGUGACA	450
1473	GUCACAUU U UCAGUCAA	224	UUGACUGA CUGAUGAGGCCGUUAGGCCGAA AAUGUGAC	451
1474	UCACAUUU U CAGUCAAA	225	UUUGACUG CUGAUGAGGCCGUUAGGCCGAA AAAUGUGA	452

TABLE III-continued

Human PTGDR Hammerhead Ribozyme and Substrate Sequence

Pos	Substrate	Seq ID	Hammerhead Ribozyme	Seq ID
1475	CACAUUUU C AGUCAAAG	226	CUUUGACU CUGAUGAGGCCGUUAGGCCGAA AAAAUGUG	453
1479	UUUUCAGU C AAAGAACC	227	GGUUCUUU CUGAUGAGGCCGUUAGGCCGAA ACUGAAAA	454

Input Sequence = PTGDR_composit.
Cut Site = UH/.
Arm Length = 8.
Core Sequence = CUGAUGAG GCCGUUAGGC CGAA
PTGDR_composit (1 to 993 of HSU31332 (PTGDR 5')+1 to 495 of HSU31099 (PTGDR 3'); 1488 nt)
Underlined region can be any X sequence or linker, as described herein.

[0231]

TABLE IV

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
11	AUUCUGGC U AUUUUCCU	455	AGGAAAAU CUGAUGAGGCCGUUAGGCCGAA ICCAGAAU	831
18	CUAUUUUC C UCCUGCCG	456	CGGCAGGA CUGAUGAGGCCGUUAGGCCGAA IAAAAUAG	832
19	UAUUUUCC U CCUGCCGU	457	ACGGCAGG CUGAUGAGGCCGUUAGGCCGAA IGAAAAUA	833
21	UUUUCCUC C UGCCGUUC	458	GAACGGCA CUGAUGAGGCCGUUAGGCCGAA IAGGAAAA	834
22	UUUCCUCC U GCCGUUCC	459	GGAACGGC CUGAUGAGGCCGUUAGGCCGAA IGAGGAAA	835
25	CCUCCUGC C GUUCCGAC	460	GUCGGAAC CUGAUCACGCCGUUAGGCCCAA ICAGGAGG	836
30	UGCCGUUC C GACUCCUC	461	GCCGAGUC CUGAUGAGGCCGUUAGGCCGAA IAACGGCA	837
34	GUUCCGAC U CGGCACCA	462	UGGUGCCG CUGAUGAGGCCGUUAGGCCGAA IUCGGAAC	838
39	GACUCGGC A CCAGAGUC	463	GACUCUGG CUGAUGAGGCCGUUAGGCCGAA ICCGAGUC	839
41	CUCGGCAC C AGAGUCUG	464	CAGACUCU CUGAUGAGGCCGUUAGGCCGAA IUGCCGAG	840
42	UCGGCACC A GAGUCUGU	465	ACAGACUC CUGAUGAGGCCGUUAGGCCGAA IGUGCCGA	841
48	CCAGAGUC U GUCUCUAC	466	GUAGAGAC CUGAUGAGGCCGUUAGGCCGAA IACUCUGG	842
52	AGUCUGUC U CUACUGAG	467	CUCAGUAG CUGAUGAGGCCGUUAGGCCGAA IACAGACU	843
54	UCUGUCUC U ACUGAGAA	468	UUCUCAGU CUGAUGAGGCCGUUAGGCCGAA IAGACAGA	844
57	GUCUCUAC U GAGAACGC	469	GCGUUCUC CUGAUGAGGCCGUUAGGCCGAA IUAGAGAC	845
66	GAGAACGC A GCGCGUCA	470	UGACGCGC CUGAUGAGGCCGUUAGGCCGAA ICGUUCUC	846
74	AGCGCGUC A GGGCCGAG	471	CUCGGCCC CUGAUGAGGCCGUUAGGCCGAA IACGCGCU	847
79	GUCAGGGC C GAGCUCUU	472	AAGAGCUC CUGAUGAGGCCGUUAGGCCGAA ICCCUGAC	848
84	GGCCGAGC U CUUCACUG	473	CAGUGAAG CUGAUGAGGCCGUUAGGCCGAA ICUCGGCC	849
86	CCGAGCUC U UCACUGGC	474	GCCAGUGA CUGAUGAGGCCGUUAGGCCGAA IAGCUCGG	850
89	AGCUCUUC A CUGGCCUG	475	CAGGCCAG CUGAUGAGGCCGUUAGGCCGAA IAAGAGCU	851
91	CUCUUCAC U GGCCUGCU	476	AGCAGGCC CUGAUGAGGCCGUUAGGCCGAA IUGAAGAG	852
95	UCACUGGC C UGCUCCGC	477	GCGGAGCA CUGAUGAGGCCGUUAGGCGGAA ICCAGUGA	853
96	CACUGGCC U GCUCCGCG	478	CGCGGAGC CUGAUGAGGCCGUUAGGCCGAA IGCCAGUG	854

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
99	UGGCCUGC U CCGCGCUC	479	GAGCGCGG CUGAUGAGGCCGUUAGGCCGAA ICAGGCCA	855
101	GCCUGCUC C GCGCUCUU	480	AAGAGCGC CUGAUGAGGCCGUUAGGCCGAA IAGCAGGC	856
106	CUCCGCGC U CUUCAAUG	481	CAUUGAAG CUGAUGAGGCCGUUAGGCCGAA ICGCGGAG	857
108	CCGCGCUC U UCAAUGCC	482	GGCAUUGA CUGAUGAGGCCGUUAGGCCGAA IAGCGCGG	858
111	CGCUCUUC A AUGCCAGC	483	GCUGGCAU CUGAUGAGGCCGUUAGGCCGAA IAAGAGCG	859
116	UUCAAUGC C AGCGCCAG	484	CUGGCGCU CUGAUGAGGCCGUUAGGCCGAA ICAUUGAA	860
117	UCAAUGCC A GCGCCAGG	485	CCUGGCGC CUGAUGAGGCCGUUAGGCCGAA IGCAUUGA	861
122	GCCAGCGC C AGGCGCUC	486	GAGCGCCU CUGAUGAGGCCGUUAGGCCGAA ICGCUGGC	862
123	CCAGCGCC A GGCGCUCA	487	UGAGCGCC CUGAUGAGGCCGUUAGGCCGAA IGCGCUGG	863
129	CCAGGCGC U CACCCUGC	488	GCAGGGUG CUGAUGAGGCCGUUAGGCCGAA ICGCCUGG	864
131	AGGCGCUC A CCCUGCAG	489	CUGCAGGG CUGAUGAGGCCGUUAGGCCGAA IAGCGCCU	865
133	GCGCUCAC C CUGCAGAG	490	CUCUGCAG CUGAUGAGGCCGUUAGGCCGAA IUGAGCGC	866
134	CGCUCACC C UGCAGAGC	491	GCUCUGCA CUGAUGAGGCCGUUAGGCCGAA IGUGAGCG	867
135	GCUCACCC U GCAGAGCG	492	CGCUCUGC CUGAUGAGGCCGUUAGGCCGAA IGGUGAGC	868
138	CACCCUGC A GAGCGUCC	493	GGACGCUC CUGAUGAGGCCGUUAGGCCGAA ICAGGGUG	869
146	AGAGCGUC C CGCCUCUC	494	GAGAGGCG CUGAUGAGGCCGUUAGGCCGAA IACGCUCU	870
147	GAGCGUCC C GCCUCUCA	495	UGAGAGGC CUGAUGAGGCCGUUAGGCCGAA IGACGCUC	871
150	CGUCCCGC C UCUCAAAG	496	CUUUGAGA CUGAUGAGGCCGUUAGGCCGAA ICGGGACG	872
151	GUCCCGCC U CUCAAAGA	497	UCUUUGAG CUGAUGAGGCCGUUAGGCCGAA IGCGGGAC	873
153	CCCGCCUC U CAAAGAGG	498	CCUCUUUG CUGAUGAGGCCGUUAGGCCGAA IAGGCGGG	874
155	CGCCUCUC A AAGAGGGG	499	CCCCUCUU CUGAUGAGGCCGUUAGGCCGAA IAGAGGCG	875
170	GGUGUGAC C CGCGAGUU	500	AACUCGCG CUGAUGAGGCCGUUAGGCCGAA IUCACACC	876
171	GUGUGACC C GCGAGUUU	501	AAACUCGC CUGAUGAGGCCGUUAGGCCGAA IGUCACAC	877
193	GGAGGUUC C UGCCCUCG	502	CCACGGCA CUCAUGAGGCCGUUAGGCCGAA IAACCUCC	878
194	GACGUUCC U GCCGUGGG	503	CCCACGGC CUGAUGAGGCCGUUAGGCCGAA IGAACCUC	879
197	GUUCCUGC C GUGGGGAA	504	UUCCCCAC CUGAUGAGGCCGUUAGGCCGAA ICAGGAAC	880
207	UGCGGAAC A CCCCGCCG	505	CCGCGGGG CUGAUGAGGCCGUUAGGCCGAA IUUCCCCA	881
209	GGGAACAC C CCGCCGCC	506	GGCGGCGG CUGAUGAGGCCGUUAGGCCGAA IUGUUCCC	882
210	GGAACACC C CGCCGCCC	507	GGGCCGCG CUGAUGAGGCCGUUAGGCCGAA IGUGUUCC	883
211	GAACACCC C GCCGCCCU	508	AGGGCGGC CUCAUGAGGCCGUUAGGCCGAA IGGUGUUC	884
214	CACCCCGC C GCCCUCGG	509	CCGAGGGC CUGAUGAGGCCGUUAGGCCGAA ICGGGGUG	885
217	CCCGCCCC C CUCGGAGC	510	GCUCCGAG CUGAUGAGGCCGUUAGGCCGAA ICGGCGGG	886
218	CCGCCGCC C UCGGAGCU	511	AGCUCCGA CUGAUGAGGCCGUUAGGCCGAA IGCGGCGG	887
219	CGCCGCCC U CGGAGCUU	512	AAGCUCCG CUGAUGAGGCCGUUAGGCCGAA IGGCGGCG	888
226	CUCGGAGC U UUUUCUGU	513	ACAGAAAA CUGAUGAGGCCGUUAGGCCGAA ICUCCGAG	889

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
232	GCUUUUUC U GUGGCGCA	514	UGCGCCAC CUGAUGAGGCCGUUAGGCCGAA IAAAAAGC	890
240	UGUGGCGC A GCUUCUCC	515	GGAGAAGC CUGAUGAGGCCGUUAGGCCGAA ICGCCACA	891
243	GGCGCAGC U UCUCCGCC	516	GGCGGAGA CUGAUGAGGCCGUUAGGCCGAA ICUGCGCC	892
246	GCAGCUUC U CCGCCCGA	517	UCGGGCGG CUGAUGAGGCCGUUAGGCCGAA IAAGCUGC	893
248	AGCUUCUC C GCCCGAGC	518	GCUCGGGC CUGAUGAGGCCGUUAGGCCGAA IAGAAGCU	894
251	UUCUCCGC C CGAGCCGC	519	GCGGCUCG CUGAUGAGGCCGUUAGGCCGAA ICGGAGAA	895
252	UCUCCGCC C GAGCCGCG	520	CGCGGCUC CUGAUGAGGCCGUUAGGCCGAA ICCUGAGA	896
257	GCCCGAGC C GCGCGCGG	521	CCGCGCGC CUGAUGAGGCCGUUAGGCCGAA ICUCGGGC	897
269	CGCGGAGC U GCCGGGGG	522	CCCCCGGC CUGAUGAGGCCGUUAGGCCGAA ICUCCGCG	898
272	GGAGCUGC C GGGGGCUC	523	GAGCCCCC CUGAUGAGGCCGUUAGGCCGAA ICAGCUCC	899
279	CCGGGGGC U CCUUAGCA	524	UGCUAAGG CUGAUGAGGCCGUUAGGCCGAA ICCCCCGG	900
281	GGGGGCUC C UUAGCACC	525	GGUGCUAA CUGAUGAGGCCGUUAGGCCGAA IAGCCCCC	901
282	GGGGCUCC U UAGCACCC	526	GGGUGCUA CUGAUGAGGCCGUUAGGCCGAA IGAGCCCC	902
287	UCCUUAGC A CCCGGGCG	527	CGCCCGGG CUGAUGAGGCCGUUAGGCCGAA ICUAAGGA	903
289	CUUAGCAC C CGGGCGCC	528	GGCGCCCG CUGAUGAGGCCGUUAGGCCGAA IUGCUAAG	904
290	UUAGCACC C GGGCGCCG	529	CGGCGCCC CUGAUGAGGCCGUUAGGCCGAA IGUGCUAA	905
297	CCGGGCGC C GGGGCCCU	530	AGGGCCCC CUGAUGAGGCCGUUAGGCCGAA ICGCCCGG	906
303	GCCGGGGC C CUCGCCCU	531	AGGGCGAG CUGAUGAGGCCGUUAGGCCGAA ICCCCGGC	907
304	CCGGGGCC C UCGCCCUU	532	AAGGGCGA CUGAUGAGGCCGUUAGGCCGAA IGCCCCGG	908
305	CGGGGCCC U CGCCCUUC	533	GAAGGGCG CUGAUGAGGCCGUUAGGCCGAA IGGCCCCG	909
309	GCCCUCGC C CUUCCGCA	534	UGCGGAAG CUGAUGAGGCCGUUAGGCCGAA ICGAGGGC	910
310	CCCUCGCC C UUCCGCAG	535	CUGCGGAA CUGAUGAGGCCGUUAGGCCGAA IGCGAGGG	911
311	CCUCGCCC U UCCGCAGC	536	GCUGCGGA CUGAUGAGGCCGUUAGGCCGAA IGGCGAGG	912
314	CGCCCUUC C GCAGCCUU	537	AAGGCUGC CUGAUGAGGCCGUUAGGCCGAA IAAGGGCG	913
317	CCUUCCGC A GCCUUCAC	538	GUGAAGGC CUGAUGAGGCCGUUAGGCCGAA ICGGAAGG	914
320	UCCGCAGC C UUCACUCC	539	GGAGUGAA CUGAUGAGGCCGUUAGGCCGAA ICUGCGGA	915
321	CCGCAGCC U UCACUCCA	540	UGGAGUGA CUGAUGAGGCCGUUAGGCCGAA IGCUGCGG	916
324	CAGCCUUC A CUCCAGCC	541	GGCUGGAG CUGAUGAGGCCGUUAGGCCGAA IAAGGCUG	917
326	GCCUUCAC U CCAGCCCU	542	AGGGCUGG CUGAUGAGGCCGUUAGGCCGAA IUGAAGGC	918
328	CUUCACUC C AGCCCUCU	543	AGAGGGCU CUGAUGAGGCCGUUAGGCCGAA IAGUGAAG	919
329	UUCACUCC A GCCCUCUG	544	CAGAGGGC CUGAUGAGGCCGUUAGGCCGAA IGAGUGAA	920
332	ACUCCAGC C CUCUGCUC	545	GAGCAGAG CUGAUGAGGCCGUUAGGCCGAA ICUGGAGU	921
333	CUCCAGCC C UCUGCUCC	546	GGAGCAGA CUGAUGAGGCCGUUAGGCCGAA IGCUGGAG	922
334	UCCAGCCC U CUGCUCCC	547	GGGAGCAG CUGAUGAGGCCGUUAGGCCGAA IGGCUGGA	923
336	CAGCCCUC U GCUCCCGC	548	GCGGGAGC CUGAUGAGGCCGUUAGGCCGAA IAGGGCUG	924
339	CCCUCUGC U CCCGCACG	549	CGUGCGGG CUGAUGAGGCCGUUAGGCCGAA ICAGAGGG	925

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
341	CUCUGCUC C CGCACGCC	550	GGCGUGCG CUGAUGAGGCCGUUAGGCCGAA IAGCAGAG	926
342	UCUGCUCC C GCACGCCA	551	UGGCGUGC CUGAUGAGGCCGUUAGGCCGAA IGAGCAGA	927
345	GCUCCCGC A CGCCAUGA	552	UCAUGGCG CUGAUGAGGCCGUUAGGCCGAA ICGGGAGC	928
349	CCGCACGC C AUGAAGUC	553	GACUUCAU CUGAUGACCCCGUUAGGCCGAA ICGUGCGC	929
350	CGCACGCC A UGAAGUCG	554	CGACUUCA CUGAUGAGGCCGUUAGGCCGAA IGCGUGCG	930
360	GAAGUCGC C GUUCUACC	555	GGUAGAAC CUGAUGAGGCCGUUAGGCCGAA ICGACUUC	931
365	CGCCGUUC U ACCGCUGC	556	GCACCGGU CUGAUGAGGCCGUUAGGCCGAA IAACGGCG	932
368	CGUUCUAC C GCUGCCAG	557	CUGGCAGC CUGAUGAGGCCGUUAGGCCGAA IUAGAACG	933
371	UCUACCUC U GCCAGAAC	558	GUUCUGGC CUGAUGAGGCCGUUAGGCCGAA ICOGUAGA	934
374	ACCGCUGC C AGAACACC	559	GGUGUUCU CUGAUGAGGCCGUUAGGCCGAA ICAGCGGU	935
375	CCGCUGCC A GAACACCA	560	UGGUGUUC CUGAUGAGGCCGUUAGGCCGAA IGCAGCGG	936
380	GCCAGAAC A CCACCUCU	561	AGAGGUGG CUGAUGAGGCCGUUAGGCCGAA IUUCUGGC	937
382	CAGAACAC C ACCUCUGU	562	ACAGAGGU CUGAUGAGGCCGUUAGGCCGAA IUGUUCUG	938
383	AGAACACC A CCUCUGUG	563	CACAGAGG CUGAUGAGGCCGUUAGGCCGAA IGUGUUCU	939
385	AACACCAC C UCUGUGGA	564	UCCACAGA CUGAUGAGGCCGUUAGGCCGAA IUGGUGUU	940
386	ACACCACC U CUGUGGAA	565	UUCCACAG CUGAUGAGGCCGUUAGGCCGAA IGUGGUGU	941
388	ACCACCUC U GUGGAAAA	566	UUUUCCAC CUGAUGAGGCCGUUAGGCCGAA IAGGUGGU	942
401	AAAAAGGC A ACUCGGCG	567	CGCCGAGU CUGAUGAGGCCGUUAGGCCGAA ICCUUUUU	943
404	AAGGCAAC U CGGCGGUG	568	CACCGCCG CUGAUGAGGCCGUUAGGCCGAA IUUGCCUU	944
426	CGGGGUGC U CUUCAGCA	569	UGCUGAAG CUGAUGAGGCCGUUAGGCCGAA ICACCCCG	945
428	GGGUGCUC U UCAGCACC	570	GGUGCUGA CUGAUGAGGCCGUUAGGCCGAA IAGCACCC	946
431	UGCUCUUC A GCACCGGC	571	GCCGGUGC CUGAUGAGGCCGUUAGGCCGAA IAAGAGCA	947
434	UCUUCAGC A CCGGCCUC	572	GAGGCCGG CUGAUGAGGCCGUUAGGCCGAA ICUGAAGA	948
436	UUCAGCAC C GGCCUCCU	573	AGGAGGCC CUGAUGAGGCCGUUAGGCCGAA IUGCUGAA	949
440	GCACCGGC C UCCUGGGC	574	GCCCAGGA CUGAUGAGGCCGUUAGGCCGAA ICCGGUGC	950
441	CACCGGCC U CCUGGGCA	575	UGCCCAGG CUGAUGAGGCCGUUAGGCCGAA IGCCGGUG	951
443	CCGGCCUC C UGGGCAAC	576	GUUGCCCA CUGAUGAGGCCGUUAGGCCGAA IAGGCCGG	952
444	CGGCCUCC U GGGCAACC	577	GGUUGCCC CUGAUGAGGCCGUUAGGCCGAA IGAGGCCG	953
449	UCCUGGGC A ACCUGCUG	578	CAGCAGGU CUGAUGAGGCCGUUAGGCCGAA ICCCAGGA	954
452	UGGGCAAC C UGCUGGCC	579	GGCCAGCA CUGAUGAGGCCGUUAGGCCGAA IUUGCCCA	955
453	GGGCAACC U GCUGGCCC	580	GGGCCAGC CUGAUGAGGCCGUUAGGCCGAA IGUUGCCC	956
456	CAACCUGC U GGCCCUGG	581	CCAGGGCC CUGAUGAGGCCGUUAGGCCGAA ICAGGUUG	957
460	CUGCUGGC C CUGGGGCU	582	AGCCCCAG CUGAUGAGGCCGUUAGGCCGAA ICCAGCAG	958
461	UGCUGGCC C UGGGGCUG	583	CAGCCCCA CUGAUGAGGCCGUUAGGCCGAA IGCCAGCA	959
462	GCUGGCCC U GGGGCUGC	584	GCAGCCCC CUGAUGAGGCCGUUAGGCCGAA IGGCCAGC	960

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
468	CCUGGGGC U GCUGGCGC	585	GCGCCAGC CUGAUGAGGCCGUUAGGCCGAA ICCCCAGG	961
471	GGGGCUGC U GGCGCGCU	586	AGCGCGCC CUGAUGAGGCCGUUAGGCCGAA ICAGCCCC	962
479	UGGCGCGC U CGGGGCUG	587	CAGCCCCG CUGAUGAGGCCGUUAGGCCGAA ICGCGCCA	963
486	CUCGGGGC U GGGGUGGU	588	ACCACCCC CUGAUGAGGCCGUUAGGCCGAA ICCCCGAG	964
497	GGUGGUGC U CGCGGCGU	589	ACGCCGCG CUGAUGAGGCCGUUAGGCCGAA ICACCACC	965
507	GCGGCGUC C ACUGCGCC	590	GGCGCAGU CUGAUGAGGCCGUUAGGCCGAA IACGCCGC	966
508	CGGCGUCC A CUGCGCCC	591	GGGCGCAG CUGAUGAGGCCGUUAGGCCGAA IGACGCCG	967
510	GCGUCCAC U GCGCCCGC	592	GCGGGCGC CUGAUGAGGCCGUUAGGCCGAA IUGGACGC	968
515	CACUGCGC C CGCUGCCC	593	GGGCAGCG CUGAUGAGGCCGUUAGGCCGAA ICGCAGUG	969
516	ACUGCGCC C GCUGCCCU	594	AGGGCAGC CUGAUGAGGCCGUUAGGCCGAA IGCGCAGU	970
519	GCGCCCGC U GCCCUCGG	595	CCGAGGGC CUGAUGAGGCCGUUAGGCCGAA ICGGGCGC	971
522	CCCGCUGC C CUCGGUCU	596	AGACCGAG CUGAUGAGGCCGUUAGGCCGAA ICAGCGGG	972
523	CCGCUGCC C UCGGUCUU	597	AAGACCGA CUGAUGAGGCCGUUAGGCCGAA IGCAGCGG	973
524	CGCUGCCC U CGGUCUUC	598	GAAGACCG CUGAUGAGGCCGUUAGGCCGAA IGGCAGCG	974
530	CCUCGGUC U UCUACAUG	599	CAUGUAGA CUGAUGAGGCCGUUAGGCCGAA IACCGAGG	975
533	CGGUCUUC U ACAUGCUG	600	CAGCAUGU CUGAUGAGGCCGUUAGGCCGAA IAAGACCG	976
536	UCUUCUAC A UGCUGGUG	601	CACCAGCA CUGAUGAGGCCGUUAGGCCGAA IUAGAAGA	977
540	CUACAUGC U GGUGUGUG	602	CACACACC CUGAUGAGGCCGUUAGGCCGAA ICAUGUAG	978
551	UGUGUGGC C UGACGGUC	603	GACCGUCA CUGAUGAGGCCGUUAGGCCGAA ICCACACA	979
552	GUGUGGCC U GACGGUCA	604	UGACCGUC CUGAUGAGGCCGUUAGGCCGAA IGCCACAC	980
560	UGACGGUC A CCGACUUG	605	CAAGUCGG CUGAUGAGGCCGUUAGGCCGAA IACCGUCA	981
562	ACGGUCAC C GACUUCCU	606	AGCAAGUC CUGAUCAGGCCGUUAGGCCGAA IUGACCGU	982
566	UCACCGAC U UGCUGGGC	607	GCCCAGCA CUGAUGAGGCCGUUAGGCCGAA IUCCGUGA	983
570	CGACUUCC U GCCCAAGU	608	ACUUGCCC CUGAUGAGGCCGUUAGGCCGAA ICAAGUCG	984
575	UGCUGGGC A AGUGCCUC	609	GAGGCACU CUGAUGAGGCCGUUAGGCCGAA ICCCAGCA	985
581	CCAAGUGC C UCCUAAGC	610	GCUUACGA CUGAUGAGGCCGUUAGGCCGAA ICACUUGC	986
582	CAAGUGCC U CCUAAGCC	611	GGCUUAGG CUGAUCACGCCGUUAGGCCGAA IGCACUUG	987
584	AGUGCCUC C UAAGCCCG	612	CGGGCUUA CUGAUGAGGCCGUUAGGCCGAA IAGGCACU	988
585	GUGCCUCC U AAGCCCGG	613	CCGGGCUU CUGAUGAGGCCGUUAGGCCGAA IGAGGCAC	989
590	UCCUAAGC C CGGUGGUG	614	CACCACCG CUGAUGAGGCCGUUAGGCCGAA ICUUAGGA	990
591	CCUAAGCC C CGUGGUGC	615	GCACCACC CUGAUGAGGCCGUUAGGCCGAA IGCUUAGG	991
600	GGUGGUGC U GGCUGCCU	616	AGGCAGCC CUGAUGAGGCCGUUAGGCCGAA ICACCACC	992
604	GUGCUCGC U CCCUACGC	617	GCGUAGGC CUCAUCAGGCCUUUAGGCCGAA ICCAGCAC	993
607	CUGGCUGC C UACGCUCA	618	UGAGCGUA CUGAUGAGGCCGUUAGGCCCAA ICAGCCAG	994
608	UCGCUGCC U ACGCUCAG	619	CUGACCGU CUGAUGAGGCCGUUAGGCCGAA IGCAGCCA	995
613	GCCUACGC U CAGAACCC	620	CGGUUCUG CUGAUGAGGCCGUUAGGCCGAA ICGUAGGC	996

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
615	CUACGCUC A GAACCGGA	621	UCCGGUUC CUGAUGAGGCCGUUAGGCCGAA IAGCGUAG	997
620	CUCAGAAC C GGAGUCUG	622	CAGACUCC CUGAUGAGGCCGUUAGGCCGAA IUUCUGAG	998
627	CCGGAGUC U GCGGGUGC	623	GCACCCGC CUGAUGAGGCCGUUAGGCCGAA IACUCCGG	999
636	GCCGGUGC U UGCGCCCG	624	CGGGCCCA CUGAUGAGGCCGUUAGGCCGAA ICACCCCC	1000
642	GCUUGCGC C CGCAUUGG	625	CCAAUGCG CUGAUGAGGCCGUUAGGCCGAA ICGCAAGC	1001
643	CUUCCGCC C GCAUUGGA	626	UCCAAUGC CUGAUGAGGCCGUUAGGCCGAA IGCGCAAC	1002
646	GCGCCCGC A UUGGACAA	627	UUGUCCAA CUGAUGAGGCCGUUACGCCGAA ICGGGCGC	1003
653	CAUUGCAC A ACUCGUUG	628	CAACGAGU CUGAUGAGGCCGUUAGGCCGAA IUCCAAUG	1004
656	UGGACAAC U CGUUGUGC	629	GCACAACG CUGAUGAGGCCGUUAGGCCGAA IUUGUCCA	1005
665	CGUUGUGC C AAGCCUUC	630	CAAGCCUU CUGAUGAGGCCGUUAGGCCGAA ICACAACG	1006
666	GUUGUGCC A AGCCUUCG	631	CGAAGGCU CUGAUGAGGCCGUUAGGCCGAA IGCACAAC	1007
670	UGCCAAGC C UUCGCCUU	632	AAGGCGAA CUGAUGAGGCCGUUACGCCCAA ICUUGGCA	1008
671	GCCAAGCC U UCGCCUUC	633	GAACGCGA CUGAUGAGGCCGUUAGGCCGAA IGCUUCGC	1009
676	GCCUUCGC C UUCUUCAU	634	AUGAAGAA CUGAUGAGCCCGUUAGGCCGAA ICGAAGGC	1010
677	CCUUCGCC U UCUUCAUG	635	CAUGAAGA CUGAUGAGGCCGUUAGGCCGAA IGCGAAGG	1011
680	UCGCCUUC U UCAUGUCC	636	GGACAUGA CUGAUGAGGCCGUUAGGCCGAA IAAGGCGA	1012
683	CCUUCUUC A UGUCCUUC	637	GAAGGACA CUGAUGAGGCCGUUAGGCCGAA IAAGAAGG	1013
688	UUCAUGUC C UUCUUUGG	638	CCAAAGAA CUGAUGAGGCCGUUAGGCCGAA IACAUGAA	1014
689	UCAUGUCC U UCUUUGGG	639	CCCAAAGA CUGAUGAGGCCGUUAGGCCGAA IGACAUGA	1015
692	UGUCCUUC U UUGGGCUC	640	GAGCCCAA CUGAUGAGGCCGUUAGGCCGAA IAAGGACA	1016
699	CUUUGGGC U CUCCUCCA	641	UCGAGGAG CUGAUGAGGCCGUUAGGCCGAA ICCCAAAG	1017
701	UUGGGCUC U CCUCGACA	642	UGUCGAGG CUGAUGAGGCCGUUAGGCCGAA IAGCCCAA	1018
703	GGGCUCUC C UCGACACU	643	AGUGUCGA CUGAUGAGGCCGUUAGGCCGAA IAGAGCCC	1019
704	GGCUCUCC U CGACACUG	644	CAGUGUCG CUGAUGAGGCCGUUAGGCCGAA IGAGAGCC	1020
709	UCCUCGAC A CUGCAACU	645	AGUUGCAG CUGAUGAGGCCGUUAGGCCGAA IUCGAGGA	1021
721	CUCGACAC U GCAACUCC	646	GGAGUUGC CUGAUGAGGCCGUUAGGCCGAA IUGUCGAG	1022
714	GACACUGG A ACUCCUGG	647	CCAGGAGU CUGAUGAGGCCGUUAGGCCGAA ICAGUGUC	1023
717	ACUGCAAC U CCUGGCCA	648	UGGCCAGG CUGAUGAGGCCGUUAGGCCGAA IUUGCAGU	1024
719	UGCAACUC C UGGCCAUG	649	CAUGGCCA CUGAUGAGGCCGUUAGGCCGAA IAGUUGCA	1025
720	GCAACUCC U GGCCAUGG	650	CCAUGGCC CUGAUGAGGCCGUUAGGCCGAA IGAGUUGC	1026
724	CUCCUGGC C AUGGCACU	651	AGUGCCAU CUGAUGAGGCCGUUAGGCCGAA ICCAGGAG	1027
725	UCCUGGCC A UGGCACUG	652	CAGUGCCA CUGAUGAGGCCGUUAGGCCGAA IGCCAGGA	1028
730	GCCAUGGC A CUGGAGUG	653	CACUCCAG CUGAUGAGGCCGUUAGGCCGAA ICCAUGGC	1029
732	CAUGGCAC U GGAGUGCU	654	AGCACUCC CUGAUGAGGCCGUUAGGCCGAA IUGCCAUG	1030
740	UCGAGUGC U GGCUCUCC	655	GGAGAGCC CUGAUGAGGCCGUUAGGCCGAA ICACUCCA	1031

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
744	GUGCUGGC U CUCCCUAG	656	CUAGGGAG CUGAUGAGGCCGUUAGGCCGAA ICCAGCAC	1032
746	GCUGCCUC U CCCUAGGG	657	CCCUAGGG CUGAUGAGGCCGUUAGGCCGAA IAGCCAGC	1033
748	UGGCUCUC C CUAGOCCA	658	UGCCCUAG CUGAUGAGGCCGUUAGGCCGAA IAGAGCCA	1034
749	GGCUCUCC C UAGGGCAC	659	GUCCCCUA CUGAUGAGGCCGUUAGGCCGAA IGAGAGCC	1035
750	GCUCUCCC U AGGGCACC	660	GGUGCCCU CUGAUGAGGCCGUUAGGCCGAA IGGAGAUC	1036
756	CCUAGGGC A CCCUUIJCU	661	AGAAAGGG CUGAUGAGGCCGUUAGGCCGAA ICCCUAGG	1037
758	UAGGGCAC C CUUUCUUC6	62	GAAGAAAG CUGAUGAGGCCGUUAGGCCGAA IUGCCCUA	1038
759	AGGGCACC C UUUCUUCU	663	AGAAGAAA CUGAUGAGGCCGUUAGGCCGAA IGUGCCCU	1039
760	GGGCACCC U UUCUUCUA	664	UAGAAGAA CUGAUGAGGCCGUUAGGCCGAA IGGUGCCC	1040
764	ACCCUUUC U UCUACCGA	665	UCGGUAGA CUGAUGAGGCCGUUAGGCCGAA TAAAGGGU	1041
767	CUUUCUUC U ACCGACGG	666	CCGUCGGU CUGAUGAGGCCGUUAGGCCGAA IAAGAAAG	1042
770	UCUUCUAC C GACGGCAC	667	GUGCCGUC CUGAUGAGCCCGUUAGGCCGAA IUAGAAGA	1043
777	CCGACGGC A CAUCACCC	668	GGGUGAUG CUGAUGAGGCCGUUAGGCCGAA ICCGUCGG	1044
779	GACGGCAC A UCACCCUG	669	CAGGGUGA CUGAUGAGGCCGUUAGGCCGAA IUGCCGUC	1045
782	GGCACAUC A CCCUGCGC	670	GCGCAGGG CUGAUGAGGCCGUUAGGCCGAA IAUGUGCC	1046
784	CACAUCAC C CUGCGCCU	671	AGGCGCAG CUGAUGAGGCCGUUAGGCCGAA TUGAUGUG	1047
785	ACAUCACC C UGCGCCUG	672	CAGGCGCA CUGAUGAGGCCGUUAGGCCGAA IGUGAUGU	1048
786	CAUCACCC U GCGCCUGG	673	CCAGGCGC CUGAUGAGGCCGUUAGGCCGAA IGGUGAUG	1049
791	CCCUGCGC C UGGGCGCA	674	UGCGCCCA CUGAUGAGGCCGUUAGGCCGAA ICGCAGGG	1050
792	CCUGCGCC U GGGCGCAC	675	GUGCGCCC CUGAUGAGGCCGUUAGGCCGAA IGCGCAGG	1051
799	CUGGGCGC A CUGGUGGC	676	GCCACCAG CUGAUGAGGCCGUUAGGCCGAA ICGCCCAG	1052
801	GGGCGCAC U GGUGGCCC	677	GGGCCACC CUGAUGAGGCCGUUAGGCCGAA IUGCGCCC	1053
808	CUGGUGGC C CCGGUGGU	678	ACCACCGG CUGAUGAGGCCGUUAGGCCGAA ICCACCAG	1054
809	UGGUGGCC C CGGUGGUG	679	CACCACCG CUGAUGAGGCCGUUAGGCCGAA IGCCACCA	1055
810	GGUGGCCC C GGUGGUGA	680	UCACCACC CUGAUGAGGCCGUUAGGCCGAA IGGCCACC	1056
823	GUGAGCGC C UUCUCCCU	681	AGGGAGAA CUGAUGAGGCCGUUAGGCCGAA ICOCUCAC	1057
824	UGAGCGCC U UCUCCCUG	682	CAUGGAGA CUGAUGAGGCCGUUAGGCCGAA IGCGCUCA	1058
827	GCGCCUUC U CCCUGGCU	683	AGCCAGGG CUGAUGAGGCCGUUAGGCCGAA IAAGGCGC	1059
829	GCCUUCUC C CUGGCUUU	684	AAAGCCAG CUGAUGAGGCCGUUAGGCCGAA IAGAAGGC	1060
830	CCUUCUCC C UGGCUUUC	685	GAAAGCCA CUGAUGAGGCCGUUAGGCCGAA IGAGAAGG	1061
831	CUUCUCCC U GGCUUUCU	686	AGAAAGCC CUGAUGAGGCCGUUAGGCCGAA IGGAGAAG	1062
835	UCCCUGGC U UUCUGCGC	687	GCGCAGAA CUGAUGAGGCCGUUAGGCCGAA ICCAGGGA	1063
839	UGGCUUUC U GCGCGCUA	688	UAGCGCGC CUGAUGAGGCCGUUAGGCCGAA IAAAGCCA	1064
846	CUGCGCGC U ACCUUUCA	689	UGAAAGGU CUGAUGAGGCCGUUAGGCCGAA ICGCGCAG	1065
849	CGCGCUAC C UUUCAUGG	690	CCAUGAAA CUGAUGAGGCCGUUAGGCCGAA IUAGCGCG	1066
850	GCGCUACC U UUCAUGGG	691	CCCAUGAA CUGAUGAGGCCGUUAGGCCGAA IGUAGCGC	1067

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
854	UACCUUUC A UGGGCUUC	692	GAAGCCCA CUGAUGAGGCCGUUAGGCCGAA IAAAGGUA	1068
860	UCAUGGGC U UCGGGAAG	693	CUUCCCGA CUGAUGAGGCCGUUAGGCCGAA ICCCAUGA	1069
876	GUUCGUGC A GUACUGCC	694	GGCAGUAC CUGAUGAGGCCGUUAGGCCGAA ICACGAAC	1070
881	UGCAGUAC U GCCCCGGC	695	GCCGGGGC CUGAUGAGGCCGUUAGGCCGAA IUACUGCA	1071
884	AGUACUGC C CCGGCACC	696	GGUGCCGG CUGAUGAGGCCGUUAGGCCGAA ICAGUACU	1072
885	GUACUGCC C CGGCACCU	697	AGGUGCCG CUGAUGAGGCCGUUAGGCCGAA IGCAGUAC	1073
886	UACUGCCC C GGCACCUG	698	CAGGUGCC CUGAUGAGGCCGUUAGGCCGAA IGGCAGUA	1074
890	GCCCCGGC A CCUGGUGC	699	GCACCAGG CUGAUGAGGCCGUUAGGCCGAA ICCGGGGC	1075
892	CCCGGCAC C UGGUGCUU	700	AAGCACCA CUGAUGAGGCCGUUAGGCCGAA IUGCCGGG	1076
893	CCGGCACC U GGUGCLRTU	701	AAAGCACC CUGAUGAGGCCGUUAGGCCGAA IGUGCCGG	1077
899	CCUGGUGC U UUAUCCAG	702	CUGGAUAA CUGAUGAGGCCGUUAGGCCGAA ICACCAGG	1078
905	GCUUUAUC C AGAUGGUC	703	GACCAUCU CUGAUGAGGCCGUUAGGCCGAA IAUAAAGC	1079
906	CUUUAUCC A GAUGGUCC	704	GGACCAUC CUGAUGAGGCCGUUAGGCCGAA IGAUAAAG	1080
914	AGAUGGUC C ACGAGGAG	705	CUCCUCGU CUGAUGAGGCCGUUAGGCCGAA IACCAUCU	1081
915	GAUCGUCC A CCAGGAGG	706	CCUCCUCG CUGAUGAGGCCGUUAGGCCGAA IGACCAUC	1082
926	AGGAGGGC U CGCUGUCG	707	CGACAGCG CUGAUGAGGCCGUUAGGCCGAA ICCCUCCU	1083
930	GGGCUCGC U GUCGGUGC	708	GCACCGAC CUGAUGAGGCCGUUAGGCCGAA ICGAGCCC	1084
939	GUCGGUGC U GGGGUACU	709	AGUACCCC CUGAUGAGGCCGUUAGGCCGAA ICACCGAC	1085
947	UGGGGUAC U CUGUCCUC	710	GAGCACAG CUGAUGAGGCCGUUAGGCCGAA IUACCCCA	1086
949	GOGUACUC U GUGCUCUA	711	UAGAGCAC CUGAUGAGGCCGUUAGGCCGAA IAGUACCC	1087
954	CUCUGUGC U CUACUCCA	712	UGGAGUAG CUGAUGAGGCCGUUAGGCCGAA ICACAGAG	1088
956	CUGUCCUC U ACUCCAGC	713	GCUGGAGU CUGAUGAGGCCGUUAGGCCGAA IAGCACAG	1089
959	UGCUCUAC U CCAGCCUC	714	GAGGCUGG CUGAUGAGGCCGUUAGGCCGAA IUAGAGCA	1090
961	CUCUACUC C AGCCUCAU	715	AUGAGGCU CUGAUGAGGCCGUUAGGCCGAA IAGUAGAG	1091
962	UCUACUCC A GCCUCAUG	716	CAUGAGGC CUGAUGAGGCCGUUAGGCCGAA IGAGUAGA	1092
965	ACUCCAGC C UCAUGGCG	717	CGCCAUGA CUGAUGAGGCCGUUAGGCCGAA ICUGGAGU	1093
966	CUCCAGCC U CAUGGCGC	718	GCGCCAUG CUGAUGAGGCCGUUAGGCCGAA IGCUGGAG	1094
968	CCAGCCUC A UGGCGCUG	719	CAGCGCCA CUGAUGAGGCCGUUAGGCCGAA IAGGCUGG	1095
975	CAUGGCGC U GCUGGUCC	720	GGACCAGC CUGAUGAGGCCGUUAGGCCGAA ICGCCAUG	1096
978	GGCGCUGC U GGUCCUCG	721	CGAGGACC CUGAUGAGGCCGUUAGGCCGAA ICAGCGCC	1097
983	UCCUGGUC C UCGCCACC	722	GGUGGCGA CUGAUGAGGCCGUUAGGCCGAA IACCAGCA	1098
984	GCUGGUCC U CGCCACCG	723	CGGUGGCG CUGAUGAGGCCGUUAGGCCGAA IGACCAGC	1099
988	GUCCUCGC C ACCGUGCU	724	AGCACGGU CUGAUGAGGCCGUUAGGCCGAA ICCAGGAC	1100
989	UCCUCGCC A CCGUGCUG	725	CAGCACGG CUGAUGAGGCCGUUAGGCCGAA IGCGAGGA	1101
991	CUCGCCAC C GUGCUGUG	726	CACAGCAC CUGAUGAGGCCGUUAGGCCGAA IUGGCGAG	1102

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
996	CACCGUGC U GUGCAACC	727	GGUUGCAC CUGAUGAGGCCGUUAGGCCGAA ICACGGUG	1103
1001	UGCUGUGC A ACCUCGGC	728	GCCGAGGU CUGAUGAGGCCGUUAGGCCGAA ICACAGCA	1104
1004	UGUGCAAC C UCGGCGCC	729	GGCGCCGA CUGAUGAGGCCGUUAGGCCGAA IUUGCACA	1105
1005	GUGCAACC U CGGCGCCA	730	UGGCGCCG CUGAUGAGGCCGUUAGGCCGAA IGUUGCAC	1106
1012	CUCGGCGC C AUGCGCAA	731	UUGCGCAU CUGAUGAGGCCGUUAGGCCGAA ICGCCGAG	1107
1013	UCGGCGCC A UGCGCAAC	732	GUUGCGCA CUGAUGAGGCCGUUAGGCCGAA IGCGCCGA	1108
1019	CCAUGCGC A ACCUCUAU	733	AUAGAGGU CUGAUGAGGCCGUUAGGCCGAA ICGCAUGG	1109
1022	UGCGCAAC C UCUAUGCG	734	CGCAUAGA CUGAUGAGGCCGUUAGGCCGAA IUUGCGCA	1110
1023	GCGCAACC U CUAUGCGA	735	UCGCAUAG CUGAUGAGGCCGUUAGGCCGAA IGUUGCGC	1111
1025	GCAACCUC U AUGCGAUG	736	CAUCGCAU CUGAUGAGGCCGUUAGGCCGAA IAGGUUGC	1112
1035	UGCGAUGC A CCGGCGGC	737	GCCGCCGG CUGAUGAGGCCGUUAGGCCGAA ICAUCGCA	1113
1037	CGAUGCAC C GGCGGCUG	738	CAGCCGCC CUGAUGAGGCCGUUAGGCCGAA IUGCAUCG	1114
1044	CCGGCGGC U GCAGCGGC	739	GCCGCUGC CUGAUGAGGCCGUUAGGCCGAA ICCGCCGG	1115
1047	GCGGCUGC A GCGGCACC	740	GGUGCCGC CUGAUGAGGCCGUUAGGCCGAA ICAGCCGC	1116
1053	GCAGCGGC A CCCGCGCU	741	AGCGCGGG CUGAUGAGGCCGUUAGGCCGAA ICCGCUGC	1117
1055	AGCGGCAC C CGCGCUCC	742	GGAGCGCG CUGAUGAGGCCGUUAGGCCGAA IUGCCGCU	1118
1056	GCGGCACC C GCGCUCCU	743	AGGAGCGC CUGAUGAGGCCGUUAGGCCGAA IGUGCCGC	1119
1061	ACCCGCGC U CCUGCACC	744	GGUGCAGG CUGAUGAGGCCGUUAGGCCGAA ICGCGGGU	1120
1063	CCGCGCUC C UCCACCAG	745	CUGGUCCA CUGAUGAGGCCGUUAGGCCGAA IAGCGCGG	1121
1064	CGCGCUCC U GCACCAGG	746	CCUGGUGC CUGAUGAGGCCGUUAGGCCGAA IGAGCGCG	1122
1067	GCUCCUGC A CCAGGGAC	747	GUCCCUGG CUGAUGAGGCCGUUAGGCCGAA ICAGGAGC	1123
1069	UCCUCCAC C AGGGACUG	748	CAGUCCCU CUGAUGAGGCCGUUAGGCCGAA IUCCAGGA	1124
1070	CCUGCACC A GGGACUGU	749	ACAGUCCC CUGAUGAGGCCGUUAGGCCGAA IGUGCAGG	1125
1076	CCAGGGAC U GUGCCGAG	750	CUCGGCAC CUGAUGAGGCCGUUAGGCCGAA IUCCCUGG	1126
1081	GACUGUGC C GAGCCGCG	751	CGCGGCUC CUGAUGAGGCCGUUAGGCCGAA ICACAGUC	1127
1086	UGCCGAGC C GCGCGCGG	752	CCGCGCGC CUGAUGAGGCCGUUAGGCCGAA ICUCGGCA	1128
1111	GAAGCGUC C CCUCAGCC	753	GGCUGAGG CUGAUGAGGCCGUUAGGCCGAA IACGCUUC	1129
1112	AAGCGUCC C CUCAGCCC	754	GGGCUGAG CUGAUGAGGCCGUUAGGCCGAA IGACGCUU	1130
1113	AGCGUCCC C UCAGCCCC	755	GGGGCUGA CUGAUGAGGCCGUUAGGCCGAA IGGACGCU	1131
1114	GCGUCCCC U CAGCCCCU	756	AGGGGCUG CUGAUGAGGCCGUUAGGCCGAA IGGGACGC	1132
1116	GUCCCCUC A GCCCCUGG	757	CCAGGGGC CUGAUGAGGCCGUUAGGCCGAA IAGGGGAC	1133
1119	CCCUCAGC C CCUCGAGG	758	CCUCCAGG CUGAUGACGCCGUUAGGCCGAA ICUGAGGG	1134
1120	CCUCAGCC C CUGGAGGA	759	UCCUCCAG CUGAUGAGGCCGUUAGGCCGAA IGCUGAGG	1135
1121	CUCAGCCC C UGGAGGAG	760	CUCCUCCA CUGAUGAGGCCGUUAGGCCGAA IGGCUGAG	1136
1122	UCAGCCCC U GGAGGAGC	761	OCUCCUCO CUGAUGAGGCCGUUAGGCCGAA IGGGCUGA	1137
1131	GGAGGAGC U GGAUCACC	762	GGUGAUCC CUGAUGAGGCCGUUAGGCCGAA ICUCCUCC	1138

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
1137	GCUGGAUC A CCUCCUGC	763	GCAGGAGG CUGAUGAGGCCGUUAGGCCGAA IAUCCAGC	1139
1139	UGGAUCAC C UCCUGCUG	764	CAGCAGGA CUGAUGAGGCCGUUAGGCCGAA IUGAUCCA	1140
1140	GGAUCACC U CCUGCUGC	765	GCAGCAGG CUGAUGAGGCCGUUAGGCCGAA TGUGAUCC	1141
1142	AUCACCUC C UGCUGCUG	766	CAGCAGCA CUGAUGAGGCCGUUAGGCCGAA IAGGUGAU	1142
1143	UCACCUCC U GCUGCUGG	767	CCAGCAGC CUGAUGAGGCCGUUAGGCCGAA IGAGGUGA	1143
1146	CCUCCUGC U GCUGGCGC	768	GCGCCAGC CUGAUGAGGCCGUUAGGCCGAA ICAGGAGG	1144
1149	CCUGCUGC U GGCGCUGA	769	UCAGCGCC CUGAUGAGGCCGUUAGGCCGAA ICAGCAGG	1145
1155	GCUGGCGC U GAUGACCG	770	CGGUCAUC CUGAUGAGGCCGUUAGGCCGAA ICGCCAGC	1146
1162	CUGAUGAC C GUGCUCUU	771	AAGAGCAC CUGAUGAGGCCGUUAGGCCGAA IUCAUCAG	1147
1167	GACCGUGC U CUUCACUA	772	UAGUGAAG CUGAUGAGGCCGUUAGGCCGAA ICACGGUC	1148
1169	CCGUGCUC U UCACUAUG	773	CAUAGUGA CUGAUGAGGCCGUUAGGCCGAA IAGCACGG	1149
1172	UGCUCUUC A CUAUGUGU	774	ACACAUAG CUGAUGAGGCCGUUAGGCCGAA IAAGAGCA	1150
1174	CUCUUCAC U AUGUGUUC	775	GAACACAU CUGAUGAGGCCGUUAGGCCGAA IUGAAGAG	1151
1183	AUGUGUUC U CUGCCCGU	776	ACGGGCAG CUGAUGAGGCCGUUAGGCCGAA IAACACAU	1152
1185	GUGUUCUC U GCCCGUAA	777	UUACGGGC CUGAUGAGGCCGUUAGGCCGAA IAGAACAC	1153
1188	UUCUCUGC C CGUAAUUU	778	AAAUUACG CUGAUGAGGCCGUUAGGCCGAA ICAGAGAA	1154
1189	UCUCUGCC C GUAAUUUA	779	UAAAUUAC CUGAUGAGGCCGUUAGGCCGAA IGCAGAGA	1155
1204	UAUCGCGC U UACUAUGG	780	CCAUAGUA CUGAUGAGGCCGUUAGGCCGAA ICGCGAUA	1156
1208	GCGCUUAC U AUGGAGCA	781	UGCUCCAU CUGAUGAGGCCGUUAGGCCGAA IUAAGCGC	1157
1216	UAUGGAGC A UUUAAGGA	782	UCCUUAAA CUGAUGAGGCCGUUAGGCCGAA ICUCCAUA	1158
1229	AGGAUGUC A AGGAGAAA	783	UUUCUCCU CUGAUGAGGCCGUUAGGCCGAA IACAUCCU	1159
1241	AGAAAAAC A GGACCUCU	784	AGAGGUCC CUGAUGAGGCCGUUAGGCCGAA IUUUUUCU	1160
1246	AACAGGAC C UCUGAAGA	785	UCUUCAGA CUGAUGAGGCCGUUAGGCCGAA IUCCUGUU	1161
1247	ACAGGACC U CUGAAGAA	786	UUCUUCAG CUGAUGAGGCCGUUAGGCCGAA IGUCCUGU	1162
1249	AGGACCUC U GAAGAAGC	787	GCUUCUUC CUGAUGAGGCCGUUAGGCCGAA IAGGUCCU	1163
1258	GAAGAAGC A GAAGACCU	788	AGGUCUUC CUGAUGAGGCCGUUAGGCCGAA ICUUCUUC	1164
1265	CAGAAGAC C UCCGAGCC	789	GGCUCGGA CUGAUGAGGCCGUUAGGCCGAA IUCUUCUG	1165
1266	AGAAGACC U CCGAGCCU	790	AGGCUCGG CUGAUGAGGCCGUUAGGCCGAA IGUCUUCU	1166
1268	AAGACCUC C GAGCCUUG	791	CAAGGCUC CUGAUGAGGCCGUUAGGCCGAA IAGGUCUU	1167
1273	CUCCGAGC C UUGCGAUU	792	AAUCGCAA CUGAUGAGGCCGUUAGGCCGAA ICUCGGAG	1168
1274	UCCGAGCC U UUGCGAUU	793	AAAUCGCA CUGAUGAGGCCGUUAGGCCGAA IGCUCGGA	1169
1284	GCGAUUUC U AUCUGUGA	794	UCACAGAU CUGAUGAGGCCGUUAGGCCGAA IAAAUCGC	1170
1288	UUUCUAUC U GUGAUUUC	795	GAAAUCAC CUGAUGAGGCCGUUAGGCCGAA IAUAGAAA	1171
1297	GUGAUUUC A AUUGUGGA	796	UCCACAAU CUGAUGAGGCCGUUAGGCCGAA IAAAUCAC	1172
1307	UUGUGGAC C CUUGGAUU	797	AAUCCAAG CUGAUGAGGCCGUUAGGCCGAA IUCCACAA	1173

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
1308	UGUGGACC C UUGGAUUU	798	AAAUCCAA CUGAUGAGGCCGUUAGGCCGAA IGUCCACA	1174
1309	GUGGACCC U UGGAUUUU	799	AAAAUCCA CUGAUGAGGCCGUUAGGCCGAA IGGUCCAC	1175
1322	UUUUUAUC A UUUUCAGA	800	UCUGAAAA CUGAUGAGGCCGUUAGGCCGAA IAUAAAAA	1176
1328	UCAUUUUC A GAUCUCCA	801	UGGAGAUC CUGAUGAGGCCGUUAGGCCGAA IAAAAUGA	1177
1333	UUCAGAUC U CCAGUAUU	802	AAUACUGG CUGAUGAGGCCGUUAGGCCGAA IAUCUGAA	1178
1335	CAGAUCUC C AGUAUUUC	803	GAAAUACU CUGAUGAGGCCGUUAGGCCGAA IAGAUCUG	1179
1336	AGAUCUCC A GUAUUUCG	804	CGAAAUAC CUGAUGAGGCCGUUAGGCCGAA IGAGAUCU	1180
1356	AUUUUUUC A CAAGAUUU	805	AAAUCUUG CUGAUGAGGCCGUUAGGCCGAA IAAAAAAU	1181
1358	UUUUUCAC A AGAUUUUC	806	GAAAAUCU CUGAUGAGGCCGUUAGGCCGAA IUGAAAAA	1182
1367	AGAUUUUC A UUAGACCU	807	AGGUCUAA CUGAUGAGGCCGUUAGGCCGAA IAAAAUCU	1183
1374	CAUUACAC C UCUUAGGU	808	ACCUAAGA CUGAUGAGGCCGUUAGCCCGAA IUCUAAUG	1184
1375	AUUAGACC U CUUAGGUA	809	UACCUAAG CUGAUGAGGCCGUUAGGCCGAA IGUCUAAU	1185
1377	UAGACCUC U UAGGUACA	810	UGUACCUA CUGAUGAGGCCGUUAGGCCGAA IAGGUCUA	1186
1385	UUAGGUAC A GGAGCCGG	811	CCGGCUCC CUGAUGAGGCCGUUAGGCCGAA IUACCUAA	1187
1391	ACAGGAGC C GGUGCAGC	812	GCUGCACC CUGAUGAGGCCGUUAGGCCGAA ICUCCUGU	1188
1397	GCCGGUGC A GCAAUUCC	813	GGAAUUGC CUGAUGAGGCCGUUAGGCCGAA ICACCGGC	1189
1400	GGUGCAGC A AUUCCACU	814	AGUGCAAU CUGAUGAGGCCGUUAGGCCGAA ICUGCACC	1190
1405	AGCAAUUC C ACUAACAU	815	AUGUUAGU CUGAUGAGGCCGUUAGGCCGAA IAAUUGCU	1191
1406	GCAAUUCC A CUAACAUG	816	CAUGUUAG CUGAUGAGGCCGUUAGCCCGAA IGAAUUGC	1192
1408	AAUUCCAC U AACAUGGA	817	UCCAUGUU CUGAUGAGGCCGUUAGGCCGAA IUGGAAUU	1193
1412	CCACUAAC A UGGAAUCC	818	GGAUUCCA CUGAUGAGGCCGUUAGGCCGAA IUUAGUGG	1194
1420	AUCGAAUC C AGUCUGUG	819	CACAGACU CUGAUGAGGCCGUUAGGCCGAA IAUUCCAU	1195
1421	UGGAAUCC A GUCUGUGA	820	UCACAGAC CUGAUGAGGCCGUUAGGCCGAA IGAUUCCA	1196
1425	AUCCAGUC U GUGACAGU	821	ACUGUCAC CUGAUGAGGCCGUUAGGCCGAA IACUGGAU	1197
1431	UCUGUGAC A GUGUUUUU	822	AAAAACAC CUGAUGAGGCCGUUAGGCCGAA IUCACAGA	1198
1441	UGUUUUUC A CUCUGUGG	823	CCACAGAG CUGAUGAGGCCGUUAGGCCGAA IAAAAACA	1199
1443	UUUUUCAC U CUGUGGUA	824	UACCACAG CUGAUGAGGCCGUUAGGCCGAA IUGAAAAA	1200
1445	UUUCACUC U GUGGUAAG	825	CUUACCAC CUGAUGAGGCCGUUAGGCCGAA IAGUGAAA	1201
1455	UGGUAAGC U GAGGAAUA	826	UAUUCCUC CUGAUGAGGCCGUUAGGCCGAA ICUUACCA	1202
1468	AAUAUGUC A CAUUUUCA	827	UGAAAAUG CUGAUGAGGCCGUUAGGCCGAA IACAUAUU	1203
1470	UAUGUCAC A UUUUCAGU	828	ACUGAAAA CUGAUGAGGCCGUUAGGCCGAA IUGACAUA	1204

TABLE IV-continued

Human PTGDR Inozyme and Substrate Sequence

Pos	Substrate	Seq ID	Inozyme	Seq ID
1476	ACAUUUUC A GUCAAAGA	829	UCUUUGAC CUGAUGAGGCCGUUAGGCCGAA IAAAAUGU	1205
1480	UUUCAGUC A AAGAACCA	830	UGGUUCUU CUGAUGAGGCCGUUAGGCCGAA IACUGAAA	1206

Input Sequence = PTGDR_composit.
Cut Site = CH/.
Arm Length = 8.
Core Sequence = CUGAUGAG GCCGUUAGGC CGAA
PTGDR_composit (1 to 993 of HSU31332 (PTGDR 5') +1 to 495 of HSU31099 (PTGDR 3'); 1488 nt)
Underlined region can be any X sequence or linker, as described herein.
I = Inosine

[0232]

TABLE V

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
9	GAAUUCUG G CUAUUUUC	1207	GAAAAUAG GCCGAAAGGCGAGUGAGGUCU CAGAAUUC	1438
23	UUCCUCCU G CCGUUCCG	1208	CGGAACGG GCCGAAAGGCGAGUGAGGUCU AGGAGGAA	1439
26	CUCCUGCC G UUCCGACU	1209	AGUCGGAA GCCGAAAGGCGAGUGAGGUCU GGCAGGAG	1440
37	CCGACUCG G CACCAGAG	1210	CUCUGGUG GCCGAAAGGCGAGUGAGGUCU CGAGUCGG	1441
45	GCACCAGA G UCUGUCUC	1211	GAGACAGA GCCGAAAGGCGAGUGAGGUCU UCUGGUGC	1442
49	CAGAGUCU G UCUCUACU	1212	AGUAGAGA GCCGAAAGGCGAGUGAGGUCU AGACUCUG	1443
64	CUGAGAAC G CAGCGCGU	1213	ACGCGCUG GCCGAAAGGCGAGUGAGGUCU GUUCUCAG	1444
67	AGAACGCA G CGCGUCAG	1214	CUGACGCG GCCGAAAGGCGAGUGAGGUCU UGCGUUCU	1445
69	AACGCAGC G CGUCAGGG	1215	CCCUGACG GCCGAAAGGCGAGUGAGGUCU GCUGCGUU	1446
71	CGCAGCGC G UCAGGGCC	1216	GGCCCUGA GCCGAAAGGCGAGUGAGGUCU GCGCUGCG	1447
77	GCGUCAGG G CCGAGCUC	1217	GAGCUCGG GCCGAAAGGCGAGUGAGGUCU CCUGACGC	1448
82	AGGGCCGA G CUCUUCAC	1218	GUGAAGAG GCCGAAAGGCGAGUGAGGUCU UCGGCCCU	1449
93	CUUCACUG G CCUGCUCC	1219	GGAGCAGG GCCGAAAGGCGAGUGAGGUCU CAGUGAAG	1450
97	ACUGGCCU G CUCCUCUC	1220	GCGCGGAG GCCGAAAGGCGAGUGAGGUCU AGGCCAGU	1451
102	CCUGCUCC G CGCUCUUC	1221	GAAGAGCG GCCGAAAGGCGAGUGAGGUCU GGAGCAGG	1452
104	UGCUCCGC G CUCUUCAA	1222	UUGAAGAG GCCGAAAGGCGAGUGAGGUCU GCGGAGCA	1453
114	UCUUCAAU G CCAGCGCC	1223	GGCGCUGG GCCUAAAGGCGAGUGAGGUCU AUUGAAUA	1454
118	CAAUGCCA G CGCCAGGC	1224	GCCUGGCG GCCGAAAGGCGAUUGAGGUCU UGGCAUUU	1455
120	AUGCCAUC G CCAGUCGC	1225	GCGCCUGG GCCGAAAGGCGAGUGAGGUCU GCUGGCAU	1456
125	AUCUCCAG G CGCUCACC	1226	GGUGAGCG GCCGAAAGGCGAGUGAGGUCU CUGGCGCU	1457
127	CGCCAGGC G CUCACCCU	1227	AUGGUGAG GCCGAAAGGCGAGUUAGGUCU GCCUGGCG	1458
136	CUCACCCU G CAGAGCGU	1228	ACUCUCUG GCCGAAAGGCGAGUGAGGUCU AGUGUGAG	1459
141	CCUUCAUA G CGUCCCGC	1229	UCUUGACU GCCGAAAGGCGAGUGAGGUCU UCUGCAGG	1460

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
143	UUCAGAGC G UCCCUCCU	1230	AGUCUGGA GCCGAAAGGCGAGUGAGGUCU UCUCUUCA	1461
148	AUCUUCCC G CCUCUCAA	1231	UUGAGAGG GCCGAAAUGCGAGUGAGGUCU GGGACGCU	1462
163	AAAGAGGG G UGUGACCC	1232	GUGUCACA GCCGAAAGGCGAGUGAGGUCU CCCUCUUU	1463
165	AUAUGUGU G UGACCCGC	1233	UCUGGUCA GCCUAAAGUCGAGUGAGGUCU ACCCCUCU	1464
172	UGUGACCC G CGAGUUUA	1234	UAAACUCG GCCGAAAGGCGAGUGAGGUCU GUGUCACA	1465
176	ACCCGCGA G UUUAGAUA	1235	UAUCUAAA GCCGAAAGGCGAGUGAGGUCU UCUCUUGU	1466
189	UAUAUUAG G UUCCUGCC	1236	GGCAGGAA GCCGAAAUGCGAGUGAGGUCU CUCCUAUC	1467
195	AGGUUCCU G CCUUUUUU	1237	CCCCACUU GCCGAAAGGCGAGUGAGGUCU AGGAACCU	1468
198	UUCCUGCC G UGGGGAAC	1238	GUUCCCCA GCCGAAAGUCUAGUGAGGUCU GGCAGGAA	1469
212	AACACCCC G CCUCCCUC	1239	GAGGUCUG GCCGAAAGGCGAGUGAGGUCU GGGGUGUU	1470
215	ACCCCGCC G CCCUCGGA	1240	UCCUAGUG GCCGAAAUUCUAGUGAGGUCU UUCUUUUU	1471
224	CCCUCGGA G CUUUUUCU	1241	AGAAAAAU UCCGAAAGGCGAGUGAUGUCU UCCGAGGG	1472
233	CUUUUUCU G UGUCUCAG	1242	CUGCGCCA UCCGAAAGGCGAGUGAGGUCU AGAAAAAG	1473
236	UUUCUGUG G CUCAUCUU	1243	AAUCUUCU UCCUAAAGGCUAUUGAUUUCU CACAGAAA	1474
238	UCUGUGUC G CAGCUUCU	1244	AGAAGCUG UCCUAAAUUCUAUUUAGGUCU UCCACAGA	1475
241	GUGUCUCA G CUUCUCCG	1245	CUUAUAAU GCCGAAAGGCUAUUUAUGUCU UGCGCCAC	1476
249	GCUUCUCC G CCCUAUCC	1246	GGCUCUUU UCCUAAAUUCGAGUUAGUUCU UGAUAAUC	1477
255	CCUCCCGA G CCGCUCUC	1247	UCGCGCUG UCCUAAAUUCUAUUUAUGUCU UCUUUCUU	1478
258	CCCUAUCC G CUCGCGGA	1248	UCCUCGCU GCCGAAAGUCGAUUUAUUUCU GUCUCGGG	1479
260	CGAGCCGC G CUCUUAUC	1249	GCUCCGCU UCCUAAAUUCUAGUGAUUUCU UCGUCUCU	1480
262	AUCCUCUC G CUUAGCUG	1250	CAGCUCCU GCCUAAAGGCGAUUUAUGUCU UCUCGGCU	1481
267	CGCGCGGA G CUUCCUUU	1251	CCCGGCAU UCCUAAAUUCUAGUGAUUUCU UCCUCUCU	1482
270	UCUUAUCU G CCGGGGGC	1252	UCCCCCUG GCCUAAAUUCUAUUUAUUUCU AUCUCCUC	1483
277	UGCCGGUU G CUCCUUAU	1253	CUAAUUAU UCCUAAAUUCGAGUGAUUUCU CCCCGUCA	1484
285	GCUCCUUA G CACCCGGG	1254	CCCGGGUG GCCGAAAGGCGAGUGAGGUCU UAAGGAGC	1485
293	GCACCCGG G CGCCGGGG	1255	CCCCGGCG GCCGAAAGGCGAGUGAGGUCU CCGGGUGC	1486
295	ACCCGGGC G CCGGGGCC	1256	GGCCCCGG GCCGAAAGGCGAGUGAGGUCU GCCCGGGU	1487
301	GCGCCGGG G CCCUCGCC	1257	GGCGAGGG GCCGAAAGGCGAGUCAGGUCU CCCGGCGC	1488
307	GGGCCCUC G CCCUUCCG	1258	CGGAAGGG GCCGAAAGGCGAGUGAGGUCU GAGGGCCC	1489
315	GCCCUUCC G CAGCCUUC	1259	GAAGGCUG GCCGAAAGGCGAGUGAGGUCU GGAAGGGC	1490
318	CUUCCGCA G CCUUCACU	1260	AGUGAAGG CCCGAAAGGCGAGUGAGGUCU UGCCGAAG	1491
330	UCACUCCA G CCCUCUGC	1261	GCAGAGGG GCCGAAAGGCGAGUGAGGUCU UGGACUGA	1492
337	AGCCCUCU G CUCCCGCA	1262	UGCGGGAG GCCGAPAGGCGAGUGAGGUCU AGAGGGCU	1493
343	CUGCUCCC G CACGCCAU	1263	AUGGCGUG GCCGAAAGGCGAGUGAGGUCU GGGAGCAC	1494
347	UCCCGCAC G CCAUGAAG	1264	CUUCAUGG GCCGAAAGGCGAGUGAGGUCU GUGCGGGA	1495

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
355	GCCAUGAA G UCGCCGUU	1265	AACGGCCA CCCGAAAGGCGAGUGAGGUCU UUCAUGGC	1496
358	AUGAAGUC G CCGUUCUA	1266	UAGAACGG GCCGAAAGCCGAGUGAGGUCU GACUUCAU	1497
361	AAGUCGCC G UUCUACCG	1267	CGGUACAA CCCGAAAGGCGAGUGAGCUCU GGCGACUU	1498
369	GUUCUACC G CUCCOAGA	1268	UCUGGCAG GCCGAAACGCGAGUGAGGUCU CGUAGAAC	1499
372	CUACCGCU G CCAGAACA	1269	UGUUCUCC GCCGAAAGGCGACUCACCUCU AGCCGUAC	1500
389	CCACCUCU G UGGAAAAA	1270	UUUUUCCA GCCCAAAGGCGAGUGAGGUCU AGAGGUOG	1501
399	GGAAAAAG G CAACUCGG	1271	CCCAGUUG GCCGAAAGGCGAGUGAGGUCU CUUUUUCC	1502
407	GCAACUCG G CUCUGAUC	1272	CAUCACCC GCCCAAAGGCGAGUGACCUCU CGAGUUGC	1503
410	ACUCGGCC G UGAUGGUC	1273	GCCCAUCA GCCGAAACCCGAGUGAGGUCU CGCCGAGU	1504
417	GGUGAUGG G CGCCCUGC	1274	CCACCCCG GCCGAAAGGCCAGUCACCUCU CCAUCACC	1505
422	UGGGCCGC G UGCUCUUC	1275	GAAGAGCA GCCCAAAGGCGAGUGAGCUCU CCCGCCCA	1506
424	CGCGGGGU G CUCUUCAG	1276	CUGAAGAG CCCGAAAGGCGAGUGAGGUCU ACCCCCCC	1507
432	GCUCUUCA G CACCGGCC	1277	GGCCGGUG CCCGAAAGGCGAGUGAGGUCU UCAAGAGC	1508
438	CAGCACCG G CCUCCUCC	1278	CCAGCAGG GCCGAAAGGCGAGUGAGGUCU CCGUGCUG	1509
447	CCUCCUCG G CAACCUGC	1279	GCAGGUUG GCCCAAAGGCGAGUGAGCUCU CCAGGAGG	1510
454	GCCAACCU G CUCGCCCU	1280	AGGGCCAG CCCGAAAGGCGAGUCAGGUCU AGGUUCCC	1511
458	ACCUCCUC G CCCUGGGG	1281	CCCCAGGC GCCCAAAGGCGAGUGACGUCU CAGCAGGU	1512
466	GCCCUGGG G CUGCUCGC	1282	GCCAGCAG GCCGAAAGGCCAGUGAGGUCU CCCAGCCC	1513
469	CUGGGGCU G CUGGCCCG	1283	CGCGCCAG GCCGAAAGGCGAGUCAGGUCU AGCCCCAC	1514
473	GGCUGCUG G CGCCCUCG	1284	CGAGCGCG GCCGAAAGGCGAGUGAGGUCU CACCAGCC	1515
475	CUGCUGGC G CCCUCCGG	1285	CCCCACCC GCCGAAACCCCACUCAGGUCU GCCACCAC	1516
477	CCUCGCGC G CUCGGCCC	1286	CCCCCCAC CCCCAAACGCGAGUCACCUCU CCGCCACC	1517
484	CCCUCCCC G CUCCGGUG	1287	CACCCCAG GCCCAAACCCCACUCAGCUCU CCCCACCC	1518
490	CCCCUGCG G UGGUCCUC	1288	CACCACCA CCCCAAACCCCACUCACCUCU CCCACCCC	1519
493	CUGCCCUC G UCCUCCCG	1289	CCCGACCA GCCCAAACCCCAGUCACCUCU CACCCCAG	1520
495	CCCCUCGU G CUCCCCCC	1290	CCCCCCAC CCCCAAAGCCGACUCACCUCU ACCACCCC	1521
499	UCCUCCUC G CCCCCUCC	1291	CCACGCCG CCCGAAACCCCACUGAGCUCU CACCACCA	1522
502	UCCUCGCG G CCUCCACU	1292	AGUCCACC CCCGAAAGGCGACUCACCUCU CGCCACCA	1523
504	CUCCCCCC G UCCACUCC	1293	GCACUCCA CCCCAAACGCGAGUCACGUCU CCCCCGAC	1524
511	CCUCCACU G CCCCCCCU	1294	ACCCCGCG GCCGAAACCCCACUCAGGUCU AGUCCACC	1525
513	UCCACUGC G CCCCCUCC	1295	CCACCCCC CCCCAAACCCCACUCACCUCU CCAGUCCA	1526
517	CUCCGCCC G CUGCCCUC	1296	CACGCCAC GCCCAAACCCGAGUCAGGUCU GGGCCCAC	1527
520	CGCCCGCU G CCCUCCGU	1297	ACCGACCG GCCGAAAGGCCAGUCACCUCU AGCCCCCC	1528
527	UGCCCUCG G UCUUCUAC	1298	GUACAACA GCCGAAACGCGAGUGAGGUCU CCACGCCA	1529
538	UUCUACAU G CUCCUCUC	1299	CACACCAG CCCGAAAGGCGAGUCAGGUCU AUCUACAA	1530
542	ACAUCCUC G UGUGUGCC	1300	GCCACACA GCCGAAACCCGACUGAGGUCU CACCAUGU	1531

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
544	AUCCUCCU G UGUCCCCU	1301	AGCCCACA GCCGAAACCCGAGUCACGUCU ACCACCAU	1532
546	GCUCCUGU G UGCCCUGA	1302	UCACGCCA CCCCAAACCCCAGUGACCUCU ACACCACC	1533
549	CCUGUCUG G CCUCACCC	1303	CCCUCACG CCCCAAACCCGACUCAGGUCU CACACACC	1534
557	GCCUGACC G UCACCGAC	1304	CUCGGUGA CCCCAAACCCGAGUGACGUCU CCUCACCC	1535
568	ACCCACUU G CUGGGCAA	1305	UUGCCCAG GCCGAAAGGCGAGUGAGGUCU AAGUCGGU	1536
573	CUUGCUGG G CAAGUGCC	1306	GGCACUUG GCCGAAAGGCGAGUGAGGUCU CCAGCAAG	1537
577	CUGGGCAA G UGCCUCCU	1307	AGGAGGCA GCCGAAAGGCGAGUGAGGUCU UUGCCCAG	1538
579	GGGCAAGU G CCUCCUAA	1308	UUAGGAGG GCCGAAAGGCGAGUGAGGUCU ACUUGCCC	1539
588	CCUCCUAA G CCCGGUGG	1309	CCACCGGG GCCGAAAGGCGAGUGAGGUCU UUAGGACG	1540
593	UAAGCCCG G UGGUGCUG	1310	CAGCACCA GCCGAAAGGCGAGUGAGGUCU CGGGCUUA	1541
596	GCCCGGUG G UGCUGGCU	1311	AGCCAGCA GCCGAAAGGCGAGUGAGGUCU CACCGGGC	1542
598	CCGGUGGU G CUGGCUGC	1312	GCAGCCAG GCCGAAAGGCGAGUGAGGUCU ACCACCGG	1543
602	UGGUGCUG G CUOCCUAC	1313	GUAGUCAG GCCGAAAGGCGAGUGAGGUCU CAGCACCA	1544
605	UGCUGGCU G CCUACGCU	1314	AGCGUAGG GCCGAAAGGCGAGUGAGGUCU AGCCAGCA	1545
611	CUGCCUAC G CUCAGAAC	1315	GUUCUGAG GCCGAAAGGCGAGUGAGGUCU GUAGGCAG	1546
624	GAACCGGA G UCUGCGGG	1316	CCCGCAGA GCCGAAAGGCGAGUGAGGUCU UCCGCUUC	1547
628	CGGAGUCU G CGGGUGCU	1317	AGCACCCG GCCGAAAGGCGAGUGAGCUCU AGACUCCG	1548
632	GUCUGCGG G UGCUUGCG	1318	CGCAAGCA GCCGAAAGGCGAGUGAGGUCU CCGCAGAC	1549
634	CUGCGGGU G CUUGCGCC	1319	GGCGCAAG GCCGAAAGGCGAGUGAGGUCU ACCCGCAG	1550
638	GGGUGCUU G CGCCCGCA	1320	UGCGGGCG GCCGAAAGGCGAGUGAGGUCU AAGCACCC	1551
640	GUGCUUGC G CCCGCAUU	1321	AAUGCGGG GCCGAAAGGCGAGUGAGGUCU GCAAGCAC	1552
644	UUGCGCCC G CAUUGGAC	1322	GUCCAAUG GCCGAAAGGCGAGUGAGGUCU GGGCGCAA	1553
658	GACAACUC G UUGUGCCA	1323	UGGCACAA GCCGAAAGGCGAGUGAGGUCU GAGUGGUC	1554
661	AACUCGUU G UGCCAAGC	1324	GCUUGGCA GCCGAAAGGCGAGUGAGGUCU AACGAGUU	1555
663	CUCGUUGU G CCAAGCCU	1325	AGGCUUGG GCCGAAAGGCGAGUGAGGUCU ACAACGAG	1556
668	UGUGCCAA G CCUUCGCC	1326	GGCGAAGG GCCGAAAGGCGAGUGAGGUCU UUGGCACA	1557
674	AAGCCUUC G CCUUCUUC	1327	GAAGAAGG GCCGAAAGGCGAGUGAGGUCU GAAGGCUU	1558
685	UUCUUCAU G UCCUUCUU	1328	AAGAAGGA GCCGAAAGGCGAGUGAGGUCU AUGAAGAA	1559
697	UUCUUUGG G CUCUCCUC	1329	GAGGAGAG GCCGAAAGGCGAGUGAGGUCU CCAAAGAA	1560
712	UCGACACU G CAACUCCU	1330	AGGAGUUG GCCGAAAGGCGAGUGAGGUCU AGUGUCGA	1561
722	AACUCCUG G CCAUGGCA	1331	UGCCAUGG GCCGAAAGGCGAGUGAGGUCU CAGGAGUU	1562
728	UGGCCAUG G CACUGGAG	1332	CUCCAGUG GCCGAAAGGCGAGUGAGGUCU CAUGOCCA	1563
736	GCACUGGA G UGCUGGCU	1333	AGCCAGCA GCCGAAAGGCGAGUGAGGUCU UCCAGUGC	1564
738	ACUGGAGU G CUGGCUCU	1334	AGAGCCAG GCCGAAAGGCGAGUGAGGUCU ACUCCAGU	1565
742	GAGUCCUG G CUCUCCCU	1335	AGGGAGAG GCCGAAAGGCGAGUGAGGUCU CACCACUC	1566

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
754	UCCCUAGG G CACCCUUU	1336	AAAGGGUG GCCGAAAGGCGAGUGAGGUCU CCUAGGGA	1567
775	UACCGACG G CACAUCAC	1337	GUGAUGUG GCCGAAAGGCGAGUGAGGUCU CGUCGGUA	1568
787	AUCACCCU G CGCCUGGG	1338	CCCAGGCG GCCGAAAGGCGAGUGAGGUCU AGGGUGAU	1569
789	CACCCUGC G CCUGGGCG	1339	CGCCCAGG GCCGAAAGGCGAGUGAGGUCU GCAGGGUG	1570
795	GCGCCUGG G CGCACUGG	1340	CCAGUGCG GCCGAAAGGCGAGUGAGGUCU CCAGGCGC	1571
797	GCCUGGGC G CACUGGUG	1341	CACCAGUG GCCGAAAGGCGAGUGAGGUCU GCCCAGGC	1572
803	GCGCACUG G UGGCCCCG	1342	CGGGGCCA GCCGAAAGGCGAGUGAGGUCU CAGUGCGC	1573
806	CACUGGUG G CCCCGGUG	1343	CACCGGGG GCCGAAAGGCGAGUGAGGUCU CACCAGUG	1574
812	UGGCCCCG G UGGUGAGC	1344	GCUCACCA GCCGAAAGGCGAGUGAGGUCU CGGGGCCA	1575
815	CCCCGGUG G UGAGCGCC	1345	GGCGCUCA GCCGAAAGGCGAGUGAGGUCU CACCGGGG	1576
819	GGUGGUGA G CGCCUUCU	1346	AGAAGGCG GCCGAAAGGCGAGUGAGGUCU UCACCACC	1577
821	UGGUGAGC G CCUUCUCC	1347	GGAGAAGG GCCGAAAGGCGAGUGAGGUCU GCUCACCA	1578
833	UCUCCCUG G CUUUCUGC	1348	GCAGAAAG GCCGAAAGGCGAGUGAGGUCU CAGGGAGA	1579
840	GGCUUUCU G CGCGCUAC	1349	GUAGCGCG GCCGAAAGGCGAGUGAGGUCU AGAAAGCC	1580
842	CUUUCUGC G CGCUACCU	1350	AGGUAGCG GCCGAAAGGCGAGUGAGGUCU GCAGAAAG	1581
844	UUCUGCGC G CUACCUUU	1351	AAAGGUAG GCCGAAAGGCGAGUGAGGUCU GCGCAGAA	1582
858	UUUCAUGG G CUUCGGGA	1352	UCCCGAAG GCCGAAAGGCGAGUGAGGUCU CCAUGAAA	1583
868	UUCGGGAA G UUCGUGCA	1353	UGCACGAA GCCGAAAGGCGAGUGAGGUCU UUCCCGAA	1584
872	GGAAGUUC G UCCAGUAC	1354	GUACUGCA GCCGAAAGGCGAGUGAGGUCU GAACUUCC	1585
874	AAGUUCGU G CAGUACUG	1355	CAGUACUG GCCGAAAGGCGAGUGAGGUCU ACGAACUU	1586
877	UUCGUGCA G UACUGCCC	1356	GGGCAGUA CCCGAAAGGCGAGUGAGGUCU UGCACGAA	1587
882	GCAGUACU G CCCCGGCA	1357	UGCCGGGG GCCGAAAGGCCAGUGAGGUCU AGUACUGC	1588
888	CUGCCCCG G CACCUGGU	1358	ACCAGGUG GCCGAAAGGCGAGUGAGGUCU CGGGGCAG	1589
895	GOCACCUG G UGCUUUAU	1359	AUAAAGCA GCCGAAAGGCGAGUGAGGUCU CAGGUGCC	1590
897	CACCUGGU G CUUUAUCC	1360	GGAUAAAG GCCGAAAGGCGAGUGAGGUCU ACCAGGUG	1591
911	UCCAGAUG G UCCACGAG	1361	CUCCUGGA GCCGAAAGGCGAGUGAGGUCU CAUCUGGA	1592
924	CGAGGAGG G CUCGCUGU	1362	ACAGCGAG GCCGAAAGGCGAGUGAGGUCU CCUCCUCG	1593
928	GAGGGCUC G CUGUCGGU	1363	ACCGACAG GCCGAAAGGCGAGUGAGGUCU GAGCCCUC	1594
931	GGCUCGCU G UCGGUGCU	1364	AGCACCGA GCCGAAAGGCGAGUGAGGUCU AGCGAGCC	1595
935	CGCUGUCG G UGCUGGGG	1365	CCCCAGCA GCCGAAAGGCGAGUGAGGUCU CGACAGCG	1596
937	CUGUCGGU G CUGCGGUA	1366	UACCCCAG GCCGAAACCCGAGUGAGGUCU ACCGACAG	1597
943	GUCCUGOG G UACUCUGU	1367	ACAGAGUA GCCGAAAGGCGAGUGAGGUCU CCCAGCAC	1598
950	CGUACUCU G UCCUCUAC	1368	GUACAGCA GCCGAAAGCCGAGUGAGGUCU AGACUACC	1599
952	UACUCUGU G CUCUACUC	1369	GAGUAGAC GCCGAAAGCCGAGUCACGUCU ACAGAGUA	1600
963	CUACUCCA G CCUCAUGG	1370	CCAUGACG CCCGAAACGCGACUGAGGUCU UGGAGUAG	1601
971	GCCUCAUG G CGCUGCUG	1371	CAGCAGCG GCCCAAAGGCGAGUGAGGUCU CAUGAGGC	1602

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
973	CUCAUGOC G CUGCUCCU	1372	ACCAGCAG GCCGAAAGGCGAGUGAGCUCU OCCAUGAG	1603
976	AUGGCGCU G CUCGUCCU	1373	AGGACCAG GCCGAAAGGCGAGUCAGGUCU AGCGCCAU	1604
980	CGCUGCUG G UCCUCGCC	1374	GGCGACGA GCCGAAAGGCGACUGAGGUCU CAGCAGCG	1605
986	UGGUCCUC G CCACCGUC	1375	CACGGUGG GCCGAAAGGCGAGUGACGUCU GAGGACCA	1606
992	UCCCCACC G UGCUGUGC	1376	GCACAGCA GCCGAAAGGCGAGUGAGGUCU GGUGGCGA	1607
994	GCCACCGU G CUGUGCAA	1377	UUGCACAG GCCGAAAGGCGAGUGACGUCU ACGGUGGC	1608
997	ACCCUGCU G UGCAACCU	1378	AGCUUGCA GCCGAAAGGCGACUGAGGUCU AGCACCCU	1609
999	CGUGCUGU G CAACCUCG	1379	CGAGGUUG GCCCAAAGGCGAGUGAGGUCU ACAGCACG	1610
1008	CAACCUCC G CCCCAUGC	1380	GCAUGGCG GCCGAAAGGCCAGUCAGGUCU CGACGUUG	1611
1010	ACCUCGGC G CCAUGCGC	1381	GCGCAUGG GCCGAAAGGCGAGUGAGGUCU CCCGAGGU	1612
1015	GGCCCCAU G CCCAACCU	1382	AGGUUGCC GCCGAAAGGCCAGUGAGGUCU AUGCCCCC	1613
1017	CGCCAUCC G CAACCUCU	1383	AGAGGUUG CCCGAPAGGCGACUGAGGUCU GCAUGGCG	1614
1028	ACCUCUAU G CGAUGCAC	1384	GUCCAUCG GCCCAAAGGCGAGUGAGCUCU AUAGAGGU	1615
1033	UAUGCGAU G CACCGCCC	1385	CGCCGGUG GCCCAAACGCGAGUGAGGUCU AUCGCAUA	1616
1039	AUGCACCC G CUCCUCCA	1386	UCCAGCCC CCCCAAAGGCGAGUCACCUCU CGGUCCAU	1617
1042	CACCCGCC G CUCCACCC	1387	CCCUGCAG CCCGAAACCCCACUGAGGUCU CCCCCCUG	1618
1045	CGGCCCCU G CACCUCCA	1388	UCCCGCUG CCCCAAAGGCGAGUCACCUCU AGCCGCCC	1619
1048	CCCCUGCA G CCCCACCC	1389	CCCUCCCC GCCGAAAGCCCACUGACGUCU UGCACCCG	1620
1051	CUCCACCC G CACCCCCG	1390	OCCUGGUC CCCCAAAGGCGAGUCAGCUCU CGCUGCAG	1621
1057	CCCCACCC G CUCUCCUC	1391	CACCACCG GCCGAAAGCCCAGUGAGCUCU CCCUCCCG	1622
1059	CCACCCCC G CUCCUCCA	1392	UCCACCAC CCCCAAAGGCGACUCACCUCU GCGGCUCC	1623
1065	GCCCUCCU G CACCACGG	1393	CCCUGGUG GCCCAAACCCCAGUCAGCUCU ACCACCUC	1624
1077	CACGGACU G UCCCCACC	1394	GCUCCCCA GCCGAAACCCGACUCAGGUCU AGUCCCUC	1625
1079	CCCACUCU G CCCAGCCC	1395	CUCCUCUC CCCCAAAGCCGAGUGACCUCU ACAGUCCC	1626
1084	UCUGCCCA G CCCCCCGC	1396	GCGCGCGG CCCCAAACCCCAGUGACGUCU UCCCCACA	1627
1087	CCCCAGCC G CUCUCUCA	1397	UCCCCCCC GCCGAAAGGCGACUCACGUCU GUCUCCUC	1628
1089	CGAGCCGC G CGCGGACG	1398	CGUCCGCG CCCCAAACCCCAGUGAGGUCU CCCGCUCG	1629
1091	AUCCUCUC G CGGACCCC	1399	CCCCUCCG GCCGAAAGGCGACUCACGUCU CCGCCCCU	1630
1106	CCAGGCAA G CCUCCCCU	1400	AGGGGACG CCCGAAACCCGAGUGAGCUCU UUCCCUCC	1631
1108	ACCCAAGC G UCCCCUCA	1401	UCAGCCCA GCCGAAAGGCCAGUCACCUCU CCUUCCCU	1632
1117	UCCCCUCA G CCCCUCGA	1402	UCCAGGUC CCCGAAACCCGAGUCAGCUCU UCAGUGGA	1633
1129	CUGGAGGA G CUCCAUCA	1403	UCAUCCAG GCCGAAACCCCACUCAGGUCU UCCUCCAC	1634
1144	CACCUCCU G CUCCUGUC	1404	UCCACCAC CCCCAAAGGCGACUGACCUCU AGGAGGUC	1635
1147	CUCCUCCU G CUGCCGCU	1405	ACCGCCAG CCCGAAACCCGAGUGAGCUCU ACCACCAG	1636
1151	UCCUCCUC G CUCUCAUG	1406	CAUCACCC GCCGAAAGCCGACUGAGGUCU CACCACCA	1637

TABLE V-continued

Human PTGDR Zinzyme and Substrate Sequence

Pos	Substrate	Seq ID	Zinzyme	Seq ID
1153	CUGCUGGC G CUGAUGAC	1407	GUCAUCAG GCCGAAAGGCGAGUGAGGUCU UCCACCAG	1638
1163	UGAUGACC G UGCUCUUC	1408	GAAGAGCA GCCGAAAGGCGAGUCAGGUCU GGUCAUCA	1639
1165	AUGACCGU G CUCUUCAC	1409	GUGAAGAG GCCGAAAGGCGAGUGAGGUCU ACGGUCAU	1640
1177	UUCACUAU G UGUUCUCU	1410	AGAGAACA GCCGAAACCCGAGUGAGGUCU AUAGUGAA	1641
1179	CACUAUGU G UUCUCUGC	1411	GCAGAGAA GCCGAAAGGCGACUGACCUCU ACAUACUC	1642
1186	UGUUCUCU G CCCGUAAU	1412	AUUACGGG GCCGAAAGGCGAGUGAGGUCU AGAGAACA	1643
1190	CUCUGCCC G UAAUUUAU	1413	AUAAAUUA GCCCAAAGGCGAGUCAGGUCU GGGCAGAG	1644
1200	AAUUUAUC G CGCUUACU	1414	AGUAAGCG GCCGAAAGGCGACUCAGGUCU GAUAAAUU	1645
1202	UUUAUCGC G CUUACUAU	1415	AUAGUAAG GCCCAAACCCCAGUGAGGUCU GCCAUAAA	1646
1214	ACUAUGCA G CAUUUAAC	1416	CUUAAAUG CCCGAAAGGCGAGUGACCUCU UCCAUACU	1647
1226	UUAAGGAU G UCAACCAG	1417	CUCCUCCA GCCGAAACGCGAGUGAGCUCU AUCCUUAA	1648
1256	CUGAAGAA G CAGAAGAC	1418	GUCUUCUG CCCCAAACCCGACUGAGCUCU UUCUUCAG	1649
1271	ACCUCCGA G CCUUGCCA	1419	UCGCAAGG GCCGAAACGCGAGUGAGCUCU UCGGAGGU	1650
1276	CCAGCCUU G CCAUUUCU	1420	AGAAAUCG GCCGAAACCCGACUGAGGUCU AACGCUCG	1651
1289	UUCUAUCU G UGAUCUCA	1421	UCAAAUCA CCCGAAAGCCCAGUGAGGUCU AGAUAGAA	1652
1301	UUUCAAUU G UGGACCCU	1422	ACCGUCCA GCCCAAACGCCAGUGAGGUCU AAUUCAAA	1653
1337	GAUCUCCA G UAUUUCCG	1423	CCGAAAUA CCCGAAAGGCGAGUGAGGUCU UGGAGAUC	1654
1381	CCUCUUAG G UACAGGAG	1424	CUCCUGUA GCCGAAAGGCGAGUGAGCUCU CUAAGAGG	1655
1389	CUACAGGA G CCGGUGCA	1425	UGCACCGC GCCGAAACCCGAGUGAGGUCU UCCUGUAC	1656
1393	AGGAGCCG G UCCAGCAA	1426	UUCCUGCA CCCCAAAGGCGAGUCACCUCU CGGCUCCU	1657
1395	CACCCCCU G CAGCAAUU	1427	AAUUCCUC GCCGAAACCCCACUGAGGUCU ACCCCCUC	1658
1398	CCGCUGCA G CAAUUCCA	1428	UGGAAUUG CCCCAAAGGCCAGUCACCUCU UGCACCCG	1659
1422	CCAAUCCA G UCUGUCAC	1429	CUCACACA CCCCAAACCCCACUGAGGUCU UCCAUUCC	1660
1426	UCCAGUCU G UCACACUC	1430	CACUGUCA CCCCAAAGGCCAGUCACCUCU AGACUGGA	1661
1432	CUCUCACA G UCUUUUUC	1431	CAAAAACA CCCGAAACCCCACUGAGCUCU UCUCACAG	1662
1434	CUGACACU G UUUUUCAC	1432	CUGAAAAA CCCGAAACGCCACUCACCUCU ACUGUCAC	1663
1446	UUCACUCU G UCCUAAGC	1433	CCUUACCA CCCCAAACGCGAGUGACCUCU AGACUGAA	1664
1449	ACUCUGUG G UAACCUCA	1434	UCACCUUA GCCGAAACCCCACUGAGCUCU CACACACU	1665
1453	UCUCCUAA G CUGAGGAA	1435	UUCCUCAC CCCGAAAGGCGACUCACCUCU UUACCACA	1666
1465	ACCAAUAU G UCACAUUU	1436	AAAUCUGA CCCCAAACCCGAGUGACCUCU AUAUUCCU	1667
1477	CAUUUUCA G UCAAACAA	1437	UUCUUUCA CCCCAAACCCCACUCACCUCU UGAAAAUC	1668

Input Sequence = PTCDR_composit.
Cut Site = G/Y
Arm Length = 8.
Core Sequence = CCcgaaagGCGaGuCaaGGuCu
PTGDR_composit (1 to 993 of HSU31332 (PTGDR 5') +1 to 495 of HSU31099 (PTCDR 3') ; 1488 nt)

[0233]

TABLE VI

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
9	GAAUUCUG G CUAUUUUC	1207	GAAAATAG GGCTAGCTACAACGA CAGAATTC	1715
12	UUCUGGCU A UUUUCCUC	1	GAGGAAAA GGCTAGCTACAACGA AGCCAGAA	1716
23	UUCCUCCU G CCGUUCCG	1208	CGGAACGG GGCTAGCTACAACGA AGGAGGAA	1717
26	CUCCUGCC G UUCCGACU	1209	AGTCGGAA GGCTAGCTACAACGA GGCAGGAG	1718
32	CCGUUCCG A CUCGGCAC	1669	GTGCCGAG GGCTAGCTACAACGA CGGAACGG	1719
37	CCGACUCG G CACCAGAG	1210	CTCTGGTG GGCTAGCTACAACGA CGAGTCGG	1720
39	GACUCGGC A CCAGAGUC	463	GACTCTGG GGCTAGCTACAACGA GCCGAGTC	1721
45	GCACCAGA G UCUGUCUC	1211	GAGACAGA GGCTAGCTACAACGA TCTGGTGC	1722
49	CAGAGUCU G UCUCUACU	1212	AGTAGAGA GGCTACCTACAACGA AGACTCTG	1723
55	CUGUCUCU A CUGAGAAC	13	GTTCTCAG GGCTAGCTACAACGA AGAGACAG	1724
62	UACUGAGA A CGCAGCGC	1670	GCGCTGCG GGCTAGCTACAACGA TCTCAGTA	1725
64	CUGAGAAC G CAGCGCGU	1213	ACGCGCTG GGCTAGCTACAACGA GTTCTCAG	1726
67	AGAACGCA G CGCGUCAG	1214	CTGACGCG GGCTAGCTACAACGA TGCGTTCT	1727
69	AACGCAGC G CGUCAGGG	1215	CCCTGACG GGCTAGCTACAACGA GCTGCGTT	1728
71	CGCAGCGC G UCAGGGCC	1216	GGCCCTGA GGCTAGCTACAACGA GCGCTGCG	1729
77	GCGUCAGG G CCGAGCUC	1217	CAGCTCGG GGCTAGCTACAACCA CCTGACGC	1730
82	AGCCCCGA G CUCUUCAC	1218	GTCAAGAC GCCTAGCTACAACGA TCGGCCCT	1731
89	AGCUCUUC A CUGGCCUG	475	CAGGCCAG GGCTAGCTACAACGA GAAGAGCT	1732
93	CUUCACUG G CCUGCUCC	1219	GCACCAGG GGCTAGCTACAACGA CAGTGAAG	1733
97	ACUCCCCU G CUCCGCGC	1220	GCGCGGAG GGCTAGCTACAACGA AGOCCACT	1734
102	CCUGCUCC G CCCUCUUC	1221	CAAGAGCG GGCTAGCTACAACGA GGACCAGG	1735
104	UGCUCCGC G CUCUUCAA	1222	TTCAAGAG GGCTAGCTACAACGA GCGGAGCA	1736
112	GCUCUUCA A UGCCAGCG	1671	CGCTGGCA GGCTAGCTACAACGA TGAAGAGC	1737
114	UCUUCAAU G CCAGCGCC	1223	GGCGCTGG GGCTAGCTACAACGA ATTGAAGA	1738
118	CAAUGCCA G CGCCAGGC	1224	GCCTGGCG GGCTAGCTACAACGA TGGCATTG	1739
120	AUGCCAGC G CCAGCCGC	1225	GCGCCTGG GGCTAGCTACAACGA GCTGCCAT	1740
125	AGCGCCAG G CGCUCACC	1226	GGTGAGCG CGCTAGCTACAACGA CTGGCGCT	1741
127	CGCCAGGC G CUCACCCU	1227	AGGGTGAG GGCTAGCTACAACGA GCCTGGCG	1742
131	AGGCGCUC A CCCUGCAG	489	CTGCAGGG GGCTAGCTACAACGA GAGCGCCT	1743
136	CUCACCCU G CAGAGCGU	1228	ACGCTCTG GGCTAGCTACAACGA AGGGTGAG	1744
141	CCUGCAGA G CGUCCCGC	1229	GCGGGACG GGCTAGCTACAACGA TCTGCAGG	1745
143	UGCAGAGC G UCCCGCCU	1230	AGGCGGGA GGCTAGCTACAACGA GCTCTGCA	1746
148	AGCGUCCC G CCUCUCAA	1231	TTGAGAGG GGCTAGCTACAACGA GGGACGCT	1747
163	AAAGAGGG G UGUGACCC	1232	GGGTCACA GGCTAGCTACAACGA CCCTCTTT	1748

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
165	AGAGGGGU G UGACCCGC	1233	GCGGGTCA GGCTAGCTACAACGA ACCCCTCT	1749
168	GCGGUGUG A CCCGCGAG	1672	CTCGCGGG GGCTAGCTACAACGA CACACCCC	1750
172	UGUGACCC G CGAGUUUA	1234	TAAACTCG GGCTAGCTACAACGA GGGTCACA	1751
176	ACCCGCGA G UUUAGAUA	1235	TATCTAAA GGCTAGCTACAACGA TCGCGGGT	1752
182	GAGUUUAG A UAGGAGGU	1673	ACCTCCTA GGCTAGCTACAACGA CTAAACTC	1753
189	GAUAGGAG G UUCCUGCC	1236	GGCAGGAA GGCTAGCTACAACGA CTCCTATC	1754
195	AGGUUCCU G CCGUGGGG	1237	CCCCACCG GGCTAGCTACAACGA AGGAACCT	1755
198	UUCCUGCC G UGGGGAAC	1238	GTTCCCCA GGCTAGCTACAACGA GCCAGGAA	1756
205	CGUGGGGA A CACCCCGC	1674	CCCGGGTG GGCTAGCTACAACGA TCCCCACG	1757
207	UGGCGAAC A CCCCGCCG	505	CGGCGGGG GGCTAGCTACAACGA GTTCCCCA	1758
212	AACACCCC G CCCCCCUC	1239	GAGCCCCG GGCTAGCTACAACGA GCGGTGTT	1759
215	ACCCCGCC G CCCUCGGA	1240	TCCGAGCG GGCTAGCTACAACGA GGCGGCGT	1760
224	CCCUCGGA G CUUUUUCU	1241	AGAAAAAG GGCTAGCTACAACGA TCCGAGGG	1761
233	CUUUUUCU G UGGCGCAG	1242	CTGCGCCA GGCTAGCTACAACGA AGAAAAAG	1762
236	UUUCUCUG G CGCAGCUU	1243	AAGCTGCC GGCTAGCTACAACGA CACAGAAA	1763
238	UCUGUGGC G CAGCUUCU	1244	AGAAGCTG GGCTAGCTACAACGA GCCACAGA	1764
241	GUGGCGCA G CUUCUCCG	1245	CGGAGAAG GCCTAGCTACAACGA TOCCCCAC	1765
249	GCUUCUCC G CCCGAGCC	1246	GGCTCGGG CGCTAGCTACAACGA GGAGAAGC	1766
255	CCGCCCGA G CCCCGCGC	1247	GCGCGCGG GGCTACCTACAACGA TCGGGCGG	1767
258	CCCGAGCC G CGCGCGGA	1248	TCCGCGCG GGCTAGCTACAACCA GGCTCCCG	1768
260	CGAGCCGC G CGCGGAGC	1249	GCTCCCCG GGCTAGCTACAACGA GCGGCTCG	1769
262	ACCCGCCC G CGGAGCUG	1250	CAGCTCCG GGCTAGCTACAACGA CCGCGCCT	1770
267	CGCGCGGA G CUCCCGCG	1251	CCCGGCAG GGCTAGCTACAACCA TCCGCGCG	1771
270	GCGCACCU G CCGGCGGC	1252	GCCCCCCG GGCTAGCTACAACGA AGCTCCGC	1772
277	UGCCGGGG G CUCCUUAG	1253	CTAAGGAC GGCTAGCTACAACCA CCCCGGCA	1773
285	CCUCCUUA G CACCCCGG	1254	CCCCGGTC GCCTAGCTACAACGA TAAGGAGC	1774
287	UCCUUAGC A CCCCGGCG	527	CCCCCGGG GGCTAGCTACAACGA CCTAAGGA	1775
293	GCACCCGG G CGCCGCCG	1255	CCCCGGCG CCCTAGCTACAACCA CCGGCTGC	1776
295	ACCCCCCC G CCGGGCCC	1256	CGCCCCGC GCCTAGCTACAACGA CCCCGGCT	1777
301	CCGCCGGC G CCCUCGCC	1257	GGCGAGGG GGCTAGCTACAACGA CCCCCCCC	1778
307	GGGCCCUC G CCCUUCCG	1258	CGCAAGCC GCCTAGCTACAACCA GAGGGCCC	1779
315	GCCCUUCC G CAGCCUUC	1259	GAAGGCTG GCCTAGCTACAACGA GGAACGGC	1780
318	CUUCCGCA G CCUUCACU	1260	ACTCAAGC GGCTACCTACAACCA TGCCGAAG	1781
324	CAGCCUUC A CUCCACCC	541	CCCTCGAG GGCTACCTACAACGA CAACCCTG	1782
330	UCACUCCA G CCCUCUGC	1261	GCACACGG GGCTAGCTACAACCA TGGACTCA	1783

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
337	ACCCCUCU G CUCCCGCA	1262	TCCGCGAG GCCTACCTACAACGA ACAGGCCT	1784
343	CUGCUCCC G CACCCCAU	1263	ATGCCGTG CCCTACCTACAACGA CCGACCAC	1785
345	GCUCCCCC A CGCCAUCA	552	TCATGCCC CGCTACCTACAACCA GCGGCAGC	1786
347	UCCCGCAC G CCAUCAAG	1264	CTTCATGC GCCTAGCTACAACCA GTGCGGGA	1787
350	CGCACGCC A UCAACUCC	554	CGACTTCA GGCTACCTACAACGA GGCGTCCG	1788
355	CCCAUCAA G UCGCCGUU	1265	AACGCCGA GGCTAGCTACAACCA TTCATCGC	1789
358	AUCAACUC G CCCUUCUA	1266	TACAACCG CGCTAGCTACAACGA GACTTCAT	1790
361	AAGUCGCC G UUCUACCC	1267	CGCTACAA GGCTAGCTACAACCA CCCGACTT	1791
366	GCCCUUCU A CCCCUGCC	55	GCCAGCGG GCCTAGCTACAACCA ACAACCGC	1792
369	GUUCUACC G CUGCCAGA	1268	TCTGCCAG GCCTACCTACAACGA GGTACAAC	1793
372	CUACCCCU G CCAGAACA	1269	TGTTCTCC GCCTAGCTACAACCA AGCCGTAG	1794
378	CUCCCACA A CACCACCU	1675	ACCTCCTC GCCTACCTACAACGA TCTCCCAC	1795
380	GCCACAAC A CCACCUCU	561	ACACCTCC CCCTACCTACAACCA CTTCTCCC	1796
383	AGAACACC A CCUCUCUG	563	CACAGAGG CCCTACCTACAACGA CCTCTTCT	1797
389	CCACCUCU G UCGAAAAA	1270	TTTTTCCA CGCTAGCTACAACCA AGAGCTCC	1798
399	CCAAAAAG G CAACUCCG	1271	CCCAGTTG CCCTACCTACAACGA CTTTTTCC	1799
402	AAAACCCA A CUCGCCCC	1676	CCCCCCAC CCCTACCTACAACCA TGCCTTTT	1800
407	CCAACUCG G CCCUCAUC	1272	CATCACCC GCCTACCTACAACCA CCACTTCC	1801
410	ACUCCCCC G UGAUCGCC	1273	CCCCATCA CCCTACCTACAACQA CGCCGACT	1802
413	CCGCCCUG A UCCCCCCC	1677	CCCCCCCA CCCTACCTACAACCA CACCCCCC	1803
417	CCUCAUCC G CCGCCUCC	1274	CCACCCCC CGCTAGCTACAACCA CCATCACC	1804
422	UCCCCCCC G UCCUCUUC	1275	CAACACCA CCCTACCTACAACCA CCCCCCCA	1805
424	CCCCCGCU G CUCUUCAG	1276	CTCAACAC CCCTACCTACAACGA ACCCCCCC	1806
432	CCUCUUCA G CACCCCCC	1277	CCCCCCTC CCCTACCTACAACCA TCAAGACC	1807
434	UCUUCACC A CCGGCCUC	572	CACGCCCC CCCTACCTACAACCA CCTCAAGA	1808
438	CACCACCG G CCUCCUCC	1278	CCACCAGC GCCTACCTACAACGA CGCTCCTC	1809
447	CCUCCUCC G CAACCUGC	1279	CCACCTTC CCCTAGCTACAACCA CCAGGAGC	1810
450	CCUGCCCA A CCUCCUCC	1678	CCACCAGC GCCTACCTACAACGA TCCCCACC	1811
454	GCCAACCU G CUGGCCCU	1280	AGGGCCAC GGCTAGCTACAACGA AGGTTGCC	1812
458	ACCUGCUG G CCCUGGGG	1281	CCCCAGGG GGCTAGCTACAACGA CAGCAGGT	1813
466	GCCCUGGG G CUGCUCGC	1282	GCCAGCAG GGCTAGCTACAACGA CCCAGCGC	1814
469	CUCGGGCU G CUGGCGCG	1283	CGCGCCAC CGCTAGCTACAACGA AGCCCCAG	1815
473	GCCUGCUG G CCCGCUCG	1284	CGAGCGCG GGCTAGCTACAACGA CAGCAGCC	1816
475	CUGCUGGC G CGCUCGGG	1285	CCCGAGCG CGCTAGCTACAACGA GCCAGCAG	1817
477	GCUCGCGC G CUCCCGGC	1286	GCCCCGAC GGCTACCTACAACGA GCGCCAGC	1818

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
484	CCCUCGGG G CUGGCGUG	1287	CACCCCAG GGCTAGCTACAACCA CCCGAGCG	1819
490	GGCCUGGC G UGCUGCUC	1288	CACCACCA GCCTACCTACAACGA CCCAGCCC	1820
493	CUCCGGUG G UGCUCCCC	1289	CGCCAGCA CCCTAGCTACAACGA CACCCCAG	1821
495	CCGGUCGU G CUCCCGGC	1290	CCCCCGAG GGCTAGCTACAACCA ACCACCCC	1822
499	UCGUGCUC G CCGCCUCC	1291	CCACCCCC GGCTAGCTACAACGA CAGCACCA	1823
502	UCCUCGCC G CCUCCACU	1292	ACTGGACG GCCTACCTACAACCA CGCCAGCA	1824
504	CUCGCGCC G UCCACUCC	1293	CCAGTCGA GGCTAGCTACAACCA GCCGCGAG	1825
508	CCCCGUCC A CUCCCCCC	591	GCGCGCAG GCCTAGCTACAACGA CGACGCCC	1826
511	CGUCCACU G CGCCCGCU	1294	AGCGGGCG GGCTAGCTACAACGA AGTCCACC	1827
513	UCCACUCC G CCCGCUGC	1295	GCACCCGC CGCTAGCTACAACCA GCACTCGA	1828
517	CUGCGCCC G CUCCCCUC	1296	CAGGUCAG GGCTACCTACAACGA GGGCGCAG	1829
520	CCCCCCCU G CCCUCCGU	1297	ACCGAGGG GGCTAGCTACAACCA AGCCCCCG	1830
527	UGCCCUCC G UCUUCUAC	1298	GTAGAAGA GCCTAGCTACAACGA CCAGGGCA	1831
534	GCUCUUCU A CAUGCUCC	69	CCACCATG GGCTAGCTACAACCA ACAAGACC	1832
536	UCUCCUAC A UGCUGCUC	601	CACCACCA CCCTACCTACAACGA GTAGAAGA	1833
538	UUCUACAU G CUGGUGUG	1299	CACACCAG CGCTAGCTACAACGA ATGTAGAA	1834
542	ACAUGCUG G UCUCUCCC	1300	CCCACACA CGCTACCTACAACCA CACCATGT	1835
544	AUGCUGGU G UGUGGCCU	1301	ACGCCACA GCCTACCTACAACGA ACCAGCAT	1836
546	CCUGGUGU G UCCCCUGA	1302	TCACGCCA GGCTAGCTACAACCA ACACCAGC	1837
549	GGUCUGUG G CCUGACGG	1303	CCGTCAGC GCCTAGCTACAACGA CACACACC	1838
554	CUGCCCUG A CCGUCACC	1679	GGTGACCC GGCTAGCTACAACGA CAGGOCAC	1839
557	CCCUCACC G UCACOGAC	1304	CTCCCTGA CCCTACCTACAACGA CCTCACCC	1840
560	UCACCCUC A CCCACUUC	605	CAACTCCC CGCTAGCTACAACCA GACCGTCA	1841
564	GGUCACCC A CUUCCUGG	1680	CCACCAAC CCCTACCTACAACCA CCCTCACC	1842
568	ACCGACUU G CUCCCCAA	1305	TTCCCCAC GCCTAGCTACAACCA AAGTCGCT	1843
573	CUUCCUCC G CAACUCCC	1306	GGCACTTC CCCTAGCTACAACCA CCACCAAG	1844
577	CUCCCCAA G UCCCUCCU	1307	ACGACGCA CCCTACCTACAACGA TTCCCCAC	1845
579	CCGCAAGU G CCUCCUAA	1308	TTACCACG CCCTACCTACAACCA ACTTGCCC	1846
588	CCUCCUAA G CCCGGUCC	1309	CCACCCCC CCCTAGCTACAACCA TTACCAGG	1847
593	UAAGCCCC G UCCUCCUG	1310	CACCACCA GGCTACCTACAACGA CGGGCTTA	1848
596	CCCCCCUG G UGCUGCCU	1311	AGCCACCA CCCTAGCTACAACCA CACCCGGC	1849
598	CCGGUGGU G CUCCCUGC	1312	CCACCCAG GGCTACCTACAACGA ACCACCCC	1850
602	UCCUCCUC G CUGCCUAC	1313	GTAGCCAC CCCTAGCTACAACCA CACCACCA	1851
605	UGCUGGCU G CCUACCCU	1314	ACCCTAGG GGCTACCTACAACGA AGCCACCA	1852
609	CCCUCCCU A CGCUCACA	74	TCTCACCC CCCTAGCTACAACCA ACCCACCC	1853

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
611	CUGCCUAC G CUCAGAAC	1315	CTTCTGAG CCCTACCTACAACGA GTACCCAG	1854
618	CGCUCAGA A CCCCACUC	1681	CACTCCCG CCCTAGCTACAACCA TCTGAGCC	1855
624	CAACCCGA G UCUCCCCC	1316	CCCCCACA CCCTACCTACAACCA TCCCCTTC	1856
628	CCCACUCU G CGCGUGCU	1317	ACCACCCG CCCTACCTACAACGA AGACTCCC	1857
632	GUCUGCGC G UCCUUCCG	1318	CCCAACCA CGCTAGCTACAACCA CCCCACAC	1858
634	CUCCCCCU G CUUGCCCC	1319	GGCGCAAG CCCTAGCTACAACGA ACCCCCAG	1859
638	CGGUGCUU G CCCCCCCA	1320	TCCCCCCG GGCTACCTACAACCA AACCACCC	1860
640	CUCCUUCC G CCCGCAUU	1321	AATCCGGG CCCTAGCTACAACGA CCAACCAC	1861
644	UUGCCCCC G CAUUCCAC	1322	GTCCAATC GCCTACCTACAACCA GGCCGCAA	1862
646	GCGCCCGC A UUGGACAA	627	TTGTCCAA GGCTAGCTACAACGA GCGGGCGC	1863
651	CGCAUUGG A CAACUCGU	1682	ACGAGTTG GGCTAGCTACAACGA CCAATGCG	1864
654	AUUGGACA A CUCGUUGU	1683	ACAACGAG GGCTAGCTACAACGA TGTCCAAT	1865
658	GACAACUC G UUGUGCCA	1323	TGGCACAA GGCTAGCTACAACGA GAGTTGTC	1866
661	AACUCGUU G UGCCAAGC	1324	GCTTGGCA GGCTAGCTACAACGA AACGAGTT	1867
663	CUCGUUGU G CCAAGCCU	1325	AGGCTTGG GGCTAGCTACAACGA ACAACGAG	1868
668	UGUGCCAA G CCUUCGCC	1326	GGCGAAGG GGCTAGCTACAACGA TTGGCACA	1869
674	AAGCCUUC G CCUUCUUC	1327	GAAGAAGG GGCTAGCTACAACGA GAAGGCTT	1870
683	CCUUCUUC A UGUCCUUC	637	GAAGGACA GGCTAGCTACAACGA GAAGAAGG	1871
685	UUCUUCAU G UCCUUCUU	1328	AAGAAGGA CGCTAGCTACAACGA ATGAAGAA	1872
697	UUCUUUGG G CUCUCCUC	1329	GAGGAGAG GGCTAGCTACAACGA CCAAAGAA	1873
707	UCUCCUCG A CACUGCAA	1684	TTGCAGTG GGCTAGCTACAACGA CUAGGAGA	1874
709	UCCUCGAC A CUGCAACU	645	AGTTGCAG GGCTAGCTACAACGA GTCGAGGA	1875
712	UCGACACU G CAACUCCU	1330	AGGAGTTG GGCTAGCTACAACGA AGTGTCGA	1876
715	ACACUGCA A CUCCUGGC	1685	GCCAGGAG GGCTAGCTACAACGA TGCAGTGT	1877
722	AACUCCUG G CCAUGGCA	1331	TGCCATGG GGCTAGCTACAACGA CAGGAGTT	1878
725	UCCUGGCC A UGGCACUG	652	CAGTGCCA GGCTAGCTACAACGA GGCCAGGA	1879
728	UGGCCAUG G CACUGGAG	1332	CTCCAGTG GGCTAGCTACAACGA CATGGCCA	1880
730	GCCAUGGC A CUGGAGUG	653	CACTCCAG GGCTAGCTACAACGA GCCATGGC	1881
736	GCACUGGA G UGCUGGCU	1333	AGCCAGCA GGCTAGCTACAACGA TCCAGTGC	1882
738	ACUGGAGU G CUGGCUCU	1334	AGAGCCAG GGCTAGCTACAACGA ACTCCAGT	1883
742	GAGUCCUG G CUCUCCCU	1335	AGGGAGAG GCCTAGCTACAACGA CAGCACTC	1884
754	UCCCUAGG G CACCCUUU	1336	AAAGGGTG GGCTAGCTACAACGA CCTAGGGA	1885
756	CCUAGGGC A CCCUUUCU	661	AGAAAGGG GGCTAGCTACAACGA GCCCTAGG	1886
768	UUUCUUCU A CCGACGGC	104	GCCGTCGG GGCTAGCTACAACGA AGAACAAA	1887
772	UUCUACCG A CGGCACAU	1686	ATGTGCCG GGCTAGCTACAACGA CGGTAGAA	1888

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
775	UACCGACG G CACAUCAC	1337	GTGATGTG GGCTAGCTACAACGA CGTCGGTA	1889
777	CCGACGGC A CAUCACCC	668	GGGTGATG GGCTAGCTACAACGA GCCGTCGG	1890
779	GACGGCAC A UCACCCUG	669	CAGGGTGA GGCTAGCTACAACGA GTCCCGTC	1891
782	CGCACAUC A CCCUGCGC	670	GCGCAGGG GGCTAGCTACAACGA GATGTGCC	1892
787	AUCACCCU G CGCCUGGG	1338	CCCAGGCG GCCTAGCTACAACGA AGGGTGAT	1893
789	CACCCUGC G CCUGGGCG	1339	CGCCCAGG GGCTACCTACAACGA GCAGCGTG	1894
795	GCGCCUGG G CGCACUGG	1340	CCAGTCCG GGCTAGCTACAACGA CCAGGCGC	1895
797	GCCUCGGC G CACUGGUG	1341	CACCAGTG GCCTAGCTACAACGA GCCCAGGC	1896
799	CUGGGCGC A CUGGUGGC	676	GCCACCAG GGCTAGCTACAACGA GCGCCCAG	1897
803	CCCCACUG G UGGCCCCC	1342	CGGGGCCA CGCTAGCTACAACGA CAGTGCGC	1898
806	CACUGGUG G CCCCGGUG	1343	CACCGGGG GGCTAGCTACAACGA CACCAGTG	1899
812	UCGCCCCG G UGGUGAGC	1344	GCTCACCA GGCTAGCTACAACGA CGGGGCCA	1900
815	CCCCGGUG G UGAGCGCC	1345	GGCGCTCA GGCTAGCTACAACGA CACCGGGC	1901
819	GGUGGUGA G CGCCUUCU	1346	AGAAGGCG CGCTAGCTACAACGA TCACCACC	1902
821	UGGUGAGC G CCUUCUCC	1347	GGAGAAGG GGCTAGCTACAACGA GCTCACCA	1903
833	UCUCCCUG G CUUUCUGC	1348	GCACAAAG GGCTAGCTACAACCA CAGGGAGA	1904
840	GGCUUUCU G CGCGCUAC	1349	GTAGCGCG CGCTAGCTACAACGA AGAAAGCC	1905
842	CUUUCUGC G CCCUACCU	1350	ACCTACCG GGCTAGCTACAACGA GCAGAAAG	1906
844	UUCUCCGC G CUACCUUU	1351	AAAGGTAG GCCTAGCTACAACCA CCGCAGAA	1907
847	UGCCCCCU A CCUUUCAU	112	ATGAAAGG GGCTACCTACAACGA AGCGCCCA	1908
854	UACCUUUC A UGCCCUUC	692	CAACCCCA GGCTAGCTACAACCA CAAAGGTA	1909
858	UUUCAUCG G CUUCGGGA	1352	TCCCGAAG GGCTAGCTACAACGA CCATGAAA	1910
868	UUCGGGAA G UUCCUGCA	1353	TGCACGAA GGCTAGCTACAACGA TTCCCGAA	1911
872	GGAAGUUC G UGCAGUAC	1354	GTACTGCA GGCTAGCTACAACGA GAACTTCC	1912
874	AAGUUCGU G CACUACUG	1355	CAGTACTG GGCTAGCTACAACGA ACGAACTT	1913
877	UUCGUGCA G UACUGCCC	1356	GGGCAGTA GGCTAGCTACAACGA TGCACGAA	1914
879	CGUGCAGU A CUGCCCCG	120	CGGGGCAG GGCTAGCTACAACGA ACTGCACG	1915
882	GCAGUACU G CCCCGGCA	1357	TGCCGGGG GGCTAGCTACAACGA AGTACTGC	1916
888	CUGCCCCG G CACCUGGU	1358	ACCAGGTG GGCTAGCTACAACGA CGGGGCAG	1917
890	GCCCCGGC A CCUGGUGC	699	GCACCAGG GGCTAGCTACAACGA GCCGGGGC	1918
895	GGCACCUG G UGCUUUAU	1359	ATAAAGCA GGCTAGCTACAACGA CAGGTGCC	1919
897	CACCUGGU G CUUUAUCC	1360	GGATAAAG GGCTAGCTACAACGA ACCAGGTG	1920
902	GGUGCUUU A UCCAGAUG	123	CATCTGGA GGCTAGCTACAACGA AAAGCACC	1921
908	UUAUCCAG A UGGUCCAC	1687	GTGGACCA GGCTAGCTACAACGA CTGGATAA	1922
911	UCCAGAUG G UCCACGAG	1361	CTCGTGGA GGCTAGCTACAACGA CATCTGGA	1923

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
915	GAUGGUCC A CGAGGAGG	706	CCTCCTCG GGCTAGCTACAACGA GGACCATC	1924
924	CGAGGAGG G CUCGCUGU	1362	ACAGCGAG GGCTAGCTACAACGA CCTCCTCG	1925
928	GAGGGCUC G CUGUCGGU	1363	ACCUACAG GGCTAGCTACAACGA GAGCCCTC	1926
931	GGCUCGCU G UCGGUGCU	1364	AGCACCGA GGCTAGCTACAACGA AGCGAGCC	1927
935	CGCUGUCG G UGCUGGGG	1365	CCCCAGCA GGCTAGCTACAACGA CGACAGCG	1928
937	CUGUCGGU G CUGGGGUA	1366	TACCCCAG GGCTAGCTACAACGA ACCGACAG	1929
943	GUGCUGGG G UACUCUGU	1367	ACAGAUTA GGCTAGCTACAACGA CCCAGCAC	1930
945	GCUGGGGU A CUCUGUGC	128	GCACAGAG GGCTAGCTACAACGA ACCCCAGC	1931
950	GGUACUCU G UGCUCUAC	1368	GTAGAGCA GGCTAGCTACAACGA AGAGTACC	1932
952	UACUCUGU G CUCUACUC	1369	GAGTAGAG GGCTAGCTACAACGA ACAGAUTA	1933
957	UGUGCUCU A CUCCAGCC	131	GGCTGGAG GGCTAGCTACAACGA AGAGCACA	1934
963	CUACUCCA G CCUCAUGG	1370	CCATGAGG GGCTAGCTACAACGA TGGAGTAG	1935
968	CCAGCCUC A UGGCGCUG	719	CAUCUCCA GGCTAGCTACAACGA GAGGCTGG	1936
971	GCCUCAUG G CGCUGCUG	1371	CAGCAGCG GGCTAGCTACAACGA CATGAGGC	1937
973	CUCAUGGC G CUGCUGGU	1372	ACCACCAG GGCTAGCTACAACGA GCCATGAG	1938
976	AUGGCGCU G CUGGUCCU	1373	AGGACCAG GGCTAGCTACAACGA AGCGCCAT	1939
980	CGCUGCUG G UCCUCGCC	1374	GGCGAGGA GGCTAGCTACAACGA CAGCAGCG	1940
986	UGGUCCUC G CCACCGUG	1375	CACGGTGG GGCTAGCTACAACGA GAGGACCA	1941
989	UCCUCGCC A CCGUGCUG	725	CAGCACGG GGCTAGCTACAACGA GGCGAGGA	1942
992	UCGCCACC G UGCUGUGC	1376	GCACAGCA GGCTAGCTACAACGA GGTGGCGA	1943
994	GCCACCGU G CUGUGCAA	1377	TTGCACAG GGCTAGCTACAACGA ACGGTGGC	1944
997	ACCGUGCU G UGCAACCU	1378	AGGTTGCA GGCTAGCTACAACGA AGCACGGT	1945
999	CGUGCUGU G CAACCUCG	1379	CGAGGTTG GGCTAGCTACAACGA ACAGCACG	1946
1002	GCUGUGCA A CCUCGGCG	1688	CGCCGAGG GGCTAGCTACAACGA TGCACAGC	1947
1008	CAACCUCG G CGCCAUGC	1380	GCATGGCG GGCTAGCTACAACGA CGAGGTTG	1948
1010	ACCUCGGC G CCAUGCGC	1381	GCGCATGG GGCTAGCTACAACGA GCCGAGGT	1949
1013	UCGGCGCC A UGCGCAAC	732	GTTGCGCA GGCTAGCTACAACGA GGCGCCGA	1950
1015	GGCGCCAU G CGCAACCU	1382	AGGTTGCG GGCTAGCTACAACGA ATGGCGCC	1951
1017	CGCCAUGC G CAACCUCU	1383	AGAGGTTG GGCTAGCTACAACGA GCATGGCG	1952
1020	CAUGCGCA A CCUCUAUG	1689	CATAGAGG GGCTAGCTACAACGA TGCGCATG	1953
1026	CAACCUCU A UGCGAUGC	138	GCATCGCA GGCTAGCTACAACGA AGAGGTTG	1954
1028	ACCUCUAU G CGAUGCAC	1384	GTGCATCG GGCTAGCTACAACGA ATAGAGGT	1955
1031	UCUAUGCG A UGCACCGG	1690	CCGGTGCA GGCTAGCTACAACGA CGCATAGA	1956
1033	UAUGCGAU G CACCGGCG	1385	CGCCGGTG GGCTAGCTACAACGA ATCGCATA	1957
1035	UGCGAUGC A CCGGCGGC	737	GCCGCCGG GGCTAGCTACAACGA GCATCGCA	1958

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
1039	AUGCACCG G CGGCUGCA	1386	TGCAGCCG GGCTAGCTACAACGA CGGTGCAT	1959
1042	CACCGGCG G CUGCAGCG	1387	CGCTGCAG GGCTAGCTACAACGA CGCCGGTG	1960
1045	CGGCGGCU G CAGCGGCA	1388	TGCCGCTG GGCTAGCTACAACGA AGCCGCCG	1961
1048	CGGCUGCA G CGGCACCC	1389	GGGTGCCG GGCTAGCTACAACGA TGCAGCCG	1962
1051	CUGCAGCG G CACCCGCG	1390	CGCGGGTG GGCTAGCTACAACGA CGCTGCAG	1963
1053	GCAGCGGC A CCCGCGCU	741	AGCGCGGG GGCTAGCTACAACGA GCCGCTGC	1964
1057	CGGCACCC G CGCUCCUG	1391	CACCAGCG GGCTAGCTACAACGA GGGTGCCG	1965
1059	GCACCCGC G CUCCUCCA	1392	TGCAGGAG GGCTACCTACAACGA GCGGGTGC	1966
1065	GCGCUCCU G CACCAGGG	1393	CCCTCCTG GGCTAGCTACAACGA AGGAGCGC	1967
1067	GCUCCUGC A CCAGGCAC	747	GTCCCTGG GGCTAGCTACAACCA GCAGGAGC	1968
1074	CACCAGGG A CUGUGCCG	1691	CGGCACAG GGCTAGCTACAACGA CCCTGGTG	1969
1077	CAGGGACU G UGCCGAGC	1394	GCTCGGCA GGCTAGCTACAACGA AGTCCCTG	1970
1079	GGGACUGU G CCGAGCCG	1395	CGGCTCGG GGCTAGCTACAACGA ACAGTCCC	1971
1084	UGUGCCCA G CCGCGCCC	1396	GCGCGCGG CGCTAGCTACAACGA TCGGCACA	1972
1087	GCCGAGCC G CGCGCGGA	1397	TCCGCGCG GGCTAGCTACAACGA GGCTCGGC	1973
1089	CGAGCCGC G CGCGGACG	1398	CGTCCGCG GGCTAGCTACAACGA GCGGCTCG	1974
1091	AGCCGCGC G CGGACGGG	1399	CCCGTCCG GGCTAGCTACAACGA GCGCGGCT	1975
1095	GCGCGCGG A CGJGAGGG	1692	CCCTCCCG GGCTAGCTACAACGA CCGCCCGC	1976
1106	GGAGCGAA G CGUCCCCU	1400	AGGGGACG GGCTAGCTACAACGA TTCCCTCC	1977
1108	AGGGAAGC G UCCCCUCA	1401	TGAGGGGA GGCTAGCTACAACGA CCTTCCCT	1978
1117	UCCCCUCA G CCCCUCGA	1402	TCCAGGGG GCCTAGCTACAACGA TGAGGGGA	1979
1129	CUGGAGGA G CUCCAUCA	1403	TGATCCAG GGCTACCTACAACGA TCCTCCAG	1980
1134	GCAGCUGG A UCACCUCC	1693	GGAGGTGA GGCTAGCTACAACGA CCAGCTCC	1981
1137	CCUGGAUC A CCUCCUGC	763	GCAGGAGG CCCTAGCTACAACCA GATCCAGC	1982
1144	CACCUCCU G CUGCUGGC	1404	GCCAGCAG GCCTAGCTACAACCA AGCAGGTG	1983
1147	CUCCUCCU G CUGCCGCU	1405	AGCCCCAG GGCTACCTACAACGA AGCACGAG	1984
1151	UGCUGCUC G CCCUGAUG	1406	CATCAGCC GCCTACCTACAACGA CAGCAGCA	1985
1153	CUGCUGGC G CUGAUGAC	1407	GTCATCAG CGCTAGCTACAACGA GCCAGCAG	1986
1157	UGGCCCUG A UGACCOUG	1694	CACGGTCA GGCTAGCTACAACGA CACCGCCA	1987
1160	CCCUGAUC A CCGUGCUC	1695	CAGCACCC GGCTAGCTACAACGA CATCAGCG	1988
1163	UCAUGACC G UGCUCUUC	1408	GAAGAGCA GCCTACCTACAACGA CGTCATCA	1989
1165	AUGACCCU G CUCUUCAC	1409	GTCAACAG CGCTAGCTACAACGA ACGGTCAT	1990
1172	UGCUCUUC A CUAUGUGU	774	ACACATAC GGCTAGCTACAACGA GAAGAGCA	1991
1175	UCUUCACU A UCUGUUCU	147	AGAACACA GCCTAGCTACAACCA AGTCAACA	1992
1177	UUCACUAU G UGUUCUCU	1410	AGAGAACA CGCTACCTACAACGA ATACTCAA	1993

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
1179	CACUAUGU G UUCUCUGC	1411	GCAGAGAA CCCTACCTACAACCA ACATAGTG	1994
1186	UCUUCUCU G CCCCUAAU	1412	ATTACGGC CGCTACCTACAACGA ACACAACA	1995
1190	CUCUGCCC G UAAUUUAU	1413	ATAAATTA GCCTACCTACAACGA GGGCAGAC	1996
1193	UCCCCGUA A UUUAUCCC	1696	CCCATAAA GGCTAGCTACAACCA TACGGGCA	1997
1197	CGUAAUUU A UCCCCCUU	154	AACCCCCA CGCTAGCTACAACGA AAATTACG	1998
1200	AAUUUAUC G CGCUUACU	1414	AGTAACCG GGCTAGCTACAACCA GATAAATT	1999
1202	UUUAUCGC G CUUACUAU	1415	ATACTAAG CGCTAGCTACAACGA GCGATAAA	2000
1206	UCGCGCUU A CUAUGCAC	157	CTCCATAG GGCTAGCTACAACCA AACCGCGA	2001
1209	CCCUUACU A UCGAGCAU	158	ATCCTCCA CGCTACCTACAACGA AGTAAGCC	2002
1214	ACUAUGGA G CAUUUAAG	1416	CTTAAATG GCCTACCTACAACCA TCCATAGT	2003
1216	UAUCCACC A UUUAAGGA	782	TCCTTAAA GGCTACCTACAACGA CCTCCATA	2004
1224	AUUUAAGC A UGUCAACG	1697	CCTTCACA CGCTACCTACAACGA CCTTAAAT	2005
1226	UUAACGAU G UCAACGAG	1417	CTCCTTGA GGCTAGCTACAACCA ATCCTTAA	2006
1239	CGAGAAAA A CAGGACCU	1698	AGGTCCTG GGCTAGCTACAACGA TTTTCTCC	2007
1244	AAAACACG A CCUCUCAA	1699	TTCAGAGG GGCTACCTACAACCA CCTCTTTT	2008
1256	CUCAACAA G CAGAAGAC	1418	CTCTTCTC CCCTACCTACAACCA TTCTTCAC	2009
1263	ACCAGAAG A CCUCCCAC	1700	CTCGCACG CGCTACCTACAACCA CTTCTGCT	2010
1271	ACCUCCCA G CCUUCCGA	1419	TCCCAACC CCCTACCTACAACGA TCCCACCT	2011
1276	CCACCCUU G CCAUUUCU	1420	ACAAATCC CCCTACCTACAACCA AAGGCTCG	2012
1279	CCCUUCCC A UUUCUAUC	1701	CATACAAA GGCTACCTACAACCA CCCAACCC	2013
1285	CCAUUUCU A UCUGUGAU	169	ATCACACA CCCTACCTACAACGA AGAAATCC	2014
1289	UUCUAUCU G UCAUUUCA	1421	TCAAATCA GCCTACCTACAACCA ACATACAA	2015
1292	UAUCUGUG A UUUCAAUU	1702	AATTGAAA GGCTAGCTACAACGA CACAGATA	2016
1298	UGAUUUCA A UHOUGGAC	1703	GTCCACAA GGCTAGCTACAACGA TGAAATCA	2017
1301	UUUCAAUU G UGGACCCU	1422	AGGGTCCA GGCTAGCTACAACGA AATTGAAA	2018
1305	AAUUGUGG A CCCUUGGA	1704	TCCAAGGG GGCTAGCTACAACGA CCACAATT	2019
1313	ACCCUUGG A UUUUUAUC	1705	GATAAAAA GGCTAGCTACAACGA CCAAGGGT	2020
1319	GGAUUUUU A UCAUUUUC	180	GAAAATGA GGCTAGCTACAACGA AAAAATCC	2021
1322	UUUUUAUC A UUUUCAGA	800	TCTGAAAA GGCTAGCTACAACGA GATAAAAA	2022
1330	AUUUUCAG A UCUCCAGU	1706	ACTUGAGA GGCTAGCTACAACGA CTGAAAAT	2023
1337	GAUCUCCA G UAUUUCGG	1423	CCGAAATA GGCTAGCTACAACGA TGGAGATC	2024
1339	UCUCCAGU A UUUCGGAU	188	ATCCGAAA GGCTAGCTACAACGA ACTGGAGA	2025
1346	UAUUUCGG A UAUUUUUU	1707	AAAAAATA GGCTAGCTACAACGA CCGAAATA	2026
1348	UUUCGGAU A UUUUUUCA	192	TGAAAAAA GGCTAGCTACAACGA ATCCGAAA	2027
1356	AUUUUUUC A CAAGAUUU	805	AAATCTTG GGCTAGCTACAACGA GAAAAAAT	2028

TABLE VI-continued

Human PTGDR DNAzyme and Substrate Sequence

Pos	Substrate	Seq ID	DNAzyme	Seq ID
1361	UUCACAAG A UUUUCAUU	1708	AATGAAAA GGCTAGCTACAACGA CTTGTGAA	2029
1367	AGAUUUUC A UUAGACCU	807	AGGTCTAA GGCTAGCTACAACGA GAAAATCT	2030
1372	UUCAUUAG A CCUCUUAG	1709	CTAAGAGG GGCTAGCTACAACGA CTAATGAA	2031
1381	CCUCUUAG G UACAGGAG	1424	CTCCTGTA GGCTAGCTACAACGA CTAAGAGG	2032
1383	UCUUAGGU A CAGGAGCC	208	GGCTCCTG GGCTAGCTACAACGA ACCTAAGA	2033
1389	GUACAGGA G CCGGUGCA	1425	TGCACCGG GGCTAGCTACAACGA TCCTGTAC	2034
1393	AGGAGCCG G UGCAGCAA	1426	TTGCTGCA GGCTAGCTACAACGA CGGCTCCT	2035
1395	GAGCCGGU G CAGCAAUU	1427	AATTGCTG GGCTAGCTACAACGA ACCGGCTC	2036
1398	CCGGUGCA G CAAUUCCA	1428	TGGAATTG GGCTAGCTACAACGA TGCACCGG	2037
1401	GUGCAGCA A UUCCACUA	1710	TAGTGGAA GGCTAGCTACAACGA TGCTGCAC	2038
1406	GCAAUUCC A CUAACAUG	816	CATGTTAG GGCTAGCTACAACGA GGAATTGC	2039
1410	UUCCACUA A CAUGGAAU	1711	ATTCCATG GGCTAGCTACAACGA TAGTGGAA	2040
1412	CCACUAAC A UGGAAUCC	818	GGATTCCA GGCTAGCTACAACGA GTTAGTGG	2041
1417	AACAUGGA A UCCAGUCU	1712	AGACTGGA GGCTAGCTACAACGA TCCATGTT	2042
1422	GGAAUCCA G UCUGUGAC	1429	GTCACAGA GGCTAGCTACAACGA TGGATTCC	2043
1426	UCCAGUCU G UGACAGUG	1430	CACTGTCA GGCTAGCTACAACGA AGACTGGA	2044
1429	AGUCUGUG A CAGUGUUU	1713	AAACACTG GGCTAGCTACAACGA CACAGACT	2045
1432	CUGUGACA G UGUUUUUC	1431	GAAAAACA GGCTAGCTACAACGA TGTCACAG	2046
1434	GUGACAGU G UUUUUCAC	1432	GTGAAAAA GGCTAGCTACAACGA ACTGTCAC	2047
1441	UGUUUUUC A CUCUGUGG	823	CCACAGAG GGCTAGCTACAACGA GAAAAACA	2048
1446	UUCACUCU G UGGUAAGC	1433	GCTTACCA GGCTAGCTACAACGA AGAGTGAA	2049
1449	ACUCUGUG G UAAGCUGA	1434	TCAGCTTA GGCTAGCTACAACGA CACAGAGT	2050
1453	UGUGGUAA G CUGAGGAA	1435	TTCCTCAG GGCTAGCTACAACGA TTACCACA	2051
1461	GCUGAGGA A UAUGUCAC	1714	GTGACATA GGCTAGCTACAACGA TCCTCAGC	2052
1463	UGAGGAAU A UGUCACAU	221	ATGTGACA GGCTAGCTACAACGA ATTCCTCA	2053
1465	AGGAAUAU G UCACAUUU	1436	AAATGTGA GGCTAGCTACAACGA ATATTCCT	2054
1468	AAUAUGUC A CAUUUUCA	827	TGAAAATG GGCTAGCTACAACGA GACATATT	2055
1470	UAUGUCAC A UUUUCAGU	828	ACTGAAAA GGCTAGCTACAACGA GTGACATA	2056
1477	CAUUUUCA G UCAAAGAA	1437	TTCTTTGA GGCTAGCTACAACGA TGAAAATG	2057

Input Sequence = PTGDR_composit.
Cut Site = R/Y
Arm Length = 8.
Core Sequence = GGCTAGCTACAACGA
PTGDR_composit (1 to 993 of HSU31332 (PTGDR 5') +1 to 495 of HSU31099 (PTGDR 3'); 1488 nt)

[0234]

TABLE VII

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
9	GAAUUCUG G CUAUUUUC	1207	GAAAAUAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGAAUUC	2247
23	UUCCUCCU G CCGUUCCG	1208	CGGAACGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGAGGAA	2248
28	CUCCUGCC G UUCCGACU	1209	AGUCGGAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCAGGAG	2249
31	GCCGUUCC G ACUCGGCA	2058	UGCCGAGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGAACGGC	2250
36	UCCGACUC G GCACCAGA	2059	UCUGGUGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAGUCGGA	2251
37	CCGACUCG G CACCAGAG	1210	CUCUGGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAGUCGG	2252
43	CGGCACCA G AGUCUGUC	2060	GACAGACU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGUGCCG	2253
45	GCACCAGA G UCUGUCUC	1211	GAGACAGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCUGGUGC	2254
49	CAGAGUCU G UCUCUACU	1212	AGUAGAGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGACUCUG	2255
58	UCUCUACU G AGAACGCA	2061	UGCGUUCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGUAGAGA	2256
60	UCUACUGA G AACGCAGC	2062	GCUGCGUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCAGUAGA	2257
64	CUGAGAAC G CAGCGCGU	1213	ACGCGCUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUUCUCAG	2258
67	AGAACGCA G CGCGUCAG	1214	CUGACGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGCGUUCU	2259
69	AACGCAGC G CGUCAGGG	1215	CCCUGACG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUGCGUU	2260
71	CGCAGCGC G UCAGGGCC	1216	GGCCCUGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGCUGCG	2261
75	GCGCGUCA G GGCCGAGC	2063	GCUCGGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGACGCGC	2262
76	CGCGUCAG G GCCGAGCU	2064	AGCUCGGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUGACGCG	2263
77	GCGUCAGG G CCGAGCUC	1217	GAGCUCGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCUGACGC	2264
80	UCAGGGCC G AGCUCUUC	2065	GAAGAGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCCCUGA	2265
82	AGGGCCGA G CUCUUCAC	1218	GUGAAGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCGGCCCU	2266
92	UCUUCACU G GCCUGCUC	2066	GAGCAGGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGUGAAGA	2267
93	CUUCACUG G CCUGCUCC	1219	GGAGCAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGUGAAG	2268
97	ACUGGCCU G CUCCGCGC	1220	GCGCGGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGCCAGU	2269
102	CCUGCUCC G CGCUCUUC	1221	GAAGAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGAGCAGG	2270
104	UGCUCCGC G CUCUUCAA	1222	UUGAAGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGGAGCA	2271
114	UCUUCAAU G CCAGCGCC	1223	GGCGCUGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUUGAAGA	2272
118	CAAUGCCA G CGCCAGGC	1224	GCCUGGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGCAUUG	2273
120	AUGCCAGC G CCAGGCGC	1225	GCGCCUGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUGGCAU	2274
124	CAGCGCCA G GCGCUCAC	2067	GUGAGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGCGCUG	2275
125	AGCGCCAG G CGCUCACC	1226	GGUGAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUGGCGCU	2276
127	CGCCAGGC G CUCACCCU	1227	AGGGUGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCCUGGCG	2277
136	CUCACCCU G CAGAGCGU	1228	ACGCUCUG GCAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGCUGAG	2278
139	ACCCUGCA G AGCGUCCC	2068	GGGACGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGCAGGGU	2279
141	CCUGCAGA G CGUCCCGC	1229	GCGGGACG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCUGCAGG	2280
143	UGCAGAGC G UCCCGCCU	1230	AGGCGGGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUCUGCA	2281

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
148	AGCGUCCC G CCUCUCAA	1231	UUGAGAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGACGCU	2282
158	CUCUCAAA G AGGGGUGU	2069	ACACCCCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUUGAGAG	2283
160	CUCAAAGA G GGGUGUGA	2070	UCACACCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCUUUGAG	2284
161	UCAAAGAG G GGUGUGAC	2071	GUCACACC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUCUUUGA	2285
162	CAAAGAGG G GUGUGACC	2072	UGUCACAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCUCUUUG	2286
163	AAAGAGGG G UGUGACCC	1232	GGGUCACA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCCUCUUU	2287
165	AGAGGGGU G UGACCCGC	1233	GCGGGUCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCCCUCU	2288
167	AGGGGUGU U ACCCGCGA	2073	UCGCGGGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACACCCCU	2289
172	UGUGACCC C CGAGUUUA	1234	UAAACUCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUGUCACA	2290
174	UGACCCGC C AGUUUAGA	2074	UCUAAACU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGGGUCA	2291
176	ACCCGCGA G UUUAGAUA	1235	UAUCUAAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCGCGGGU	2292
181	CGAGUUUA G AUAGGAGG	2075	CCUCCUAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UAAACUCG	2293
185	UUUAGAUA C GAGGUUCC	2076	GGAACCUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UAUCUAAA	2294
186	UUAGAUAG G AGGUUCCU	2077	AGGAACCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUAUCUAA	2295
188	AGAUAGGA G GUUCCUGC	2078	GCAGGAAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCUAUCU	2296
189	GAUAGGAG G UUCCUGCC	1236	GGCAGGAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUCCUAUC	2297
195	AGGUUCCU G CCGUGGGG	1237	CCCCACGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGAACCU	2298
198	UUCCUGCC G UGGGGAAC	1238	GUUCCCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCAGGAA	2299
200	CCUGCCGU G GGGAACAC	2079	GUGUUCCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACGGCAGG	2300
201	CUGCCGUG G GGAACACC	2080	GGUGUUCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACGGCAG	2301
202	UGCCGUGG C GAACACCC	2081	CCGUGUUC GCAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCACGGCA	2302
203	GCCGUGGG G AACACCCC	2082	GGGGUGUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCCACGGC	2303
212	AACACCCC G CCGCCCUC	1239	GAGGGCGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGCUCUU	2304
215	ACCCCGCC G CCCUCGCA	1240	UCCGAGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCGGGGU	2305
221	CCGCCCUC G GAGCUUUU	2083	AAAAGCUC GGAGCAAACUCC CU UCAAGGACAUCGUCCGGG GAGGUCUG	2306
222	CGCCCUCG G AGCUUUUU	2084	AAAAAGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAGGGCG	2307
224	CCCUCGGA G CUUUUUCU	1241	AGAAAAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCGAGGG	2308
233	CUUUUUCU G UGGCGCAG	1242	CUGCGCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAAAAAG	2309
235	UUUUCUGU G GCGCAGCU	2085	AGCUGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGAAPA	2310
236	UUUCUGUG G CGCAGCUU	1243	AAGCUGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACAGAAA	2311
238	UCUGUGGC C CAGCUUCU	1244	AGAAGCUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCCACAGA	2312
241	GUGGCGCA G CUUCUCCG	1245	CGGACAAG GGAGGAAACUCC CU UCAAGCACAUCGUCCGGG UGCGCCAC	2313
249	GCUUCUCC G CCCGAGCC	1246	GGCUCGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGAGAAGC	2314
253	CUCCGCCC C AGCCGCGC	2086	GCGCGGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGCGGAG	2315
255	CCGCCCGA G CCGCGCGC	1247	GCGCGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCGGGCGG	2316

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
258	CCCGAGCC C CGCGCGGA	1248	UCCGCGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCUCGGG	2317
260	CGAGCCCC C CCCGGAGC	1249	GCUCCGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGGCUCG	2318
262	AGCCGCGC G CGGAGCUG	1250	CAGCUCCG CGAGCAAACUCC CU UCAACCACAUCGUCCCGG CCGCGGCU	2319
264	CCGCGCGC C CAGCUCCC	2087	GCCACCUC CCACGAAACUCC CU UCAACGACAUCGUCCCCG CCGCCCCG	2320
265	CGCGCCCG C AGCUCCCG	2088	CGCCAGCU GGAGCAAACUCC CU UCAAGCACAUCGUCCGGC CCCGCCCC	2321
267	CCCCCCGA G CUGCCCGC	1251	CCCGGCAG GCACGAAACUCC CU UCAACGACAUCGUCCGGG UCCCCCCG	2322
270	GCCCACCU G CCGGGGGC	1252	CCCCCCCC GCACGAAACUCC CU UCAAGGACAUCCUCCCGG AGCUCCCC	2323
273	CACCUGCC C CGGGCUCC	2089	CGAGCCCC GCACCAAACUCC CU UCAAGCACAUCCUCCGGC GCCAGCUC	2324
274	AGCUGCCG G GCGCUCCU	2090	AGCACCCC GCAGGAAACUCC CU UCAAGCACAUCGUCCGGG CCCCACCU	2325
275	CCUGCCGC C CCCUCCUU	2091	AAGCACCC CGACGAAACUCC CU UCAAGGACAUCCUCCGGG CCCGCAGC	2326
276	CUGCCCGG C GCUCCUUA	2092	UAACGACC GGAGCAAACUCC CU UCAACGACAUCGUCCCGC CCCGGCAG	2327
277	UGCCGGCC C CUCCUUAG	1253	CUAACGAC GCAGCAAACUCC CU UCAAGCACAUCGUCCGGG CCCCCCCA	2328
285	GCUCCUUA G CACCCGCG	1254	CCCCCCUC CGAGGAAACUCC CU UCAACCACAUCGUCCGGG UAACGAGC	2329
291	UAGCACCC G GCCGCCGC	2093	CCGGCCCC CCACCAAACUCC CU UCAACGACAUCCUCCCGG GCGUGCUA	2330
292	ACCACCCG C CCGCCCCG	2094	CCCGGCCC GCACCAAACUCC CU UCAAGCACAUCCUCCGGC CCGCUGCU	2331
293	GCACCCGC C CGCCCGCG	1255	CCCCCGCG CGACGAAACUCC CU UCAAGGACAUCGUCCGCG CCGGGUGC	2332
295	ACCCCCCC C CCCCCGCC	1256	CGCCCCCC CCACCAAACUCC CU UCAACCACAUCCUCCCCC CCCCCCCU	2333
298	CCCCCCCC C CGCCCCUC	2095	CACCCCCC CCAGCAAACUCC CU UCAACCACAUCCUCCCCC CCCGCCCC	2334
299	CCCCCCCC C CCCCCUCC	2096	CCACCCCC CGACCAAACUCC CU UCAACCACAUCGUCCGCC CGCCCCCC	2335
300	CCCCCCCG C CCCCUCCC	2097	CCCACCCC CCACGAAACUCC CU UCAACCACAUCCUCCCCC CCCCCCCC	2336
301	CCCCCCCC C CCCUCCCC	1257	CCCCACCC CCACCAAACUCC CU UCAACGACAUCCUCCCCC CCCCCCCC	2337
307	CCCCCCUC C CCCUUCCG	1258	CCCAACCC CCACGAAACUCC CU UCAACGACAUCCUCCCCC CACCCCCC	2338
315	GCCCUUCC C CACCCUUC	1259	CAAGCCUC CCACCAAACUCC CU UCAACCACAUCCUCCCGC CCAACCGC	2339
318	CUUCCCCA C CCUUCACU	1260	ACUCAACG CCACCAAACUCC CU UCAACCACAUCCUCCCCC UCCCCAAC	2340
330	UCACUCCA C CCCUCUCC	1261	CCACACCG GCACCAAACUCC CU UCAAGCACAUCCUCCGCG UCCACUCA	2341
337	AGCCCUCU G CUCCCGCA	1262	UGCGGGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAGGGCU	2342
343	CUGCUCCC G CACGCCAU	1263	AUGGCGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGAGCAG	2343
347	UCCCGCAC G CCAUGAAG	1264	CUUCAUGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUGCGGGA	2344
352	CACGCCAU G AAGUCGCC	2098	GGCGACUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUGGCGUG	2345
355	GCCAUGAA G UCGCCGUU	1265	AACGGCGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUCAUGGC	2346
358	AUGAAGUC G CCGUUCUA	1266	UAGAACGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GACUUCAU	2347
361	AAGUCGCC U UUCUACCG	1267	CGGUAGAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCGACUU	2348
369	GUUCUACC U CUGCCAUA	1268	UCUGGCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGUG GGUAGAAC	2349
372	CUACCGCU U CCAGAACA	1269	UGUUCUGG GUAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCGGUAG	2350
376	CGCUGCCA G AACACCAC	2099	GUGGUGUU GUAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGUCAGCG	2351
389	CCACCUCU G UGGAAAAA	1270	UUUUUCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAGUUGG	2352

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
391	ACCUCUUU G GAAAAAGG	2100	CCUUUUUC GGAGUAAACUCC CU UCAAGGACAUCGUCCGUG ACAGAGGU	2353
392	CCUCUGUG U AAAAAGUC	2101	GCCUUUUU GGAUUAAACUCC CU UCAAGGACAUCUUCCGUU CACAGAGG	2354
398	UGGAAAAA U UCAACUCU	2102	CGAGUUGC GGAGGAAACUCC CU UCAAGUACAUCGUCCGGU UUUUUCCA	2355
399	GUAAAAAU G CAACUCGU	1271	CCGAUUUG GGAGUAAACUCC CU UCAAGUACAUCGUCCGGG CUUUUUCC	2356
406	UUCAACUC U GCGUUGAU	2103	AUCACCUC UGAGUAAACUCC CU UCAAGGACAUCGUCCUUG GAGUUGCC	2357
407	GCAACUCU U CUGUGAUG	1272	CAUCACCU UGAGGAAACUCC CU UCAAGGACAUCGUCCGUU CGAUUUGC	2358
409	AACUCGGC G UUGAUUGU	2104	CCCAUCAC GGAGGAAACUCC CU UCAAUGACAUCGUCCUUG GCCUAUUU	2359
410	ACUCGUCG G UGAUGGUC	1273	UCCCAUCA UGAGGAAACUCC CU UCAAGGACAUCGUCCGUU CUCCUAGU	2360
412	UCGUCGGU U AUGGUCGG	2105	CCGCCCAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGUG ACCGCCGA	2361
415	GCGGUUAU U UUCGGGGU	2106	ACCCCGCC GGAUGAAACUCC CU UCAAUGACAUCGUCCGGG AUCACCGC	2362
416	CGGUUAUG U UCUGUGUG	2107	CACCCCGC UGAUGAAACUCC CU UCAAGGACAUCGUCCGGG CAUCACCG	2363
417	GGUUAUUG U CGUGUUGC	1274	GCACCCCG GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG CCAUCACC	2364
419	UUAUUGGC U GGUUGCUC	2108	GAGCACCC UGAUGAAACUCC CU UCAAGGACAUCGUCCGGG GCCCAUCA	2365
420	GAUGGGCG U GGUUCUCU	2109	AGAGCACC GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG CGCCCAUC	2366
421	AUGGUCUG U GUGCUCUU	2110	AAGAGCAC GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG CCGCCCAU	2367
422	UGGGCGUG U UUCUCUUC	1275	GAAGAUCA GUAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCCGCCCA	2368
424	GGCGGGGU U CUCUUCAG	1276	CUGAAGAG GGAGGAAACUCC CU UCAAGGACAUCUUCCUGU ACCCCGCC	2369
432	GCUCUUCA G CACCGGCC	1277	GUCCUGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGAAGAGC	2370
437	UCAGCACC U UCCUCCUG	2111	CAGGAGGC GUAGGAAACUCC CU UCAAGGACAUCUUCCGGG GUUGCUGA	2371
438	CAUCACCG U CCUCCUGG	1278	CCAGUAGG GGAGGAAACUCC CU UCAAGUACAUCGUCCGGG CGGUGCUU	2372
445	GUCCUCCU U GGCAACCU	2112	AGGUUGCC GGAGGAAACUCC CU UCAAGUACAUCGUCCGGU AUGAGUCC	2373
446	GCCUCCUG U GCAACCUU	2113	CAUGUUUC UUAUUAAACUCC CU UCAAGUACAUCUUCCUUU CAGUAUUC	2374
447	CCUCCUGG G CAACCUGC	1279	GCAGGUUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAGGAGG	2375
454	GGCAACCU G CUGGCCCU	1280	AGGGCCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGUUGCC	2376
457	AACCUGCU G GCCCUGGG	2114	CCCAGGGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCAGGUU	2377
458	ACCUGCUG G CCCUGGGG	1281	CCCCAGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCAGGU	2378
463	CUGGCCCU G GGGCUGCU	2115	AGCAGCCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGGCCAG	2379
464	UGGCCCUG U GGCUGCUG	2116	CAGCAGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGGGCCA	2380
465	GGCCCUGG G GCUGCUGG	2117	CCAGCAGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAGGGCC	2381
466	GCCCUGGG G CUGCUGGC	1282	UCCAUCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCCAGGGC	2382
469	CUGGGGCU G CUGGCGCG	1283	CGCGCCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCCCCAG	2383
472	GGGCUGCU G GCGCGCUC	2118	GAGCGCUC GGAGGAAACUCC CU UCAAGUACAUCGUCCGUG AGCAGCCC	2384
473	GGCUGCUG U CGCGCUCG	1284	CGAGCGCG GGAGGAAACUCC CU UCAAGUACAUCGUCCGUG CAGCAGCC	2385
475	CUGCUGUC U CGCUCUGU	1285	CCCGAGCG GGAGGAAACUCC CU UCAAUGACAUCGUCCGUG GCCAGCAG	2386
477	GCUGGCGC U CUCGGGGC	1286	GCCCCGAU GGAUGAAACUCC CU UCAAUGACAUCGUCCGGG UCUCCAUC	2387

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
481	GCGCGCUC G GUGCUGUU	2119	CCCAGCCC GUAUGAAACUCC CU UCAAUUACAUCGUCCGGG GAUCUCGC	2388
482	CGCGCUCG G GGCUGGGG	2120	CCCCAGCC GUAUGAAACUCC CU UCAAGUACAUCGUCCGGG CUAUCGCG	2389
483	GCGCUCGG G GCUGGGGU	2121	ACCCCAGC GUAUGAAACUCC CU UCAAGGACAUCGUCCGGG CCUAUCGC	2390
484	CGCUCGGG G CUGGGGUG	1287	CACCCCAG GUAUUAAACUCC CU UCAAUUACAUCGUCCUGU CCCGAGCG	2391
487	UCGGGGCU G GGGUGUUG	2122	CACCACCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCCCCGA	2392
488	CUGGUCUG U GGUGGUGC	2123	GCACCACC GGAUUAAACUCC CU UCAAUUACAUCGUCCUGU CAGCCCCG	2393
489	GUUGCUUU U GUGGUGCU	2124	AGCACCAC GGAGUAAACUCC CU UCAAUUACAUCGUCCUGG CCAGCCCC	2394
490	UGGCUGUG U UGGUGCUC	1288	UAGCACCA UGAGUAAACUCC CU UCAAGUACAUCGUCCGGG CCCAGCCC	2395
492	GCUGUGGU U UUGCUCGC	2125	UCGAGCAC GGAGUAAACUCC CU UCAAGGACAUCGUCCGUG ACCCCAGC	2396
493	CUGGGGUG U UGCUCGCU	1289	CGCGAGCA UGAGGAAACUCC CU UCAAUUACAUCUUCCUUU CACCCCAU	2397
495	UGGGUUGU G CUCGCGGC	1290	GCCGCGAU UGAGGAAACUCC CU UCAAUUACAUCGUCCUUU ACCACCCC	2398
499	UGGUCCUC U CGUCGUCC	1291	GGACUCCG GGAGUAAACUCC CU UCAAUGACAUCGUCCUGG GAUCACCA	2399
501	UUGCUCUC U UCUUCCAC	2126	GUUGACGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUAGCAC	2400
502	UGCUCGCG U CGUCCACU	1292	AGUGUACG GGAGGAAACUCC CU UCAAUGACAUCGUCCUGG CGCGAGCA	2401
504	CUCGCGGC U UCCACUGC	1293	GCAGUUGA UGAGGAAACUCC CU UCAAGGACAUCGUCCGUU GCCGCGAG	2402
511	CGUCCACU G CGCCCGCU	1294	AUCGUUCU GUAUGAAACUCC CU UCAAGGACAUCUUCCGUG AGUGUACG	2403
513	UCCACUGC U CCCGCUGC	1295	GCAGCGGU GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG UCAGUGGA	2404
517	CUGCUCCC U CUUCCCUC	1296	GAUGUCAG GGAGUAAACUCC CU UCAAGGACAUCUUCCGUG UGUCUCAG	2405
520	CGCCCGCU U CCCUCUGU	1297	ACCUAGUG GGAGGAAACUCC CU UCAAUGACAUCUUCCUGU AGCGUGCU	2406
526	CUGCCCUC U GUCUUCUA	2127	UAGAAGAC GGAGUAAACUCC CU UCAAGGACAUCUUCCGGU GAUGUCAG	2407
527	UGCCCUCG G UCUUCUAC	1298	GUAGAAGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAGGGCA	2408
538	UUCUACAU G CUGGUGUG	1299	CACACCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUGUAGAA	2409
541	UACAUGCU G GUGUGUGG	2128	CCACACAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCAUGUA	2410
542	ACAUGCUG G UGUGUGGC	1300	GCCACACA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCAUGU	2411
544	AUGCUGGU G UGUGGCCU	1301	AGOCCACA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCAGCAU	2412
546	GCUGGUGU G UGGCCUGA	1302	UCAGGCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACACCAGC	2413
548	UGGUGUGU G GCCUGACG	2129	CGUCAGGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACACACCA	2414
549	GGUGUGUG G CCUGACGG	1303	CCGUCAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACACACC	2415
553	UGUGGCCU G ACGGUCAC	2130	GUGACCGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGCCACA	2416
556	GGCCUGAC G GUCACCGA	2131	UCGGUGAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUCAGGCC	2417
557	GCCUGACG G UCACCGAC	1304	GUCGGUGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGUCAGGC	2418
563	CGGUCACC G ACUUGCUG	2132	CAGCAAGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGUGACCG	2419
568	ACCGACUU G CUGGGCAA	1305	UUGCCCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AAGUCGGU	2420
571	GACUUGCU G GGCAAGUG	2133	CACUUGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCAAGUC	2421
572	ACUUGCUG G GCAAGUGC	2134	GCACUUGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCAAGU	2422
573	CUUGCUGG G CAAGUGCC	1306	GGCACUUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAGCAAG	2423

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
577	CUGGGCAA G UGCCUCCU	1307	AGGAGGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUGCCCAG	2424
579	GGGCAAGU G CCUCCUAA	1308	UUAGGAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACUUGCCC	2425
588	CCUCCUAA G CCCGGUGG	1309	CCACCGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUAGGAGG	2426
592	CUAAGCCC G GUGGUGCU	2135	AGCACCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGCUUAG	2427
593	UAAGCCCG G UGGUGCUG	1310	CAGCACCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGGGCUUA	2428
595	AGCCCGGU G GUGCUGGC	2136	GCCAGCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCGGGCU	2429
596	GCCCGGUG G UGCUGGCU	1311	AGCCAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACCGGGC	2430
598	CCGGUGGU G CUGGCUGC	1312	GCAGCCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCACCGG	2431
601	GUGGUGCU G GCUGCCUA	2137	UAGGCAGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCACCAC	2432
602	UGGUGCUG G CUGCCUAC	1313	GUAGGCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCACCA	2433
605	UGCUGGCU G CCUACGCU	1314	AGCGUAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCCAGCA	2434
611	CUGCCUAC G CUCAGAAC	1315	GUUCUGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUAGGOAG	2435
616	UACGCUCA G AACCGGAG	2138	CUCCGGUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGAGCGUA	2436
621	UCAGAACC G GAGUCUGC	2139	GCAGACUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGUUCUGA	2437
622	CAGAACCG G AGUCUGCG	2140	CGCAGACU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGGUUCUG	2438
624	GAACCGGA G UCUGCGGG	1316	CCCGCAGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCGGUUC	2439
628	CGGAGUCU G CGGGUGCU	1317	AGCACCCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGACUCCG	2440
630	GAGUCUGC G GGUGCUUG	2141	CAAGCACC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAGACUC	2441
631	AGUCUGCG G GUGCUUGC	2142	GCAAGCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGCAGACU	2442
632	GUCUGCGG G UGCUUGCG	1318	CGCAAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCGCAGAC	2443
634	CUGCGGGU G CUUGCGCC	1319	GGCGCAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCCGCAG	2444
638	GGGUGCUU C CGCCCGCA	1320	UGCGGGCG GGAGGAAACUCC CU UCAAGGACAUCCUCCGGG AAGCACCC	2445
640	GUGCUUGC G CCCGCAUU	1321	AAUGCGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAAGCAC	2446
644	UUGCGCCC G CAUUGGAC	1322	GUCCAAUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGCGCAA	2447
649	CCCGCAUU G GACAACUC	2143	GAGUUGUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AAUGCGGG	2448
650	CCGCAUUG C ACAACUCG	2144	CGAGUUGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAAUGCGC	2449
658	CACAACUC G UUGUGCCA	1323	UGGCACAA GGACGAAACUCC CU UCAACGACAUCGUCCCGG GACUUGUC	2450
661	AACUCGUU G UGCCAAGC	1324	GCUUGGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGCG AACCACUU	2451
663	CUCGUUGU G CCAACCCU	1325	ACGCUUGG CGAGGAAACUCC CU UCAAGGACAUCGUCCCGC ACAACGAC	2452
668	UGUGCCAA G CCUUCCCC	1326	CCCGAAGC CGACGAAACUCC CU UCAACGACAUCGUCCGGC UUGGCACA	2453
674	AACCCUUC C CCUUCUUC	1327	GAAGAAGG CGACGAAACUCC CU UCAAGGACAUCCUCCGCG CAACCCUU	2454
685	UUCUUCAU G UCCUUCUU	1328	AACAACGA GGACGAAACUCC CU UCAAGGACAUCGUCCGGG AUGAAGAA	2455
695	CCUUCUUU G GGCUCUCC	2145	CCAGACCC GGACGAAACUCC CU UCAACGACAUCGUCCGGG AAAGAACC	2456
696	CUUCUUUG G GCUCUCCU	2146	ACCACAGC GGACGAAACUCC CU UCAACGACAUCCUCCCCG CAAACAAG	2457
697	UUCUUUGG G CUCUCCUC	1329	GAGGACAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGCG CCAAAGAA	2458

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
706	CUCUCCUC G ACACUGCA	2147	UCCAGUGU GGAGGAAACUCC CU UCAACGACAUCGUCCGGG GAGGAGAG	2459
712	UCGACACU C CAACUCCU	1330	ACCACUUC CCAGGAAACUCC CU UCAAGGACAUCGUCCGCG AGUGUCGA	2460
721	CAACUCCU C CCCAUGCC	2148	CCCAUCGC GCACGAAACUCC CU UCAACCACAUCGUCCGCG ACCACUUC	2461
722	AACUCCUC G CCAUGGCA	1331	UGCCAUGG CGACGAAACUCC CU UCAAGGACAUCGUCCCGG CACGAGUU	2462
727	CUGGCCAU C GCACUCGA	2149	UCCACUGC GGAGGAAACUCC CU UCAAGGACAUCGUCCCCC AUGGCCAG	2463
728	UGCCCAUC C CACUGGAC	1332	CUCCACUC GGACGAAACUCC CU UCAAGCACAUCGUCCGCG CAUCCCCA	2464
733	AUCCCACU C CACUGCUC	2150	CACCACUC GGACGAAACUCC CU UCAAGCACAUCGUCCGGG AGUGCCAU	2465
734	UCCCACUC C ACUGCUGG	2151	CCAGCACU CCACCAAACUCC CU UCAACCACAUCCUCCCGC CACUGCCA	2466
736	CCACUCGA C UCCUCCCU	1333	AGCCAGCA GCAGGAAACUCC CU UCAACCACAUCCUCCCCC UCCACUCC	2467
738	ACUCCAGU C CUGCCUCU	1334	ACACCCAC CCACCAAACUCC CU UCAACCACAUCCUCCCGC ACUCCACU	2468
741	CCACUCCU C CCUCUCCC	2152	GGGAGAGC GCAGGAAACUCC CU UCAACCACAUCCUCCCGC ACCACUCC	2469
742	CACUCCUC C CUCUCCCU	1335	ACGCAGAC GCACGAAACUCC CU UCAACCACAUCCUCCCCC CACCACUC	2470
752	UCUCCCUA C CCCACCCU	2153	ACCCUCCC CCACCAAACUCC CU UCAACCACAUCCUCCCCC UACCCACA	2471
753	CUCCCUAC C GCACCCUU	2154	AAGGGUGC GCAGGAAACUCC CU UCAACCACAUCCUCCGGC CUAGGCAG	2472
754	UCCCUAGC C CACCCUUU	1336	AAACGCUC CCACGAAACUCC CU UCAACCACAUCCUCCCCC CCUAGCGA	2473
771	CUUCUACC G ACGGCACA	2155	UGUGCCGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGUAGAAG	2474
774	CUACCGAC G GCACAUCA	2156	UGAUGUGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUCGGUAG	2475
775	UACCGACG G CACAUCAC	1337	GUGAUGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGUCGGUA	2476
787	AUCACCCU G CGCCUGGG	1338	CCCAGGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGGUGAU	2477
789	CACCCUGC G CCUGGGCG	1339	CGCCCAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAGGGUG	2478
793	CUGCGCCU G GGCGCACU	2157	AGUGCGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGCGCAG	2479
794	UGCGCCUG G GCGCACUG	2158	CAGUGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGGCGCA	2480
795	GCGCCUGG G CGCACUGG	1340	CCAGUGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAGGCGC	2481
797	GCCUGGGC G CACUGGUG	1341	CACCAGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCCCAGGC	2482
802	GGCGCACU G GUGGCCCC	2159	GGGGCCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGUGCGCC	2483
803	GCGCACUG G UGGCCCCG	1342	CGGGGCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGUGCGC	2484
805	GCACUGGU G GCCCCGGU	2160	ACCGGGGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCAGUGC	2485
806	CACUGGUG G CCCCGGUG	1343	CACCGGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACCAGUG	2486
811	GUGGCCCC G GUGGUGAG	2161	CUCACCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGGCCAC	2487
812	UGGCCCCG G UGGUGAGC	1344	UCUCACCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGGGGCCA	2488
814	GCCCCGGU G GUGAGCGC	2162	GCGCUCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCGGGGC	2489
815	CCCCGGUG G UGAGCGCC	1345	GGCGCUCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACCGGGG	2490
817	CCGGUGGU G AGCGCCUU	2163	AAGGCGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCACCGG	2491
819	GGUGGUGA G CGCCUUCU	1346	AGAAGGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCACCACC	2492
821	UGGUGAGC G CCUUCUCC	1347	GGAGAAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUCACCA	2493
832	UUCUCCCU G GCUUUCUG	2164	CAGAAAGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGGAGAA	2494

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
833	UCUCCCUG G CUUUCUGC	1348	GCAGAAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGGGAGA	2495
840	GGCUUUCU G CGCGCUAC	1349	GUAGCGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAAAGCC	2496
842	CUUUCUGC G CGCUACCU	1350	AGGUAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAGAAAG	2497
844	UUCUGCGC G CUACCUUU	1351	AAAGGUAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGCAGAA	2498
856	CCUUUCAU G GGCUUCGG	2165	CCGAAGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUGAAAGG	2499
857	CUUUCAUG G GCUUCGGG	2166	CCCGAAGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAUGAAAG	2500
858	UUUCAUGG G CUUCGGGA	1352	UCCCGAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAUGAAA	2501
863	UGGGCUUC G GGAAGUUC	2167	GAACUUCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAAGCCCA	2502
864	GGGCUUCG G GAAGUUCG	2168	CGAACUUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAAGCCC	2503
865	GGCUUCGG G AAGUUCGU	2169	ACGAACUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCGAAGCC	2504
868	UUCGGGAA G UUCGUGCA	1353	UGCACGAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUCCCGAA	2505
872	GGAAGUUC G UGCAGUAC	1354	GUACUGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAACUUCC	2506
874	AAGUUCGU G CAGUACUG	1355	CAGUACUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACGAACUU	2507
877	UUCGUGCA G UACUGCCC	1356	GGGCAGUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGCACGAA	2508
882	GCAGUACU G CCCCGGCA	1357	UGCCGGGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGUACUGC	2509
887	ACUGCCCC G GCACCUGG	2170	CCAGGUGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGGCAGU	2510
888	CUGCCCCG G CACCUGGU	1358	ACCAGGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGGGGCAG	2511
894	CGGCACCU G GUGCUUUA	2171	UAAAGCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGGUGCCG	2512
895	GGCACCUG G UGCUUUAU	1359	AUAAAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGGUGCC	2513
897	CACCUGGU G CUUUAUCC	1360	GGAUAAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCAGGUG	2514
907	UUUAUCCA G AUGGUCCA	2172	UGGACCAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGAUAAA	2515
910	AUCCAGAU G GUCCACGA	2173	UCGUGGAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUCUGGAU	2516
911	UCCAGAUG G UCCACGAG	1361	CUCGUGGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAUCUGGA	2517
917	UGGUCCAC G AGGAGGGC	2174	GCCCUCCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUGGACCA	2518
919	GUCCACGA G GAGGGCUC	2175	GAGCCCUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCGUGGAC	2519
920	UCCACGAG G AGGGCUCG	2176	CGAGCCCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUCGUGGA	2520
922	CACGAGGA G GGCUCGCU	2177	AGCGAGCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCUCGUG	2521
923	ACGAGGAG G GCUCGCUG	2178	CAGCGAGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUCCUCGU	2522
924	CGAGGAGG G CUCGCUGU	1362	ACAGCGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCUCCUCG	2523
928	GAGGGCUC G CUGUCGGU	1363	ACCGACAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAGCCCUC	2524
931	GGCUCGCU G UCGGUGCU	1364	AGCACCGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCGAGCC	2525
934	UCGCUGUC G GUGCUGGG	2179	CCCAGCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GACAGCGA	2526
935	CGCUGUCG G UGCUGGGG	1365	CCCCAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGACAGCG	2527
937	CUGUCGGU G CUGGGGUA	1366	UACCCCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCGACAG	2528
940	UCGGUGCU G GGGUACUC	2180	GAGUACCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCACCGA	2529

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
941	CGGUGCUG G GGUACUCU	2181	AGAGUACC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCACCG	2530
942	GGUGCUGG G GUACUCUG	2182	CAGAGUAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCAGCACC	2531
943	GUGCUGGG G UACUCUGU	1367	ACAGAGUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CCCAGCAC	2532
950	GGUACUCU G UGCUCUAC	1368	GUAGAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAGUACC	2533
952	UACUCUGU G CUCUACUC	1369	GAGUAGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGAGUA	2534
963	CUACUCCA G CCUCAUGG	1370	CCAUGAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGAGUAG	2535
970	AGCCUCAU G GCGCUGCU	2183	AGCAGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUGAGGCU	2536
971	GCCUCAUG G CGCUGCUG	1371	CAGCAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAUGAGGC	2537
973	CUCAUGGC G CUGCUGGU	1372	ACCAGCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCCAUGAG	2538
976	AUGGCGCU G CUGGUCCU	1373	AGGACCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCGCCAU	2539
979	GCGCUGCU G GUCCUCGC	2184	GCGAGGAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCAGCGC	2540
980	CGCUGCUG G UCCUCGCC	1374	GGCGAGGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAGCAGCG	2541
986	UGGUCCUC G CCACCGUG	1375	CACGGUGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAGGACCA	2542
992	UCGCCACC G UGCUGUGC	1376	GCACAGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGUGGCGA	2543
994	GCCACCGU U CUGUGCAA	1377	UUGCACAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACGGUGGC	2544
997	ACCGUGCU G UGCAACCU	1378	AGGUUGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCACGGU	2545
999	CGUGCUGU G CAACCUCG	1379	CGAGGUUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGCACG	2546
1007	GCAACCUC U GCGCCAUG	2185	CAUGGCGC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAGGUUGC	2547
1008	CAACCUCG G CGCCAUGC	1380	GCAUGGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAGGUUG	2548
1010	ACCUCGGC G CCAUGCGC	1381	GCGCAUGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCCGAGGU	2549
1015	GGCGCCAU G CGCAACCU	1382	AGGUUUCU GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG AUGGCGCC	2550
1017	CGCCAUUC G CAACCUCU	1383	AUAGGUUG GGAGGAAACUCC CU UCAAGGACAUCUUCCGGG GCAUGGCG	2551
1028	ACCUCUAU G CGAUGCAC	1384	GUGCAUCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUAGAGGU	2552
1030	CUCUAUGC U AUGCACCG	2186	CGGUGCAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAUAGAG	2553
1033	UAUGCGAU G CACCGGCG	1385	CGCCGGUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUCGCAUA	2554
1038	UAUGCACC G GCUGCUGC	2187	UCAGCCGC GUAGGAAACUCC CU UCAAGGACAUCGUCCGUG GGUGCAUC	2555
1039	AUGCACCG G CGUCUGCA	1386	UGCAGCCG GGAGUAAACUCC CU UCAAGGACAUCGUCCGUG CGGUGCAU	2556
1041	GCACCGGC U UCUGCAUC	2188	GCUGCAGC GGAGGAAACUCC CU UCAAUGACAUCGUCCGGG GCCGGUUC	2557
1042	CACCGUCG U CUUCAUCG	1387	CGCUGCAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGCCGGUG	2558
1045	CGGCGUCU G CAUCUGCA	1388	UUCCGCUG GGAGGAAACUCC CU UCAAGUACAUCGUCCGGG AGCCGCCU	2559
1048	CUUCUGCA G CGGCACCC	1389	GGGUGCCG GGAGGAAACUCC CU UCAAGGACAUCGUCCUGG UGCAGCCG	2560
1050	GCUUCAGC U UCACCCGC	2189	GCGUGUGC UUAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCUGCAGC	2561
1051	CUGCAGCG G CACCCGCU	1390	CGCUGGUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGU CGCUGCAG	2562
1057	CGUCACCC U CGCUCCUG	1391	CAGGAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGUGCCG	2563
1059	GCACCCUC U CUCCUGCA	1392	UGCAGGAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGGGUGC	2564
1065	GCGCUCCU G CACCAGGG	1393	CCCUUGUG GGAUGAAACUCC CU UCAAGGACAUCGUCCGGG AGGAGCGC	2565

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
1071	CUGCACCA G GUACUGUG	2190	CACAGUCC UGAGUAAACUCC CU UCAAGUACAUCGUCCGGG UGGUGCAG	2566
1072	UGCACCAG U GACUGUGC	2191	GCACAUUC GGAGUAAACUCC CU UCAAGUACAUCGUCCGGG CUGGUGCA	2567
1073	GCACCAGG U ACUGUGCC	2192	GUCACAGU GGAGGAAACUCC CU UCAAGUACAUCGUCCGGG CCUGGUGC	2568
1077	CAGGGACU U UGCCGAGC	1394	GCUCGGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGUCCCUG	2569
1079	GGGACUGU U CCGAGCCG	1395	CUGCUCGG UGAGGAAACUCC CU UCAAGGACAUCGUCCGGU ACAGUCCC	2570
1082	ACUUUUCC U AUCCUCUC	2193	GCUCGUCU UUAUGAAACUCC CU UCAAUGACAUCUUCCUGU UUCACAGU	2571
1084	UUUUCCUA U CCUCUCGC	1396	UCUCUCUG UUAUGAAACUCC CU UCAAUGACAUCUUCCUUU UCGUCACA	2572
1087	GCCGAGCC G CGCGCGGA	1397	UCCGCGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCUCGGC	2573
1089	CGAGCCGC G CGCGGACG	1398	CGUCCGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGGCUCG	2574
1091	AGCCGCGC G CGGACGGG	1399	CCCGUCCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGCGGCU	2575
1093	CCGCGCGC G GACGGGAG	2194	CUCCCGUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGCGCGG	2576
1094	CGCGCGCG G ACGGGAGG	2195	CCUCCCGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGCGCGCG	2577
1097	GCGCGGAC G GGAGGGAA	2196	UUCCCUCC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GUCCGCGC	2578
1098	CGCGGACG C GAGGGAAG	2197	CUUCCCUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGUCCGCG	2579
1099	GCGGACGG C AGGGAAGC	2198	CCUUCCCU GCACGAAACUCC CU UCAAGCACAUCCUCCGGG CCCUCCGC	2580
1101	CGACCCGA C CCAAGCCU	2199	ACCCUUCC GCAGGAAACUCC CU UCAAGGACAUCGUCCCCG UCCCCUCC	2581
1102	CACGGCAC G GAAGCGUC	2200	GACGCUUC GGAGGAAACUCC CU UCAAGGACAUCGUCCCCG CUCCCGUC	2582
1103	ACCGCAGC C AACCGUCC	2201	GGACCCUU GCACGAAACUCC CU UCAAGCACAUCCUCCCCG CCUCCCGU	2583
1106	GGAGGCAA G CCUCCCCU	1400	AGCGCACG GGAGGAAACUCC CU UCAAGGACAUCGUCCCGG UUCCCUCC	2584
1108	AGGCAACC C UCCCCUCA	1401	UGAGGGCA GGAGGAAACUCC CU UCAACCACAUCGUCCCGG GCUUCCCU	2585
1117	UCCCCUCA C CCCCUGGA	1402	UCCACGGG GGACGAAACUCC CU UCAAGGACAUCGUCCCGG UCACCGGA	2586
1123	CAGCCCCU C CACGAGCU	2202	AGCUCCUC GGACGAAACUCC CU UCAAGGACAUCGUCCGGG ACGGGCUG	2587
1124	ACCCCCUG C ACGAGCUG	2203	CAGCUCCU GGAGGAAACUCC CU UCAAGGACAUCGUCCCCG CAGGCGCU	2588
1126	CCCCUCGA C GAGCUGGA	2204	UCCACCUC GCACGAAACUCC CU UCAAGGACAUCGUCCGCG UCCACGCG	2589
1127	CCCUCCAC C AGCUGGAU	2205	AUCCAGCU GCAGGAAACUCC CU UCAACGACAUCCUCCGCG CUCCAGGG	2590
1129	CUGGAGGA C CUGGAUCA	1403	UCAUCCAG GCACGAAACUCC CU UCAAGCACAUCGUCCGCG UCCUCCAG	2591
1132	GAGGAGCU C CAUCACCU	2206	ACCUGAUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCUCCUC	2592
1133	AGCACCUC C AUCACCUC	2207	CACGUGAU GCACGAAACUCC CU UCAAGCACAUCCUCCGGG CACCUCCU	2593
1144	CACCUCCU C CUCCUGCC	1404	CCCACCAG GCACGAAACUCC CU UCAAGCACAUCCUCCGGG ACCAGGUG	2594
1147	CUCCUGCU C CUGGCGCU	1405	AGCGCCAG GGACGAAACUCC CU UCAAGGACAUCCUCCGGG ACCACGAG	2595
1150	CUCCUCCU C GCGCUGAU	2208	AUCACCCC GCAGGAAACUCC CU UCAAGCACAUCCUCCGCG ACCACCAG	2596
1151	UCCUCCUC C CGCUCAUG	1406	CAUCAGCG GCACGAAACUCC CU UCAAGGACAUCGUCCGGG CACCAGCA	2597
1153	CUCCUGGC C CUGAUGAC	1407	GUCAUCAG GCAGGAAACUCC CU UCAAGCACAUCCUCCGCG GCCAGCAG	2598
1156	CUCCCCCU C AUCACCCU	2209	ACCGUCAU GCAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCGCCAG	2599
1159	CCCCUCAU C ACCCUCCU	2210	AGCACGCU GCACCAAACUCC CU UCAAGCACAUCGUCCGCG AUCACCCC	2600

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
1163	UGAUCACC C UGCUCUUC	1408	CAAGAGCA GCAGGAAACUCC CU UCAAGCACAUCCUCCGGG GCUCAUCA	2601
1165	AUGACCGU C CUCCUCAC	1409	GUCAAGAG GGAGCAAACUCC CU UCAAGCACAUCCUCCGCG ACGGUCAU	2602
1177	UUCACUAU C UGUUCUCU	1410	AGACAACA CGAGCAAACUCC CU UCAAGCACAUCCUCCGGG AUACUCAA	2603
1179	CACUAUGU C UUCUCUGC	1411	GCAGAGAA GGAGGAAACUCC CU UCAAGCACAUCCUCCGCG ACAUACUG	2604
1186	UGUUCUCU C CCCGUAAU	1412	AUUACGGC CGAGGAAACUCC CU UCAAGCACAUCCUCCCCG AGAGAACA	2605
1190	CUCUGCCC G UAAUUUAU	1413	AUAAAUUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGGCAGAG	2606
1200	AAUUUAUC G CGCUUACU	1414	AGUAAGCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAUAAAUU	2607
1202	UUUAUCGC G CUUACUAU	1415	AUAGUAAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCGAUAAA	2608
1211	CUUACUAU G CAGCAUUU	2211	AAAUGCUC GGAGGAAACUCC CU UCAAOGACAUCGUCCGGG AUAGUAAG	2609
1212	UUACUAUG G AGCAUUUA	2212	UAAAUGCU GGAGGAAACUCC CU UCAA0GACAUCGUCCG0G CAUAGUAA	2610
1214	ACUAUGGA G CAUUUAAG	1416	CUUAAAUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCAUAGU	2611
1222	GCAUUUAA G GAUGUCAA	2213	UUGACAUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUAAAUGC	2612
1223	CAUUUAAG G AUGUCAAG	2214	CUUGACAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUUAAAUG	2613
1226	UUAAGGAU G UCAAGGAG	1417	CUCCUUGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUCCUUAA	2614
1231	GAUGUCAA G GAGAAAAA	2215	UUUUUCUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUGACAUC	2615
1232	AUGUCAAG G AGAAAAAC	2216	GUUUUUCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUUGACAU	2616
1234	GUCAAGGA G AAAAACAG	2217	CUGUUUUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCUUGAC	2617
1242	GAAAAACA G GACCUCUG	2218	CAGAGGUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGUUUUUC	2618
1243	AAAAACAG G ACCUCUGA	2219	UCAGAGGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUGUUUUU	2619
1250	GGACCUCU G AAGAAGCA	2220	UGCUUCUU GGAGGAAACUCC CU UCAAGGACAUCGUCC0GG AGAGGUCC	2620
1253	CCUCUGAA G AAGCAGAA	2221	UUCUGCUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUCAGAGG	2621
1256	CUGAAGAA G CAGAAGAC	1418	GUCGUCUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUCUUCAG	2622
1259	AAGAAGCA G AAGACCUC	2222	GAGGUCUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGCUUCUU	2623
1262	AAGCAGAA G ACCUCCGA	2223	UCGGAGGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUCUGCUU	2624
1269	AGACCUCC G AGCCUUGC	2224	GCAAGGCU GGAGGAAACUCC CU UCAAG0ACAUCGUCCGGG GGAGGUCU	2625
1271	ACCUCCGA G CCUUGCGA	1419	UCGCAAGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCGGAGGU	2626
1276	CGAGCCUU G CGAUUUCU	1420	AGAAAUCG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AAGGCUCG	2627
1278	AGCCUUGC G AUUUCUAU	2225	AUAGAAAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GCAAGGCU	2628
1289	UUCUAUCU G UGAUUUCA	1421	UGAAAUCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAUAGAA	2629
1291	CUAUCUGU G AUUUCAAU	2226	AUUGAAAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGAUAG	2630
1301	UUUCAAUU G UGGACCCU	1422	AGGGUCCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AAUUGAAA	2631
1303	UCAAUUGU G GACCCUUG	2227	CAAGGGUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAAUUGA	2632
1304	CAAUUGUG G ACCCUUGG	2228	CCAAGGGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACAAUUG	2633
1311	GGACCCUU G GAUUUUUA	2229	UAAAAAUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AAGGGUCC	2634
1312	GACCCUUG G AUUUUUAU	2230	AUAAAAAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAAGGGUC	2635
1329	CAUUUUCA G AUCUCCAG	2231	CUGGAGAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGAAAAUG	2636

TABLE VII-continued

Human PTGDR Amberzyme and Substrate Sequence

Pos	Substrate	Seq ID	Amberzyme	Seq ID
1337	GAUCUCCA G UAUUUCGG	1423	CCGAAAUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGAGAUC	2637
1344	AGUAUUUC G GAUAUUUU	2232	AAAAUAUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GAAAUACU	2638
1345	GUAUUUCG G AUAUUUUU	2233	AAAAAUAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGAAAUAC	2639
1360	UUUCACAA G AUUUUCAU	2234	AUGAAAAU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUGUGAAA	2640
1371	UUUCAUUA G ACCUCUUA	2235	UAAGAGGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UAAUGAAA	2641
1380	ACCUCUUA G GUACAGGA	2236	UCCUGUAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UAAGAGGU	2642
1381	CCUCUUAG G UACAGGAG	1424	CUCCUGUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUAAGAGG	2643
1386	UAGGUACA G GAGCCGGU	2237	ACCGGCUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGUACCUA	2644
1387	AGGUACAG G AGCCGGUG	2238	CACCGGCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUGUACCU	2645
1389	GUACAGGA G CCGGUGCA	1425	UGCACCGG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCCUGUAC	2646
1392	CAGGAGCC G GUGCAGCA	2239	UGCUGCAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG GGCUCCUG	2647
1393	AGGAGCCG G UGCAGCAA	1426	UUGCUGCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CGGCUCCU	2648
1395	GAGCCGGU G CAGCAAUU	1427	AAUUGCUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACCGGCUC	2649
1398	CCGGUGCA G CAAUUCCA	1428	UGGAAUUG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGCACCGG	2650
1414	ACUAACAU G GAAUCCAG	2240	CUGGAUUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUGUUAGU	2651
1415	CUAACAUG G AAUCCAGU	2241	ACUGGAUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CAUGUUAG	2652
1422	GGAAUCCA G UCUGUGAC	1429	GUCACAGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGGAUUCC	2653
1426	UCCAGUCU G UGACAGUG	1430	CACUGUCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGACUGGA	2654
1428	CAGUCUGU G ACAGUGUU	2242	AACACUGU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGACUG	2655
1432	CUGUGACA G UGUUUUUC	1431	GAAAAACA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGUCACAG	2656
1434	GUGACAGU G UUUUUCAC	1432	GUGAAAAA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACUGUCAC	2657
1446	UUCACUCU G UGGUAAGC	1433	GCUUACCA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGAGUGAA	2658
1448	CACUCUGU G GUAAGCUG	2243	CAGCUUAC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG ACAGAGUG	2659
1449	ACUCUGUG G UAAGCUGA	1434	UCAGCUUA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CACAGAGU	2660
1453	UGUGGUAA G CUGAGGAA	1435	UUCCUCAG GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UUACCACA	2661
1456	GGUAAGCU G AGGAAUAU	2244	AUAUUCCU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AGCUUACC	2662
1458	UAAGCUGA G GAAUAUGU	2245	ACAUAUUC GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UCAGCUUA	2663
1459	AAGCUGAG G AAUAUGUC	2246	GACAUAUU GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG CUCAGCUU	2664
1465	AGGAAUAU G UCACAUUU	1436	AAAUGUGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG AUAUUCCU	2665
1477	CAUUUUCA G UCAAAGAA	1437	UUCUUUGA GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG UGAAAAUG	2666

Input Sequence = PTGDR_composit.
Cut Site = G/.
Arm Length = 8.
Core Sequence = GGAGGAAACUCC CU UCAAGGACAUCGUCCGGG
PTGDR_composit (1 to 993 of HSU31332 (PTGDR 5') + 1 to 495 of HSU31099 (PTGDR 3'); 1488 nt)

What we claim is:

1. A nucleic acid molecule that down regulates expression of a prostaglandin D2 receptor (PTGDR) gene.

2. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule is an enzymatic nucleic acid molecule.

3. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule is an antisense nucleic acid molecule.

4. The enzymatic nucleic acid molecule of claim 2, wherein said enzymatic nucleic acid molecule comprises a sequence selected from the group of sequences consisting of SEQ ID NOs: 228-454, 831-1206, 1438-1668, 1715-2057, and 2247-2666.

5. The enzymatic nucleic acid molecule of claim 2, wherein said enzymatic nucleic acid molecule comprises at least one binding arm wherein one or more of said binding arms comprises a sequence complementary to a sequence selected from the group of sequences consisting of SEQ ID NOs: 1-227, 455-830, 1207-1437, 1669-1714, and 2058-2246.

6. The antisense nucleic acid molecule of claim 3, wherein said antisense nucleic acid molecule comprises a sequence complementary to a sequence selected from the group of sequences consisting of SEQ ID NOs: 1-227, 455-830, 1207-1437, 1669-1714, and 2058-2246.

7. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule is adapted to treat asthma.

8. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises at least one 2'-sugar modification.

9. The nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises at least one phosphate backbone modification.

10. A method of reducing PTGDR activity in a cell, comprising contacting said cell with the nucleic acid molecule of claim 1 under conditions suitable for said reduction.

11. A method of treatment of a patient having a condition associated with the level of PTGDR, comprising contacting cells of said patient with the nucleic acid molecule of claim 1, under conditions suitable for said treatment.

12. The method of claim 11 further comprising the use of one or more drug therapies under conditions suitable for said treatment.

13. A pharmaceutical composition comprising an enzymatic nucleic acid molecule of claim 1.

14. A method of administering to a mammal the nucleic acid molecule of claim 1, comprising contacting said mammal with the molecule under conditions suitable for said administration.

15. The method of claim 14, wherein said mammal is a human.

16. The method of claim 14 wherein said administration is in the presence of a delivery reagent.

17. The method of claim 16, wherein said delivery reagent is a lipid.

18. The method of claim 17, wherein said lipid is a cationic lipid.

19. The method of claim 17, wherein said lipid is a phospholipid.

20. The method of claim 17, wherein said delivery reagent is a liposome.

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