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(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **MEADE, Bryan**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **MURRAY, Justin K.**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **RULIFSON, Ingrid**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **HOMANN, Oliver**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

(74) Agent: **KARABINIS, Melissa**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

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(54) **Title:** RNAI CONSTRUCTS FOR INHIBITING PNPLA3 EXPRESSION AND METHODS OF USE THEREOF

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37555-1	113	AGCUGCUGC GGAUCAGG ACC{invAb}	1069	asgscugcUfgCfGfGf Afucaggaccs{invAb}	1699	AGGUCCUGAU CCGCAGCAGC UUU	2329	asGfsguccUf gauccgCfaGf cagcususu	2959
37556-1	115	CUGCUGCGG AUCAGGACC CG{invAb}	1070	csusgcugCfgGfAfUf Cfaggacccgs{invAb}	1700	UCGGGUCCUG AUCCGCAGCA GUU	2330	usCfsggguCf cugaucCfgCf agcagsusu	2960
37557-1	121	CGGAUCAG GACCCGAGC CGA{invAb}	1071	csgsgaucAfgGfAfCf Cfcgagccgas{invAb}	1701	AUCGGCUCGG GUCCUGAUCC GUU	2331	asUfscggcUf cgggucCfuGf auccgsusu	2961
37558-1	122	GGAUCAGG ACCCGAGCC GAU{invAb}	1072	gsgsaucaGfgAfCfCf Cfgagccgaus{invAb}	1702	AAUCGGCUCG GGUCCUGAUC CUU	2332	asAfsucggCf ucgggucCfcUf gauccsusu	2962
37559-1	204	CAGAGCGCG GCUGGAGC UUG{invAb}	1073	csasgagcGfcGfGfCf Ufggagcuugs{invAb}	1703	ACAAGCUCCA GCCGCGCUCU GUU	2333	asCfsaagcUf ccagccGfcGf cucugsusu	2963
37560-1	205	AGAGCGCG GCUGGAGC UUGU{invAb}	1074	asgsagcgCfgGfCfUf Gfgagcuugus{invAb}	1704	AACAAGCUCC AGCCGCGCUC UUU	2334	asAfscaagCf uccagcCfgCf gcucususu	2964
37561-1	206	GAGCGCGGC UGGAGCUU GUC{invAb}	1075	gsasgcgcGfgCfUfGf Gfagcuugucs{invAb}	1705	AGACAAGCUC CAGCCGCGCU CUU	2335	asGfsacaaGf cuccagCfcGf cgcucsusu	2965

(57) **Abstract:** The disclosure relates to RNAi constructs, such as siRNA, for reducing expression of the Patatin-Like Phospholipase Domain Containing 3 (PNPLA3) gene. Further disclosed are RNAi constructs comprising sense strand and antisense strand sequences, and PNPLA3 mRNA sequences. Methods of using such RNAi constructs to treat or prevent liver disease, such as nonalcoholic fatty liver disease (NAFLD), are also described.

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RNAI CONSTRUCTS FOR INHIBITING PNPLA3 EXPRESSION AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

[0001] The present disclosure relates to compositions and methods for modulating liver expression of patatin-like phospholipase domain-containing 3 (PNPLA3). In particular, the present disclosure relates to nucleic acid-based therapeutics for reducing PNPLA3 expression via RNA interference and methods of using such nucleic acid-based therapeutics to treat or prevent liver disease, such as nonalcoholic fatty liver disease (NAFLD).

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 1,930 kilobyte XML document named "A-2910-WO01-SEC.xml," created on March 20, 2023.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0003] This application claims the benefit of U.S. Provisional Application No. 63/322,845, filed on March 23, 2022.

BACKGROUND

[0004] Comprising a spectrum of hepatic pathologies, nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, the prevalence of which doubled in the last 20 years and now is estimated to affect approximately 20% of the world's population (Sattar et al. (2014) BMJ 349: g4596; Loomba and Sanyal (2013) Nature Reviews Gastroenterology & hepatology 10(11):686-690; Kim and Kim (2017) Clin Gastroenterol Hepatol 15(4):474-485; Petta et al. (2016) Dig Liver Dis 48(3):333-342). NAFLD begins with the accumulation of triglyceride in the liver and is defined by the presence of cytoplasmic lipid droplets in more than 5% of hepatocytes in an individual 1) without a history of significant alcohol consumption and 2) in which the diagnosis of other types of liver disease have been excluded (Zhu et al (2016) World J Gastroenterol 22(36):8226-33; Rinella (2015) JAMA 313(22):2263-73; Yki-Jarvinen (2016) Diabetologia 59(6):1104-11). In some individuals the accumulation of ectopic fat in the liver, called steatosis, triggers inflammation and hepatocellular injury leading to a more advanced stage of

disease called nonalcoholic steatohepatitis (NASH) (Rinella, *supra*). As of 2015, 75-100 million Americans are predicted to have NAFLD, with NASH accounting for approximately 10-30% of NAFLD diagnoses (Rinella, *supra*; Younossi et al (2016) Hepatology 64(5):1577-1586).

[0005] Patatin-like phospholipase domain-containing 3 (PNPLA3), formerly known as adiponutrin (ADPN) and calcium-independent phospholipase A2-epsilon (iPLA(2)ε), is a type II transmembrane protein (Wilson et al (2006) J Lipid Res 47(9):1940-9; Jenkins et al (2004) J Biol Chem 279(47):48968-75). Initially identified in adipose cells as a membrane-associated, adipose-enriched protein induced during adipogenesis in mice, it is now well characterized to be expressed in other tissues, including the liver (Wilson et al, *supra*; Baulande et al. (2001) J Biol Chem 276(36):33336-44; Moldes et al. (2006) Eur J Endocrinol 155(3):461-8; Faraj et al. (2006) J Endocrinol 191(2):427-35; Liu et al. (2004) J Clin Endocrinol Metab 89(6) :2684-9; Lake et al. (2005) J Lipid Res 46(11) :2477-87). In cell-free biochemical systems, recombinant PNPLA3 protein can exhibit either triacylglycerol lipase or transacylation activity (Jenkins et al., *supra*; Kumari et al. (2012) Cell Metab 15(5):691-702; He et al. (2010) J Biol Chem 285(9):6706-15). In hepatocytes, PNPLA3 is expressed on the endoplasmic reticulum and lipid membranes and predominantly exhibits triacylglycerol hydrolase activity (He et al., *supra*; Huang et al. (2010) Proc Natl Acad Sci USA 107(17):7892-7; Ruhanen et al. (2014) J Lipid Res 55(4):739-46; Pingitore et al. (2014) Biochim Biophys Acta 1841(4):574-80). Although PNPLA3 lacks a secretory signal, data indicates that it is secreted and can be found in human plasma as disulfide-bond dependent multimers (Winberg et al. (2014) Biochem Biophys Res Commun 446(4):1114-9).

[0006] Currently, NAFLD symptoms are managed via weight loss and treatment of any secondary conditions, as no pharmacologic treatments have been approved. Thus, there is a need for compositions and methods that treat NAFLD in affected individuals.

SUMMARY OF THE INVENTION

[0007] The present disclosure provides an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is complementary to a PNPLA3 mRNA sequence, such as a PNPLA3 mRNA sequence set forth in Table 1, and wherein the RNAi construct inhibits the expression of PNPLA3. In certain embodiments, the RNAi construct comprises a region having at least 15 contiguous

nucleotides differing by no more than 3 nucleotides from an antisense sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588. In some embodiments, the antisense strand hybridizes to a PNPLA3 mRNA sequence listed in Table 1.

[0008] In some embodiments, the sense strand of the RNAi constructs described herein comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length. In these and other embodiments, the sense and antisense strands each are about 15 to about 30 nucleotides in length. In some embodiments, the RNAi constructs comprise at least one blunt end. In other embodiments, the RNAi constructs comprise at least one nucleotide overhang. Such nucleotide overhangs may comprise at least 1 to 6 unpaired nucleotides and can be located at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense and antisense strand. In certain embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the sense strand and the 3' end of the antisense strand. In other embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3' end of the antisense strand and a blunt end of the 3' end of the sense strand/5' end of the antisense strand.

[0009] The RNAi constructs of the disclosure may comprise one or more modified nucleotides, including nucleotides having modifications to the ribose ring, nucleobase, or phosphodiester backbone. In some embodiments, the RNAi constructs comprise one or more 2'-modified nucleotides. Such 2'-modified nucleotides can include 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acids (BNA), glycol nucleic acids (GNAs), inverted bases (e.g. inverted adenosine) or combinations thereof. In one particular embodiment, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, or combinations thereof. In some embodiments, all of the nucleotides in the sense and antisense strand of the RNAi construct are modified nucleotides.

[0010] In some embodiments, the RNAi constructs comprise at least one backbone modification, such as a modified internucleotide or internucleoside linkage. In certain embodiments, the RNAi constructs described herein comprise at least one phosphorothioate internucleotide linkage. In particular embodiments, the phosphorothioate internucleotide linkages may be positioned at the 3' or 5' ends of the sense and/or antisense strands.

[0011] In some embodiments, the antisense strand and/or the sense strand of the RNAi constructs of the disclosure may comprise or consist of a sequence from the antisense and sense sequences listed in Figures 1 or 2. In certain embodiments, the RNAi construct may

comprise a duplex compound comprising an antisense strand and a sense strand, wherein the antisense strand comprises a sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588 and the sense strand comprises a sequence selected from SEQ ID NOs: 61-564 and SEQ ID NOs: 1069-2328.

[0012] The disclosure also provides a composition comprising the aforementioned RNAi construct and a pharmaceutically acceptable carrier, excipient, or diluent, as well as methods of reducing the expression of PNPLA3 in a patient in need thereof comprising administering to the patient the aforementioned RNAi construct or composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 is a table listing unmodified and modified siRNA sequences directed to PNPLA3 tested in the *in vitro* experiments described in Example 2. All sequences are shown in 5'-3' orientation.

[0014] Figure 2 is a table listing unmodified and modified siRNA sequences directed to PNPLA3 tested in the *in vivo* studies described in Example 3. All sequences are shown in 5'-3' orientation.

[0015] Figure 3 is a table showing results of siRNA inhibition of PNPLA3 in an AAV-based mouse model containing the full human PNPLA3 coding sequence (CDS).

[0016] Figure 4 is a table showing results of siRNA inhibition of PNPLA3 in an AAV-based mouse model containing portions of the 3' untranslated region (UTR) of human PNPLA3.

[0017] Figure 5 is a table showing results of siRNA inhibition of PNPLA3 in a homozygous h*PNPLA3*^{I148M} knock-in (h*PNPLA3*^{I148M} KI) mouse model.

[0018] The nucleotide sequences in Figures 1-5 and other parts of the application are listed according to the following notations: A, U, G, and C =corresponding ribonucleotide; dT = deoxythymidine; dA = deoxyadenosine; dC = deoxycytidine; dG = deoxyguanosine; invAb = inverted A basic; invDT = inverted deoxythymidine; invDA = inverted deoxyadenosine; invDC = inverted deoxycytidine; invDG = inverted deoxyguanosin; a, u, g, and c = corresponding 2'-O-methyl ribonucleotide; Af, Uf, Gf, and Cf = corresponding 2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide; Ab = Abasic; MeO-I = 2' methoxy inosine; GNA = glycol nucleic acid; sGNA = glycol nucleic acid with 3' phosphorothioate; LNA = locked nucleic acid. Insertion of an "s" in the sequence indicates that the two adjacent nucleotides are connected by a phosphorothiodiester group (e.g. a phosphorothioate

internucleotide linkage). Unless indicated otherwise, all other nucleotides are connected by 3'-5' phosphodiester groups.

DETAILED DESCRIPTION

[0019] The present disclosure is based, in part, on the design and generation of RNAi constructs that target the PNPLA3 gene and reduce expression of PNPLA3 in liver cells in a non-sequence specific manner. The non-sequence specific inhibition of PNPLA3 expression is useful for treating or preventing conditions associated with PNPLA3 expression, including liver-related diseases, such as, for example, simple fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis (irreversible, advanced scarring of the liver), or PNPLA3-related obesity.

[0020] The disclosure provides compositions and methods for regulating the expression of the Patatin-Like Phospholipase Domain Containing 3 (PNPLA3) gene. In some embodiments, the gene may be within a cell or subject, such as a mammal (e.g., a human). In some embodiments, compositions of the disclosure comprise RNAi constructs that target a PNPLA3 mRNA and reduce PNPLA3 expression in a cell or mammal. Such RNAi constructs are useful for treating or preventing various forms of liver-related diseases, such as, for example, simple fatty liver (steatosis), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), cirrhosis (irreversible, advanced scarring of the liver), or PNPLA3-related obesity.

[0021] In 2008, a genome wide association study (GWAS) exploring nonsynonymous sequence variations, or single nucleotide polymorphisms (SNPs), associated with NAFLD identified a variant in PNPLA3, (rs738409[G], encoding I148M; which can be referred to as PNPLA3-rs738409, PNPLA3-ma, or PNPLA3-minor allele), as significantly associated with hepatic fat content. Since this initial report, subsequent GWAS confirmed PNPLA3 rs738409 as the major genetic determinant of NAFLD, significantly associated with 1) increased levels of the serum biomarker for liver damage, alanine transaminase (ALT), 2) NAFLD incidence, progression, and severity, 3) both obese and lean individuals, and 4) the only known SNP shown to be significantly associated with all stages of NAFLD: steatosis, NASH, cirrhosis and hepatic cell carcinoma. The consensus among numerous GWAS indicates that the association of PNPLA3 rs738409 with NAFLD is independent of age, gender, ethnicity, metabolic syndrome, body mass index, insulin resistance, and serum lipids. Furthermore, statistical analyses from multiple sources estimate approximately 50% of NAFLD patients carry the PNPLA3 rs738409 mutation. Patients can be homozygous or

heterozygous for the PNPLA3 rs738409 mutation. Additionally, it has been discovered that patients having the PNPLA3 rs738409 mutation often also carry an rs738408 mutation 3 base pairs away (Tian et al (2010) Nature Genetics 42:21-23). Thus, a patient can have a PNPLA3-rs738409 minor allele, a PNPLA3-rs738408 minor allele or a PNPLA3-rs738409-rs738408 double minor allele mutation (PNPLA3-dma).

[0022] Investigators have developed mouse models for exploring PNPLA3 function *in vivo*. To date, no detectable metabolic phenotype has been identified as the result of PNPLA3-deficiency or PNPLA3 over-expression. In contrast, expression of PNPLA3I148M in both transgenic mice and knock-in mice led to increased hepatic triglyceride levels akin to NAFLD. Thus, the combined *in vivo* mouse model data points to expression of the mutant PNPLA3I148M protein, and not over-expression of the wild-type protein, as the driver of the disease phenotype. These findings, in addition to the high frequency of the minor allele in NAFLD-affected individuals and prevailing association with the disease, underline PNPLA3 rs738409 as a prime therapeutic target for NAFLD.

[0023] RNA interference (RNAi) is the process of introducing exogeneous RNA into a cell leading to specific degradation of the mRNA encoding the targeted protein with a resultant decrease in protein expression. Advances in both the RNAi technology and hepatic delivery, as well as growing positive outcomes with other RNAi-based therapies, suggest RNAi as a compelling means to therapeutically treat NAFLD by directly targeting PNPLA3.

[0024] As used herein, the term "RNAi construct" refers to an agent comprising an RNA molecule that is capable of downregulating expression of a target gene (e.g. PNPLA3) via an RNA interference mechanism when introduced into a cell. "RNA interference" is the process by which a nucleic acid molecule induces the cleavage and degradation of a target RNA molecule (e.g. messenger RNA or mRNA molecule) in a sequence-specific manner, e.g., through an RNA induced silencing complex (RISC) pathway. In some embodiments, the RNAi construct comprises a double-stranded RNA (dsRNA) molecule comprising two antiparallel strands of contiguous nucleotides that are sufficiently complementary to each other to hybridize to form a duplex region. A double-stranded RNAi construct also may be referred to as an RNAi "trigger." The terms "hybridize" or "hybridization" refer to the pairing of complementary polynucleotides, typically via hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary bases in the two polynucleotides. The strand comprising a region having a sequence that is substantially complementary to a target sequence (e.g., target mRNA) is referred to as the "antisense strand." The "sense strand" refers to the strand that includes a region that is

substantially complementary to a region of the antisense strand. In some embodiments, the sense strand may comprise a region that has a sequence that is substantially identical to the target sequence.

[0025] In certain embodiments, the sense strand and antisense strand of the double-stranded RNA may be two separate molecules that hybridize to form a duplex region but are otherwise unconnected. Such double-stranded RNA molecules formed from two separate strands are referred to as "small interfering RNAs" or "short interfering RNAs" (siRNAs). siRNAs are a class of non-coding, double-stranded RNA molecules that are typically about 20-27 base pairs and are central to RNAi. Thus, in some embodiments, the RNAi constructs of the disclosure comprise an siRNA. In other embodiments, the RNAi construct may be a microRNA (also known as "miRNA" or "mature miRNA"). miRNAs are small (approximately 18-24 nucleotides in length), non-coding RNA molecules present in plants, animals, and some viruses. miRNAs resemble siRNA, but miRNAs originate from hairpin mRNA structures. miRNAs regulate gene expression by base-pairing to complementary regions of target mRNAs.

[0026] In some embodiments, the disclosure provides an RNAi construct directed to PNPLA3. In some embodiments, the RNAi construct is an siRNA that comprises a sense strand and an antisense strand, wherein the antisense strand comprises a region that is complementary to PNPLA3 mRNA sequence. The region of the RNAi antisense strand may be complementary to any suitable region of a PNPLA3 mRNA sequence. For example, the antisense strand may comprise a region that is complementary to the coding region or the 3' untranslated region (UTR) of a PNPLA3 mRNA sequence. Exemplary PNPLA3 target sequences within the coding region (reference sequence GenBank Accession No. NM_025225.2) and 3' UTR are set forth in Table 1. The antisense strand of the RNAi construct desirably hybridizes to a PNPLA3 mRNA sequence listed in Table 1.

Table 1. PNPLA3 siRNA Target Sites

PNPLA3 Target Region	**23mer Target Site**	**PNPLA3 Location (reference sequence NM_025225.2)**	**SEQ ID NO:**
Coding Region	CTGCAGGTCCTCTCAGATCTTGT	391	1
Coding Region	GAGAGATATGCCTTCGAGGATAT	899	2
Coding Region	CGCGGCTGGAGCTTGTCCTTCGC	211	3
Coding Region	AGATATGCCTTCGAGGATATTTG	902	4
Coding Region	TGCAGGTCCTCTCAGATCTTGTG	392	5
Coding Region	GGTCCAAAGACGAAGTCGTGGAT	593	6

PNPLA3 Target Region	23mer Target Site	PNPLA3 Location (reference sequence NM_025225.2)	SEQ ID NO:
Coding Region	CCTTCTACAGTGGCCTTATCCCT	641	7
Coding Region	TTTGCAACTTGCTACCCATTAGG	1220	8
Coding Region	GTGACAACGTACCCTTCATTGAT	704	9
Coding Region	CGACGCGCGCATGTTGTTCGGCG	309	10
Coding Region	AGATTTGCAACTTGCTACCCATT	1217	11
Coding Region	GGGAGAGATATGCCTTCGAGGAT	897	12
Coding Region	CTCCTTCCTTCAGAGGCGTGCGA	662	13
Coding Region	TGACAACGTACCCTTCATTGATG	705	14
Coding Region	GACAACGTACCCTTCATTGATGC	706	15
Coding Region	TACGACATCTGCCCTAAAGTCAA	766	16
Coding Region	ACTTGCTACCCATTAGGATAATG	1226	17
Coding Region	CTATGGGGAGTACGACATCTGCC	756	18
Coding Region	TGGAATCTGCCATTGCGATTGTC	1280	19
Coding Region	ACGACATCTGCCCTAAAGTCAAG	767	20
Coding Region	TATGCCTTCGAGGATATTTGGAT	905	21
Coding Region	TGAGCTGCTAGACCACCTGCGTC	1092	22
Coding Region	GCAACTTGCTACCCATTAGGATA	1223	23
Coding Region	CAACTTGCTACCCATTAGGATAA	1224	24
Coding Region	TGCACTGCGTCGGCGTCCTCTCC	347	25
Coding Region	AGCTTGTCCTTCGCGGGCTGCGG	220	26
Coding Region	TTCCAGATATGCCCGACGATGTC	1322	27
Coding Region	GATGGGGAAAACGTTCTGGTGTC	562	28
Coding Region	ATGGGGAAAACGTTCTGGTGTCT	563	29
Coding Region	CCCCGGATCTCAAGGTGCTGGGA	878	30
Coding Region	TCAGAGGCGTGCGATATGTGGAT	671	31
Coding Region	CGCCTCTGCACAGGGAACCTCTA	832	32
Coding Region	CGACATCTGCCCTAAAGTCAAGT	768	33
Coding Region	GGTGGATACATGAGCAAGATTTG	1201	34
Coding Region	AGCAAGATTTGCAACTTGCTACC	1213	35
Coding Region	TGCTGGGAGAGATATGCCTTCGA	893	36
Coding Region	GTCCAGAGACTGGTGACATGGCT	1300	37
Coding Region	GAAAACGTTCTGGTGTCTGACTT	568	38
Coding Region	TTCGGTCCAAAGACGAAGTCGTG	590	39
Coding Region	ATTTGCAACTTGCTACCCATTAG	1219	40
Coding Region	GAGTGAGTGACAACGTACCCTTC	698	41
Coding Region	GCTGGGAGAGATATGCCTTCGAG	894	42
Coding Region	CTGGGAGAGATATGCCTTCGAGG	895	43
Coding Region	ATGAAAGACAAAGGTGGATACAT	1189	44
Coding Region	TGAGTGACAACGTACCCTTCATT	701	45
Coding Region	CTCCACCTTTCCCAGTTTTTCAC	1602	46
Coding Region	TCCACCTTTCCCAGTTTTTCACT	1603	47
Coding Region	AGTACGACATCTGCCCTAAAGTC	764	48
3'UTR	AGAACACCTTTTTCACCTAACTA	2197	49

PNPLA3 Target Region	23mer Target Site	PNPLA3 Location (reference sequence NM_025225.2)	SEQ ID NO:
3'UTR	CCTCTGAGCTGAGTTGGTTTTAT	1760	50
3'UTR	CTGAGCTGAGTTGGTTTTATGAA	1763	51
3'UTR	TGAGCTGAGTTGGTTTTATGAAA	1764	52
3'UTR	AGTTGGTTTTATGAAAAGCTAGG	1771	53
3'UTR	TGCAGAGGGTCCCTTACTGACTG	1890	54
3'UTR	GAACACCTTTTTCACCTAACTAA	2198	55
3'UTR	AACACCTTTTTCACCTAACTAAA	2199	56
3'UTR	ACACCTTTTTCACCTAACTAAAA	2200	57
3'UTR	CACCTTTTTCACCTAACTAAAAT	2201	58
3'UTR	ACCTTTTTCACCTAACTAAAATA	2202	59
3'UTR	CTTTTTCACCTAACTAAAATAAT	2204	60

[0027] The disclosed RNAi construct is not required to hybridize to a particular PNPLA3 SNP. In such aspects, the RNAi construct may bind to the 3' UTR of PNPLA3. As discussed above, non-sequence specific PNPLA3 RNAi may have broader therapeutic applications for diseases associated with PNPLA3 expression, including for example, simple fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis (irreversible, advanced scarring of the liver), or PNPLA3-related obesity. In some embodiments, the RNAi construct is an siRNA molecule that contains any of the sequences set forth in Figures 1 or 2 (e.g., an antisense strand comprising a sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588 and/or a sense strand comprising a sequence selected from SEQ ID NOs: 61-564 and SEQ ID NOs: 1069-2328).

[0028] A double-stranded RNAi molecule may include chemical modifications to ribonucleotides, including modifications to the ribose sugar, base, or backbone components of the ribonucleotides, such as those described herein or known in the art. Any such modifications, as used in a double-stranded RNA molecule (e.g. siRNA, shRNA, or the like), are encompassed by the term "double-stranded RNA" for the purposes of this disclosure.

[0029] As used herein, a first sequence is "complementary" to a second sequence if a polynucleotide comprising the first sequence can hybridize to a polynucleotide comprising the second sequence to form a duplex region under certain conditions, such as physiological conditions. Other such conditions can include moderate or stringent hybridization conditions, which are known to those of skill in the art. A first sequence is considered to be fully complementary (100% complementary) to a second sequence if a polynucleotide comprising the first sequence base pairs with a polynucleotide comprising the second

sequence over the entire length of one or both nucleotide sequences without any mismatches. A sequence is "substantially complementary" to a target sequence if the sequence is at least about 80%, 85%, 90%, 95%,96%, 97%, 98%, 99% or 100% complementary to a target sequence. Percent complementarity can be calculated by dividing the number of bases in a first sequence that are complementary to bases at corresponding positions in a second or target sequence by the total length of the first sequence. A sequence may also be said to be substantially complementary to another sequence if there are no more than 5, 4, 3, 2, or 1 mismatch over a 30 base pair duplex region when the two sequences are hybridized. Generally, if any nucleotide overhangs, as defined herein, are present, the sequence of such overhangs is not considered in determining the degree of complementarity between two sequences. By way of example, a sense strand of 21 nucleotides in length and an antisense strand of 21 nucleotides in length that hybridize to form a 19 base pair duplex region with a 2-nucleotide overhang at the 3' end of each strand would be considered to be fully complementary as the term is used herein.

[0030] In some embodiments, a region of the antisense strand comprises a sequence that is fully complementary to a region of the target RNA sequence (e.g. PNPLA3 mRNA). In such embodiments, the sense strand may comprise a sequence that is fully complementary to the sequence of the antisense strand. In other such embodiments, the sense strand may comprise a sequence that is substantially complementary to the sequence of the antisense strand, e.g., having 1, 2, 3, 4, or 5 mismatches in the duplex region formed by the sense and antisense strands. In certain embodiments, it is preferred that any mismatches occur within the terminal regions (e.g. within 6, 5, 4, 3, 2, or 1 nucleotides of the 5' and/or 3' ends of the strands). In one embodiment, any mismatches in the duplex region formed from the sense and antisense strands desirably occur within 6, 5, 4, 3, 2, or 1 nucleotides of the 5' end of the antisense strand.

[0031] Where the two substantially complementary strands of a dsRNA are comprised of separate RNA molecules, those molecules need not, but can be, covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3 '-end of one strand and the 5' -end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs in the duplex is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs.

[0032] In other embodiments, the sense strand and the antisense strand that hybridize to form a duplex region may be part of a single RNA molecule, i.e., the sense and antisense strands are part of a self-complementary region of a single RNA molecule. In such cases, a single RNA molecule comprises a duplex region (also referred to as a stem region) and a loop region. The 3' end of the sense strand is connected to the 5' end of the antisense strand by a contiguous sequence of unpaired nucleotides, which will form the loop region. The loop region is typically of a sufficient length to allow the RNA molecule to fold back on itself such that the antisense strand can base pair with the sense strand to form the duplex or stem region. The loop region can comprise from about 3 to about 25, from about 5 to about 15, or from about 8 to about 12 unpaired nucleotides. As noted herein, such RNA molecules with at least partially self-complementary regions are referred to as "short hairpin RNAs" (shRNAs). In some embodiments, the loop region can comprise at least 1, 2, 3, 4, 5, 10, 20, or 25 unpaired nucleotides. In other embodiments, the loop region can have 10, 9, 8, 7, 6, 5, 4, 3, 2, or fewer unpaired nucleotides. In certain embodiments, the RNAi constructs of the disclosure comprise an shRNA. The length of a single, at least partially self-complementary RNA molecule can be from about 35 nucleotides to about 100 nucleotides, from about 45 nucleotides to about 85 nucleotides, or from about 50 to about 60 nucleotides and comprise a duplex region and loop region each having the lengths recited herein.

[0033] In some embodiments, the RNAi constructs of the disclosure comprise a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially or fully complementary to a PNPLA3 messenger RNA (mRNA) sequence. As used herein, a "PNPLA3 mRNA sequence" refers to any messenger RNA sequence, including splice variants, encoding a PNPLA3 protein, including PNPLA3 protein variants or isoforms from any species (e.g. mouse, rat, non-human primate, human). PNPLA3 protein is also known as adiponutrin (ADPN) and calcium-independent phospholipase A2-epsilon (iPLA(2)ε)).

[0034] A PNPLA3 mRNA sequence also includes the transcript sequence expressed as its complementary DNA (cDNA) sequence. A cDNA sequence refers to the sequence of an mRNA transcript expressed as DNA bases (e.g. guanine, adenine, thymine, and cytosine) rather than RNA bases (e.g. guanine, adenine, uracil, and cytosine). Thus, the antisense strand of the RNAi constructs of the disclosure may comprise a region having a sequence that is substantially or fully complementary to a target PNPLA3 mRNA sequence or PNPLA3 cDNA sequence. A PNPLA3 mRNA or cDNA sequence can include, but is not

limited to, any PNPLA3 mRNA or cDNA sequence such as can be derived from the NCBI Reference sequence NM_025225.2.

[0035] A region of the antisense strand can be substantially complementary or fully complementary to at least 15 consecutive nucleotides of the PNPLA3 mRNA sequence. In some embodiments, the target region of the PNPLA3 mRNA sequence to which the antisense strand comprises a region of complementarity can range from about 15 to about 30 consecutive nucleotides, from about 16 to about 28 consecutive nucleotides, from about 18 to about 26 consecutive nucleotides, from about 17 to about 24 consecutive nucleotides, from about 19 to about 25 consecutive nucleotides, from about 19 to about 23 consecutive nucleotides, or from about 19 to about 21 consecutive nucleotides. In certain embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to a PNPLA3 mRNA sequence may, in some embodiments, comprise at least 15 contiguous nucleotides from an antisense sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588 (see Figures 1 or 2). In other embodiments, the antisense sequence comprises at least 16, at least 17, at least 18, or at least 19 contiguous nucleotides from an antisense sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588. In some embodiments, the sense and/or antisense sequence comprises at least 15 nucleotides from a sequence listed in Figures 1 or 2 with no more than 1, 2, or 3 nucleotide mismatches.

[0036] The sense strand of the RNAi construct typically comprises a sequence that is sufficiently complementary to the sequence of the antisense strand such that the two strands hybridize under physiological conditions to form a duplex region. A "duplex region" refers to the region in two complementary or substantially complementary polynucleotides that form base pairs with one another, either by Watson-Crick base pairing or other hydrogen bonding interaction, to create a duplex between the two polynucleotides. The duplex region of the RNAi construct should be of sufficient length to allow the RNAi construct to enter the RNA interference pathway, e.g. by engaging the Dicer enzyme and/or the RISC complex (described below). For instance, in some embodiments, the duplex region is about 15 to about 30 base pairs in length. Other lengths for the duplex region within this range are also suitable, such as about 15 to about 28 base pairs, about 15 to about 26 base pairs, about 15 to about 24 base pairs, about 15 to about 22 base pairs, about 17 to about 28 base pairs, about 17 to about 26 base pairs, about 17 to about 24 base pairs, about 17 to about 23 base pairs, about 17 to about 21 base pairs, about 19 to about 25 base pairs, about 19 to about 23 base pairs, about 20 to about 25 base pairs, or about 19 to about 21 base pairs. In one

embodiment, the duplex region is about 17 to about 24 base pairs in length. In another embodiment, the duplex region is about 19 to about 21 base pairs in length.

[0037] In some embodiments, an siRNA construct of the disclosure contains a duplex region of about 18 to about 30 nucleotides that interacts with a target RNA sequence, e.g., a PNPLA3 target mRNA sequence, to direct the cleavage of the target RNA. For example, the siRNA may comprise a duplex region of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 nucleotides that interacts with a PNPLA3 target mRNA sequence. Without wishing to be bound by theory, long double-stranded RNA introduced into cells can be broken down into siRNA by a Type III endonuclease known as Dicer (Sharp et al. (2001) Genes Dev. 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, et al., (2001) Nature 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, et al., (2001) Cell 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, et al., (2001) Genes Dev. 15: 188).

[0038] For embodiments in which the sense strand and antisense strand are two separate molecules (e.g., an siRNA RNAi construct), the sense strand and antisense strand need not be the same length as the length of the duplex region. For instance, one or both strands maybe longer than the duplex region and have one or more unpaired nucleotides or mismatches flanking the duplex region. Thus, in some embodiments, the RNAi construct comprises at least one nucleotide overhang. As used herein, a "nucleotide overhang" refers to the unpaired nucleotide or nucleotides that extend beyond the duplex region at the terminal ends of the strands. Nucleotide overhangs are typically created when the 3' end of one strand extends beyond the 5' end of the other strand or when the 5' end of one strand extends beyond the 3' end of the other strand. The length of a nucleotide overhang is generally between 1 and 6 nucleotides, 1 and 5 nucleotides, 1 and 4 nucleotides, 1 and 3 nucleotides, 2 and 6 nucleotides, 2 and 5 nucleotides, or 2 and 4 nucleotides. In some embodiments, the nucleotide overhang comprises 1, 2, 3, 4, 5, or 6 nucleotides. In one particular embodiment, the nucleotide overhang comprises 1 to 4 nucleotides. In certain embodiments, the nucleotide overhang comprises 2 nucleotides. The nucleotides in the overhang can be ribonucleotides, deoxyribonucleotides, or modified nucleotides as described herein. In some embodiments, the overhang comprises a 5'-uridineuridine-3' (5'-UU-3') dinucleotide. In such embodiments, the UU dinucleotide may comprise ribonucleotides or modified

nucleotides, e.g., 2'-modified nucleotides. In other embodiments, the overhang comprises a 5'-deoxythymidine-deoxythymidine-3' (5'-dTdT-3') dinucleotide.

[0039] The nucleotide overhang can be at the 5' end or 3' end of one or both strands. For example, in one embodiment, the RNAi construct comprises a nucleotide overhang at the 5' end and the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises a nucleotide overhang at the 5' end and the 3' end of the sense strand. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 5' end of the sense strand and the 5' end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand and the 3' end of the antisense strand.

[0040] The RNAi constructs may comprise a single nucleotide overhang at one end of the double-stranded RNA molecule and a blunt end at the other. A "blunt end" means that the sense strand and antisense strand are fully base-paired at the end of the molecule and there are no unpaired nucleotides that extend beyond the duplex region. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand and a blunt end at the 5' end of the sense strand and 3' end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3' end of the antisense strand and a blunt end at the 5' end of the antisense strand and the 3' end of the sense strand. In certain embodiments, the RNAi construct comprises a blunt end at both ends of the double-stranded RNA molecule. In such embodiments, the sense strand and antisense strand have the same length and the duplex region is the same length as the sense and antisense strands (i.e., the molecule is double-stranded over its entire length).

[0041] The sense strand and antisense strand can each independently be any suitable length, such as about 15 to about 30 nucleotides in length, about 18 to about 28 nucleotides in length, about 19 to about 27 nucleotides in length, about 19 to about 25 nucleotides in length, about 19 to about 23 nucleotides in length, about 20 to about 25 nucleotides in length, or about 21 to about 23 nucleotides in length. In certain embodiments, the sense strand and antisense strand are each about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 nucleotides in length. In some embodiments, the sense strand and antisense strand are of the same length but form a duplex region that is shorter than the strands such that the RNAi construct has two nucleotide overhangs. For instance, in one embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 21 nucleotides in length, (ii) a duplex region that is 19 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3' end of the sense strand and the 3' end of

the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 23 nucleotides in length, (ii) a duplex region that is 21 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3' end of the sense strand and the 3' end of the antisense strand. In other embodiments, the sense strand and antisense strand have the same length and form a duplex region over their entire length such that there are no nucleotide overhangs on either end of the double-stranded molecule. In one such embodiment, the RNAi construct is blunt ended and comprises (i) a sense strand and an antisense strand, each of which is 21 nucleotides in length, and (ii) a duplex region that is 21 base pairs in length. In another embodiment, the RNAi construct is blunt ended and comprises (i) a sense strand and an antisense strand, each of which is 23 nucleotides in length, and (ii) a duplex region that is 23 base pairs in length.

[0042] In other embodiments, the sense strand or the antisense strand is longer than the other strand and the two strands form a duplex region having a length equal to that of the shorter strand such that the RNAi construct comprises at least one nucleotide overhang. For example, in one embodiment, the RNAi construct comprises (i) a sense strand that is 19 nucleotides in length, (ii) an antisense strand that is 21 nucleotides in length, (iii) a duplex region of 19 base pairs in length, and (iv) a single nucleotide overhang of 2 unpaired nucleotides at the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand that is 21 nucleotides in length, (ii) an antisense strand that is 23 nucleotides in length, (iii) a duplex region of 21 base pairs in length, and (iv) a single nucleotide overhang of 2 unpaired nucleotides at the 3' end of the antisense strand.

[0043] The antisense strand of the RNAi constructs of the disclosure can comprise the sequence of any one of the antisense sequences listed in Figure 1 or Figure 2 (e.g., any one of SEQ ID NOs: 565-816 or SEQ ID NOs: 2329-2958), or the sequence of nucleotides 1-21 of any of these antisense sequences. Each of the antisense sequences of SEQ ID NOs: 565-816 and SEQ ID NOs: 2329-2958 comprises a sequence of 20 or 21 consecutive nucleotides (first 20 or 21 nucleotides counting from the 5' end) that is complementary to a PNPLA3 mRNA sequence, plus an optional two-nucleotide overhang sequence. Thus, in some embodiments, the antisense strand comprises a sequence of nucleotides 1-20 or 1-21 of any one of SEQ ID NOs: 565-816 or SEQ ID NOs: 2329-2958.

Modified Nucleotides

[0044] The RNAi constructs of the disclosure may comprise one or more modified nucleotides. A "modified nucleotide" refers to a nucleotide that has one or more chemical

modifications to the nucleoside, nucleobase, pentose ring, or phosphate group. As used herein, modified nucleotides do not encompass ribonucleotides containing adenosine monophosphate, guanosine monophosphate, uridine monophosphate, and cytidine monophosphate, and deoxyribonucleotides containing deoxyadenosine monophosphate, deoxyguanosine monophosphate, deoxythymidine monophosphate, and deoxycytidine monophosphate. However, the RNAi constructs may comprise combinations of modified nucleotides, ribonucleotides, and deoxyribonucleotides. Incorporation of modified nucleotides into one or both strands of double-stranded RNA molecules can improve the *in vivo* stability of the RNA molecules, e.g., by reducing the molecules' susceptibility to nucleases and other degradation processes. The potency of RNAi constructs for reducing expression of the target gene can also be enhanced by incorporation of modified nucleotides.

[0045] In certain embodiments, the modified nucleotides have a modification of the ribose sugar. These sugar modifications can include modifications at the 2' and/or 5' position of the pentose ring as well as bicyclic sugar modifications. A 2'-modified nucleotide refers to a nucleotide having a pentose ring with a substituent at the 2' position other than H or OH. Such 2' modifications include, but are not limited to, 2'-O-alkyl (e.g. O-C1-C10 or O-C1-C10 substituted alkyl), 2'-O-allyl (O-CH2CH=CH2), 2'-C-allyl, 2'-fluoro, 2'-O-methyl (OCH3), 2'-O-methoxyethyl (O-(CH2)2OCH3), 2'-OCF3, 2'-O(CH2)2SCH3, 2'-O-aminoalkyl, 2'-amino (e.g., NH_2), 2'-O-ethylamine, and 2'-azido. Modifications at the 5' position of the pentose ring include, but are not limited to, 5'-methyl (R or S); 5'-vinyl, and 5'-methoxy.

[0046] A "bicyclic sugar modification" refers to a modification of the pentose ring where a bridge connects two atoms of the ring to form a second ring resulting in a bicyclic sugar structure. In some embodiments, the bicyclic sugar modification comprises a bridge between the 4' and 2' carbons of the pentose ring. Nucleotides comprising a sugar moiety with a bicyclic sugar modification are referred to herein as "bicyclic nucleic acids" or "BNAs." Exemplary bicyclic sugar modifications include, but are not limited to, α-L-Methyleneoxy (4'- CH_2-O-2') bicyclicnucleic acid (BNA); β-D-Methyleneoxy (4'-CH_2-O-2') BNA (also referred to as a locked nucleic acid or LNA); Ethyleneoxy (4'-(CH_2)2-O-2') BNA; Aminooxy (4'- CH_2-O-N(R)- 2')BNA; Oxyamino (4'- CH_2-N(R)-O-2') BNA; Methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA (also referred to as constrained ethyl or cEt); methylene-thio (4'- CH_2-S-2') BNA; methylene-amino (4'- CH_2-N(R)-2') BNA; methyl carbocyclic (4'- CH_2-CH(CH3)-2') BNA; propylene carbocyclic (4'-(CH_2)3-2') BNA; and Methoxy(ethyleneoxy) (4'-$CH(CH_2OMe)$-O-2')BNA (also referred to as

constrained MOE or cMOE). These and other sugar-modified nucleotides that can be incorporated into the RNAi constructs of the disclosure are described in, e.g., U.S. Patent 9,181,551, U.S. Patent Publication No. 2016/0122761, and Deleavey and Damha, *Chemistry and Biology*, *19*: 937-954 (2012).

[0047] In some embodiments, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, 2'-O-allyl modified nucleotides, bicyclic nucleic acids (BNAs), or combinations thereof. In certain embodiments, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, 2'-O-methoxyethyl modified nucleotides, or combinations thereof. In one particular embodiment, the RNAi constructs comprise one or more 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, or combinations thereof.

[0048] Both the sense and antisense strands of the RNAi constructs can comprise one or multiple modified nucleotides. For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In certain embodiments, all nucleotides in the sense strand are modified nucleotides. In some embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In other embodiments, all nucleotides in the antisense strand are modified nucleotides. In certain other embodiments, all nucleotides in the sense strand and all nucleotides in the antisense strand are modified nucleotides. In these and other embodiments, the modified nucleotides can be 2'-fluoro modified nucleotides, 2'-O-methyl modified nucleotides, or combinations thereof.

[0049] In some embodiments, all pyrimidine nucleotides preceding an adenosine nucleotide in the sense strand and/or in the antisense strand are modified nucleotides. For example, where the sequence 5'-CA-3' or 5'-UA-3' appears in either strand, the cytidine and uridine nucleotides are modified nucleotides, preferably 2'-O-methyl modified nucleotides. In certain embodiments, all pyrimidine nucleotides in the sense strand are modified nucleotides (e.g. 2'-O-methyl modified nucleotides), and the 5' nucleotide in all occurrences of the sequence 5'-CA-3' or 5'-UA-3' in the antisense strand are modified nucleotides (e.g. 2'-O-methyl modified nucleotides). In other embodiments, all nucleotides in the duplex region are modified nucleotides. In such embodiments, the modified nucleotides are preferably 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

[0050] In embodiments in which the RNAi construct comprises a nucleotide overhang, the nucleotides in the overhang can be ribonucleotides, deoxyribonucleotides, or modified nucleotides. In one embodiment, the nucleotides in the overhang are deoxyribonucleotides, e.g., deoxythymidine. In another embodiment, the nucleotides in the overhang are modified nucleotides. For instance, in some embodiments, the nucleotides in the overhang are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, 2'-methoxyethyl modified nucleotides, or combinations thereof.

[0051] The RNAi constructs of the disclosure may also comprise one or more modified internucleotide linkages. As used herein, the term "modified internucleotide linkage" refers to an internucleotide linkage other than the natural 3' to 5' phosphodiester linkage. In some embodiments, the modified internucleotide linkage is a phosphorous-containing internucleotide linkage, such as a phosphotriester, an aminoalkyl phosphotriester, an alkylphosphonate (e.g., methylphosphonate, 3'-alkylene phosphonate), a phosphinate, a phosphoramidate (e.g., 3'-aminophosphoramidate and aminoalkylphosphoramidate), a phosphorothioate (P=S), a chiralphosphorothioate, a phosphorodithioate, a thionophosphoramidate, a thionoalkylphosphonate, athionoalkylphosphotriester, and a boranophosphate. In one embodiment, a modified internucleotide linkage is a 2' to 5' phosphodiester linkage. In other embodiments, the modified internucleotide linkage is a non-phosphorous-containing internucleotide linkage and thus can be referred to as a modified internucleoside linkage. Such non-phosphorous-containing linkages include, but are not limited to, morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane linkages (-O-Si(H)$_2$-O-); sulfide, sulfoxide and sulfone linkages; formacetyl and thioformacetyl linkages; alkene containing backbones; sulfamate backbones; methylenemethylimino (-CH$_2$-N(CH$_3$)-O-CH$_2$-) and methylenehydrazino linkages; sulfonate and sulfonamide linkages; amide linkages; and others having mixed N, O, S and CH$_2$ component parts. In one embodiment, the modified internucleoside linkage is a peptide-based linkage (e.g., aminoethylglycine) to create a peptide nucleic acid or PNA, such as those described in U.S. Patents 5,539,082; 5,714,331; and 5,719,262. Other suitable modified internucleotide and internucleoside linkages that may be employed in the disclosed RNAi constructs are described in U.S. Patents 6,693,187 and 9,181,551, U.S. Patent Publication No. 2016/0122761, and Deleavey and Damha, *supra*.

[0052] In certain embodiments, the RNAi constructs comprise one or more phosphorothioate internucleotide linkages. The phosphorothioate internucleotide linkages may be present in the sense strand, antisense strand, or both strands of the RNAi constructs.

For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. In other embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7,8, or more phosphorothioate internucleotide linkages. In still other embodiments, both strands comprise 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. The RNAi constructs can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both the 3'- and 5'- ends of the sense strand, the antisense strand, or both strands. For instance, in certain embodiments, the RNAi construct comprises about 1 to about 6 or more (e.g., about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 3'-end of the sense strand, the antisense strand, or both strands. In other embodiments, the RNAi construct comprises about 1 to about 6 or more (e.g., about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In one embodiment, the RNAi construct comprises a single phosphorothioate internucleotide linkage at the 3' end of the sense strand and a single phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3' end of the antisense strand (i.e., a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at the 3' end of the antisense strand). In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the antisense strand. In yet another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at the 5' end of the sense strand. In still another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the sense strand (i.e. a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5' and 3' ends of the antisense strand and a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5' and 3' ends of the sense strand). In any of the embodiments in which one or both strands comprise one or more phosphorothioate internucleotide linkages, the remaining internucleotide linkages within the strands can be the natural 3' to 5' phosphodiester linkages. For instance, in some embodiments, each internucleotide linkage of the sense and antisense strands is

selected from phosphodiester and phosphorothioate, wherein at least one internucleotide linkage is a phosphorothioate.

[0053] In embodiments in which the RNAi construct comprises a nucleotide overhang, two or more of the unpaired nucleotides in the overhang can be connected by a phosphorothioate internucleotide linkage. In certain embodiments, all the unpaired nucleotides in a nucleotide overhang at the 3' end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In other embodiments, all the unpaired nucleotides in a nucleotide overhang at the 5' end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In still other embodiments, all the unpaired nucleotides in any nucleotide overhang are connected by phosphorothioate internucleotide linkages.

[0054] In certain embodiments, the modified nucleotides incorporated into one or both of the strands of the RNAi constructs of the disclosure have a modification of the nucleobase (also referred to herein as "base"). A "modified nucleobase" or "modified base" refers to a base other than the naturally occurring purine bases adenine (A) and guanine (G) and pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases can be synthetic or naturally occurring modifications and include, but are not limited to, universal bases, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine (X), hypoxanthine (I), 2-aminoadenine, 6-methyladenine, 6-methylguanine, and other alkyl derivatives of adenine and guanine, 2-propyland other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine, and 3-deazaadenine.

[0055] In some embodiments, the modified base is a universal base. A "universal base" refers to a base analog that indiscriminately forms base pairs with all of the natural bases in RNA and DNA without altering the double helical structure of the resulting duplex region. Universal bases are known to those of skill in the art and include, but are not limited to, inosine, C-phenyl, C-naphthyl and other aromatic derivatives, azole carboxamides, and nitroazole derivatives, such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole.

[0056] Other suitable modified bases that can be incorporated into the disclosed RNAi constructs include those described in, for example, Herdewijn, Antisense Nucleic Acid Drug

Dev., 10: 297-310 (2000) and Peacock et al., J. Org. Chern., 76: 7295-7300 (2011). The skilled person is well aware that guanine, cytosine, adenine, thymine, and uracil may be replaced by other nucleobases, such as the modified nucleobases described above, without substantially altering the base pairing properties of a polynucleotide comprising a nucleotide bearing such replacement nucleobase.

[0057] In some embodiments, the 5' end of the sense strand, antisense strand, or both the antisense and sense strands of the disclosed RNAi constructs comprises a phosphate moiety. As used herein, the term "phosphate moiety" refers to a terminal phosphate group that includes unmodified phosphates (-O-P=O)(OH)OH) as well as modified phosphates. Modified phosphates include phosphates in which one or more of the O and OH groups are replaced with H, O, S, N(R) or alkyl where R is H, an amino protecting group or unsubstituted or substituted alkyl. Exemplary phosphate moieties include, but are not limited to, 5'-monophosphate; 5'diphosphate; 5'-triphosphate; 5'-guanosine cap (7-methylated or non-methylated); 5'-adenosinecap or any other modified or unmodified nucleotide cap structure; 5'-monothiophosphate (phosphorothioate); 5'-monodithiophosphate (phosphorodithioate); 5'-alpha-thiotriphosphate; 5'-gamma-thiotriphosphate, 5'-phosphoramidates; 5'-vinylphosphates; 5'-alkylphosphonates (wherein "alkyl" can be methyl, ethyl, isopropyl, propyl, etc.); and 5'-alkyletherphosphonates (wherein "alkylether" can be methoxymethyl, ethoxymethyl, etc.).

[0058] The modified nucleotides that can be incorporated into the RNAi constructs of the disclosure may have more than one chemical modification described herein. For instance, the modified nucleotide may have a modification to the ribose sugar as well as a modification to the nucleobase. By way of example, a modified nucleotide may comprise a 2' sugar modification (e.g., 2'-fluoro or 2'-methyl) and comprise a modified base (e.g., 5-methyl cytosine or pseudouracil). In other embodiments, the modified nucleotide may comprise a sugar modification in combination with a modification to the 5' phosphate that would create a modified internucleotide or internucleoside linkage when the modified nucleotide was incorporated into a polynucleotide. For instance, in some embodiments, the modified nucleotide may comprise a sugar modification, such as a 2'-fluoro modification, a 2'-O-methyl modification, or a bicyclic sugar modification, as well as a 5' phosphorothioate group. Accordingly, in some embodiments, one or both strands of the RNAi constructs of the disclosure comprise a combination of 2' modified nucleotides or BNAs and phosphorothioate internucleotide linkages. In certain embodiments, both the sense and antisense strands of the RNAi constructs of the disclosure comprise a combination of 2'-

fluoro modified nucleotides, 2'-O-methyl modified nucleotides, and phosphorothioate internucleotide linkages. Exemplary siRNA constructs comprising modified nucleotides and internucleotide linkages are shown in Figure 1 and Figure 2.

[0059] The antisense strand of the RNAi constructs of the disclosure can comprise the sequence of any one of the modified antisense sequences listed in Figure 1 or Figure 2 (e.g., any one of SEQ ID NOs: 817-1068 or SEQ ID NOs: 2959-3588), or the sequence of nucleotides 1-21 of any of these antisense sequences. In some embodiments, the antisense strand comprises a sequence of nucleotides 1-20 or 1-21 of any one of SEQ ID NOs: 817-1068 or SEQ ID NOs: 2959-3588.

Function of RNAi Constructs

[0060] The disclosed RNAi constructs desirably reduce or inhibit the expression of PNPLA3 in cells, particularly liver cells. Accordingly, in one embodiment, the present disclosure provides a method of reducing PNPLA3 expression in a cell by contacting the cell with any RNAi construct described herein. The cell may be *in vitro* or *in vivo*. PNPLA3 expression can be assessed by measuring the amount or level of PNPLA3 mRNA, PNPLA3 protein, or another biomarker linked to PNPLA3 expression. The reduction of PNPLA3 expression in cells or animals treated with an RNAi construct of the disclosure can be determined relative to the PNPLA3 expression in cells or animals not treated with the RNAi construct or treated with a control RNAi construct. For instance, in some embodiments, reduction of PNPLA3 expression is assessed by (a) measuring the amount or level of PNPLA3 mRNA in liver cells treated with a RNAi construct of the disclosure, (b) measuring the amount or level of PNPLA3 mRNA in liver cells treated with a control RNAi construct (e.g., RNAi construct directed to a RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured PNPLA3 mRNA levels from treated cells in (a) to the measured PNPLA3 mRNA levels from control cells in (b). The PNPLA3 mRNA levels in the treated cells and controls cells can be normalized to RNA levels for a control gene (e.g., 18S ribosomal RNA) prior to comparison. PNPLA3 mRNA levels can be measured by a variety of methods, including Northern blot analysis, nuclease protection assays, fluorescence *in situ* hybridization (FISH), reverse-transcriptase (RT)-PCR, real-time RT-PCR, quantitative PCR, and the like.

[0061] In other embodiments, reduction of PNPLA3 expression is assessed by (a) measuring the amount or level of PNPLA3 protein in liver cells treated with a RNAi construct described herein, (b) measuring the amount or level of PNPLA3 protein in liver

cells treated with a control RNAi construct (e.g., RNAi construct directed to a RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured PNPLA3 protein levels from treated cells in (a) to the measured PNPLA3 protein levels from control cells in (b). PNPLA3 protein levels can be measured using any suitable method known to those of skill in the art, including but not limited to, western blots, immunoassays (e.g., ELISA), and flow cytometry. Any suitable method of measuring PNPLA3 mRNA or protein can be used to assess the efficacy of the RNAi constructs described herein.

[0062] In some embodiments, the methods to assess PNPLA3 expression levels are performed *in vitro* in cells that natively express PNPLA3 (e.g., liver cells) or cells that have been engineered to express PNPLA3. In certain embodiments, the methods are performed *in vitro* in liver cells. Suitable liver cells include, but are not limited to, primary hepatocytes (e.g. human, non-human primate, or rodent hepatocytes), HepAD38 cells, HuH-6 cells, HuH-7 cells, HuH-5-2 cells, BNLCL2 cells, Hep3B cells, or HepG2 cells. In one embodiment, the liver cells are Hep3B cells. In another embodiment, the liver cells are HepG2 cells.

[0063] In other embodiments, the methods to assess PNPLA3 expression levels are performed *in vivo*. For example, the RNAi constructs and any control RNAi constructs can be administered to an animal (e.g., rodent or non-human primate), and PNPLA3 mRNA or protein levels may be assessed in liver tissue harvested from the animal following treatment. Alternatively or additionally, a biomarker or functional phenotype associated with PNPLA3 expression can be assessed in the treated animals.

[0064] In certain embodiments, expression of PNPLA3 is reduced in liver cells by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% by an RNAi construct described herein. In some embodiments, expression of PNPLA3 is reduced in liver cells by at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, or at least 85% by an RNAi construct described herein. In other embodiments, the expression of PNPLA3 is reduced in liver cells by about 90% or more, e.g., 91%, 92%, 93%, 94%, 95%, 96%,97%, 98%, 99%, or more by an RNAi construct described herein. The percent reduction of PNPLA3 expression can be measured by any of the methods described herein or otherwise known in the art. For instance, in certain embodiments, the RNAi constructs described herein inhibit at least 60% of PNPLA3 expression at 5 nM in Hep3B cells (contains wild type PNPLA3) *in vitro*. In related embodiments, the RNAi constructs described herein inhibit at least 65%, at least 70%, at

least 75%, at least 80%, at least 85%, or at least 90% of PNPLA3 expression at 5 nM in Hep3B cells *in vitro*. In other embodiments, the RNAi constructs described herein inhibit at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of PNPLA3 expression at 5 nM in Hep3B cells *in vitro*. In certain embodiments, the RNAi constructs described herein inhibit at least 60% of PNPLA3 expression at 5 nM in HepG2 cells (contains wild type PNPLA3) *in vitro*. In related embodiments, the RNAi constructs described herein inhibit at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90% of PNPLA3 expression at 5 nM in HepG2 cells *in vitro*. In other embodiments, the RNAi constructs described herein inhibit at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of PNPLA3 expression at 5 nM in HepG2 cells *in vitro*. Reduction of PNPLA3 can be measured using a variety of techniques including, for example, RNA FISH or droplet digital PCR (see, e.g., Kamitaki et al., *Digital PCR. Methods in Molecular Biology*, *1768*: 401-422 (2018). doi:10.1007/978-1-4939-7778-9_23).

[0065] In some embodiments, an IC_{50} value is calculated to assess the potency of an RNAi construct described herein for inhibiting PNPLA3 expression in liver cells. An "IC_{50} value" is the dose/concentration required to achieve 50% inhibition of a biological or biochemical function. The IC_{50} value of any substance or antagonist can be determined by constructing a dose-response curve and examining the effect of different concentrations of the substance or antagonist on expression levels or functional activity in any assay. IC_{50} values can be calculated for a given antagonist or substance by determining the concentration needed to inhibit half of the maximum biological response or native expression levels. Thus, the IC_{50} value for any RNAi construct can be calculated by determining the concentration of the RNAi construct needed to inhibit half of the native PNPLA3 expression level in liver cells (e.g., PNPLA3 expression level in control liver cells) in any assay, such as an immunoassay, RNA FISH assay, or a droplet digital PCR assay. The RNAi constructs described herein may inhibit PNPLA3 expression in liver cells (e.g. Hep3B cells or HepG2 cells) with an IC_{50} of less than about 40 nM (e.g., less than about 35, nM, 30 nM, 25nM, 20 nM, 15 nM, 10 nM, 5 nM, or 1 nM). For example, the disclosed RNAi constructs may inhibit PNPLA3 expression in liver cells with an IC_{50} of about 0.001 nM to about 40 nM, about 0.001 nM to about 30 nM, about 0.001 nM to about 20 nM, about 0.001 nM to about 10 nM, about 0.001 nM to about 5 nM, about 0.001 nM to about 1 nM, about 0.1 nM to about 10 nM, about 0.1 nM to about 5 nM, or about 0.1 nM to about 1 nM.

[0066] The RNAi constructs described herein can readily be made using techniques known in the art, such as, for example, conventional nucleic acid solid phase synthesis. The polynucleotides of the RNAi constructs can be assembled on a suitable nucleic acid synthesizer utilizing standard nucleotide or nucleoside precursors (e.g., phosphoramidites). Automated nucleic acid synthesizers are sold commercially by several vendors, including DNA/RNA synthesizers from Applied Biosystems (Foster City, CA), MerMade synthesizers from BioAutomation (Irving, TX), and OligoPilot synthesizers from GE Healthcare Life Sciences (Pittsburgh, PA).

[0067] The 2' silyl protecting group can be used in conjunction with acid labile dimethoxytrityl (DMT) at the 5' position of ribonucleosides to synthesize oligonucleotides via phosphoramidite chemistry. Final deprotection conditions are known not to significantly degrade RNA products. All syntheses can be conducted in any automated or manual synthesizer on large, medium, or small scale. The syntheses may also be carried out in multiple well plates, columns, or glass slides.

[0068] The 2'-O-silyl group can be removed via exposure to fluoride ions, which can include any source of fluoride ion, e.g., those salts containing fluoride ion paired with inorganic counterions, e.g., cesium fluoride and potassium fluoride or those salts containing fluoride ion paired with an organic counterion, e.g., a tetraalkylammonium fluoride. A crown ether catalyst can be utilized in combination with the inorganic fluoride in the deprotection reaction. Exemplary fluoride ion sources include, but are not limited to, tetrabutylammonium fluoride or aminohydrofluorides (e.g., combining aqueous HF with triethylamine in a dipolar aprotic solvent, e.g., dimethylformamide).

[0069] The choice of protecting groups for use on the phosphite triesters and phosphotriesters can alter the stability of the triesters towards fluoride. Methyl protection of the phosphotriester or phosphitetriester can stabilize the linkage against fluoride ions and improve process yields.

[0070] Since ribonucleosides have a reactive 2' hydroxyl substituent, it may be desirable to protect the reactive 2' position in RNA with a protecting group that is orthogonal to a 5'-O-dimethoxytrityl protecting group, e.g., one stable to treatment with acid. Silyl protecting groups meet this criterion and can be readily removed in a final fluoride deprotection step that can result in minimal RNA degradation.

[0071] Tetrazole catalysts can be used in the standard phosphoramidite coupling reaction. Exemplary catalysts include, e.g., tetrazole, S-ethyl-tetrazole, benzylthiotetrazole, and pnitrophenyltetrazole.

[0072] Additional methods of synthesizing the RNAi constructs described herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Other synthetic chemistry transformations, protecting groups (e.g., for hydroxyl, amino, etc., present on the bases) and protecting group methodologies (protection and deprotection) useful in synthesizing the RNAi constructs described herein are known in the art and include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof. Custom synthesis of RNAi constructs is also available from several commercial vendors, including Dharmacon, Inc. (Lafayette, CO), AxoLabs GmbH (Kulmbach, Germany), and Ambion, Inc. (Foster City, CA).

[0073] The RNAi constructs described herein may comprise a ligand. As used herein, a "ligand" refers to any compound or molecule that can interact with another compound or molecule, either directly or indirectly. The interaction of a ligand with another compound or molecule may elicit a biological response (e.g., initiate a signal transduction cascade, induce receptor mediated endocytosis) or may just be a physical association. The ligand can modify one or more properties of the double-stranded RNA molecule to which is attached, such as the pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties of the RNA molecule.

[0074] The ligand may comprise a serum protein (e.g., human serum albumin, low-density lipoprotein, globulin), a cholesterol moiety, a vitamin (e.g., biotin, vitamin E, vitamin B12), a folate moiety, a steroid, a bile acid (e.g., cholic acid), a fatty acid (e.g., palmitic acid, myristic acid), a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid), a glycoside, a phospholipid, or an antibody or binding fragment thereof (e.g., a whole antibody or binding fragment that targets the RNAi construct to a specific cell type, such as liver cells). Other examples of ligands include dyes, intercalating agents (e.g., acridines), cross-linkers (e.g., psoralene, mitomycin C), porphyrins (e.g., TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g., EDTA), lipophilic molecules (e.g., adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-BisO(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, 03-(

oleoyl)lithocholic acid, 03-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), peptides (e.g., antennapedia peptide, Tat peptide, RGD peptides), alkylating agents, polymers (e.g., polyethylene glycol (PEG), PEG-40K), poly amino acids, and polyamines (e.g., spermine, spermidine).

[0075] In certain embodiments, the ligands have endosomolytic properties. The endosomolytic ligands promote the lysis of the endosome and/or transport of the RNAi construct described herein, or its components, from the endosome to the cytoplasm of the cell. The endosomolytic ligand may be a polycationic peptide or peptidomimetic which shows pH-dependent membrane activity and fusogenicity. In one embodiment, the endosomolytic ligand assumes its active conformation at endosomal pH. The "active" conformation is that conformation in which the endosomolytic ligand promotes lysis of the endosome and/or transport of the RNAi construct described herein, or its components, from the endosome to the cytoplasm of the cell. Exemplary endosomolytic ligands include the GALA peptide (Subbarao et al., Biochemistry, Vol. 26: 2964-2972, 1987), the EALA peptide (Vogel et al., J. Am. Chern. Soc., Vol. 118: 1581-1586, 1996), and their derivatives (Turk et al., Biochem. Biophys. Acta, Vol. 1559: 56-68, 2002). In one embodiment, the endosomolytic component may contain a chemical group (e.g., an amino acid) which will undergo a change in charge or protonation in response to a change in pH. The endosomolytic component may be linear or branched.

[0076] In some embodiments, the ligand comprises a lipid or other hydrophobic molecule. In one embodiment, the ligand comprises a cholesterol moiety or other steroid. Cholesterol conjugated oligonucleotides have been reported to be more active than their unconjugated counterparts (Manoharan, Antisense Nucleic Acid Drug Development, Vol. 12: 103-228, 2002). Ligands comprising cholesterol moieties and other lipids for conjugation to nucleic acid molecules have also been described in U.S. Patents 7,851,615; 7,745,608; and 7,833,992. In another embodiment, the ligand may comprise a folate moiety. Polynucleotides conjugated to folate moieties can be taken up by cells via a receptor-mediated endocytosis pathway. Such folate-polynucleotide conjugates are described in, e.g., U.S. Patent 8,188,247.

[0077] Given that PNPLA3 is expressed in liver cells (e.g., hepatocytes), in certain embodiments, it is desirable to specifically deliver the RNAi construct to liver cells. In some embodiments, RNAi constructs can be specifically targeted to the liver by employing ligands that bind to or interact with proteins expressed on the surface of liver cells. For example, in certain embodiments, a ligand may comprise one or more antigen binding

proteins (e.g. antibodies or binding fragments thereof (e.g. Fab, scFv)) that specifically bind to a receptor expressed on hepatocytes.

[0078] In certain embodiments, the ligand comprises a carbohydrate. A "carbohydrate" refers to a compound made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched, or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Carbohydrates include, but are not limited to, sugars (e.g., monosaccharides, disaccharides, trisaccharides, tetrasaccharides, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides, such as starches, glycogen, cellulose, and polysaccharide gums. In some embodiments, the carbohydrate incorporated into the ligand is a monosaccharide selected from a pentose, hexose, or heptose and di- and tri-saccharides including such monosaccharide units. In other embodiments, the carbohydrate incorporated into the ligand is an amino sugar, such as galactosamine, glucosamine, N-acetylgalactosamine, and N-acetylglucosamine.

[0079] In some embodiments, the ligand comprises a hexose or hexosamine. The hexose may be selected from glucose, galactose, mannose, fucose, or fructose. The hexosamine may be selected from fructosamine, galactosamine, glucosamine, or mannosamine. In certain embodiments, the ligand comprises glucose, galactose, galactosamine, or glucosamine. In one embodiment, the ligand comprises glucose, glucosamine, or N-acetylglucosamine. In another embodiment, the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine. In particular embodiments, the ligand comprises N-acetyl-galactosamine. Ligands comprising glucose, galactose, and N-acetyl-galactosamine (GalNAc) are particularly effective in targeting compounds to liver cells (see, e.g., D'Souza and Devarajan, J. Control Release, Vol. 203: 126-139, 2015). Examples of GalNAc- or galactose-containing ligands that can be incorporated into the RNAi constructs described herein are described in U.S. Patents 7,491,805; 8,106,022; and 8,877,917; U.S. Patent Publication No. 2003/0130186; and WIPO Publication No. WO 2013/166155.

[0080] In certain embodiments, the ligand comprises a multivalent carbohydrate moiety. As used herein, a "multivalent carbohydrate moiety" refers to a moiety comprising two or more carbohydrate units capable of independently binding or interacting with other molecules. For example, a multivalent carbohydrate moiety comprises two or more binding domains comprised of carbohydrates that can bind to two or more different molecules or two or more different sites on the same molecule. The valency of the carbohydrate moiety denotes the number of individual binding domains within the carbohydrate moiety. For instance, the terms "monovalent," "bivalent," "trivalent," and "tetravalent" with reference to

the carbohydrate moiety refer to carbohydrate moieties with one, two, three, and four binding domains, respectively. The multivalent carbohydrate moiety may comprise a multivalent lactose moiety, a multivalent galactose moiety, a multivalent glucose moiety, a multivalent N-acetyl-galactosamine moiety, a multivalent N-acetyl-glucosamine moiety, a multivalent mannose moiety, or a multivalent fucose moiety. In some embodiments, the ligand comprises a multivalent galactose moiety. In other embodiments, the ligand comprises a multivalent N-acetyl-galactosamine moiety. In these and other embodiments, the multivalent carbohydrate moiety is bivalent, trivalent, or tetravalent. In such embodiments, the multivalent carbohydrate moiety can be bi-antennary or tri-antennary. In one particular embodiment, the multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent. In another particular embodiment, the multivalent galactose moiety is trivalent or tetravalent. Exemplary trivalent and tetravalent GalNAc-containing ligands for incorporation into the RNAi constructs are described in detail below.

[0081] The ligand can be attached or conjugated to the RNA molecule of the RNAi construct directly or indirectly. For instance, in some embodiments, the ligand is covalently attached directly to the sense or antisense strand of the RNAi construct. In other embodiments, the ligand is covalently attached via a linker to the sense or antisense strand of the RNAi construct. The ligand can be attached to nucleobases, sugar moieties, or internucleotide linkages of polynucleotides (e.g., sense strand or antisense strand) of the RNAi constructs described herein. Conjugation or attachment to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In certain embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a ligand. Conjugation or attachment to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2, 5-, and 6-positions of a pyrimidine nucleobase can be attached to a ligand. Conjugation or attachment to sugar moieties of nucleotides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a ligand include the 2', 3', and 5' carbon atoms. The 1' position can also be attached to a ligand, such as in a basic residue. Internucleotide linkages can also support ligand attachments. For phosphorus-containing linkages (e.g., phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the ligand can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleoside linkages (e.g., PNA), the ligand can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

[0082] In certain embodiments, the ligand may be attached to the 3' or 5' end of either the sense or antisense strand. In certain embodiments, the ligand is covalently attached to the 5' end of the sense strand. In other embodiments, the ligand is covalently attached to the 3' end of the sense strand. For example, in some embodiments, the ligand is attached to the 3'-terminal nucleotide of the sense strand. In certain such embodiments, the ligand is attached at the 3'-position of the 3'-terminal nucleotide of the sense strand. In alternative embodiments, the ligand is attached near the 3' end of the sense strand, but before one or more terminal nucleotides (i.e. before 1, 2, 3, or 4 terminal nucleotides). In some embodiments, the ligand is attached at the 2'-position of the sugar of the 3'-terminal nucleotide of the sense strand.

[0083] In certain embodiments, the ligand is attached to the sense or antisense strand via a linker. A "linker" is an atom or group of atoms that covalently joins a ligand to a polynucleotide component of the RNAi construct. The linker may be from about 1 to about 30 atoms in length, from about 2 to about 28 atoms in length, from about 3 to about 26 atoms in length, from about 4to about 24 atoms in length, from about 6 to about 20 atoms in length, from about 7 to about 20atoms in length, from about 8 to about 20 atoms in length, from about 8 to about 18 atoms in length, from about 10 to about 18 atoms in length, and from about 12 to about 18 atoms in length. In some embodiments, the linker may comprise a bifunctional linking moiety, which generally comprises an alkyl moiety with two functional groups. One of the functional groups is selected to bind to the compound of interest (e.g., sense or antisense strand of the RNAi construct) and the other is selected to bind essentially any selected group, such as a ligand as described herein. In certain embodiments, the linker comprises a chain structure or an oligomer of repeating units, such as ethylene glycol or amino acid units. Examples of functional groups that are typically employed in a bifunctional linking moiety include, but are not limited to, electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In some embodiments, bifunctional linking moieties include amino, hydroxyl, carboxylic acid, thiol, unsaturations (e.g., double or triple bonds), and the like.

[0084] Linkers that may be used to attach a ligand to the sense or antisense strand in the RNAi constructs described herein include, but are not limited to, pyrrolidine, 8-amino-3,6-di oxaoctanoic acid, succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 6-aminohexanoic acid, substituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl. Preferred substituent groups for such linkers

include, but are not limited to, hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, and alkynyl.

[0085] In certain embodiments, the linkers are cleavable. A cleavable linker is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In some embodiments, the cleavable linker is cleaved at least 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, or more, or at least 100 times faster in the target cell or under a first reference condition (which can, e.g., be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, e.g., be selected to mimic or represent conditions found in the blood or serum).

[0086] Cleavable linkers are susceptible to cleavage agents, e.g., pH, redox potential, or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, e.g., oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linker by reduction; esterases; endosomes or agents that can create an acidic environment, e.g., those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linker by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0087] A cleavable linker may comprise a moiety that is susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable group that is cleaved at a preferred pH, thereby releasing the RNA molecule from the ligand inside the cell, or into the desired compartment of the cell.

[0088] A linker can include a cleavable group that is cleavable by a particular enzyme. The type of cleavable group incorporated into a linker can depend on the cell to be targeted. For example, liver-targeting ligands can be linked to RNA molecules through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other types of cells rich in esterases include cells of the lung, renal cortex, and testis. Linkers that contain peptide bonds can be used when targeting cells rich in peptidases, such as liver cells and synoviocytes.

[0089] In general, the suitability of a candidate cleavable linker can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linker. It will also be desirable to also test the candidate cleavable linker for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, e.g., blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It may be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In some embodiments, useful candidate linkers are cleaved at least 2, 4, 10, 20, 50, 70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

[0090] In other embodiments, redox cleavable linkers are utilized. Redox cleavable linkers are cleaved upon reduction or oxidation. An example of reductively cleavable group is a disulfide linking group (-S-S-). To determine if a candidate cleavable linker is a suitable "reductively cleavable linker," or, for example, is suitable for use with a particular RNAi construct and particular ligand, one or more methods described herein can be used. For example, a candidate linker can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent known in the art, which mimics the rate of cleavage that would be observed in a cell, e.g., a target cell. The candidate linkers can also be evaluated under conditions which are selected to mimic blood or serum conditions. In a specific embodiment, candidate linkers are cleaved by at most 10% in the blood. In other embodiments, useful candidate linkers are degraded at least 2, 4, 10, 20, 50,70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions).

[0091] In yet other embodiments, phosphate-based cleavable linkers are cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that hydrolyzes phosphate groups in cells are enzymes, such as phosphatases in cells. Examples of phosphate-based cleavable groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Specific embodiments include -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-

P(S)(OH)-S-, -SP(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O-, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. Another specific embodiment is -O-P(O)(OH)-O-. These candidate linkers can be evaluated using methods analogous to those described above.

[0092] In other embodiments, the linkers may comprise acid cleavable groups, which are groups that are cleaved under acidic conditions. In some embodiments, acid cleavable groups are cleaved in an acidic environment with a pH of about 6.5 or lower (e.g., about 6.0, 5.5, 5.0, or lower), or by agents, such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes, can provide a cleaving environment for acid cleavable groups. Examples of acid cleavable linking groups include, but are not limited to, hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). A specific embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiaryalkyl group such as dimethyl, pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

[0093] In other embodiments, the linkers may comprise ester-based cleavable groups, which are cleaved by enzymes, such as esterases and amidases in cells. Examples of ester-based cleavable groups include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups. Ester cleavable groups have the general formula -C(O)O-, or -OC(O) -. These candidate linkers can be evaluated using methods analogous to those described above.

[0094] In further embodiments, the linkers may comprise peptide-based cleavable groups, which are cleaved by enzymes, such as peptidases and proteases in cells. Peptide-based cleavable groups are peptide bonds formed between amino acids to yield oligopeptides (e.g., dipeptides, tripeptides etc.) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide-based cleavage group is generally limited to the peptide bond (i.e., the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula -NHCHRAC(O)NHCHRBC(O)-, where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

[0095] Other types of linkers suitable for attaching ligands to the sense or antisense strands in the RNAi constructs described herein are known in the art and can include the

linkers described in, e.g., U.S. Patents 7,723,509; 8,017,762; 8,828,956; 8,877,917; and 9,181,551.

[0096] In certain embodiments, the ligand covalently attached to the sense or antisense strand of the RNAi constructs described herein comprises a GalNAc moiety, e.g, a multivalent GalNAc moiety. In some embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 3' end of the sense strand. In other embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 5' end of the sense strand. In yet other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 3' end of the sense strand. In still other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 5' end of the sense strand.

[0097] In some embodiments, the RNAi constructs described herein may be delivered to a cell or tissue of interest by administering a vector that encodes and controls the intracellular expression of the RNAi construct. A "vector" (also referred to herein as an "expression vector") is a composition of matter which can be used to deliver a nucleic acid of interest to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated viral vectors, retroviral vectors, and the like. A vector can be replicated in a living cell, or it can be made synthetically.

[0098] Generally, a vector for expressing an RNAi construct described herein will comprise one or more promoters operably linked to sequences encoding the RNAi construct. The phrases "operably linked," "operatively linked," or "under transcriptional control" may be used interchangeably herein to indicate when a promoter is in the correct location and orientation in relation to a polynucleotide sequence to control the initiation of transcription by RNA polymerase and expression of the polynucleotide sequence. A "promoter" refers to a sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene sequence. Suitable promoters include, but are not limited to, RNA pol I, pol II, HI or U6 RNA pol III, and viral promoters (e.g., human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, and the Rous sarcoma virus long terminal repeat). In some embodiments, an HI or U6RNA pol III promoter is employed. The promoter can be a tissue-specific or inducible promoter. Of particular interest are liver-specific promoters, such as promoter

sequences from the human alpha-1 antitrypsin gene, albumin gene, hemopexin gene, and hepatic lipase gene. Inducible promoters include, for example, promoters regulated by ecdysone, estrogen, progesterone, tetracycline, and isopropyl-PD1-thiogalactopyranoside (IPTG).

[0099] When the RNAi construct comprises an siRNA, the two separate strands (sense and antisense strand) can be expressed from a single vector or two separate vectors. For example, in some embodiments, the sequence encoding the sense strand is operably linked to a promoter on a first vector and the sequence encoding the antisense strand is operably linked to a promoter on a second vector. In such an embodiment, the first and second vectors are co-introduced, e.g., by infection or transfection, into a target cell, such that the sense and antisense strands, once transcribed, will hybridize intracellularly to form the siRNA molecule. In another embodiment, the sense and antisense strands are transcribed from two separate promoters located in a single vector. In such embodiments, the sequence encoding the sense strand may be operably linked to a first promoter and the sequence encoding the antisense strand may be operably linked to a second promoter, wherein the first and second promoters are located in a single vector. In one embodiment, the vector comprises a first promoter operably linked to a sequence encoding the siRNA molecule, and a second promoter operably linked to the same sequence in the opposite direction, such that transcription of the sequence from the first promoter results in the synthesis of the sense strand of the siRNA molecule and transcription of the sequence from the second promoter results in synthesis of the antisense strand of the siRNA molecule.

[0100] When the RNAi construct comprises a shRNA, a sequence encoding the single, at least partially self-complementary RNA molecule is operably linked to a promoter to produce a single transcript. In some embodiments, the sequence encoding the shRNA comprises an inverted repeat joined by a linker polynucleotide sequence to produce the stem and loop structure of the shRNA following transcription.

[0101] In some embodiments, the vector encoding an RNAi construct described herein is a viral vector. Various viral vector systems that are suitable to express the RNAi constructs described herein include, but are not limited to, adenoviral vectors, retroviral vectors (e.g., lentiviral vectors, maloney murine leukemia virus), adeno-associated viral vectors; herpes simplex viral vectors; SV40 vectors; polyoma viral vectors; papilloma viral vectors; picornaviral vectors; and pox viral vectors (e.g., vaccinia virus). In certain embodiments, the viral vector is a retroviral vector (e.g., lentiviral vector).

[0102] Various vectors suitable for use in the present disclosure, methods for inserting nucleic acid sequences encoding siRNA or shRNA molecules into vectors, and methods of delivering the vectors to the cells of interest are known in the art (see, e.g., Dornburg , Gene Therap., Vol. 2: 301-310, 1995; Eglitis, Biotechniques, Vol. 6: 608-614, 1988; Miller, HumGene Therap., Vol. 1: 5-14, 1990; Anderson, Nature, Vol. 392: 25-30, 1998; Rubinson D A et al., Nat. Genet., Vol. 33: 401-406, 2003; Brummelkamp et al., Science, Vol. 296: 550-553, 2002; Brummelkamp et al., Cancer Cell, Vol. 2: 243-247, 2002; Lee et al., Nat Biotechnol, Vol. 20: 500-505, 2002; Miyagishi et al., Nat Biotechnol, Vol. 20: 497-500, 2002; Paddison et al., GenesDev, Vol. 16: 948-958, 2002; Paul et al., Nat Biotechnol, Vol. 20: 505-508, 2002; Sui et al., Proc Natl Acad Sci USA, Vol. 99: 5515-5520, 2002; and Yu et al., Proc Natl Acad Sci USA, Vol. 99: 6047-6052, 2002).

Compositions

[0103] The disclosure also provides compositions and formulations comprising the RNAi constructs described herein and pharmaceutically acceptable carriers, excipients, or diluents. Such compositions and formulations are useful for reducing expression of PNPLA3 in a subject in need thereof. Where clinical applications are contemplated, pharmaceutical compositions and formulations will be prepared in a form appropriate for the intended application. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

[0104] The phrases "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable carrier, excipient, or diluent" includes solvents, buffers, solutions, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, etc., acceptable for use in formulating pharmaceuticals, such as pharmaceuticals suitable for administration to humans. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the RNAi constructs described herein, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions, provided they do not inactivate the vectors or RNAi constructs of the compositions.

[0105] Compositions and methods for the formulation of pharmaceutical compositions depend on several criteria, including, but not limited to, route of administration, type and

extent of disease or disorder to be treated, and dose to be administered. In some embodiments, the pharmaceutical compositions are formulated based on the intended route of delivery. For instance, in certain embodiments, the pharmaceutical compositions are formulated for parenteral delivery. Parenteral forms of delivery include intravenous, intraarterial, subcutaneous, intrathecal, intraperitoneal, and intramuscular injection or infusion. In one embodiment, the pharmaceutical composition is formulated for intravenous delivery. In such an embodiment, the pharmaceutical composition may include a lipid-based delivery vehicle. In another embodiment, the pharmaceutical composition is formulated for subcutaneous delivery. In such an embodiment, the pharmaceutical composition may include a targeting ligand (e.g., GalNAc-containing ligands described herein).

[0106] In some embodiments, the pharmaceutical compositions comprise an effective amount of an RNAi construct described herein. An "effective amount" is an amount sufficient to produce a beneficial or desired clinical result. In some embodiments, an effective amount is an amount sufficient to reduce PNPLA3 expression in hepatocytes of a subject. In some embodiments, an effective amount may be an amount sufficient to only partially reduce PNPLA3 expression, for example, to a level comparable to expression of the wild-type PNPLA3 allele in human heterozygotes. Human heterozygous carriers of loss of function PNPLA3 variant alleles were reported to have lower serum levels of non- HDL cholesterol and a lower risk of coronary artery disease and myocardial infarction as compared to non-carriers (Nioi et al., New England Journal of Medicine, Vol. 374(22): 2131-2141, 2016). Thus, without being bound by theory, it is believed that partial reduction of PNPLA3 expression may be sufficient to achieve the beneficial reduction of serum non-HDL cholesterol and reduction of risk of coronary artery disease and myocardial infarction.

[0107] An effective amount of an RNAi construct may be from about 0.01 mg/kg body weight to about 100 mg/kg body weight, about 0.05 mg/kg body weight to about 75mg/kg body weight, about 0.1 mg/kg body weight to about 50 mg/kg body weight, about 1 mg/kg to about 30 mg/kg body weight, about 2.5 mg/kg of body weight to about 20 mg/kg bodyweight, or about 5 mg/kg body weight to about 15 mg/kg body weight. In certain embodiments, a single effective dose of an RNAi construct may be about 0.1 mg/kg, about 0.5mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, or about 10 mg/kg. The pharmaceutical composition comprising an effective amount of RNAi construct can be administered weekly, biweekly, monthly, quarterly, or biannually. The precise determination of what would be considered an effective amount and frequency of administration may be

based on several factors, including a patient's size, age, gender, type of disorder to be treated (e.g., myocardial infarction, heart failure, coronary artery disease, hypercholesterolemia), particular RNAi construct employed, and route of administration. Estimates of effective dosages and *in vivo* half-lives for any particular RNAi construct described herein can be ascertained using conventional methods and/or testing in appropriate animal models.

[0108] Colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes, may be used as delivery vehicles for the RNAi constructs described herein or vectors encoding such constructs. Commercially available fat emulsions that are suitable for delivering the nucleic acids described herein include INTRALIPID®, LIPOSYN®, LIPOSYN®II, LIPOSYN®III, NUTRILIPID, and other similar lipid emulsions. A preferred colloidal system for use as a delivery vehicle *in vivo* is a liposome (i.e., an artificial membrane vesicle). The RNAi constructs described herein may be encapsulated within liposomes, such as cationic liposomes. Alternatively, RNAi constructs may be complexed to lipids, such as cationic lipids. Suitable lipids and liposomes include neutral (e.g., dioleoylphosphatidyl ethanolamine (DOPE), dimyristoylphosphatidyl choline (DMPC), and dipalmitoyl phosphatidylcholine (DPPC)), distearolyphosphatidyl choline), negative (e.g., dimyristoylphosphatidyl glycerol (DMPG)), and cationic (e.g., dioleoyltetramethylaminopropyl (DOTAP) and dioleoylphosphatidyl ethanolamine (DOTMA)). The preparation and use of such colloidal dispersion systems is well known in the art. Exemplary formulations also are disclosed in, e.g., U.S. Patents 5,783,565; 5,837,533; 5,981,505; 6,127,170; 6,217,900; 6,379,965; 6,383,512; 6,747,014; 7,202,227; and WO 03/093449.

[0109] In some embodiments, the RNAi constructs are fully encapsulated in a lipid formulation, e.g., to form a SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle. As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle, including SPLP. As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle. SNALPs and SPLPs typically contain a cationic lipid, a noncationic lipid, and a lipid that prevents aggregation of the particle (e.g., a PEG-lipid conjugate). SNALPs and SPLPs are exceptionally useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous injection and accumulate at distal sites (e.g., sites physically separated from the administration site). SPLPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The nucleic acid-lipid particles typically have a

mean diameter of about 50 nm to about 150 nm, about 60 nm to about 130 nm, about 70 nm to about 110 nm, or about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids present in the nucleic acid-lipid particles desirably are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patents 5,976,567; 5,981,501; 6,534,484; 6,586,410; and 6,815,432; and PCT Publication No. WO 96/40964.

[0110] Pharmaceutical compositions suitable for injections include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Generally, these preparations are sterile and fluid to the extent that easy injectability exists. Preparations should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. Appropriate solvents or dispersion media may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by using a coating (such as lecithin), by maintaining the required particle size (in the case of dispersion), and/or by using surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, such as, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, isotonic agents (e.g., sugars or sodium chloride) may be included in the composition. Prolonged absorption of the injectable compositions can be brought about by including absorption-delaying agents, such as, for example, aluminum monostearate and gelatin.

[0111] Sterile injectable solutions may be prepared by incorporating an appropriate amount of the RNAi construct (alone or complexed with a ligand) into a solvent along with any other ingredients (such as described above) as desired, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the desired other ingredients. In the case of sterile powders for the preparation of sterile injectable solutions, suitable methods of preparation include vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0112] The compositions provided herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include, for example, acid addition salts (formed with free amino groups) derived from inorganic acids (e.g., hydrochloric or phosphoric acids), or from

organic acids (e.g., acetic, oxalic, tartaric, mandelic, and the like). Salts formed with free carboxyl groups can also be derived from inorganic bases (e.g., sodium, potassium, ammonium, calcium, or ferric hydroxides) or from organic bases (e.g., isopropylamine, trimethylamine, histidine, procaine, and the like).

[0113] For parenteral administration in an aqueous solution, for example, a solution generally is suitably buffered and a liquid diluent is first rendered isotonic with, e.g., sufficient saline or glucose. Such aqueous solutions may be used, for example, for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. Sterile aqueous media desirably are employed as is known to those of skill in the art. By way of illustration, a single dose may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA standards. In certain embodiments, a pharmaceutical composition described herein comprises or consists of a sterile saline solution and an RNAi construct described herein. In other embodiments, a pharmaceutical composition described herein comprises or consists of an RNAi construct described herein and sterile water (e.g. water for injection, WFI). In still other embodiments, a pharmaceutical composition described herein comprises or consists of an RNAi construct described herein and phosphate-buffered saline (PBS).

[0114] In some embodiments, the pharmaceutical compositions are packaged with or stored within a device for administration. Devices for injectable formulations include, but are not limited to, injection ports, pre-filled syringes, auto injectors, injection pumps, on-body injectors, and injection pens. Devices for aerosolized or powder formulations include, but are not limited to, inhalers, insufflators, aspirators, and the like. Thus, the present disclosure includes administration devices comprising a pharmaceutical composition described herein for treating or preventing one or more of the disorders described herein.

Methods for Inhibiting PNPLA3 Expression

[0115] The present disclosure also provides methods of inhibiting expression of a PNPLA3 gene in a cell. The methods include contacting a cell with an RNAi construct, e.g., double-stranded RNAi construct, in an amount effective to inhibit expression of PNPLA3 in the cell, thereby inhibiting expression of PNPLA3 in the cell. Contacting a cell with an RNAi construct, e.g., a double-stranded RNAi construct, may be done *in vitro* or *in vivo*.

Contacting a cell *in vivo* with the RNAi construct includes contacting a cell or group of cells within a subject, e.g., a human subject, with the RNAi construct. Combinations of *in vitro* and *in vivo* methods of contacting a cell also are within the scope of the present disclosure.

[0116] The present disclosure provides methods for reducing or inhibiting expression of PNPLA3 in a subject in need thereof as well as methods of treating or preventing conditions, diseases, or disorders associated with PNPLA3 expression or activity. A "condition, disease, or disorder associated with PNPLA3 expression" refers to conditions, diseases, or disorders in which PNPLA3 expression levels are altered or where elevated expression levels of PNPLA3 are associated with an increased risk of developing the condition, disease, or disorder.

[0117] Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand, including any ligand described herein or known in the art. In preferred embodiments, the targeting ligand is a carbohydrate moiety, e.g., a GalNAc3 ligand, or any other ligand that directs the RNAi construct to a site of interest.

[0118] In one embodiment, contacting a cell with an RNAi includes "introducing" or "delivering the RNAi into the cell" by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an RNAi can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. For *in vivo* introduction, for example, RNAi can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell may be accomplished using methods known in the art, such as electroporation and lipofection. Additional approaches are described herein below and/or are known in the art.

[0119] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

[0120] The phrase "inhibiting expression of a PNPLA3" is intended to refer to inhibition of expression of any PNPLA3 gene (such as, e.g., a mouse PNPLA3 gene, a rat PNPLA3 gene, a monkey PNPLA3 gene, or a human PNPLA3 gene) as well as variants or mutants of a PNPLA3 gene. Thus, the PNPLA3 gene may be a wild-type PNPLA3 gene, a mutant PNPLA3 gene (such as a mutant PNPLA3 gene giving rise to amyloid deposition), or a transgenic PNPLA3 gene in the context of a genetically manipulated cell, group of cells, or organism.

[0121] "Inhibiting expression of a PNPLA3 gene" includes any level of inhibition of a PNPLA3 gene, e.g., at least partial suppression of the expression of a PNPLA3 gene. The

expression of the PNPLA3 gene may be assessed based on the level, or the change in the level, of any variable associated with PNPLA3 gene expression, e.g., PNPLA3 mRNA level, PNPLA3 protein level, or the number or extent of amyloid deposits. This level may be assessed in an individual cell or in a group of cells, including, for example, a sample derived from a subject.

[0122] Inhibition may be assessed by a decrease in an absolute or relative level of one or more variables that are associated with PNPLA3 expression compared with a control level. The control level may be any type of control level that is utilized in the art, e.g., a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, e.g., buffer only control or inactive agent control). In some embodiments, expression of a PNPLA3 gene is inhibited by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%,at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%. at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

[0123] Inhibition of the expression of a PNPLA3 gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a PNPLA3 gene is transcribed and which has or have been treated (e.g., by contacting the cell or cells with an RNAi construct described herein, or by administering an RNAi construct described herein to a subject in which the cells are or were present), such that the expression of a PNPLA3 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s)). Inhibition may be assessed by expressing the level of mRNA in treated cells as a percentage of the level of mRNA in control cells, using the following formula:

$$\frac{(mRNA\ in\ control\ cells) - (mRNA\ in\ treated\ cells)}{mRNA\ in\ control\ cells} \times 100\%$$

[0124] Alternatively, inhibition of the expression of a PNPLA3 gene may be assessed in terms of a reduction of a parameter that is functionally linked to PNPLA3 gene expression, e.g., PNPLA3 protein expression or Hedgehog pathway protein activities. PNPLA3 gene

silencing may be determined in any cell expressing PNPLA3, either endogenously or recombinantly, by any assay known in the art.

[0125] Inhibition of the expression of a PNPLA3 protein may be manifested by a reduction in the level of the PNPLA3 protein that is expressed by a cell or group of cells (e.g., the level of protein expressed in a sample obtained from a subject). As explained above, for the assessment of mRNA suppression, the inhibition of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

[0126] A control cell or group of cells that may be used to assess the inhibition of the expression of a PNPLA3 gene includes a cell or group of cells that has not yet been contacted with an RNAi construct described herein. For example, the control cell or group of cells may be derived from an individual subject (e.g., a human or animal subject) prior to treatment of the subject with an RNAi construct.

[0127] The level of PNPLA3 mRNA that is expressed by a cell or group of cells, or the level of circulating PNPLA3 mRNA, may be determined using any method known in the art for assessing mRNA expression, such as those mentioned above. In some embodiments, the level of expression of PNPLA3 in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, e.g., mRNA of the PNPLA3 gene. In this regard, for example, RNA may be extracted from cells using RNA extraction techniques including, for example, acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy RNA preparation kits (Qiagen), or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays (Melton et al., Nuc. Acids Res., 12:7035), northern blotting, *in situ* hybridization, and microarray analysis. Circulating PNPLA3 mRNA may be detected using methods described in WO 2012/177906.

[0128] In one embodiment, the level of expression of PNPLA3 is determined using a nucleic acid probe. The term "probe," as used herein, refers to any molecule that is capable of selectively binding to a specific PNPLA3 sequence. Probes can be synthesized by one of skill in the art or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

[0129] Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses, and probe arrays. One method for the determination of mRNA levels involves

contacting isolated mRNA with a nucleic acid molecule (probe) that can hybridize to PNPLA3 mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of PNPLA3 mRNA.

[0130] An alternative method for determining the level of expression of PNPLA3 in a sample involves the process of nucleic acid amplification and/or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, e.g., by RT-PCR (see, e.g., U.S. Patent 4,683,202), ligase chain reaction (Barany (1991) Proc. Natl. Acad. Sci. USA 88: 189-193), self-sustained sequence replication (Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87: 1874-1878), transcriptional amplification system (Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86: 1173-1177), Q-Beta Replicase (Lizardi et al. (1988) Bio/Technology 6: 1197), rolling circle replication (Lizardi et al., *supra*; and U.S Patent 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In some aspects of the disclosure, the level of expression of PNPLA3 may be determined by quantitative fluorogenic RT-PCR {i.e., the TAQMAN™ System). The expression levels of PNPLA3 mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids) (see, e.g., U.S. Patents 5,445,934; 5,677,195; 5,770,722; 5,744,305; and 5,874,219). The determination of PNPLA3 expression level may also comprise using nucleic acid probes in solution. In certain embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR).

[0131] The level of PNPLA3 protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, Western blotting,

radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, etc.

[0132] In some embodiments, the efficacy of the methods described herein can be monitored by detecting or monitoring a reduction in a symptom of a PNPLA3 disease, such as reduction in edema swelling of the extremities, face, larynx, upper respiratory tract, abdomen, trunk, and genitals, prodrome; laryngeal swelling; nonpruritic rash; nausea; vomiting; or abdominal pain. These symptoms may be assessed *in vitro* or *in vivo* using any method known in the art.

[0133] In some embodiments, the RNAi construct or a composition comprising the RNAi construct is administered to a subject such that the RNAi construct is delivered to a specific site within the subject. The inhibition of expression of PNPLA3 may be assessed using measurements of the level or change in the level of PNPLA3 mRNA or PNPLA3 protein in a sample derived from fluid or tissue from the specific site within the subject. In some embodiments, the RNAi construct may be delivered to a site such as the liver, choroid plexus, retina, and pancreas. The site may also be a subsection or subgroup of cells from any one of the aforementioned sites. The site may also include cells that express a particular type of receptor.

Methods of Treating or Preventing PNPLA3-Associated Diseases

[0134] The present disclosure provides therapeutic and prophylactic methods which include administering to a subject with a PNPLA3 -associated disease, disorder, and/or condition, or prone to developing, a PNPLA3- associated disease, disorder, and/or condition, an RNAi construct, compositions (e.g., pharmaceutical compositions) comprising an RNAi construct, or vectors comprising an RNAi construct as described herein. Non-limiting examples of PNPLA3- associated diseases include, for example, fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), cirrhosis of the liver, accumulation of fat in the liver, inflammation of the liver, hepatocellular necrosis, liver fibrosis, obesity, and nonalcoholic fatty liver disease (NAFLD). In one embodiment, the PNPLA3-associated disease is NAFLD. In another embodiment, the PNPLA3-associated disease is NASH. In another embodiment, the PNPLA3-associated disease is fatty liver (steatosis). In another embodiment, the PNPLA3-associated disease is insulin resistance. In another embodiment, the PNPLA3-associated disease is not insulin resistance.

[0135] In certain embodiments, the present disclosure provides a method for reducing the expression of PNPLA3 in a patient in need thereof comprising administering to the patient any of the RNAi constructs described herein. The term "patient," as used herein, refers to a

mammal, including humans, and can be used interchangeably with the term "subject." The expression level of PNPLA3 in hepatocytes in the patient desirably is reduced following administration of the RNAi construct as compared to the PNPLA3 expression level in a patient not receiving the RNAi construct.

[0136] The methods described herein are useful for treating a subject having a PNPLA3-associated disease, e.g., a subject that would benefit from reduction in PNPLA3 gene expression and/or PNPLA3 protein production. In one aspect, the present disclosure provides methods of reducing the level of Patatin-Like Phospholipase Domain Containing 3 (PNPLA3) gene expression in a subject having nonalcoholic fatty liver disease (NAFLD). In another aspect, the present disclosure provides methods of reducing the level of PNPLA3 protein in a subject with NAFLD. The present disclosure also provides methods of reducing the level of activity of the hedgehog pathway in a subject with NAFLD.

[0137] The treatment methods (and uses) described herein include administering to the subject, e.g., a human, a therapeutically effective amount of the disclosed RNAi construct targeting a PNPLA3 gene, a pharmaceutical composition comprising the RNAi construct, or a vector comprising the RNAi construct.

[0138] In one aspect, the disclosure provides methods of preventing at least one symptom in a subject having NAFLD, e.g., the presence of elevated hedgehog signaling pathways, fatigue, weakness, weight loss, loss of apetite, nausea, abdominal pain, spider-like blood vessels, yellowing of the skin and eyes (jaundice), itching, fluid buildup and swelling of the legs (edema), abdomen swelling (ascites), and mental confusion. The methods include administering to the subject a prophylactically effective amount of the RNAi construct, e.g., dsRNA, pharmaceutical compositions comprising the RNAi construct, or vectors encoding the RNAi construct, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in PNPLA3 gene expression. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired prophylactic result (e.g., prevention of disease onset).

[0139] In another aspect, the present disclosure provides uses of a therapeutically effective amount of an RNAi construct described herein for treating a subject, e.g., a subject that would benefit from a reduction and/or inhibition of PNPLA3 gene expression. In a further aspect, the present disclosure provides uses of an RNAi construct, e.g., a dsRNA, targeting an PNPLA3 gene or pharmaceutical composition comprising an RNAi construct targeting an PNPLA3 gene in the manufacture of a medicament for treating a subject, e.g., a subject that would benefit from a reduction and/or inhibition of PNPLA3 gene expression

and/or PNPLA3 protein production, such as a subject having a disorder that would benefit from reduction in PNPLA3 gene expression, e.g., a PNPLA3-associated disease.

[0140] The disclosure provides uses of an RNAi construct, e.g., a dsRNA, for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of PNPLA3 gene expression and/or PNPLA3 protein production. For example, the disclosure provides uses of the RNAi construct described herein, compositions comprising same, and vectors comprising same, in the treatment of NAFLD.

[0141] In a further aspect, the present invention provides uses of the disclosed RNAi construct, compositions comprising same, or a vector comprising same, in the manufacture of a medicament for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of PNPLA3 gene expression and/or PNPLA3 protein production, such as a PNPLA3-associated disease.

[0142] In one embodiment, an RNAi construct targeting PNPLA3 is administered to a subject having a PNPLA3-associated disease, e.g., nonalcoholic fatty liver disease (NAFLD), such that the expression of a PNPLA3 gene, e.g., in a cell, tissue, blood or other tissue or fluid of the subject are reduced by at least about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 62%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% or more when the RNAi construct is administered to the subject.

[0143] The methods and uses provided herein include administering a composition described herein such that expression of the target PNPLA3 gene is decreased for any suitable amount of time, such as for about 1, 2, 3, 4 5, 6, 7, 8, 12, 16, 18, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, or about 80 hours. In one embodiment, expression of the target PNPLA3 gene is decreased for an extended duration, e.g., at least about two, three, four, five, six, seven days or more, e.g., about one week, two weeks, three weeks, or about four weeks or longer.

[0144] Administration of the RNAi construct according to the methods and uses of the described herein may result in a reduction of the severity, signs, symptoms, and/or markers of such diseases or disorders in a patient with a PNPLA3-associated disease, e.g., NAFLD. By "reduction" in this context is meant a statistically significant decrease in such level. The

reduction can be, for example, at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%. Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of NAFLD may be assessed, for example, by periodic monitoring of NAFLD symptoms, liver fat levels, or expression of downstream genes. Comparison of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an RNAi targeting PNPLA3 or pharmaceutical composition thereof, "effective against" an PNPLA3 -associated disease indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating NAFLD and/or an PNPLA3 -associated disease and the related causes.

[0145] A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given RNAi drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

[0146] Subjects can be administered any therapeutically effective amount of the RNAi construct. Exemplary therapeutically effective amounts of the RNAi construct include, but are not limited to, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.35 mg/kg, 0.4 mg/kg, 0.45 mg/kg, 0.5 mg/kg, 0.55 mg/kg, 0.6 mg/kg, 0.65 mg/kg, 0.7 mg/kg, 0.75 mg/kg, 0.8 mg/kg, 0.85 mg/kg,

0.9 mg/kg, 0.95 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4.0 mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5.0 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg dsRNA, 5.9 mg/kg, 6.0 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7.0 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8.0 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9.0 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, 9.0 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, or about 50 mg/kg. In one embodiment, subjects can be administered 0.5 mg/kg of the RNAi construct. Values and ranges intermediate to the recited values also are encompassed by the present disclosure.

[0147] Administration of the RNAi construct, or a composition comprising same, can reduce the presence of PNPLA3 protein levels, e.g., in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31 %, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% or more.

[0148] Before administration of a full dose of the RNAi, patients can be administered a smaller dose, such as a 5% infusion, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (e.g., TNF-alpha or INF-alpha) levels.

[0149] Owing to the inhibitory effects on PNPLA3 expression, a composition according to the disclosure or a pharmaceutical composition prepared therefrom can enhance the quality of life.

[0150] An RNAi described herein may be administered in "naked" form, where the modified or unmodified RNAi construct is directly suspended in aqueous or suitable buffer solvent, as a "free RNAi." A free RNAi is administered in the absence of a pharmaceutical

composition. The free RNAi may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolality of the buffer solution containing the RNAi can be adjusted such that it is suitable for administering to a subject.

[0151] Alternatively, an RNAi described herein may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

[0152] Subjects that would benefit from a reduction and/or inhibition of PNPLA3 gene expression are those having nonalcoholic fatty liver disease (NAFLD) and/or an PNPLA3-associated disease or disorder as described herein.

[0153] Treatment of a subject that would benefit from a reduction and/or inhibition of PNPLA3 gene expression includes therapeutic and prophylactic treatment.

[0154] The disclosure further provides methods and uses of an RNAi construct or a pharmaceutical composition thereof for treating a subject that would benefit from reduction and/or inhibition of PNPLA3 gene expression, e.g., a subject having a PNPLA3-associated disease, in combination with other pharmaceuticals and/or other therapeutic methods, e.g., with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders.

[0155] For example, in certain embodiments, an RNAi targeting a PNPLA3 gene is administered in combination with, e.g., an agent useful in treating an PNPLA3-associated disease. For example, additional therapeutics and therapeutic methods suitable for treating a subject that would benefit from reduction in PNPLA3 expression, e.g., a subject having a PNPLA3-associated disease, include an RNAi construct targeting a different portion of the PNPLA3 gene, a therapeutic agent, and/or procedures for treating a PNPLA3 -associated disease or a combination of any of the foregoing.

[0156] In certain embodiments, a first RNAi construct targeting a PNPLA3 gene is administered in combination with a second RNAi construct targeting a different portion of the PNPLA3 gene. For example, the first RNAi construct may comprise a first sense strand and a first antisense strand forming a double stranded region, wherein substantially all of the nucleotides of said first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein said first sense strand is conjugated to a ligand attached at the 3'- terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and the second RNAi construct may comprise a second sense strand and a second antisense strand forming a

double stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3 '-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In one embodiment, all of the nucleotides of the first and second sense strand and/or all of the nucleotides of the first and second antisense strand comprise a modification. The modified nucleotides may be any one or combination of the modified nucleotides described herein.

[0157] In other embodiments, a first RNAi construct targeting a PNPLA3 gene is administered in combination with a second RNAi construct targeting a gene that is different from the PNPLA3 gene. For example, the RNAi construct targeting the PNPLA3 gene may be administered in combination with an RNAi construct targeting the SCAP gene. SCAP (SREBP Cleavage Activating Protein) is the only known regulator of the transcription factors of the SREBP family. The SREBP (Sterol Response Element Binding Protein) family play important roles in regulating *de novo* lipogenesis and triglyceride (TG) accumulation within the liver. The first RNAi construct targeting a PNPLA3 gene and the second RNAi construct targeting a different gene, e.g., the SCAP gene, may be administered as parts of the same pharmaceutical composition. Alternatively, the first RNAi construct targeting a PNPLA3 gene and the second RNAi construct targeting a different gene, e.g., the SCAP gene, may be administered as parts of different pharmaceutical compositions.

[0158] The RNAi construct and an additional therapeutic agent and/or treatment may be administered at the same time and/or in the same combination, e.g., parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times and/or by another method known in the art or described herein.

[0159] The present disclosure also provides methods of using an RNAi construct and/or a composition containing an RNAi construct to reduce and/or inhibit PNPLA3 expression (gene or protein expression) in a cell. In yet other aspects, use of an RNAi construct and/or a composition comprising an RNAi construct for the manufacture of a medicament for reducing and/or inhibiting PNPLA3 gene expression in a cell are provided. In still other aspects, the present disclosure provides an RNAi described herein and/or a composition comprising an RNAi construct described herein for use in reducing and/or inhibiting PNPLA3 protein production in a cell. In yet other aspects, use of an RNAi construct and/or a composition comprising an RNAi construct for the manufacture of a medicament for reducing and/or inhibiting PNPLA3 protein production in a cell are provided. The methods

and uses include contacting the cell with an RNAi construct, e.g., a dsRNA, and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a PNPLA3 gene, thereby inhibiting expression of the PNPLA3 gene or inhibiting PNPLA3 protein production in the cell. Reduction in gene expression can be assessed by any methods known in the art or described herein for determining mRNA or protein levels.

[0160] In the methods and uses described herein, the cell may be contacted *in vitro* or *in vivo*, i.e., the cell may be outside (e.g., in cell culture) or within a subject. A cell suitable for treatment using the methods described herein may be any cell that expresses an PNPLA3 gene, e.g., a cell from a subject having NAFLD or a cell comprising an expression vector comprising a PNPLA3 gene or portion of a PNPLA3 gene. A suitable cell for use in the disclosed methods includes, for example, a mammalian cell, e.g., a primate cell (such as a human cell or a non-human primate cell, e.g., a monkey cell or a chimpanzee cell), a non-primate cell (such as a cow cell, a pig cell, a camel cell, a llama cell, a horse cell, a goat cell, a rabbit cell, a sheep cell, a hamster, a guinea pig cell, a cat cell, a dog cell, a rat cell, a mouse cell, a lion cell, a tiger cell, a bear cell, or a buffalo cell), a bird cell (e.g., a duck cell or a goose cell), or a whale cell. In one embodiment, the cell is a human cell.

[0161] PNPLA3 gene expression may be inhibited in the cell by at least about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or about 100%.

[0162] PNPLA3 protein production may be inhibited in the cell by at least about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or about 100%.

[0163] The *in vivo* methods and uses described herein may include administering to a subject a composition containing an RNAi construct, where the RNAi construct includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the PNPLA3 gene of the subject. When the organism to be treated is a human, the composition

can be administered by any means known in the art including, but not limited to subcutaneous, intravenous, oral, intraperitoneal, or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal, and intrathecal), intramuscular, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by subcutaneous or intravenous infusion or injection. In one embodiment, the compositions are administered by subcutaneous injection.

[0164] In some embodiments, the administration is via a depot injection. A depot injection may release the RNAi construct in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, e.g., a desired inhibition of PNPLA3, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In some embodiments, the depot injection is a subcutaneous injection.

[0165] In some embodiments, the administration is via a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the RNAi to the subject.

[0166] The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

[0167] The methods and uses include administering to the mammal, e.g., a human, a composition comprising an RNAi construct, e.g., an siRNA, that targets an PNPLA3 gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the PNPLA3 gene, thereby inhibiting expression of the PNPLA3 gene in the mammal. Reduction in gene expression and/or protein expression can be assessed in a sample obtained from the RNAi construct-administered subject by any method known in the art or described herein. In one embodiment, a tissue sample serves as the tissue material for monitoring the reduction in PNPLA3 gene and/or protein expression. In another embodiment, a blood sample serves as the tissue material for monitoring the reduction in PNPLA3 gene and/or protein expression.

[0168] In some embodiments, verification of RISC-mediated cleavage of a target mRNA (e.g., PNPLA3 mRNA) *in vivo* following administration of an RNAi construct may be assessed by performing 5 '-RACE or modifications of the protocol as known in the art (Lasham A et al., (2010) Nucleic Acid Res., 38 (3) p-el9; and Zimmermann et al. (2006) Nature 441: 111-4).

[0169] It is understood that all ribonucleic acid sequences disclosed herein can be converted to deoxyribonucleic acid sequences by substituting a thymine base for a uracil base in the sequence. Likewise, all deoxyribonucleic acid sequences disclosed herein can be converted to ribonucleic acid sequences by substituting a uracil base for a thymine base in the sequence. Deoxyribonucleic acid sequences, ribonucleic acid sequences, and sequences containing mixtures of deoxyribonucleotides and ribonucleotides of all sequences disclosed herein are encompassed by the present disclosure.

[0170] Additionally, any nucleic acid sequences disclosed herein may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified polynucleotides is, in certain instances, arbitrary. For example, a polynucleotide comprising a nucleotide having a 2'-OH substituent on the ribose sugar and a thymine base could be described as a DNA molecule having a modified sugar (2'-OH for the natural 2'-H of DNA) or as an RNA molecule having a modified base (thymine (methylated uracil) for natural uracil of RNA).

[0171] Accordingly, nucleic acid sequences provided herein, including but not limited to those set forth in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to, such nucleic acids having modified nucleobases. By way of a further example and without limitation, a polynucleotide having the sequence "ATCGATCG" (encompasses any polynucleotides having such a sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG," and polynucleotides having other modified bases, such as "ATmeCGAUCG," wherein meC indicates a cytosine base comprising a methyl group at the 5-position.

[0172] The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the scope of the appended claims.

EXAMPLES

[0173] All animal experiments described herein were approved by the Institutional Animal Care and Use Committee (IACUC) of Amgen and cared for in accordance to the Guide for the Care and Use of Laboratory Animals, 8th Edition (National Research Council (U.S.)). Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research (U.S.), and National Academies Press (U.S.) (2011) *Guide for the care and use of laboratory animals. 8th Ed.,* National Academies Press, Washington, D.C. Mice were single-housed in an air-conditioned room at 22±2°C with a twelve-hour light; twelve-hour darkness cycle (0600-1800 hours). Animals had *ad libitum* access to a regular chow diet (Envigo, 2920X, or a diet as stated otherwise) and to water (reverse osmosis-purified) via automatic watering system, unless otherwise indicated. At termination, blood was collected by cardiac puncture under deep anesthesia, and then, following Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) guidelines, euthanized by a secondary physical method.

EXAMPLE 1: Selection, Design and Synthesis of Modified PNPLA3 siRNA molecules

[0174] The identification and selection of optimal sequences for therapeutic siRNA molecules targeting patatin-like phospholipase domain-containing 3 (PNPLA3) were identified using bioinformatics analysis of a human PNPLA3 transcript (GenBank Accession No. NM_025225.2). The bioinformatics analysis identified more than 450 suitable human/cynomolgus triggers across the entire PNPLA3 transcript and revealed an extended 3'UTR of approximately 4,500 bp that has yet to be explored. Table 1 lists PNPLA3 mRNA target sequences identified as having therapeutic properties.

[0175] More than 600 siRNA molecules directed against the sequences listed in Table 1 were synthesized, and these sequences were modified to include a single chemical modification to improve the potency and *in vivo* stability of PNPLA3 siRNA sequences. The sense and antisense sequences for each of the unmodified and modified PNPLA3 siRNAs are shown in Figure1 and Figure 2.

[0176] A panel of 194 siRNA molecules (or "triggers") selective for human and cynomolgus (human/cyno) PNPLA3 spanning the coding region (CDR) and annotated 3'UTR were generated, along with an additional 162 human/cyno triggers targeting the extended 3'UTR and 64 human/marmoset triggers. Human-only triggers targeting the coding region also were prepared.

EXAMPLE 2: Efficacy of select PNPLA3 siRNA molecules in RNA FISH assay

[0177] siRNA molecules synthesized in Example 1 with a single modification pattern (shown in Figure 1) were screened in an *in vitro* siRNA transfection assay followed by a fluorescent *in situ* hybridization assay targeting ribonucleic acid molecules (RNA FISH) to determine IC_{50} and maximum activity values. HepG2 cells (purchased from ATCC) were cultured in minimal essential medium EMEM from ATCC supplemented with 10% fetal bovine serum (FBS, Sigma) and 1% penicillin-streptomycin (P-S, Corning).

[0178] The siRNA transfection was performed as follows: 1 μL of test siRNAs and 4 μL of plain EMEM were added to PDL-coated CellCarrier-384 Ultra assay plates (PerkinElmer) by Bravo Automated Liquid Handling (Agilent). 5 μL of Lipofectamine RNAiMAX (Thermo Fisher Scientific), pre-diluted in EMEM (specifically 0.06 μL of RNAiMAX in 5 μL EMEM), was then dispensed into the assay plates by Multidrop Combi Reagent Dispenser (Thermo Fisher Scientific). After a 20 minute incubation of the siRNA/RNAiMAX mixture at room temperature (RT), 30 μL of HepG2 cells (2000 cells per well) in EMEM supplemented with 10% FBS and 1% P-S were added to the transfection complex using Multidrop Combi Reagent Dispenser. The assay plates were incubated for 20 minutes at RT prior to being placed in an incubator. Cells were then incubated for 72 hours at 37 °C and 5% CO_2.

[0179] The RNA FISH assay was performed using the Affymetrix QUANTIGENE® View RNA HC Screening Assay kit (QVP0011), the Affymetrix View HC Signal Amplification Kit 3-plex (QVP0213), and Affymetrix gene specific probes: Human PNPLA3 (VA6-20279-01) and Human PPIB (VA1-10148-01), following the manufacturer's protocol using an in-house assembled automated FISH assay platform for liquid handling.

[0180] In brief, cells were fixed in 4% formaldehyde (Thermo Fisher Scientific) for 15 minutes at RT, permeabilized with detergent for 3 minutes at RT and then treated with protease solution for 10 minutes at RT. Incubation of PNPLA3 and PPIB probe pairs was done for 3 hours, while for Preamplifiers, Amplifiers and Label Probes were for 1 hr each. All hybridization steps were carried out at 40 °C in a Cytomat 2 C-LIN automated incubator (Thermo Fisher Scientific). After hybridization reactions, cells were stained for 30 minutes with Hoechst and CellMask Blue (Thermo Fisher Scientific).

[0181] All plates were imaged on an Opera Phenix High Content Screening System (PerkinElmer), using the UV Channel for Hoechst 33342 and Cell Mask Blue, the 488 Channel for PPIB probes, and the 647 Channel for PNPLA3 probes.

[0182] The images were analyzed using Columbus Image Data Storage and Analysis System (PerkinElmer) to obtain mean spot counts per cell. The spot counts were normalized using the high (containing phosphate-buffered saline, Corning) and low (without target probe pairs) control wells. The normalized values against the total siRNA concentrations were plotted and the data were fit to a four-parameter sigmoidal model in Genedata Screener (Genedata) to obtain IC_{50} and maximum activity. The results for all siRNAs generated are shown in Table 2. Results for the panel of 194 human/cyno siRNA molecules spanning the PNPLA3 CDR and annotated 3'UTR are shown in Table 3. Results for the panel of 162 human/cyno siRNA molecules targeting the extended 3'UTR are shown in Table 4, and results for the panel 64 human/marmoset siRNA molecules are shown in Table 5.

[0183] PNPLA3 knockdown provides a percentage of knockdown compared to control. Negative values indicate a decrease in PNPLA3 levels. 22 siRNA triggers achieved >75% mRNA knockdown. In comparison, a minor allele-specific siRNA directed to PNPLA3 I148M (described in WO 2020/123508) reduces the expression of PNPLA3 mRNA by approximately 81%. The top 48 triggers were synthesized as GalNAc-siRNA conjugates.

Table 2

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
44956-1	1233	-97.0	1.61
45212-1	571	-90.8	16.80
44928-1	1367	-90.5	1.39
44912-1	449	-88.2	1.99
45207-1	1564	-87.8	9.98
45221-1	1379	-86.7	38.80
44911-1	445	-85.8	1.37
41946-1	844	-85.8	1.59
44957-1	1234	-84.3	0.33
42048-1	1561	-83.6	1.92
41955-1	909	-82.8	3.84
37781-1	698	-82.7	2.69
44939-1	991	-82.5	17.70
42064-1	1240	-82.3	1.21
44908-1	396	-82.3	2.88
41921-1	574	-81.9	2.43

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
37893-1	768	-81.8	5.28
41932-1	692	-81.1	5.52
37600-1	347	-80.9	1.77
37930-1	1219	-80.9	2.11
38215-1	2198	-80.2	1.78
45218-1	1184	-79.8	19.00
37785-1	704	-79.6	1.85
37744-1	391	-79.6	2.68
45220-1	1185	-79.5	19.30
38217-1	2200	-79.4	1.93
41942-1	811	-79.4	0.53
38216-1	2199	-79.4	2.63
37745-1	392	-79.3	2.49
44922-1	1359	-79.0	4.64
44955-1	1168	-79.0	4.93
41949-1	853	-79.0	3.37
45201-1	1562	-78.8	4.34
44905-1	812	-78.8	2.95
45216-1	842	-78.7	10.80
44910-1	442	-78.7	13.40
41935-1	776	-78.6	4.31
44909-1	397	-78.6	2.14
44915-1	1328	-78.6	4.53
41919-1	572	-78.6	4.54
44946-1	1024	-78.3	1.31
44949-1	1029	-78.2	9.80
44940-1	994	-78.0	4.38
42062-1	1236	-78.0	2.04
45200-1	696	-77.9	9.55
41950-1	854	-77.9	11.75
44923-1	1361	-77.9	14.60
37889-1	764	-77.7	2.12
44914-1	459	-76.9	3.20
42066-1	1266	-76.7	14.70
37789-1	756	-76.5	1.88
44950-1	1042	-76.5	4.28
37588-1	309	-76.4	1.50
37786-1	705	-76.4	1.56
37864-1	1602	-76.3	2.46
45199-1	695	-76.2	6.84
37907-1	893	-75.8	1.58
41954-1	907	-75.6	5.08
41960-1	923	-75.4	5.48

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41953-1	906	-75.4	4.68
37763-1	590	-75.3	2.50
44927-1	1366	-75.1	0.91
44918-1	1334	-75.0	5.36
37915-1	905	-75.0	11.08
41917-1	540	-74.9	2.83
37843-1	1224	-74.8	4.86
41920-1	573	-74.8	4.89
37563-1	211	-74.7	5.64
45217-1	790	-74.6	22.90
45219-1	1262	-74.3	29.80
37787-1	706	-74.2	1.70
37846-1	1280	-74.1	2.70
44951-1	1051	-73.9	2.67
37765-1	593	-73.7	2.61
42047-1	1560	-73.7	15.82
42060-1	1229	-73.7	1.96
37886-1	2197	-73.6	2.11
44925-1	1364	-73.6	5.41
37842-1	1223	-73.3	2.30
44906-1	353	-73.3	47.70
44920-1	1356	-73.3	10.60
41922-1	576	-73.3	1.17
45210-1	546	-73.2	9.79
44917-1	1332	-73.2	2.06
37567-1	220	-73.0	2.02
37932-1	1220	-72.9	2.69
38218-1	2201	-72.6	1.64
37892-1	767	-72.3	1.06
37908-1	894	-72.3	2.04
41951-1	855	-72.2	4.09
41947-1	845	-72.2	1.21
42063-1	1237	-72.1	0.52
38214-1	1092	-71.3	4.71
37770-1	662	-71.3	3.87
37865-1	1603	-71.2	1.45
38210-1	1189	-71.2	3.68
37758-1	562	-71.2	2.61
37759-1	563	-71.0	1.80
37913-1	902	-70.8	2.32
37880-1	1890	-70.5	3.03
44924-1	1363	-70.5	3.45
41939-1	786	-70.3	7.09

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
37858-1	1322	-70.1	2.11
41945-1	817	-70.1	1.36
44921-1	1358	-69.8	6.09
44926-1	1365	-69.8	4.52
45241-1	1013	-69.6	26.60
37782-1	701	-69.3	2.64
42054-1	989	-69.3	14.45
37845-1	1226	-69.2	5.66
37927-1	1201	-69.1	2.08
42043-1	1554	-69.1	2.53
37762-1	568	-69.1	5.37
44947-1	1027	-69.0	7.08
41952-1	856	-68.7	2.23
42067-1	1268	-68.5	3.03
42052-1	1618	-68.3	2.86
42046-1	1558	-68.0	9.21
42035-1	1376	-68.0	3.19
42049-1	1607	-67.9	5.67
40810-1	4193	-67.9	1.81
37849-1	1300	-67.9	1.60
38213-1	897	-67.8	2.38
37897-1	832	-67.6	1.64
37929-1	1213	-67.6	1.10
37777-1	671	-67.5	3.47
42034-1	1371	-67.4	3.19
41910-1	510	-67.2	7.79
42056-1	995	-67.0	1.19
37874-1	1771	-67.0	2.17
38220-1	2204	-66.9	1.73
37903-1	878	-66.8	1.84
37767-1	641	-66.7	4.83
37912-1	899	-66.7	9.32
42042-1	1553	-66.7	7.24
41927-1	604	-66.6	10.83
38212-1	1217	-66.6	3.50
37871-1	1763	-66.6	2.21
45263-1	458	-66.4	38.60
44943-1	1020	-66.4	16.40
44932-1	1446	-66.2	3.83
42065-1	1250	-66.2	3.16
38219-1	2202	-66.2	1.75
37909-1	895	-66.1	2.49
42061-1	1230	-65.9	2.15

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
44937-1	966	-65.9	11.50
40789-1	3858	-65.9	1.60
44948-1	1028	-65.8	5.49
37870-1	1760	-65.6	1.27
45203-1	822	-65.5	9.72
45334-1	451	-65.4	0.78
40788-1	3857	-65.2	1.00
41163-1	2187	-65.2	0.94
40817-1	4260	-65.2	2.35
37757-1	560	-65.1	2.46
37872-1	1764	-65.1	2.17
37756-1	557	-65.0	5.74
37888-1	762	-65.0	1.55
41031-1	5640	-65.0	20.16
45215-1	1413	-64.9	3.96
37753-1	497	-64.9	5.10
41179-1	4117	-64.8	1.68
41175-1	4112	-64.7	1.08
41150-1	715	-64.6	1.28
41959-1	919	-64.6	3.24
37877-1	1852	-64.5	3.61
41178-1	4116	-64.5	0.25
45225-1	1333	-64.2	Undefined
42050-1	1612	-64.0	1.76
41914-1	514	-63.9	6.33
37905-1	887	-63.8	6.37
41174-1	3893	-63.7	1.02
37866-1	1604	-63.6	2.05
44944-1	1021	-63.6	2.68
37920-1	1101	-63.5	5.96
37760-1	564	-63.4	11.50
42044-1	1556	-63.3	17.39
37890-1	765	-63.3	1.34
37921-1	1104	-63.1	1.88
41943-1	813	-63.1	3.87
41149-1	714	-63.0	1.68
44929-1	1373	-63.0	9.61
41908-1	360	-62.6	13.30
37764-1	591	-62.3	21.50
41145-1	422	-62.3	0.78
37561-1	206	-62.2	3.42
42055-1	992	-62.1	2.82
37754-1	555	-62.1	4.56

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
37570-1	245	-61.7	3.21
37595-1	339	-61.5	1.78
45250-1	1357	-61.4	Undefined
37878-1	1855	-61.3	2.78
40884-1	4500	-61.2	5.64
44935-1	1500	-61.0	24.20
44903-1	312	-60.8	12.60
37583-1	302	-60.6	3.39
38208-1	763	-60.4	3.37
37585-1	305	-60.3	22.60
37587-1	307	-60.3	3.42
40866-1	4290	-60.1	2.00
41152-1	718	-60.1	0.35
37779-1	675	-60.1	13.70
37761-1	567	-60.0	2.81
45232-1	857	-60.0	33.20
41928-1	605	-60.0	2.81
41170-1	2269	-59.9	2.02
37896-1	805	-59.8	4.08
45257-1	608	-59.8	Undefined
37891-1	766	-59.8	1.09
37569-1	244	-59.8	2.19
37910-1	896	-59.7	8.15
44938-1	967	-59.6	Undefined
41070-1	6594	-59.6	1.76
37852-1	1312	-59.4	4.67
37586-1	306	-59.3	1.80
37580-1	291	-59.1	7.76
37911-1	898	-59.1	1.82
44952-1	1148	-59.0	27.70
37581-1	293	-58.8	3.74
42040-1	1516	-58.6	14.84
37850-1	1310	-58.4	3.73
41146-1	423	-58.4	2.01
37565-1	213	-58.1	13.90
37844-1	1225	-58.0	3.70
37568-1	243	-57.9	2.01
41941-1	807	-57.8	1.86
41039-1	5674	-57.7	1.12
37594-1	338	-57.6	8.13
41142-1	266	-57.6	2.01
37788-1	708	-57.5	2.82
44904-1	774	-57.5	5.83

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
37750-1	415	-57.5	22.70
41934-1	694	-57.3	1.26
45247-1	1494	-57.3	Undefined
41915-1	515	-57.3	8.83
40906-1	5578	-57.3	2.78
41053-1	6199	-57.2	0.25
41042-1	5680	-57.0	1.20
40783-1	3813	-56.9	3.54
37906-1	889	-56.8	Undefined
40899-1	5012	-56.8	3.59
41288-1	6644	-56.7	1.74
41171-1	2273	-56.7	2.83
37848-1	1296	-56.2	2.86
37885-1	2014	-56.1	2.87
37584-1	303	-56.1	5.70
37873-1	1765	-55.8	2.29
40907-1	5579	-55.6	1.52
38221-1	2216	-55.6	2.60
44919-1	1344	-55.6	6.36
41052-1	6163	-55.5	0.39
41155-1	723	-55.5	0.23
37869-1	1757	-55.4	2.63
41048-1	5741	-55.2	1.72
37863-1	1596	-55.1	2.53
44916-1	1329	-55.1	15.50
41424-1	4119	-55.0	1.83
37593-1	337	-54.8	7.08
41050-1	6153	-54.5	1.62
37578-1	272	-54.5	4.98
37851-1	1311	-54.0	2.55
44942-1	1010	-53.8	22.60
37881-1	1917	-53.7	6.86
37776-1	669	-53.7	20.80
41162-1	1860	-53.7	0.95
41944-1	814	-53.6	0.76
41176-1	4113	-53.4	1.27
41161-1	1858	-53.3	0.68
37895-1	770	-53.3	1.92
41911-1	511	-53.1	2.80
41066-1	6573	-53.0	0.23
40806-1	4140	-52.9	2.26
37774-1	666	-52.6	2.97
41153-1	721	-52.5	1.43

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
42039-1	1504	-52.3	3.54
41956-1	912	-52.1	4.01
45246-1	1277	-51.6	Undefined
40882-1	4495	-51.3	3.01
44930-1	1416	-51.2	Undefined
41916-1	538	-51.2	2.64
37868-1	1754	-51.1	2.21
41295-1	6635	-51.1	0.62
37847-1	1289	-51.0	Undefined
37597-1	341	-51.0	3.81
38209-1	1095	-51.0	3.54
37867-1	1666	-50.9	2.42
44945-1	1022	-50.9	16.00
44954-1	1152	-50.8	Undefined
37876-1	1851	-50.7	Undefined
41413-1	5820	-50.6	1.46
41414-1	5819	-50.6	1.19
37755-1	556	-50.5	2.73
37572-1	248	-50.5	10.30
37571-1	246	-50.5	6.47
45239-1	988	-50.5	Undefined
45211-1	1347	-50.3	Undefined
41418-1	5771	-50.3	1.73
37784-1	703	-50.3	13.30
37775-1	667	-50.3	7.64
41069-1	6576	-50.3	1.26
45202-1	493	-50.3	Undefined
37574-1	251	-50.2	7.09
37861-1	1402	-50.1	3.16
41299-1	6611	-49.9	3.01
37562-1	207	-49.8	3.77
37853-1	1317	-49.8	Undefined
41057-1	6265	-49.7	0.76
37747-1	412	-49.6	2.21
40893-1	4958	-49.6	7.06
37919-1	1094	-49.6	8.21
41925-1	585	-49.3	8.51
40782-1	3796	-49.3	3.35
37768-1	660	-49.3	1.70
37859-1	1352	-49.0	4.78
44953-1	1149	-49.0	Undefined
37766-1	595	-48.8	2.62
41065-1	6571	-48.7	1.96

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41931-1	691	-48.6	1.18
41177-1	4115	-48.4	2.23
37899-1	867	-48.3	5.69
42041-1	1517	-48.3	6.18
41924-1	584	-48.2	6.92
41957-1	916	-47.9	0.73
41294-1	6636	-47.9	1.72
45259-1	351	-47.8	40.30
42045-1	1557	-47.8	5.43
37884-1	2013	-47.3	2.45
37769-1	661	-47.3	Undefined
41289-1	6643	-47.2	0.78
45233-1	354	-47.2	Undefined
40885-1	4543	-47.2	3.40
45258-1	606	-47.1	Undefined
37557-1	121	-47.0	3.90
45204-1	460	-46.8	12.60
40865-1	4289	-46.7	2.97
37875-1	1775	-46.7	2.43
37841-1	1221	-46.5	4.28
41307-1	4046	-46.2	3.56
37882-1	1918	-46.2	3.15
41426-1	258	-46.1	2.53
37749-1	414	-45.9	4.85
37559-1	204	-45.8	3.19
40898-1	4968	-45.8	1.01
40900-1	5026	-45.7	0.91
37783-1	702	-45.7	5.25
37560-1	205	-45.4	3.29
42038-1	1450	-45.4	1.28
41410-1	5824	-45.4	2.16
37772-1	664	-45.3	1.66
37599-1	344	-45.2	12.00
40892-1	4957	-45.2	3.78
41151-1	716	-45.1	3.55
37917-1	939	-45.1	1.76
41408-1	6601	-45.0	6.07
37926-1	1200	-45.0	Undefined
37752-1	419	-44.8	26.80
41293-1	6637	-44.7	0.72
41948-1	848	-44.6	1.07
40777-1	3775	-44.6	8.56
40784-1	3820	-44.5	10.52

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41308-1	4008	-44.5	4.12
42069-1	1324	-44.5	0.51
41933-1	693	-44.2	1.02
44907-1	357	-44.1	13.10
41169-1	2268	-43.9	0.39
41030-1	5601	-43.4	1.14
37748-1	413	-43.2	3.55
37901-1	869	-42.7	Undefined
37856-1	1320	-42.6	3.47
45264-1	197	-42.5	Undefined
41157-1	730	-42.5	1.26
41290-1	6641	-42.5	0.78
41912-1	512	-42.2	1.75
45229-1	782	-42.0	Undefined
41280-1	6686	-41.8	0.92
41936-1	777	-41.6	0.72
37883-1	2012	-41.5	13.70
40791-1	3862	-41.3	2.68
40779-1	3793	-41.1	1.67
41937-1	778	-41.0	1.49
41300-1	6610	-41.0	12.53
37582-1	294	-40.9	Undefined
37904-1	886	-40.8	8.22
37857-1	1321	-40.7	1.62
41420-1	5707	-40.5	2.86
41419-1	5770	-40.5	1.77
38211-1	1210	-39.9	Undefined
45248-1	1439	-39.7	45.30
45236-1	402	-39.7	Undefined
42053-1	985	-39.6	Undefined
37879-1	1857	-39.6	Undefined
41040-1	5676	-39.3	9.14
37746-1	411	-39.2	32.60
37743-1	369	-39.2	7.55
37924-1	1125	-39.0	14.50
45213-1	1081	-38.8	Undefined
37751-1	416	-38.8	21.10
42059-1	1044	-38.6	10.70
37564-1	212	-38.1	Undefined
45249-1	1039	-38.0	Undefined
41298-1	6612	-38.0	0.25
40903-1	5571	-38.0	3.19
40818-1	4261	-37.9	Undefined

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41923-1	583	-37.8	1.98
41909-1	490	-37.4	2.42
42037-1	1445	-37.3	Undefined
37773-1	665	-37.2	>100
40864-1	4286	-37.1	1.59
41291-1	6640	-36.8	0.58
41281-1	6685	-36.8	0.70
41287-1	6669	-36.8	1.42
37566-1	219	-36.7	Undefined
41958-1	918	-36.7	0.18
45256-1	352	-36.5	Undefined
37771-1	663	-36.4	>100
41049-1	5967	-36.4	1.18
40795-1	3958	-36.1	2.49
41284-1	6676	-36.1	0.18
41305-1	5642	-36.0	Undefined
40790-1	3860	-36.0	1.85
41301-1	6162	-35.8	Undefined
41166-1	2191	-35.8	0.31
40796-1	4006	-35.8	2.18
41309-1	3773	-35.7	2.48
41285-1	6671	-35.5	1.14
41158-1	1136	-35.3	3.51
40888-1	4903	-35.2	Undefined
41282-1	6684	-35.0	0.22
40792-1	3920	-34.9	2.40
41046-1	5736	-34.2	0.60
41913-1	513	-34.2	4.74
40891-1	4906	-34.1	1.86
41156-1	729	-34.1	0.26
41421-1	4983	-33.6	Undefined
41286-1	6670	-33.6	0.38
40808-1	4186	-33.5	Undefined
40780-1	3794	-33.1	1.49
40878-1	4484	-33.1	7.66
40785-1	3851	-33.0	3.36
41297-1	6613	-32.9	0.39
45209-1	1038	-32.6	Undefined
40875-1	4402	-32.2	3.47
41173-1	2639	-32.2	4.98
41051-1	6157	-32.1	1.39
41147-1	424	-32.0	1.80
41415-1	5774	-31.6	0.93

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41154-1	722	-31.4	1.72
40805-1	4139	-31.3	2.89
41044-1	5692	-31.3	0.33
37780-1	679	-31.1	40.40
41306-1	4097	-31.0	1.16
41159-1	1137	-30.9	0.30
37855-1	1319	-30.8	>100
40797-1	4020	-30.7	1.24
41160-1	1162	-30.6	2.11
41045-1	5705	-30.5	Undefined
41068-1	6575	-30.4	1.82
44941-1	1003	-30.3	18.20
40902-1	5569	-30.1	1.05
41180-1	4118	-30.0	0.73
41283-1	6683	-30.0	0.34
40887-1	4902	-29.9	22.40
40896-1	4965	-29.9	Undefined
41054-1	6201	-29.3	0.76
41168-1	2267	-29.3	Undefined
41033-1	5668	-29.0	2.21
37590-1	334	-28.3	>100
41296-1	6614	-28.3	1.30
41918-1	542	-28.2	Undefined
37862-1	1431	-28.2	Undefined
45237-1	448	-28.2	Undefined
41292-1	6638	-28.0	0.44
45240-1	1006	-27.9	Undefined
37898-1	866	-27.7	>100
41411-1	5823	-27.5	Undefined
45222-1	194	-27.3	Undefined
40803-1	4137	-27.2	2.73
41043-1	5681	-26.7	0.51
37558-1	122	-26.7	>100
41059-1	6268	-26.6	0.24
40868-1	4318	-26.4	2.72
41422-1	4441	-26.4	1.72
40880-1	4488	-26.2	1.92
40816-1	4259	-25.9	4.50
41302-1	6158	-25.8	1.97
37596-1	340	-25.5	>100
37914-1	904	-25.2	Undefined
41032-1	5641	-25.1	2.63
40881-1	4491	-25.1	1.40

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
37598-1	343	-24.8	>100
41409-1	5857	-24.8	>33.3
41416-1	5773	-24.5	>100
41038-1	5673	-23.7	>33.3
40786-1	3853	-23.4	>33.3
41062-1	6280	-23.2	Undefined
40811-1	4199	-23.1	>100
45235-1	364	-23.0	>100
37556-1	115	-22.8	>100
40883-1	4496	-22.6	>100
40793-1	3921	-22.5	>100
40781-1	3795	-22.4	>100
45226-1	317	-22.2	>100
44931-1	1435	-21.9	>100
40813-1	4203	-21.9	>100
45254-1	358	-21.8	>100
45255-1	356	-21.5	>100
45243-1	1239	-21.4	>100
40809-1	4191	-20.7	3.46
41417-1	5772	-20.6	>100
40895-1	4963	-20.5	>100
40890-1	4905	-20.1	>100
45230-1	783	-19.8	>100
40799-1	4129	-19.4	>33.3
40801-1	4132	-19.4	>100
45214-1	792	-19.4	>100
41930-1	688	-19.2	>100
45234-1	355	-18.7	>100
40876-1	4403	-18.7	>100
37900-1	868	-18.6	>100
41058-1	6267	-18.5	>100
41055-1	6202	-18.1	>100
41063-1	6503	-17.9	0.69
41165-1	2190	-17.9	>100
45206-1	492	-17.8	>100
41041-1	5679	-17.5	>100
42057-1	1009	-16.9	>100
40870-1	4361	-16.8	>100
37592-1	336	-16.7	>100
37589-1	329	-16.5	>100
37854-1	1318	-16.4	>100
40897-1	4966	-16.4	>100
45242-1	1235	-16.3	>100

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
42058-1	1040	-16.2	>100
45238-1	1501	-16.1	>100
38207-1	112	-15.7	>100
41143-1	269	-15.7	0.43
41423-1	4160	-15.6	>100
40807-1	4184	-15.2	>100
40905-1	5576	-15.0	>100
41061-1	6279	-14.6	>100
41056-1	6243	-14.3	>100
40778-1	3776	-14.2	>100
37591-1	335	-14.2	>100
40889-1	4904	-13.7	>100
37887-1	757	-13.4	1.18
40901-1	5215	-12.9	>100
40802-1	4135	-12.8	>100
45260-1	318	-12.6	>100
40879-1	4487	-12.5	>100
42051-1	1614	-12.3	>100
40863-1	4283	-12.3	>100
40877-1	4404	-12.1	>100
37923-1	1121	-11.5	>100
45253-1	395	-11.3	>100
40800-1	4130	-11.0	>100
41035-1	5670	-10.6	>100
45208-1	327	-10.3	>100
45251-1	1354	-10.0	>100
44934-1	1497	-9.8	>100
45245-1	1264	-9.4	>100
37577-1	254	-8.7	>100
45262-1	315	-8.5	>100
40794-1	3923	-8.5	>100
41060-1	6271	-7.7	>100
41167-1	2193	-7.6	>100
41940-1	788	-7.6	>100
40886-1	4901	-7.4	>100
45261-1	467	-7.3	>100
40814-1	4251	-7.2	>100
40869-1	4360	-7.1	>100
40867-1	4291	-6.6	>100
45228-1	601	-6.4	>100
37902-1	870	-6.1	>100
45227-1	321	-6.1	>100
37860-1	1399	-6.0	>100

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41430-1	21	-5.5	>100
40871-1	4362	-4.7	>100
44936-1	1520	-4.3	>100
41172-1	2274	-4.2	>100
44913-1	450	-3.2	>100
40908-1	5600	-3.0	>100
41429-1	22	-2.6	>100
45252-1	446	-2.1	>100
37576-1	253	-2.0	>100
45223-1	452	-1.8	>100
41047-1	5740	-0.9	>100
40798-1	4095	-0.8	>100
41427-1	257	-0.7	>100
45231-1	843	-0.6	>100
40815-1	4254	-0.6	>100
45205-1	491	-0.5	>100
40812-1	4202	-0.4	>100
37778-1	673	0.3	>100
37573-1	249	0.5	>100
42036-1	1417	0.9	>100
40904-1	5575	2.2	>100
40894-1	4962	2.3	>100
37555-1	113	3.6	>100
37579-1	281	3.7	>100
40872-1	4363	4.2	>100
37894-1	769	5.0	>100
40819-1	4262	5.4	>100
41141-1	143	5.4	>100
41938-1	781	5.4	>100
41148-1	586	5.5	>100
41064-1	6568	5.5	>100
41144-1	420	6.9	>100
41303-1	6154	8.5	>100
45224-1	489	8.7	>100
40874-1	4398	9.5	>100
45244-1	1248	10.3	>100
41140-1	138	10.5	>100
40787-1	3854	11.5	>100
41036-1	5671	11.6	>100
42068-1	1269	12.4	>100
44933-1	1451	13.6	>100
37575-1	252	13.8	>100
40862-1	4263	14.2	>100

Duplex No.	PNPLA3 Location	% Avg Max Activity	Avg IC_{50} (nM)
41929-1	615	15.9	>100
41164-1	2189	20.4	>100
41428-1	142	21.1	>100
41304-1	5691	21.2	>100
40804-1	4138	34.1	>100
41412-1	5822	34.3	>100
41067-1	6574	36.3	>100
40873-1	4369	37.6	>100
41037-1	5672	38.0	>100
41425-1	262	39.7	>100
41034-1	5669	40.4	>100
41926-1	603	46.7	>100

Table 3. RNA FISH Assay with Human/Cyno PNPLA3-Spanning siRNA

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
38207-1	112	-15.7
37555-1	113	3.6
37556-1	115	-22.8
37557-1	121	-47.0
37558-1	122	-26.7
37559-1	204	-45.8
37560-1	205	-45.4
37561-1	206	-62.2
37562-1	207	-49.8
37563-1	211	-74.7
37564-1	212	-38.1
37565-1	213	-58.1
37566-1	219	-36.7
37567-1	220	-73.0
37568-1	243	-57.9
37569-1	244	-59.8
37570-1	245	-61.7
37571-1	246	-50.5
37572-1	248	-50.5
37573-1	249	0.5
37574-1	251	-50.2
37575-1	252	13.8
37576-1	253	-2.0
37577-1	254	-4.4
37578-1	272	-54.5

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
37579-1	281	3.7
37580-1	291	-59.1
37581-1	293	-58.8
37582-1	294	-40.9
37583-1	302	-60.6
37584-1	303	-56.1
37585-1	305	-60.3
37586-1	306	-59.3
37587-1	307	-60.3
37588-1	309	-76.4
37589-1	329	-17.8
37590-1	334	-28.3
37591-1	335	-14.2
37592-1	336	-16.7
37593-1	337	-54.8
37594-1	338	-57.6
37595-1	339	-61.5
37596-1	340	-25.5
37597-1	341	-51.0
37598-1	343	-24.8
37599-1	344	-45.2
37600-1	347	-80.9
37743-1	369	-32.7
37744-1	391	-79.6
37745-1	392	-77.0
37746-1	411	-39.2
37747-1	412	-49.6
37748-1	413	-43.2
37749-1	414	-45.9
37750-1	415	-57.5
37751-1	416	-38.8
37752-1	419	-44.8
37753-1	497	-64.9
37754-1	555	-62.1
37755-1	556	-50.5
37756-1	557	-65.0
37757-1	560	-65.1
37758-1	562	-71.2
37759-1	563	-71.0
37760-1	564	-63.4
37761-1	567	-60.0
37762-1	568	-69.1
37763-1	590	-75.3

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
37764-1	591	-62.3
37765-1	593	-73.7
37766-1	595	-48.8
37767-1	641	-66.7
37768-1	660	-49.3
37769-1	661	-47.3
37770-1	662	-71.3
37771-1	663	-36.4
37772-1	664	-45.3
37773-1	665	-37.2
37774-1	666	-52.6
37775-1	667	-50.3
37776-1	669	-53.7
37777-1	671	-67.5
37778-1	673	0.3
37779-1	675	-60.1
37780-1	679	-39.6
37781-1	698	-76.0
37782-1	701	-69.3
37783-1	702	-45.7
37784-1	703	-50.3
37785-1	704	-79.6
37786-1	705	-76.4
37787-1	706	-74.2
37788-1	708	-57.5
37789-1	756	-76.5
37887-1	757	-13.4
37888-1	762	-65.0
38208-1	763	-60.4
37889-1	764	-77.7
37890-1	765	-63.3
37891-1	766	-59.8
37892-1	767	-72.3
37893-1	768	-81.8
37894-1	769	5.0
37895-1	770	-53.3
37896-1	805	-59.8
37897-1	832	-67.6
37898-1	866	-27.7
37899-1	867	-48.3
37900-1	868	-18.6
37901-1	869	-42.7
37902-1	870	-6.1

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
37903-1	878	-66.8
37904-1	886	-40.8
37905-1	887	-63.8
37906-1	889	-56.8
37907-1	893	-75.8
37908-1	894	-72.3
37909-1	895	-66.1
37910-1	896	-59.7
38213-1	897	-67.8
37911-1	898	-59.1
37912-1	899	-66.7
37913-1	902	-70.8
37914-1	904	-25.2
37915-1	905	-67.7
37917-1	939	-45.1
38214-1	1092	-71.3
37919-1	1094	-49.6
38209-1	1095	-51.0
37920-1	1101	-63.5
37921-1	1104	-63.1
37923-1	1121	-11.5
37924-1	1125	-39.0
38210-1	1189	-71.2
37926-1	1200	-45.0
37927-1	1201	-69.1
38211-1	1210	-39.9
37929-1	1213	-67.6
38212-1	1217	-66.6
37930-1	1219	-80.9
37932-1	1220	-72.9
37841-1	1221	-46.5
37842-1	1223	-73.3
37843-1	1224	-74.8
37844-1	1225	-58.0
37845-1	1226	-73.0
37846-1	1280	-74.1
37847-1	1289	-51.0
37848-1	1296	-56.2
37849-1	1300	-67.9
37850-1	1310	-58.4
37851-1	1311	-54.0
37852-1	1312	-59.4
37853-1	1317	-49.8

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
37854-1	1318	-16.4
37855-1	1319	-30.8
37856-1	1320	-42.6
37857-1	1321	-40.7
37858-1	1322	-70.1
37859-1	1352	-62.5
37860-1	1399	-20.3
37861-1	1402	-50.1
37862-1	1431	-28.2
37863-1	1596	-55.1
37864-1	1602	-76.3
37865-1	1603	-71.2
37866-1	1604	-63.6
37867-1	1666	-50.9
37868-1	1754	-51.1
37869-1	1757	-55.4
37870-1	1760	-65.6
37871-1	1763	-66.6
37872-1	1764	-65.1
37873-1	1765	-55.8
37874-1	1771	-67.0
37875-1	1775	-46.7
37876-1	1851	-50.7
37877-1	1852	-64.5
37878-1	1855	-61.3
37879-1	1857	-39.6
37880-1	1890	-70.5
37881-1	1917	-53.7
37882-1	1918	-46.2
37883-1	2012	-41.5
37884-1	2013	-47.3
37885-1	2014	-56.1
37886-1	2197	-73.6
38215-1	2198	-80.2
38216-1	2199	-79.4
38217-1	2200	-79.4
38218-1	2201	-72.6
38219-1	2202	-66.2
38220-1	2204	-66.9
38221-1	2216	-55.6

Table 4. RNA FISH Assay with Human/Cyno PNPLA3 Extended 3' UTR siRNA

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
41309-1	3773	-35.7
40777-1	3775	-51.4
40778-1	3776	-14.2
40779-1	3793	-45.5
40780-1	3794	-33.1
40781-1	3795	-22.4
40782-1	3796	-43.5
40783-1	3813	-49.7
40784-1	3820	-41.5
40785-1	3851	-33.0
40786-1	3853	-23.4
40787-1	3854	11.5
40788-1	3857	-60.2
40789-1	3858	-66.3
40790-1	3860	-36.0
40791-1	3862	-38.3
40792-1	3920	-34.9
40793-1	3921	-22.5
40794-1	3923	-8.5
40795-1	3958	-42.7
40796-1	4006	-35.8
41308-1	4008	-41.7
40797-1	4020	-30.7
41307-1	4046	-48.3
40798-1	4095	-0.8
41306-1	4097	-31.0
40799-1	4129	-19.4
40800-1	4130	-11.0
40801-1	4132	-19.4
40802-1	4135	-12.8
40803-1	4137	-27.2
40804-1	4138	34.1
40805-1	4139	-31.3
40806-1	4140	-47.1
40807-1	4184	-15.2
40808-1	4186	-33.5
40809-1	4191	-47.8
40810-1	4193	-67.3
40811-1	4199	-23.1
40812-1	4202	-0.4
40813-1	4203	-21.9
40814-1	4251	-7.2

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
40815-1	4254	-0.6
40816-1	4259	-25.9
40817-1	4260	-50.9
40818-1	4261	-37.9
40819-1	4262	5.4
40862-1	4263	14.2
40863-1	4283	-12.3
40864-1	4286	-37.1
40865-1	4289	-42.4
40866-1	4290	-61.5
40867-1	4291	-6.6
40868-1	4318	-26.4
40869-1	4360	-7.1
40870-1	4361	-16.8
40871-1	4362	-4.7
40872-1	4363	4.2
40873-1	4369	37.6
40874-1	4398	9.5
40875-1	4402	-42.4
40876-1	4403	-18.7
40877-1	4404	-12.1
40878-1	4484	-33.1
40879-1	4487	-12.5
40880-1	4488	-26.2
40881-1	4491	-25.1
40882-1	4495	-52.1
40883-1	4496	-22.6
40884-1	4500	-57.0
40885-1	4543	-47.2
40886-1	4901	-7.4
40887-1	4902	-29.9
40888-1	4903	-35.2
40889-1	4904	-13.7
40890-1	4905	-20.1
40891-1	4906	-34.1
40892-1	4957	-38.1
40893-1	4958	-41.3
40894-1	4962	2.3
40895-1	4963	-20.5
40896-1	4965	-29.9
40897-1	4966	-16.4
40898-1	4968	-42.4
40899-1	5012	-46.0

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
40900-1	5026	-42.2
40901-1	5215	-12.9
40902-1	5569	-30.1
40903-1	5571	-54.7
40904-1	5575	2.2
40905-1	5576	-15.0
40906-1	5578	-49.9
40907-1	5579	-57.2
40908-1	5600	-3.0
41030-1	5601	-40.8
41031-1	5640	-44.1
41032-1	5641	-25.1
41305-1	5642	-36.0
41033-1	5668	-29.0
41034-1	5669	40.4
41035-1	5670	-10.6
41036-1	5671	11.6
41037-1	5672	38.0
41038-1	5673	-23.7
41039-1	5674	-54.9
41040-1	5676	-46.4
41041-1	5679	-17.5
41042-1	5680	-55.6
41043-1	5681	-26.7
41304-1	5691	21.2
41044-1	5692	-31.3
41045-1	5705	-30.5
41046-1	5736	-49.3
41047-1	5740	-0.9
41048-1	5741	-49.7
41049-1	5967	-36.4
41050-1	6153	-56.7
41303-1	6154	8.5
41051-1	6157	-32.1
41302-1	6158	-25.8
41301-1	6162	-35.8
41052-1	6163	-52.9
41053-1	6199	-57.4
41054-1	6201	-29.3
41055-1	6202	-18.1
41056-1	6243	-14.3
41057-1	6265	-43.7
41058-1	6267	-18.5

Duplex No.	PNPLA3 Location	PNPLA3 knockdown (%)
41059-1	6268	-26.6
41060-1	6271	-7.7
41061-1	6279	-14.6
41062-1	6280	-23.2
41063-1	6503	-39.8
41064-1	6568	5.5
41065-1	6571	-45.0
41066-1	6573	-56.1
41067-1	6574	36.3
41068-1	6575	-30.4
41069-1	6576	-44.4
41070-1	6594	-44.0
41300-1	6610	-43.8
41299-1	6611	-43.6
41298-1	6612	-38.0
41297-1	6613	-32.9
41296-1	6614	-28.3
41295-1	6635	-54.2
41294-1	6636	-52.8
41293-1	6637	-42.4
41292-1	6638	-28.0
41291-1	6640	-36.8
41290-1	6641	-44.6
41289-1	6643	-45.9
41288-1	6644	-52.3
41287-1	6669	-36.8
41286-1	6670	-33.6
41285-1	6671	-35.5
41284-1	6676	-36.1
41283-1	6683	-30.0
41282-1	6684	-35.0
41281-1	6685	-36.8
41280-1	6686	-38.6

Table 5. RNA FISH Assay with Human/Marmoset PNPLA3 siRNA

Duplex No.	PNPLA3 Location	PNPLA3 Knockdown (%)
41430-1	21	-5.5
41429-1	22	-2.6
41140-1	138	10.5
41428-1	142	21.1

Duplex No.	PNPLA3 Location	PNPLA3 Knockdown (%)
41141-1	143	5.4
41427-1	257	7.3
41426-1	258	-40.1
41425-1	262	57.8
41142-1	266	-56.7
41143-1	269	-4.0
41144-1	420	19.6
41145-1	422	-55.4
41146-1	423	-52.7
41147-1	424	-30.1
41148-1	586	1.7
41149-1	714	-57.8
41150-1	715	-58.6
41151-1	716	-39.0
41152-1	718	-57.2
41153-1	721	-54.6
41154-1	722	-33.4
41155-1	723	-52.9
41156-1	729	-33.9
41157-1	730	-36.7
41158-1	1136	-25.9
41159-1	1137	-32.9
41160-1	1162	-28.0
41161-1	1858	-53.3
41162-1	1860	-62.0
41163-1	2187	-59.0
41164-1	2189	20.4
41165-1	2190	-17.9
41166-1	2191	-39.5
41167-1	2193	-7.6
41168-1	2267	-29.3
41169-1	2268	-36.5
41170-1	2269	-48.3
41171-1	2273	-49.3
41172-1	2274	-4.2
41173-1	2639	-32.2
41174-1	3893	-61.4
41175-1	4112	-57.5
41176-1	4113	-54.6
41177-1	4115	-41.7
41178-1	4116	-63.4
41179-1	4117	-66.1
41180-1	4118	-30.0

Duplex No.	PNPLA3 Location	PNPLA3 Knockdown (%)
41424-1	4119	-57.0
41423-1	4160	-15.6
41422-1	4441	-26.4
41421-1	4983	-33.6
41420-1	5707	-38.5
41419-1	5770	-37.0
41418-1	5771	-43.1
41417-1	5772	-20.6
41416-1	5773	-24.5
41415-1	5774	-31.6
41414-1	5819	-47.9
41413-1	5820	-51.7
41412-1	5822	35.8
41411-1	5823	-27.5
41410-1	5824	-38.3
41409-1	5857	-24.8
41408-1	6601	-38.2

Example 3: Efficacy screening of select PNPLA3 siRNA molecules in AAV-based mouse models containing human PNPLA3 sequences

[0184] Adeno-associated adenovirus (AAV; serotype AAVDJ8; endotoxin-free, prepared internally by Amgen) diluted in phosphate buffered saline (Thermo Fisher Scientific,14190-136) was administered at $1x10^{12}$ viral particles per animal into the tail vein of C57BL/6NCrl male or female mice (Charles River Laboratories Inc.) to drive expression of human PNPLA3 sequences in the liver. Four AAV constructs were designed from the ENST00000216180.7 PNPLA3 transcript for *in vivo* screening; one containing the full-length coding sequence for PNPLA3$^{rs738409\text{-}rs738408}$ (AAV-CDS), and three enhanced green fluorescence protein (eGFP) reporter constructs containing stretches of the 3' untranslated region (nucleotides (nt) 1620-3410 (AAV-A), nt 3310-5100 (AAV-B), and nt 5000-6689 (AAV-C). Each AAV construct also contained a benchmark sequence to compare siRNA-mediated knockdown efficacy across AAVs and studies.

[0185] GalNAc-conjugated siRNAs shown in Figure 2 were tested against PNPLA3$^{rs738409\text{-}rs738408}$, AAV-A, AAV-B or AAV-C. Figure 2 also shows the unmodified versions of these siRNA sequences. Two weeks after AAV injection, mice (generally 8-12 weeks of age and an n=3-4 animals per group) were treated with a single dose of siRNA via subcutaneous injection, at 0.5, 1.0, or 3.0 milligrams per kilogram of animal, diluted in

phosphate buffered saline (Thermo Fisher Scientific,14190-136). After 28 days post-siRNA injection, animals were euthanized, and livers were collected from the animals and snap-frozen in liquid nitrogen. A portion of the liver was processed for purified RNA using a QIACube Classic instrument (Qiagen, 9001292) and RNeasy Mini kits (Qiagen, 74106) according to manufacturer's instructions. Samples were analyzed using a NanoDroppTM 8000 Spectrophotometer (Thermo Scientific, ND-8000-GL). RNA was treated with RQ1 RNase-Free DNase (Promega, M6101) and prepared for Real-Time qPCR using the TAQMAN™ RNA-to-CT™ 1-Step kit (Applied Biosystems, 4392656). Real-Time qPCR was run on a QuantStudio Real-Time PCR machine. Results were based on gene expression of human *PNPLA3* (Invitrogen, hs00228747_m1), *GFP1* (IDT custom assay: Forward primer: CTATGTGCAGGAGAGAACCATC (Sense; SEQ ID NO: 3589), Reverse primer: GCCCTTCAGCTCGATTCTATT (AntiSense; SEQ ID NO: 3590), Probe: 5'-6FAM-TACAAGACCCGCGCTGAAGTCAAG TAMRA-3' (Sense; SEQ ID NO: 3591)), *GFP2* (IDT custom assay: Forward primer: TCATCTGCACCACTGGAAAG (Sense; SEQ ID NO: 3592), Reverse primer: CTGCTTCATATGGTCTGGGTATC (AntiSense; SEQ ID NO: 3593), Probe: 5'-6FAM CCAACACTGGTCACTACCCTCACC TAMRA-3' (Sense; SEQ ID NO: 3594), and/or bovine growth hormone polyadenylation (*BghpA*, which is included in each AAV construct; IDT custom assay: Forward: 5'-GCCAGCCATCTGTTGT-3' (SEQ ID NO: 3595), Reverse: 5'-GGAGTGGCACCTTCCA-3' (SEQ ID NO: 3596), Probe: 5'-6FAM-TCCCCCGTGCCTTCCTTGACC TAMRA-3' (SEQ ID NO: 3597), as normalized to mouse TATA-binding protein (Tbp) (IDT, Hex Mm.PT.39a.22214839), and presented as the relative percent knockdown of human *PNPLA3*, *GFP*, and/or *BghpA* mRNA expression, normalized to mouse *Tbp*, compared to vehicle-treated control animals. For some groups, another portion of the snap-frozen liver was homogenized in Pierce IP buffer (Thermo Scientific, 87787) including 1x HALT™ Protease and Phosphatase Inhibitor Cocktail (Thermo Scientific, 78441) to make a 50mg tissue/ml lysis buffer solution. Protein concentrations were determined using a DIRECT DETECT™ infrared spectrometer (Millipore). GFP protein analysis was performed on a PEGGY SUE™ Simple Western System (Protein Simple, 004-800) using a 12-230 kDa PEGGY SUE or SALLY SUE Separation Module (Protein Simple, SM-S001), or a WES™ Simple Western System (Protein Simple, 004-600) using a 12-230 kDa Jess or Wes Separation Module, 8 x 25 capillary cartridges (Protein Simple, SM-W004). All β-actin protein detection was performed using the WES™ Simple Western System and components. The results of these experiments are shown Figure 3 (AAV-CDS) and Figure 4 (AAV-A, AAV-B, and AAV-C).

[0186] To evaluate relative percent knockdown of endogenous levels of the human PNPLA3 transcript by PNPLA3 siRNA molecules, a homozygous h*PNPLA3*^{I148M} knock-in (h*PNPLA3*^{I148M} KI) mouse model was used (developed by Amgen; colony maintained at Charles River Laboratories, Inc.). In this model, the wild type mouse *Pnpla3* gene was replaced by the full-length coding region of the human *PNPLA3*^{I148M} gene while utilizing the mouse transcriptional regulatory promoter region to drive expression.

[0187] Single housed, male h*PNPLA3*^{I148M} KI mice, typically 8-10 weeks of age, were maintained on a standard chow diet ad libitum until the start of the study, at which point they were converted to a modified rodent obesity diet supplemented with hydrogenated vegetable oil, added fructose, and enriched with 0.2% added cholesterol (Envigo, TD.190883 or TD.200212; the latter is an irradiated version of the former). After two weeks on the diet, body weights were recorded, and the mice were randomized into groups of 5-6 mice based on even weight distribution. The mice were subcutaneously injected with a single dose of PNPLA3 siRNA molecules at 1 or 3 mg/kg of animal diluted in phosphate buffered saline (Thermo Fisher Scientific, 14190-136) or saline only. After 28 days post-treatment, mice were euthanized, and the livers collected from the animals and snap-frozen in liquid nitrogen. A portion of the liver was processed for purified RNA and for some groups a portion was processed for protein analysis.

[0188] Due to the relatively low endogenous expression of *PNPLA3* transcript, mRNA analysis from KI mouse livers was prepared as described but analyzed by treating with a High-Capacity cDNA Reverse Transcription kit (Applied Biosystems, 4368813) and run on a QIAcuity Eight Platform Digital PCR System (Qiagen, 911056) which is more sensitive than traditional qPCR.

[0189] For targeted measurement of hPNPLA3 protein, approximately 100 to 200 mg of frozen liver tissue from each mouse was homogenized independently in cold PIERCE™ IP Lysis Buffer (Thermo Fisher, 87787). Samples were treated with 1X PIERCE™ Protease Inhibitor Tablets (Thermo Fisher, A32963) and BENZONASE® Nuclease (Millipore-Sigma, E1014). Human PNPLA3 protein (peptide: VSDGENVLVSDFR (SEQ ID NO: 3598); New England Peptide) was captured using immunoaffinity (IA) techniques and an anti-human PNPLA3 mAb (developed by Amgen Inc.), trypsin-digested on beads, and analyzed by liquid chromatography-with tandem mass spectrometry (LC-MS/MS; Thermo Fisher, Orbitrap FUSION™ LUMOS™ TRIBRID™ Mass Spectometer). Reagent-free LC MS/MS was used to measure mouse glyceraldehyde 3-phosphate dehydrogenase (mGAPDH; peptide: LISWYDNEYGYSNR (SEQ ID NO: 3599); New England Peptide), a housekeeping protein,

in liver tissue recovered from each animal. The peptide signals across all samples were determined using the LC-MS data analysis software, ANALYST® (SCIEX, v1.6.2). The results of the knock-in experiments are shown in Figure 5.

[0190] siRNA triggers that cluster within certain regions of the PNPLA3 coding sequence and demonstrated efficacy *in vivo* were selected for further investigation. Two selected siRNA molecules ("PNPLA3-T704_M1282_3G3-5'" (Duplex No. 43806-1) and "PNPLA3-T706-g.1g>a_M867_3G3-5'" (Duplex No. 41321-1) in Figure 5) selectively target both human and cynomolgus PNPLA3 mRNA, while the other two selected siRNA molecules ("PNPLA3(Human-Only)-T1234_M867_3G3-5'" (Duplex No. 52317-1) and "PNPLA3(Human-Only)-T1240_M867_3G3-5'" (Duplex No. 52307-1 in Figure 5) target only human PNPLA3 mRNA. The sequences of the sense and antisense strands of each of the selected siRNA molecules is set forth in Table 6.

Table 6

siRNA	Duplex No.	PNPLA3 Location	Sense SEQ ID NO: (Unmodified)	Antisense SEQ ID NO: (Unmodified)	Sense SEQ ID NO: (Modified)	Antisense SEQ ID NO: (Modified)
PNPLA3-T704_M1282_3G3-5'	43806-1	704	151	655	403	907
PNPLA3-T706-g.1g>a_M867_3G3-5'	41321-1	706	90	594	342	846
PNPLA3(Human-Only)-T1234_M867_3G3-5'	52317-1	1234	263	767	515	1019
PNPLA3(Human-Only)-T1240_M867_3G3-5	52307-1	1240	253	757	505	1009

[0191] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention. To the extent that

any of the definitions or terms provided in the references incorporated by reference differ from the terms and discussion provided herein, the present terms and definitions control.

[0192] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and examples detail certain preferred embodiments of the invention and describe the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

What is Claimed

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region that is complementary to a Patatin-Like Phospholipase Domain Containing 3 (PNPLA3) mRNA sequence comprising any one of SEQ ID NOs: 1-60, and wherein the RNAi construct inhibits the expression of PNPLA3.

2. The RNAi construct of claim 1, which comprises a region having at least 15 contiguous nucleotides differing by no more than 3 nucleotides from an antisense sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588.

3. The RNAi construct of claim 1 or claim 2, wherein the antisense strand hybridizes to a PNPLA3 mRNA sequence comprising any one of SEQ ID NOs: 1-60.

4. The RNAi construct of any one of claims 1-3, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length.

5. The RNAi construct of claim 4, wherein the duplex region is about 17 to about 24 base pairs in length.

6. The RNAi construct of claim 4, wherein the duplex region is about 19 to about 21 base pairs in length.

7. The RNAi construct of claim 6, wherein the duplex region is 19 base pairs in length.

8. The RNAi construct of claim 6, wherein the duplex region is 20 base pairs in length.

9. The RNAi construct of claim 6, wherein the duplex region is 21 base pairs in length.

10. The RNAi construct of any one of claims 4-10, wherein the sense strand and the antisense strand are each about 15 to about 30 nucleotides in length.

11. The RNAi construct of claim 10, wherein the sense strand and the antisense strand are each about 19 to about 27 nucleotides in length.

12. The RNAi construct of claim 10, wherein the sense strand and the antisense strand are each about 20 to about 25 nucleotides in length.

13. The RNAi construct of claim 12, wherein the sense strand and the antisense strand are each about 20 to about 23 nucleotides in length.

14. The RNAi construct of any one of claims 1 to 13, which comprises at least one blunt end.

15. The RNAi construct of any one of claims 1 to 13, which comprises at least one nucleotide overhang of 1 to 4 unpaired nucleotides.

16. The RNAi construct of claim 15, wherein the nucleotide overhang has two unpaired nucleotides.

17. The RNAi construct of claim 15 or 16, wherein the RNAi construct comprises a nucleotide overhang at the 3' end of the sense strand, the 3' end of the antisense strand, or the 3' end of both the sense strand and the antisense strand.

18. The RNAi construct of any one of claims 15-17, wherein the nucleotide overhang comprises a 5'-UU-3' dinucleotide or a 5'-dTdT-3' dinucleotide.

19. The RNAi construct of any one of claims 1-18, wherein the RNAi construct comprises at least one modified nucleotide.

20. The RNAi construct of claim 19, wherein the modified nucleotide is a 2'-modified nucleotide.

21. The RNAi construct of claim 19, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-O-allyl modified nucleotide, a bicyclic nucleic acid (BNA), a glycol nucleic acid, an inverted base, or combinations thereof.

22. The RNAi construct of claim 21, wherein the modified nucleotide is a 2'-O-methyl modified nucleotide, a 2'-O-methoxyethyl modified nucleotide, a 2'-fluoro modified nucleotide, or combinations thereof.

23. The RNAi construct of claim 19, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.

24. The RNAi construct of claim 23, wherein the modified nucleotides are 2'-O-methylmodified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

25. The RNAi construct of any one of claims 1-24, which comprises at least one phosphorothioate internucleotide linkage.

26. The RNAi construct of claim 25, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3' end of the antisense strand.

27. The RNAi construct of claim 25, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3' and 5' ends of the antisense strand

and two consecutive phosphorothioate internucleotide linkages at the 5' end of the sense strand.

28. The RNAi construct of any one of claims 1-27, wherein the antisense strand comprises a sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588.

29. The RNAi construct of claim 28, wherein the sense strand comprises a sequence selected from SEQ ID NOs: 61-564 and SEQ ID NOs: 1069-2328.

30. The RNAi construct of any one of claims 1-29, wherein the RNAi construct is a duplex compound comprising an antisense strand and a sense strand, wherein the antisense strand comprises a sequence selected from SEQ ID NOs: 565-1068 and SEQ ID NOs: 2329-3588 and the sense strand comprises a sequence selected from SEQ ID NOs: 61-564 and SEQ ID NOs: 1069-2328.

31. The RNAi construct of claim 30, which comprises:

    a. an antisense strand comprising SEQ ID NO: 594 and a sense strand comprising SEQ ID NO: 90;

    b. an antisense strand comprising SEQ ID NO: 846 and a sense strand comprising SEQ ID NO: 342;

    c. an antisense strand comprising SEQ ID NO: 655 and a sense strand comprising SEQ ID NO: 151;

    d. an antisense strand comprising SEQ ID NO: 907 and a sense strand comprising SEQ ID NO: 403;

    e. an antisense strand comprising SEQ ID NO: 757 and a sense strand comprising SEQ ID NO: 253;

    f. an antisense strand comprising SEQ ID NO: 1009 and a sense strand comprising SEQ ID NO: 505;

    g. an antisense strand comprising SEQ ID NO: 767 and a sense strand comprising SEQ ID NO: 263; or

    h. an antisense strand comprising SEQ ID NO: 1019 and a sense strand comprising SEQ ID NO: 515.

32. The RNAi construct of any one of claims 1-31, wherein the RNAi construct reduces the expression level of PNPLA3 in liver cells following incubation with the RNAi construct as

compared to the PNPLA3 expression level in liver cells that have been incubated with a control RNAi construct.

33. The RNAi construct of claim 32, wherein the liver cells are Hep3B or HepG2 cells.

34. The RNAi construct of any one of claims 1-33, wherein the RNAi construct inhibits at least 60% of PNPLA3 expression at 5 nM in Hep3B cells *in vitro*.

35. The RNAi construct of any one of claims 1-34, wherein the RNAi construct inhibits at least 60% of PNPLA3 expression at 5 nM in HepG2 cells *in vitro*.

36. The RNAi construct of any one of claims 1-35, wherein the RNAi construct inhibits PNPLA3 expression in Hep3B cells with an IC_{50} of less than about 1 nM.

37. The RNAi construct of any one of claims 1-36, wherein the RNAi construct inhibits PNPLA3 expression in HepG2 cells with an IC_{50} of less than about 1 nM.

38. The RNAi construct of any one of claims 1-37, further comprising a ligand that binds to one or more proteins expressed on the surface of liver cells.

39. A composition comprising the RNAi construct of any one of claims 1-38 and a pharmaceutically acceptable carrier, excipient, or diluent.

40. A method for reducing the expression of PNPLA3 in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1-39.

41. A method for reducing the expression of PNPLA3 in a patient in need thereof comprising administering to the patient the composition of claim 39.

42. The method of claim 40 or claim 41, wherein the expression level of PNPLA3 in hepatocytes is reduced in the patient following administration of the RNAi construct as compared to the PNPLA3 expression level in a patient not receiving the RNAi construct.

43. The method of any one of claims 40-42, wherein the patient suffers from nonalcoholic fatty liver disease (NAFLD).

44. The method of claim 43, wherein the patient suffers from non-alcoholic steatohepatitis (NASH).

45. An RNAi construct of any one of claims 1-38 or a composition of claim 39 for use in the treatment of NAFLD.

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37555-1	113	AGCUGCUGC GGAUCAGG ACC{invAb}	1069	asgscugcUfgCfGfGf Afucaggaccs{invAb}	1699	AGGUCCUGAU CCGCAGCAGC UUU	2329	asGfsguccUf gauccgCfaGf cagcususu	2959
37556-1	115	CUGCUGCGG AUCAGGACC CG{invAb}	1070	csusgcugCfgGfAfUf Cfaggacccgs{invAb}	1700	UCGGGUCCUG AUCCGCAGCA GUU	2330	usCfsggguCf cugaucCfgCf agcagsusu	2960
37557-1	121	CGGAUCAG GACCCGAGC CGA{invAb}	1071	csgsgaucAfgGfAfCf Cfcgagccgas{invAb}	1701	AUCGGCUCGG GUCCUGAUCC GUU	2331	asUfscggcUf cgggucCfuGf auccgsusu	2961
37558-1	122	GGAUCAGG ACCCGAGCC GAU{invAb}	1072	gsgsaucaGfgAfCfCf Cfgagccgaus{invAb}	1702	AAUCGGCUCG GGUCCUGAUC CUU	2332	asAfsucggCf ucggguCfcUf gauccsusu	2962
37559-1	204	CAGAGCGCG GCUGGAGC UUG{invAb}	1073	csasgagcGfcGfGfCf Ufggagcuugs{invAb}	1703	ACAAGCUCCA GCCGCGCUCU GUU	2333	asCfsaagcUf ccagccGfcGf cucugsusu	2963
37560-1	205	AGAGCGCG GCUGGAGC UUGU{invAb}	1074	asgsagcgCfgGfCfUf Gfgagcuugus{invAb}	1704	AACAAGCUCC AGCCGCGCUC UUU	2334	asAfscaagCf uccagcCfgCf gcucususu	2964
37561-1	206	GAGCGCGGC UGGAGCUU GUC{invAb}	1075	gsasgcgcGfgCfUfGf Gfagcuugucs{invAb}	1705	AGACAAGCUC CAGCCGCGCU CUU	2335	asGfsacaaGf cuccagCfcGf cgcucsusu	2965

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37562-1	207	AGCGCGGCU GGAGCUUG UCC{invAb}	1076	asgscgcgGfcUfGfGf Afgcuuguccs{invAb}	1706	AGGACAAGCU CCAGCCGCGC UUU	2336	asGfsgacaAf gcuccaGfcCf gcgcususu	2966
37563-1	211	CGGCUGGA GCUUGUCCU UCG{invAb}	1077	csgsgcugGfaGfCfUf Ufguccuucgs{invAb}	1707	ACGAAGGACA AGCUCCAGCC GUU	2337	asCfsgaagGf acaagcUfcCf agccgsusu	2967
37564-1	212	GGCUGGAG CUUGUCCUU CGC{invAb}	1078	gsgscuggAfgCfUfUf Gfuccuucgcs{invAb}	1708	AGCGAAGGAC AAGCUCCAGC CUU	2338	asGfscgaaGf gacaagCfuCf cagccsusu	2968
37565-1	213	GCUGGAGC UUGUCCUUC GCG{invAb}	1079	gscsuggaGfcUfUfGf Ufccuucgcgs{invAb}	1709	ACGCGAAGGA CAAGCUCCAG CUU	2339	asCfsgcgaAf ggacaaGfcUf ccagcsusu	2969
37566-1	219	GCUUGUCCU UCGCGGGCU GC{invAb}	1080	gscsuuguCfcUfUfCf Gfcgggcugcs{invAb}	1710	AGCAGCCCGC GAAGGACAAG CUU	2340	asGfscagcCf cgcgaaGfgAf caagcsusu	2970
37567-1	220	CUUGUCCUU CGCGGGCUG CG{invAb}	1081	csusuguccCfuUfCfGf Cfgggcugcgs{invAb}	1711	ACGCAGCCCG CGAAGGACAA GUU	2341	asCfsgcagCf ccgcgaAfgGf acaagsusu	2971
37568-1	243	UCCUGGGCU UCUACCACG UC{invAb}	1082	uscscuggGfcUfUfCf Ufaccacgucs{invAb}	1712	AGACGUGGUA GAAGCCCAGG AUU	2342	asGfsacguGf guagaaGfcCf caggasusu	2972

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Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37569-1	244	CCUGGGCUU CUACCACGU CG{invAb}	1083	cscsugggCfuUfCfUf AfccacgucgsUf{invAb}	1713	ACGACGUGGU AGAAGCCCAG GUU	2343	asCfsgacgUf gguagaAfgCf ccaggsusu	2973
37570-1	245	CUGGGCUUC UACCACGUC GG{invAb}	1084	csusgggcUfuCfUfAf CfcacgucggsUf{invAb}	1714	ACCGACGUGG UAGAAGCCCA GUU	2344	asCfscgacGf ugguagAfaGf cccagsusu	2974
37571-1	246	UGGGCUUC UACCACGUC GGG{invAb}	1085	usgsgggcuUfcUfAfCf CfacgucgggsUf{invAb}	1715	ACCCGACGUG GUAGAAGCCC AUU	2345	asCfsccgaCf gugguaGfaAf gcccasusu	2975
37572-1	248	GGCUUCUAC CACGUCGGG GC{invAb}	1086	gsgscuucUfaCfCfAf CfgucggggcsUf{invAb}	1716	AGCCCCGACG UGGUAGAAGC CUU	2346	asGfsccccGf acgugGfuAf aagccsusu	2976
37573-1	249	GCUUCUACC ACGUCGGG GCG{invAb}	1087	gscsuucuAfcCfAfCf GfucggggcgsUf{invAb}	1717	UCGCCCCGAC GUGGUAGAAG CUU	2347	usCfsgcccCf gacgugGfuAf gaagcsusu	2977
37574-1	251	UUCUACCAC GUCGGGGC GAC{invAb}	1088	ususcuacCfaCfGfUfC fggggcgacsUf{invAb}	1718	AGUCGCCCCG ACGUGGUAGA AUU	2348	asGfsucgcCf ccgacgUfgGf uagaasusu	2978
37575-1	252	UCUACCACG UCGGGGCG ACC{invAb}	1089	uscsuaccAfcGfUfCf GfgggcgaccsUf{invAb}	1719	AGGUCGCCCC GACGUGGUAG AUU	2349	asGfsgucgCf cccgacGfuGf guagasusu	2979

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37576-1	253	CUACCACGU CGGGGCGAC CC{invAb}	1090	csusaccaCfgUfCfGfG fggcgaccs{invAb}	1720	AGGGUCGGCCC CGACGUGGGUA GUU	2350	asGfsggucGf ccccgaCfgUf gguagsusu	2980
37577-1	254	UACCACGUC GGGGCGACC CG{invAb}	1091	usasccacGfuCfGfGf Gfgcgacccgs{invAb}	1721	ACGGGUCGCC CCGACGUGGU AUU	2351	asCfsggguCf gccccgAfcGf ugguasusu	2981
37578-1	272	CGCUGCCUG AGCGAGCAC GC{invAb}	1092	csgscugcCfuGfAfGf Cfgagcacgcs{invAb}	1722	AGCGUGCUCG CUCAGGCAGC GUU	2352	asGfscgugCf ucgcucAfgGf cagcgsusu	2982
37579-1	281	AGCGAGCAC GCCCCGCAC CU{invAb}	1093	asgscgagCfaCfGfCfC fccgcaccus{invAb}	1723	AAGGUGCGGG GCGUGCUCGC UUU	2353	asAfsggugCf ggggcgUfgCf ucgcususu	2983
37580-1	291	CCCCGCACC UCCUCCGCG AC{invAb}	1094	cscscegcAfcCfUfCfC fuccgcgacs{invAb}	1724	AGUCGCGGAG GAGGUGCGGG GUU	2354	asGfsucgcGf gaggagGfuGf cggggsusu	2984
37581-1	293	CCGCACCUC CUCCGCGAC GC{invAb}	1095	cscsgcacCfuCfCfUfC fcgcgacgcs{invAb}	1725	AGCGUCGCGG AGGAGGUGCG GUU	2355	asGfscgucGf cggaggAfgGf ugcggsusu	2985
37582-1	294	CGCACCUCC UCCGCGACG CG{invAb}	1096	csgscaccUfcCfUfCfC fgcgacgcgs{invAb}	1726	ACGCGUCGCG GAGGAGGUGC GUU	2356	asCfsgcguCf gcggagGfaGf gugcgsusu	2986

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37583-1	302	CUCCGCGACGCGCGCAUGUU{invAb}	1097	csusccgcGfaCfGfCfCfGfcgcauguus{invAb}	1727	AAACAUGCGCGCGUCGCGGAGUU	2357	asAfsacauGfcgcgcgUfcGfcggagsusu	2987
37584-1	303	UCCGCGACGCGCGCAUGUUG{invAb}	1098	uscscgcgAfcGfCfGfCfgcauguugs{invAb}	1728	ACAACAUGCGCGCGUCGCGGAUU	2358	asCfsaacaUfgcgcgcGfuCfgcggasusu	2988
37585-1	305	CGCGACGCGCGCAUGUUGUU{invAb}	1099	csgscgacGfcGfCfCfGfCfauguuguus{invAb}	1729	AAACAACAUGCGCGCGUCGCGUU	2359	asAfsacaaCfaugcgcGfcGfucgcgsusu	2989
37586-1	306	GCGACGCGCGCAUGUUGUUC{invAb}	1100	gscsgacgCfgCfGfCfCfAfuguuguucs{invAb}	1730	AGAACAACAUGCGCGCGUCGCUU	2360	asGfsaacaAfcaugcgCfgCfgucgcsusu	2990
37587-1	307	CGACGCGCGCAUGUUGUUCG{invAb}	1101	csgsacgcGfcGfCfCfAfUfguuguucgs{invAb}	1731	ACGAACAACAUGCGCGCGUCGUU	2361	asCfsgaacAfacaugcGfcGfcgucgsusu	2991
37588-1	309	ACGCGCGCAUGUUGUUCGGC{invAb}	1102	ascsgcgcGfcAfUfUfGfUfuguucggcs{invAb}	1732	AGCCGAACAACAUGCGCGCGUUU	2362	asGfscgaAfcaacauGfcGfcgcgususu	2992
37589-1	329	GCUUCGGCCGGGCGCGUUGCA{invAb}	1103	gscsuucgGfcCfGfGfGfcgcguugcas{invAb}	1733	AUGCAACGCCCCGGCCGAAGCUU	2363	asUfsgcaaCfgccccgGfcCfgaagcsusu	2993

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37590-1	334	GGCCGGGGC GUUGCACU GCG{invAb}	1104	gsgsccggGfgCfGfUf Ufgcacugcgs{invAb}	1734	ACGCAGUGCA ACGCCCCCGGCC UU	2364	asCfsgcagUf gcaacgCfcCf cggccsusu	2994
37591-1	335	GCCGGGGCG UUGCACUGC GU{invAb}	1105	gscscgggGfcGfUfUf Gfcacugcgus{invAb}	1735	AACGCAGUGC AACGCCCCGG CUU	2365	asAfscgcaGf ugcaacGfcCf ccggcsusu	2995
37592-1	336	CCGGGGCGU UGCACUGCG UC{invAb}	1106	cscsggggCfgUfUfGf Cfacugcgucs{invAb}	1736	AGACGCAGUG CAACGCCCCG GUU	2366	asGfsacgcAf gugcaaCfgCf cccggsusu	2996
37593-1	337	CGGGGCGU UGCACUGCG UCG{invAb}	1107	csgsgggcGfuUfGfCf Afcugcgucgs{invAb}	1737	ACGACGCAGU GCAACGCCCC GUU	2367	asCfsgacgCf agugcaAfcGf cccgsusu	2997
37594-1	338	GGGGCGUU GCACUGCGU CGG{invAb}	1108	gsgsggcgUfuGfCfAf Cfugcgucggs{invAb}	1738	ACCGACGCAG UGCAACGCCC CUU	2368	asCfscgacGf cagugcAfaCf gcccsusu	2998
37595-1	339	GGGCGUUG CACUGCGUC GGC{invAb}	1109	gsgsgcguUfgCfAfCf Ufgcgucggcs{invAb}	1739	AGCCGACGCA GUGCAACGCC CUU	2369	asGfsccgaCf gcagugCfaAf cgcccsusu	2999
37596-1	340	GGCGUUGC ACUGCGUCG GCG{invAb}	1110	gsgscguuGfcAfCfUf Gfcgucggcgs{invAb}	1740	ACGCCGACGC AGUGCAACGC CUU	2370	asCfsgccgAf cgcaguGfcAf acgccsusu	3000

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37597-1	341	GCGUUGCAC UGCGUCGGC GU{invAb}	1111	gscsguugCfaCfUfGf Cfgucggcgus{invAb}	1741	AACGCCGACG CAGUGCAACG CUU	2371	asAfscgccGf acgcagUfgCf aacgcsusu	3001
37598-1	343	GUUGCACU GCGUCGGCG UCC{invAb}	1112	gsusugcaCfuGfCfGf Ufcggcguccs{invAb}	1742	AGGACGCCGA CGCAGUGCAA CUU	2372	asGfsgacgCf cgacgcAfgUf gcaacsusu	3002
37599-1	344	UUGCACUGC GUCGGCGUC CU{invAb}	1113	ususgcacUfgCfGfUf Cfggcguccus{invAb}	1743	AAGGACGCCG ACGCAGUGCA AUU	2373	asAfsggacGf ccgacgCfaGf ugcaasusu	3003
37600-1	347	CACUGCGUC GGCGUCCUC UC{invAb}	1114	csascugcGfuCfGfGf Cfguccucucs{invAb}	1744	AGAGAGGACG CCGACGCAGU GUU	2374	asGfsagagGf acgccgAfcGf cagugsusu	3004
37743-1	369	GUAUCCCGC UGGAGCAG ACU{invAb}	1115	gsusauccCfgCfUfGf Gfagcagacus{invAb}	1745	AAGUCUGCUC CAGCGGGAUA CUU	2375	asAfsgucuGf cuccagCfgGf gauacsusu	3005
37744-1	391	GCAGGUCCU CUCAGAUCU UG{invAb}	1116	gscsagguCfcUfCfUf Cfagaucuugs{invAb}	1746	ACAAGAUCUG AGAGGACCUG CUU	2376	asCfsaagaUf cugagaGfgAf ccugcsusu	3006
37745-1	392	CAGGUCCUC UCAGAUCU UGU{invAb}	1117	csasggucCfuCfUfCf Afgaucuugus{invAb}	1747	AACAAGAUCU GAGAGGACCU GUU	2377	asAfscaagAf ucugagAfgGf accugsusu	3007

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Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37746-1	411	UGCGGAAG GCCAGGAG UCGG{invAb}	1118	usgscggaAfgGfCfCf Afggagucggs{invAb}	1748	UCCGACUCCU GGCCUUCCGC AUU	2378	usCfscgacUf ccuggcCfuUf ccgcasusu	3008
37747-1	412	GCGGAAGG CCAGGAGUC GGA{invAb}	1119	gscsggaaGfgCfCfAf Gfgagucggas{invAb}	1749	UUCCGACUCC UGGCCUUCCG CUU	2379	usUfsccgaCf uccuggCfcUf uccgcsusu	3009
37748-1	413	CGGAAGGCC AGGAGUCG GAA{invAb}	1120	csgsgaagGfcCfAfGf Gfagucggaas{invAb}	1750	AUUCCGACUC CUGGCCUUCC GUU	2380	asUfsuccgAf cuccugGfcCf uuccgsusu	3010
37749-1	414	GGAAGGCC AGGAGUCG GAAC{invAb}	1121	gsgsaaggCfcAfGfGf Afgucggaacs{invAb}	1751	UGUUCCGACU CCUGGCCUUC CUU	2381	usGfsuuccGf acuccuGfgCf cuuccsusu	3011
37750-1	415	GAAGGCCA GGAGUCGG AACA{invAb}	1122	gsasaggcCfaGfGfAf Gfucggaacas{invAb}	1752	AUGUUCCGAC UCCUGGCCUU CUU	2382	asUfsguucCf gacuccUfgGf ccuucsusu	3012
37751-1	416	AAGGCCAG GAGUCGGA ACAU{invAb}	1123	asasggccAfgGfAfGf Ufcggaacaus{invAb}	1753	AAUGUUCCGA CUCCUGGCCU UUU	2383	asAfsuguuCf cgacucCfuGf gccuususu	3013
37752-1	419	GCCAGGAG UCGGAACA UUGG{invAb}	1124	gscscaggAfgUfCfGf Gfaacauuggs{invAb}	1754	ACCAAUGUUC CGACUCCUGG CUU	2384	asCfscaauGf uuccgaCfuCf cuggcsusu	3014

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Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37753-1	497	CUCCCGGCC AAUGUCCAC CA{invAb}	1125	csuscccgGfcCfcAfaAf Ufguccaccas{invAb}	1755	AUGGUGGACA UUGGCCGGGA GUU	2385	asUfsggugGf acauugGfcCf gggagsusu	3015
37754-1	555	UGUCUGAU GGGGAAAA CGUU{invAb}	1126	usgsucugAfuGfGfGf Gfaaaacguus{invAb}	1756	AAACGUUUUC CCCAUCAGAC AUU	2386	asAfsacguUf uuccccAfuCf agacasusu	3016
37755-1	556	GUCUGAUG GGGAAAAC GUUC{invAb}	1127	gsuscugaUfgGfGfGf Afaaacguucs{invAb}	1757	AGAACGUUUU CCCCAUCAGA CUU	2387	asGfsaacgUf uuucccCfaUf cagacsusu	3017
37756-1	557	UCUGAUGG GGAAAACG UUCU{invAb}	1128	uscsugauGfgGfGfAf Afaacguucus{invAb}	1758	AAGAACGUUU UCCCCAUCAG AUU	2388	asAfsgaacGf uuuuccCfcAf ucagasusu	3018
37757-1	560	GAUGGGGA AAACGUUC UGGU{invAb}	1129	gsasugggGfaAfAfAf Cfguucuggus{invAb}	1759	AACCAGAACG UUUUCCCCAU CUU	2389	asAfsccagAf acguuuUfcCf ccaucsusu	3019
37758-1	562	UGGGGAAA ACGUUCUG GUGU{invAb}	1130	usgsgggaAfaAfCfGf Ufucuggugus{invAb}	1760	AACACCAGAA CGUUUUCCCC AUU	2390	asAfscaccAf gaacguUfuUf ccccasusu	3020
37759-1	563	GGGGAAAA CGUUCUGG UGUC{invAb}	1131	gsgsggaaAfaCfGfUf Ufcuggugucs{invAb}	1761	AGACACCAGA ACGUUUUCCC CUU	2391	asGfsacacCfa gaacgUfuUfu ccccsusu	3021

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37760-1	564	GGGAAAAC GUUCUGGU GUCU{invAb}	1132	gsgsgaaaAfcGfUfUf Cfuggugucus{invAb}	1762	AAGACACCAG AACGUUUUCC CUU	2392	asAfsgacaCf cagaacGfuUf uucccsusu	3022
37761-1	567	AAAACGUU CUGGUGUC UGAC{invAb}	1133	asasaacgUfuCfUfGf Gfugucugacs{invAb}	1763	AGUCAGACAC CAGAACGUUU UUU	2393	asGfsucagAf caccagAfaCf guuuususu	3023
37762-1	568	AAACGUUC UGGUGUCU GACU{invAb}	1134	asasacguUfcUfGfGf Ufgucugacus{invAb}	1764	AAGUCAGACA CCAGAACGUU UUU	2394	asAfsgucaGf acaccaGfaAf cguuususu	3024
37763-1	590	CGGUCCAAA GACGAAGU CGU{invAb}	1135	csgsguccAfaAfGfAf Cfgaagucgus{invAb}	1765	AACGACUUCG UCUUUGGACC GUU	2395	asAfscgacUf ucgucuUfuGf gaccgsusu	3025
37764-1	591	GGUCCAAA GACGAAGU CGUG{invAb}	1136	gsgsuccaAfaGfAfCf Gfaagucgugs{invAb}	1766	ACACGACUUC GUCUUUGGAC CUU	2396	asCfsacgaCf uucgucUfuUf ggaccsusu	3026
37765-1	593	UCCAAAGAC GAAGUCGU GGA{invAb}	1137	uscscaaaGfaCfGfAfA fgucguggas{invAb}	1767	AUCCACGACU UCGUCUUUGG AUU	2397	asUfsccacGf acuucgUfcUf uuggasusu	3027
37766-1	595	CAAAGACG AAGUCGUG GAUG{invAb}	1138	csasaagaCfgAfAfGf Ufcguggaugs{invAb}	1768	ACAUCCACGA CUUCGUCUUU GUU	2398	asCfsauccAf cgacuuCfgUf cuuugsusu	3028

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37767-1	641	UUCUACAG UGGCCUUA UCCC{invAb}	1139	ususcuacAfgUfGfGf Cfcuuaucccs{invAb}	1769	AGGGAUAAGG CCACUGUAGA AUU	2399	asGfsggauAf aggccaCfuGf uagaasusu	3029
37768-1	660	CUCCUUCCU UCAGAGGC GUG{invAb}	1140	csusccuuCfcUfUfCf Afgaggcgugs{invAb}	1770	ACACGCCUCU GAAGGAAGGA GUU	2400	asCfsacgcCf ucugaaGfgAf aggagsusu	3030
37769-1	661	UCCUUCCUU CAGAGGCG UGC{invAb}	1141	uscscuucCfuUfCfAf Gfaggcgugcs{invAb}	1771	AGCACGCCUC UGAAGGAAGG AUU	2401	asGfscacgCf cucugaAfgGf aaggasusu	3031
37770-1	662	CCUUCCUUC AGAGGCGU GCG{invAb}	1142	cscsuuccUfuCfAfGf Afggcgugcgs{invAb}	1772	UCGCACGCCU CUGAAGGAAG GUU	2402	usCfsgcacGf ccucugAfaGf gaaggsusu	3032
37771-1	663	CUUCCUUCA GAGGCGUG CGA{invAb}	1143	csusuccuUfcAfGfAf Gfgcgugcgas{invAb}	1773	AUCGCACGCC UCUGAAGGAA GUU	2403	asUfscgcaCf gccucuGfaAf ggaagsusu	3033
37772-1	664	UUCCUUCAG AGGCGUGC GAU{invAb}	1144	ususccuuCfaGfAfGf Gfcgugcgaus{invAb}	1774	UAUCGCACGC CUCUGAAGGA AUU	2404	usAfsucgcAf cgccucUfgAf aggaasusu	3034
37773-1	665	UCCUUCAGA GGCGUGCG AUA{invAb}	1145	uscscuucAfgAfGfGf Cfgugcgauas{invAb}	1775	AUAUCGCACG CCUCUGAAGG AUU	2405	asUfsaucgCf acgccuCfuGf aaggasusu	3035

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37774-1	666	CCUUCAGAG GCGUGCGA UAU{invAb}	1146	cscsuucaGfaGfGfCf Gfugcgauaus{invAb}	1776	AAUAUCGCAC GCCUCUGAAG GUU	2406	asAfsuaucGf cacgccUfcUf gaaggsusu	3036
37775-1	667	CUUCAGAG GCGUGCGA UAUG{invAb}	1147	csusucagAfgGfCfGf Ufgcgauaugs{invAb}	1777	ACAUAUCGCA CGCCUCUGAA GUU	2407	asCfsauauCf gcacgcCfuCf ugaagsusu	3037
37776-1	669	UCAGAGGC GUGCGAUA UGUG{invAb}	1148	uscsagagGfcGfUfGf Cfgauaugugs{invAb}	1778	ACACAUAUCG CACGCCUCUG AUU	2408	asCfsacauAf ucgcacGfcCf ucugasusu	3038
37777-1	671	AGAGGCGU GCGAUAUG UGGA{invAb}	1149	asgsaggcGfuGfCfGf Afuauguggas{invAb}	1779	AUCCACAUAU CGCACGCCUC UUU	2409	asUfsccacAf uaucgcAfcGf ccucususu	3039
37778-1	673	AGGCGUGC GAUAUGUG GAUG{invAb}	1150	asgsgcguGfcGfAfUf Afuguggaugs{invAb}	1780	ACAUCCACAU AUCGCACGCC UUU	2410	asCfsauccAf cauaucGfcAf cgccususu	3040
37779-1	675	GCGUGCGA UAUGUGGA UGGA{invAb}	1151	gscsgugcGfaUfAfUf Gfuggauggas{invAb}	1781	AUCCAUCCAC AUAUCGCACG CUU	2411	asUfsccauCf cacauaUfcGf cacgcsusu	3041
37780-1	679	GCGAUAUG UGGAUGGA GGAG{invAb}	1152	gscsgauaUfgUfGfGf Afuggaggags{invAb}	1782	ACUCCUCCAU CCACAUAUCG CUU	2412	asCfsuccuCf cauccaCfaUf aucgcsusu	3042

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Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37781-1	698	GUGAGUGA CAACGUACC CUU{invAb}	1153	gsusgaguGfaCfAfAf Cfguacccuus{invAb}	1783	AAAGGGUACG UUGUCACUCA CUU	2413	asAfsagggUf acguugUfcAf cucacsusu	3043
37782-1	701	AGUGACAA CGUACCCUU CAU{invAb}	1154	asgsugacAfaCfGfUf Afcccuucaus{invAb}	1784	AAUGAAGGGU ACGUUGUCAC UUU	2414	asAfsugaaGf gguacgUfuGf ucacususu	3044
37783-1	702	GUGACAAC GUACCCUUC AUU{invAb}	1155	gsusgacaAfcGfUfAf Cfccuucauus{invAb}	1785	AAAUGAAGGG UACGUUGUCA CUU	2415	asAfsaugaAf ggguacGfuUf gucacsusu	3045
37784-1	703	UGACAACG UACCCUUCA UUG{invAb}	1156	usgsacaaCfgUfAfCfC fcuucauugs{invAb}	1786	UCAAUGAAGG GUACGUUGUC AUU	2416	usCfsaaugAf aggguaCfgUf ugucasusu	3046
37785-1	704	GACAACGU ACCCUUCAU UGA{invAb}	1157	gsascaacGfuAfCfCfC fuucauugas{invAb}	1787	AUCAAUGAAG GGUACGUUGU CUU	2417	asUfscaauGf aaggguAfcGf uugucsusu	3047
37786-1	705	ACAACGUAC CCUUCAUUG AU{invAb}	1158	ascsaacgUfaCfCfCfU fucauugaus{invAb}	1788	AAUCAAUGAA GGGUACGUUG UUU	2418	asAfsucaaUf gaagggUfaCf guugususu	3048
37787-1	706	CAACGUACC CUUCAUUG AUG{invAb}	1159	csasacguAfcCfCfUfU fcauugaugs{invAb}	1789	ACAUCAAUGA AGGGUACGUU GUU	2419	asCfsaucaAf ugaaggGfuAf cguugsusu	3049

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37788-1	708	ACGUACCCU UCAUUGAU GCC{invAb}	1160	ascsguacCfcUfUfCfA fuugaugccs{invAb}	1790	UGGCAUCAAU GAAGGGUACG UUU	2420	usGfsgcauCf aaugaaGfgGf uacgususu	3050
37789-1	756	AUGGGGAG UACGACAUC UGC{invAb}	1161	asusggggAfgUfAfCf Gfacaucugcs{invAb}	1791	AGCAGAUGUC GUACUCCCCA UUU	2421	asGfscagaUf gucguaCfuCf cccaususu	3051
37887-1	757	UGGGGAGU ACGACAUCU GCC{invAb}	1162	usgsgggaGfuAfCfGf Afcaucugccs{invAb}	1792	AGGCAGAUGU CGUACUCCCC AUU	2422	asGfsgcagAf ugucguAfcUf ccccasusu	3052
37888-1	762	AGUACGAC AUCUGCCCU AAA{invAb}	1163	asgsuacgAfcAfUfCf Ufgcccuaaas{invAb}	1793	AUUUAGGGCA GAUGUCGUAC UUU	2423	asUfsuuagGf gcagauGfuCf guacususu	3053
37889-1	764	UACGACAUC UGCCCUAAA GU{invAb}	1164	usascgacAfuCfUfGf Cfccuaaagus{invAb}	1794	AACUUUAGGG CAGAUGUCGU AUU	2424	asAfscuuuAf gggcagAfuGf ucguasusu	3054
37890-1	765	ACGACAUCU GCCCUAAAG UC{invAb}	1165	ascsgacaUfcUfGfCfC fcuaaagucs{invAb}	1795	UGACUUUAGG GCAGAUGUCG UUU	2425	usGfsacuuUf agggcaGfaUf gucgususu	3055
37891-1	766	CGACAUCUG CCCUAAAGU CA{invAb}	1166	csgsacauCfuGfCfCfC fuaaagucas{invAb}	1796	UUGACUUUAG GGCAGAUGUC GUU	2426	usUfsgacuUf uagggcAfgAf ugucgsusu	3056

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Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37892-1	767	GACAUCUGC CCUAAAGUC AA{invAb}	1167	gsascaucUfgCfCfCfU faaagucaas{invAb}	1797	AUUGACUUUA GGGCAGAUGU CUU	2427	asUfsugacUf uuagggCfaGf augucsusu	3057
37893-1	768	ACAUCUGCC CUAAAGUC AAG{invAb}	1168	ascsaucuGfcCfCfUfA faagucaags{invAb}	1798	ACUUGACUUU AGGGCAGAUG UUU	2428	asCfsuugaCf uuuaggGfcAf gaugususu	3058
37894-1	769	CAUCUGCCC UAAAGUCA AGU{invAb}	1169	csasucugCfcCfUfAf Afagucaagus{invAb}	1799	AACUUGACUU UAGGGCAGAU GUU	2429	asAfscuugAf cuuuagGfgCf agaugsusu	3059
37895-1	770	AUCUGCCCU AAAGUCAA GUC{invAb}	1170	asuscugcCfcUfAfAf Afgucaagucs{invAb}	1800	AGACUUGACU UUAGGGCAGA UUU	2430	asGfsacuuGf acuuuaGfgGf cagaususu	3060
37896-1	805	UGUGGACA UCACCAAGC UCA{invAb}	1171	usgsuggaCfaUfCfAf Cfcaagcucas{invAb}	1801	AUGAGCUUGG UGAUGUCCAC AUU	2431	asUfsgagcUf uggugaUfgU fccacasusu	3061
37897-1	832	CCUCUGCAC AGGGAACC UCU{invAb}	1172	cscsucugCfaCfAfGf Gfgaaccucus{invAb}	1802	UAGAGGUUCC CUGUGCAGAG GUU	2432	usAfsgaggUf ucccugUfgCf agaggsusu	3062
37898-1	866	GCUUUUGU CCCCCCGGA UCU{invAb}	1173	gscsuuuuGfuCfCfCf Cfccggaucus{invAb}	1803	AAGAUCCGGG GGGACAAAAG CUU	2433	asAfsgaucCf ggggggAfcA faaagcsusu	3063

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37899-1	867	CUUUUGUCC CCCCGGAUC UC{invAb}	1174	csusuuugUfcCfCfCf Cfcggaucucs{invAb}	1804	UGAGAUCCGG GGGGACAAAA GUU	2434	usGfsagauCf cgggggGfaCf aaaagsusu	3064
37900-1	868	UUUUGUCCC CCCGGAUCU CA{invAb}	1175	ususuuguCfcCfCfCf Cfggaucucas{invAb}	1805	UUGAGAUCCG GGGGGACAAA AUU	2435	usUfsgagaUf ccgggggGfgAf caaaasusu	3065
37901-1	869	UUUGUCCCC CCGGAUCUC AA{invAb}	1176	ususuguccCfcCfCfCf Gfgaucucaas{invAb}	1806	AUUGAGAUCC GGGGGGACAA AUU	2436	asUfsugagAf uccgggGfgGf acaaasusu	3066
37902-1	870	UUGUCCCCC CGGAUCUCA AG{invAb}	1177	ususguccCfcCfCfGf Gfaucucaags{invAb}	1807	ACUUGAGAUC CGGGGGGACA AUU	2437	asCfsuugaGf auccggGfgGf gacaasusu	3067
37903-1	878	CCGGAUCUC AAGGUGCU GGG{invAb}	1178	cscsggauCfuCfAfAf Gfgugcugggs{invAb}	1808	UCCCAGCACC UUGAGAUCCG GUU	2438	usCfsccagCf accuugAfgAf uccggsusu	3068
37904-1	886	CAAGGUGC UGGGAGAG AUAU{invAb}	1179	csasagguGfcUfGfGf Gfagagauaus{invAb}	1809	AAUAUCUCUC CCAGCACCUU GUU	2439	asAfsuaucUf cucccaGfcAf ccuugsusu	3069
37905-1	887	AAGGUGCU GGGAGAGA UAUG{invAb}	1180	asasgguGfcUfGfGfGf Afgagauaugs{invAb}	1810	ACAUAUCUCU CCCAGCACCU UUU	2440	asCfsauauCf ucucccAfgCf accususu	3070

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37906-1	889	GGUGCUGG GAGAGAUA UGCC{invAb}	1181	gsgsugcuGfgGfAfGf Afgauaugccs{invAb}	1811	AGGCAUAUCU CUCCCAGCACC UU	2441	asGfsgcauAf ucucucCfcAf gcaccsusu	3071
37907-1	893	CUGGGAGA GAUAUGCC UUCG{invAb}	1182	csusgggaGfaGfAfUf Afugccuucgs{invAb}	1812	UCGAAGGCAU AUCUCUCCCA GUU	2442	usCfsgaagGf cauaucUfcUf cccagsusu	3072
37908-1	894	UGGGAGAG AUAUGCCU UCGA{invAb}	1183	usgsgsgagAfgAfUfAf Ufgccuucgas{invAb}	1813	AUCGAAGGCA UAUCUCUCCC AUU	2443	asUfsgcgaaGf gcauauCfuCf ucccasusu	3073
37909-1	895	GGGAGAGA UAUGCCUUC GAG{invAb}	1184	gsgsgagaGfaUfAfUf Gfccuucgags{invAb}	1814	ACUCGAAGGC AUAUCUCUCC CUU	2444	asCfsucgaAf ggcauaUfcUf cucccsusu	3074
37910-1	896	GGAGAGAU AUGCCUUCG AGG{invAb}	1185	gsgsagagAfuAfUfGf Cfcuucgaggs{invAb}	1815	UCCUCGAAGG CAUAUCUCUC CUU	2445	usCfscucgAf aggcauAfuCf ucuccsusu	3075
37911-1	898	AGAGAUAU GCCUUCGAG GAU{invAb}	1186	asgsagauAfuGfCfCf Ufucgaggaus{invAb}	1816	UAUCCUCGAA GGCAUAUCUC UUU	2446	usAfsuccuCf gaaggcAfuAf ucucususu	3076
37912-1	899	GAGAUAUG CCUUCGAGG AUA{invAb}	1187	gsasgauaUfgCfCfUf Ufcgaggauas{invAb}	1817	AUAUCCUCGA AGGCAUAUCU CUU	2447	asUfsauccUf cgaaggCfaUf aucucsusu	3077

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37913-1	902	AUAUGCCU UCGAGGAU AUUU{invAb}	1188	asusaugcCfuUfCfGf Afggauauuus{invAb}	1818	AAAAUAUCCU CGAAGGCAUA UUU	2448	asAfsauaUf ccucgaAfgGf cauaususu	3078
37914-1	904	AUGCCUUCG AGGAUAUU UGG{invAb}	1189	asusgccuUfcGfAfGf Gfauauuuggs{invAb}	1819	UCCAAAUAUC CUCGAAGGCA UUU	2449	usCfscaaaUf auccucGfaAf ggcaususu	3079
37915-1	905	UGCCUUCGA GGAUAUUU GGA{invAb}	1190	usgsccuuCfgAfGfGf Afuauuuggas{invAb}	1820	AUCCAAAUAU CCUCGAAGGC AUU	2450	asUfsccaaAf uauccuCfgAf aggcasusu	3080
37917-1	939	UGGAAGAG AAGGGCAU CUGC{invAb}	1191	usgsgaagAfgAfAfGf Gfgcaucugcs{invAb}	1821	UGCAGAUGCC CUUCUCUUCC AUU	2451	usGfscagaUf gcccuuCfuCf uuccasusu	3081
37919-1	1094	CUGCUAGAC CACCUGCGU CU{invAb}	1192	csusgcuaGfaCfCfAfC fcugcgucus{invAb}	1822	AAGACGCAGG UGGUCUAGCA GUU	2452	asAfsgacgCf agguggUfcUf agcagsusu	3082
37920-1	1101	ACCACCUGC GUCUCAGCA UC{invAb}	1193	ascscaccUfgCfGfUfC fucagcaucs{invAb}	1823	AGAUGCUGAG ACGCAGGUGG UUU	2453	asGfsaugcUf gagacgCfaGf guggususu	3083
37921-1	1104	ACCUGCGUC UCAGCAUCC UG{invAb}	1194	ascscugcGfuCfUfCf Afgcauccugs{invAb}	1824	ACAGGAUGCU GAGACGCAGG UUU	2454	asCfsaggaUf gcugagAfcGf caggususu	3084

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Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37923-1	1121	CUGCCCUGG GAUGAGAG CAU{invAb}	1195	csusgcccUfgGfGfAf Ufgagagcaus{invAb}	1825	AAUGCUCUCA UCCCAGGGCA GUU	2455	asAfsugcuCf ucauccCfaGf ggcagsusu	3085
37924-1	1125	CCUGGGAU GAGAGCAU CCUG{invAb}	1196	cscsugggAfuGfAfGf Afgcauccugs{invAb}	1826	ACAGGAUGCU CUCAUCCCAG GUU	2456	asCfsaggaUf gcucucAfuCf ccaggsusu	3086
37926-1	1200	GUGGAUAC AUGAGCAA GAUU{invAb}	1197	gsusggauAfcAfUfGf Afgcaagauus{invAb}	1827	AAAUCUUGCU CAUGUAUCCA CUU	2457	asAfsaucuUf gcucauGfuAf uccacsusu	3087
37927-1	1201	UGGAUACA UGAGCAAG AUUU{invAb}	1198	usgsgauaCfaUfGfAf Gfcaagauuus{invAb}	1828	AAAAUCUUGC UCAUGUAUCC AUU	2458	asAfsaaucUf ugcucaUfgUf auccasusu	3088
37929-1	1213	CAAGAUUU GCAACUUGC UAC{invAb}	1199	csasagauUfuGfCfAf Afcuugcuacs{invAb}	1829	AGUAGCAAGU UGCAAAUCUU GUU	2459	asGfsuagcAf aguugcAfaAf ucuugsusu	3089
37930-1	1219	UUGCAACU UGCUACCCA UUA{invAb}	1200	ususgcaaCfuUfGfCf Ufacccauuas{invAb}	1830	AUAAUGGGUA GCAAGUUGCA AUU	2460	asUfsaaugGf guagcaAfgUf ugcaasusu	3090
37932-1	1220	UGCAACUU GCUACCCAU UAG{invAb}	1201	usgscaacUfuGfCfUf Afcccauuags{invAb}	1831	ACUAAUGGGU AGCAAGUUGC AUU	2461	asCfsuaauGf gguagcAfaGf uugcasusu	3091

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37841-1	1221	GCAACUUGC UACCCAUUA GG{invAb}	1202	gscsaacuUfgCfUfAf Cfccauuaggs{invAb}	1832	UCCUAAUGGG UAGCAAGUUG CUU	2462	usCfscuaaUf ggguagCfaAf guugcsusu	3092
37842-1	1223	AACUUGCU ACCCAUUAG GAU{invAb}	1203	asascuugCfuAfCfCfC fauuaggaus{invAb}	1833	UAUCCUAAUG GGUAGCAAGU UUU	2463	usAfsuccuAf augguAfgCf aaguususu	3093
37843-1	1224	ACUUGCUAC CCAUUAGG AUA{invAb}	1204	ascsuugcUfaCfCfCfA fuuaggauas{invAb}	1834	UUAUCCUAAU GGGUAGCAAG UUU	2464	usUfsauccUf aaugggUfaGf caagususu	3094
37844-1	1225	CUUGCUACC CAUUAGGA UAA{invAb}	1205	csusugcuAfcCfCfAf Ufuaggauaas{invAb}	1835	AUUAUCCUAA UGGGUAGCAA GUU	2465	asUfsuaucCf uaauggGfuAf gcaagsusu	3095
37845-1	1226	UUGCUACCC AUUAGGAU AAU{invAb}	1206	ususgcuaCfcCfAfUf Ufaggauaaus{invAb}	1836	AAUUAUCCUA AUGGGUAGCA AUU	2466	asAfsuuauCf cuaaugGfgUf agcaasusu	3096
37846-1	1280	GAAUCUGCC AUUGCGAU UGU{invAb}	1207	gsasaucuGfcCfAfUf Ufgcgauugus{invAb}	1837	AACAAUCGCA AUGGCAGAUU CUU	2467	asAfscaauCf gcaaugGfcAf gauucsusu	3097
37847-1	1289	AUUGCGAU UGUCCAGA GACU{invAb}	1208	asusugcgAfuUfGfUf Cfcagagacus{invAb}	1838	AAGUCUCUGG ACAAUCGCAA UUU	2468	asAfsgucuCf uggacaAfuCf gcaaususu	3098

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37848-1	1296	UUGUCCAG AGACUGGU GACA{invAb}	1209	ususguccAfgAfGfAf Cfugugacas{invAb}	1839	AUGUCACCAG UCUCUGGACA AUU	2469	asUfsgucaCf cagucuCfuGf gacaasusu	3099
37849-1	1300	CCAGAGACU GGUGACAU GGC{invAb}	1210	cscsagagAfcUfGfGf Ufgacauggcs{invAb}	1840	AGCCAUGUCA CCAGUCUCUG GUU	2470	asGfsccauGf ucaccaGfuCf ucuggsusu	3100
37850-1	1310	GUGACAUG GCUUCCAGA UAU{invAb}	1211	gsusgacaUfgGfCfUf Ufccagauaus{invAb}	1841	AAUAUCUGGA AGCCAUGUCA CUU	2471	asAfsuaucUf ggaagcCfaUf gucacsusu	3101
37851-1	1311	UGACAUGG CUUCCAGAU AUG{invAb}	1212	usgsacauGfgCfUfUf Cfcagauaugs{invAb}	1842	ACAUAUCUGG AAGCCAUGUC AUU	2472	asCfsauauCf uggaagCfcAf ugucasusu	3102
37852-1	1312	GACAUGGC UUCCAGAU AUGC{invAb}	1213	gsascaugGfcUfUfUfCf Cfagauaugcs{invAb}	1843	AGCAUAUCUG GAAGCCAUGU CUU	2473	asGfscauaUf cuggaaGfcCf augucsusu	3103
37853-1	1317	GGCUUCCAG AUAUGCCCG AC{invAb}	1214	gsgscuucCfaGfAfUf Afugcccgacs{invAb}	1844	AGUCGGGCAU AUCUGGAAGC CUU	2474	asGfsucggGf cauaucUfgGf aagccsusu	3104
37854-1	1318	GCUUCCAGA UAUGCCCGA CG{invAb}	1215	gscsuuccAfgAfUfAf Ufgcccgacgs{invAb}	1845	UCGUCGGGCA UAUCUGGAAG CUU	2475	usCfsgucgGf gcauauCfuGf gaagcsusu	3105

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37855-1	1319	CUUCCAGAU AUGCCCGAC GA{invAb}	1216	csusuccaGfaUfAfUf Gfcccgacgas{invAb}	1846	AUCGUCGGGC AUAUCUGGAA GUU	2476	asUfscgucGf ggcauaUfcUf ggaagsusu	3106
37856-1	1320	UUCCAGAU AUGCCCGAC GAU{invAb}	1217	ususccagAfuAfUfGf Cfccgacgaus{invAb}	1847	AAUCGUCGGG CAUAUCUGGA AUU	2477	asAfsucguCf gggcauAfuCf uggaasusu	3107
37857-1	1321	UCCAGAUA UGCCCGACG AUG{invAb}	1218	uscscagaUfaUfGfCfC fcgacgaugs{invAb}	1848	ACAUCGUCGG GCAUAUCUGG AUU	2478	asCfsaucgUf cgggcaUfaUf cuggasusu	3108
37858-1	1322	CCAGAUAU GCCCGACGA UGU{invAb}	1219	cscsagauAfuGfCfCfC fgacgaugus{invAb}	1849	AACAUCGUCG GGCAUAUCUG GUU	2479	asAfscaucGf ucgggcAfuAf ucuggsusu	3109
37859-1	1352	CAGUGGU GACCUCACA GGU{invAb}	1220	csasguggGfuGfAfCf Cfucacaggus{invAb}	1850	AACCUGUGAG GUCACCCACU GUU	2480	asAfsccugUf gaggucAfcCf cacugsusu	3110
37860-1	1399	CCCCGCCUC CAGGUCCCA AA{invAb}	1221	cscsccgcCfuCfCfAfG fgucccaaas{invAb}	1851	AUUUGGGACC UGGAGGCGGG GUU	2481	asUfsuuggGf accuggAfgGf cggggsusu	3111
37861-1	1402	CGCCUCCAG GUCCCAAAU GC{invAb}	1222	csgsccucCfaGfGfUfC fccaaaugcs{invAb}	1852	AGCAUUUGGG ACCUGGAGGC GUU	2482	asGfscauuUf gggaccUfgGf aggcgsusu	3112

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37862-1	1431	GCCAACAGG CCUCCCCAU GC{invAb}	1223	gscscaacAfgGfCfCfU fcccaugcs{invAb}	1853	UGCAUGGGGA GGCCUGUUGG CUU	2483	usGfscaugGf ggaggcCfuGf uuggcsusu	3113
37863-1	1596	GGCUCUCCA CCUUUCCCA GU{invAb}	1224	gsgscucuCfcAfCfCf Ufuucccagus{invAb}	1854	AACUGGGAAA GGUGGAGAGC CUU	2484	asAfscuggGf aaagguGfgAf gagccsusu	3114
37864-1	1602	CCACCUUUC CCAGUUUU UCA{invAb}	1225	cscsaccuUfuCfCfCfA fguuuuucas{invAb}	1855	AUGAAAAACU GGGAAAGGUG GUU	2485	asUfsgaaaAf acugggAfaAf gguggsusu	3115
37865-1	1603	CACCUUUCC CAGUUUUU CAC{invAb}	1226	csasccuuUfcCfCfAfG fuuuuucacs{invAb}	1856	AGUGAAAAAC UGGGAAAGGU GUU	2486	asGfsugaaAf aacuggGfaAf aggugsusu	3116
37866-1	1604	ACCUUUCCC AGUUUUUC ACU{invAb}	1227	ascscuuuCfcCfAfGf Ufuuuucacus{invAb}	1857	UAGUGAAAAA CUGGGAAAGG UUU	2487	usAfsgugaAf aaacugGfgAf aagggususu	3117
37867-1	1666	AUUCUUUC AGAGGUGC UAAA{invAb}	1228	asusucuuUfcAfGfAf Gfgugcuaaas{invAb}	1858	AUUUAGCACC UCUGAAAGAA UUU	2488	asUfsuuagCf accucuGfaAf agaaususu	3118
37868-1	1754	CCAGCCUCU GAGCUGAG UUG{invAb}	1229	cscsagccUfcUfGfAf Gfcugaguugs{invAb}	1859	ACAACUCAGC UCAGAGGCUG GUU	2489	asCfsaacuCfa gcucaGfaGfg cuggsusu	3119

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37869-1	1757	GCCUCUGAG CUGAGUUG GUU{invAb}	1230	gscscucuGfaGfCfUf Gfaguuggguus{invAb}	1860	AAACCAACUC AGCUCAGAGG CUU	2490	asAfsaccaAf cucagcUfcAf gaggcsusu	3120
37870-1	1760	UCUGAGCU GAGUUGGU UUUA{invAb}	1231	uscsugagCfuGfAfGf Ufuggguuuas{invAb}	1861	AUAAAACCAA CUCAGCUCAG AUU	2491	asUfsaaaaCfc aacucAfgCfu cagasusu	3121
37871-1	1763	GAGCUGAG UUGGUUUU AUGA{invAb}	1232	gsasgcugAfgUfUfGf Gfuuuuaugas{invAb}	1862	UUCAUAAAAC CAACUCAGCU CUU	2492	usUfscauaAf aaccaaCfuCf agcucsusu	3122
37872-1	1764	AGCUGAGU UGGUUUUA UGAA{invAb}	1233	asgscugaGfuUfGfGf Ufuuuaugaas{invAb}	1863	UUUCAUAAAA CCAACUCAGC UUU	2493	usUfsucauAf aaaccaAfcUf cagcususu	3123
37873-1	1765	GCUGAGUU GGUUUUAU GAAA{invAb}	1234	gscsugagUfuGfGfUf Ufuuaugaaas{invAb}	1864	UUUUCAUAAA ACCAACUCAG CUU	2494	usUfsuucaUf aaaaccAfaCf ucagcsusu	3124
37874-1	1771	UUGGUUUU AUGAAAAG CUAG{invAb}	1235	ususgguuUfuAfUfUfGf Afaaagcuags{invAb}	1865	ACUAGCUUUU CAUAAAACCA AUU	2495	asCfsuagcUf uuucauAfaAf accaasusu	3125
37875-1	1775	UUUUAUGA AAAGCUAG GAAG{invAb}	1236	ususuuauGfaAfAfAf Gfcuaggaags{invAb}	1866	ACUUCCUAGC UUUUCAUAAA AUU	2496	asCfsuuccUf agcuuuUfcAf uaaaasusu	3126

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37876-1	1851	AAUUCAGC UGGUUGGG AAAU{invAb}	1237	asasuucaGfcUfGfGf Ufugggaaaus{invAb}	1867	AAUUUCCCAA CCAGCUGAAU UUU	2497	asAfsuuucCf caaccaGfcUf gaauususu	3127
37877-1	1852	AUUCAGCU GGUUGGGA AAUG{invAb}	1238	asusucagCfuGfGfUf Ufgggaaaugs{invAb}	1868	UCAUUUCCCA ACCAGCUGAA UUU	2498	usCfsauuuCf ccaaccAfgCf ugaaususu	3128
37878-1	1855	CAGCUGGU UGGGAAAU GACA{invAb}	1239	csasgcugGfuUfGfGf Gfaaaugacas{invAb}	1869	AUGUCAUUUC CCAACCAGCU GUU	2499	asUfsgucaUf uucccaAfcCf agcugsusu	3129
37879-1	1857	GCUGGUUG GGAAAUGA CACC{invAb}	1240	gscsugguUfgGfGfAf Afaugacaccs{invAb}	1870	UGGUGUCAUU UCCCAACCAG CUU	2500	usGfsguguCf auuuccCfaAf ccagcsusu	3130
37880-1	1890	CAGAGGGU CCCUUACUG ACU{invAb}	1241	csasgaggGfuCfCfCf Ufuacugacus{invAb}	1871	AAGUCAGUAA GGGACCCUCU GUU	2501	asAfsgucaGf uaagggAfcCf cucugsusu	3131
37881-1	1917	GGCCCUAUU AAUGGUCA GAC{invAb}	1242	gsgscccuAfuUfAfAf Ufggucagacs{invAb}	1872	AGUCUGACCA UUAAUAGGGC CUU	2502	asGfsucugAf ccauuaAfuAf gggccsusu	3132
37882-1	1918	GCCCUAUUA AUGGUCAG ACU{invAb}	1243	gscsccuaUfuAfAfUf Gfgucagacus{invAb}	1873	AAGUCUGACC AUUAAUAGGG CUU	2503	asAfsgucuGf accauuAfaUf agggcsusu	3133

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37883-1	2012	AUGUGUGA UCUUGUGG GGUG{invAb}	1244	asusguguGfaUfCfUf Ufgugggugs{invAb}	1874	ACACCCCACA AGAUCACACA UUU	2504	asCfsacccCfa caagaUfcAfc acaususu	3134
37884-1	2013	UGUGUGAU CUUGUGGG GUGG{invAb}	1245	usgsugugAfuCfUfUf Gfugggguggs{invAb}	1875	UCCACCCCACA AGAUCACACA UU	2505	usCfscaccCfc acaagAfuCfa cacasusu	3135
37885-1	2014	GUGUGAUC UUGUGGGG UGGA{invAb}	1246	gsusgugaUfcUfUfGf Ufgggguggas{invAb}	1876	AUCCACCCCAC AAGAUCACAC UU	2506	asUfsccacCfc cacaaGfaUfc acacsusu	3136
37886-1	2197	AACACCUUU UUCACCUAA CU{invAb}	1247	asascaccUfuUfUfUfC faccuaacus{invAb}	1877	UAGUUAGGUG AAAAAGGUGU UUU	2507	usAfsguuaGf gugaaaAfaGf guguususu	3137
38207-1	112	GAGCUGCU GCGGAUCA GGAC{invAb}	1248	gsasgcugCfuGfCfGf Gfaucaggacs{invAb}	1878	AGUCCUGAUC CGCAGCAGCU CUU	2508	asGfsuccuGf auccgcAfgCf agcucsusu	3138
38208-1	763	GUACGACA UCUGCCCUA AAG{invAb}	1249	gsusacgaCfaUfCfUf Gfcccuaaags{invAb}	1879	ACUUUAGGGC AGAUGUCGUA CUU	2509	asCfsuuuaGf ggcagaUfgUf cguacsusu	3139
38209-1	1095	UGCUAGACC ACCUGCGUC UC{invAb}	1250	usgscuagAfcCfAfCf Cfugcgucucs{invAb}	1880	UGAGACGCAG GUGGUCUAGC AUU	2510	usGfsagacGf caggugGfuCf uagcasusu	3140

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
38210-1	1189	GAAAGACA AAGGUGGA UACA{invAb}	1251	gsasaagaCfaAfAfGf Gfuggauacas{invAb}	1881	AUGUAUCCAC CUUUGUCUUU CUU	2511	asUfsguauCf caccuuUfgUf cuuucsusu	3141
38211-1	1210	GAGCAAGA UUUGCAAC UUGC{invAb}	1252	gsasgcaaGfaUfUfUf Gfcaacuugcs{invAb}	1882	AGCAAGUUGC AAAUCUUGCU CUU	2512	asGfscaagUf ugcaaaUfcUf ugcucsusu	3142
38212-1	1217	AUUUGCAA CUUGCUACC CAU{invAb}	1253	asusuugcAfaCfUfUf Gfcuacccaus{invAb}	1883	AAUGGGUAGC AAGUUGCAAA UUU	2513	asAfsugggUf agcaagUfuGf caaaususu	3143
38213-1	897	GAGAGAUA UGCCUUCGA GGA{invAb}	1254	gsasgagaUfaUfGfCf Cfuucgaggas{invAb}	1884	AUCCUCGAAG GCAUAUCUCU CUU	2514	asUfsccucGf aaggcaUfaUf cucucsusu	3144
38214-1	1092	AGCUGCUA GACCACCUG CGU{invAb}	1255	asgscugcUfaGfAfCf Cfaccugcgus{invAb}	1885	AACGCAGGUG GUCUAGCAGC UUU	2515	asAfscgcaGf guggucUfaGf cagcususu	3145
38215-1	2198	ACACCUUUU UCACCUAAC UA{invAb}	1256	ascsaccuUfuUfUfCf Afccuaacuas{invAb}	1886	UUAGUUAGGU GAAAAAGGUG UUU	2516	usUfsaguuAf ggugaaAfaAf ggugususu	3146
38216-1	2199	CACCUUUUU CACCUAACU AA{invAb}	1257	csasccuuUfuUfCfAf Cfcuaacuaas{invAb}	1887	UUUAGUUAGG UGAAAAAGGU GUU	2517	usUfsuaguUf aggugaAfaAf aggugsusu	3147

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
38217-1	2200	ACCUUUUUC ACCUAACUA AA{invAb}	1258	ascscuuuUfuCfAfCf Cfuaacuaaas{invAb}	1888	UUUUAGUUAG GUGAAAAAGG UUU	2518	usUfsuuagUf uaggugAfaAf aaggususu	3148
38218-1	2201	CCUUUUUCA CCUAACUAA AA{invAb}	1259	cscsuuuuUfcAfCfCf Ufaacuaaaas{invAb}	1889	AUUUUAGUUA GGUGAAAAAG GUU	2519	asUfsuuuaGf uuagguGfaAf aaaggsusu	3149
38219-1	2202	CUUUUUCAC CUAACUAA AAU{invAb}	1260	csusuuuuCfaCfCfUf Afacuaaaaus{invAb}	1890	UAUUUUUAGUU AGGUGAAAAA GUU	2520	usAfsuuuuAf guuaggUfgA faaaagsusu	3150
38220-1	2204	UUUUCACCU AACUAAAA UAA{invAb}	1261	ususuucaCfcUfAfAf Cfuaaaauaas{invAb}	1891	AUUAUUUUAG UUAGGUGAAA AUU	2521	asUfsuauuUf uaguuaGfgUf gaaaasusu	3151
38221-1	2216	UAAAAUAA UGUUUAAA GAGU{invAb}	1262	usasaaauAfaUfGfUf Ufuaaagagus{invAb}	1892	AACUCUUUAA ACAUUAUUUU AUU	2522	asAfscucuUf uaaacaUfuAf uuuuasusu	3152
40777-1	3775	UGGUCUGC GUUCUUUU UUUC{invAb}	1263	usgsgucuGfcGfUfUf Cfuuuuuuucs{invAb}	1893	AGAAAAAAAG AACGCAGACC AUU	2523	asGfsaaaaAf aagaacGfcAf gaccasusu	3153
40778-1	3776	GGUCUGCG UUCUUUUU UUCU{invAb}	1264	gsgsucugCfgUfUfCf Ufuuuuuucus{invAb}	1894	AAGAAAAAAA GAACGCAGAC CUU	2524	asAfsgaaaAf aaagaaCfgCf agaccsusu	3154

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40779-1	3793	UCUCCUUGC AUCUUCUCA UU{invAb}	1265	uscsuccuUfgCfAfUf CfuucucauusU{invAb}	1895	AAAUGAGAAG AUGCAAGGAG AUU	2525	asAfsaugaGf aagaugCfaAf ggagasusu	3155
40780-1	3794	CUCCUUGCA UCUUCUCAU UC{invAb}	1266	csusccuuGfcAfUfCf UfucucauucsU{invAb}	1896	AGAAUGAGAA GAUGCAAGGA GUU	2526	asGfsaaugAf gaagauGfcAf aggagsusu	3156
40781-1	3795	UCCUUGCAU CUUCUCAUU CU{invAb}	1267	uscscuugCfaUfCfUf UfcucauucusU{invAb}	1897	AAGAAUGAGA AGAUGCAAGG AUU	2527	asAfsgaauGf agaagaUfgCf aaggasusu	3157
40782-1	3796	CCUUGCAUC UUCUCAUUC UC{invAb}	1268	cscsuugcAfuCfUfUf CfucauucucsU{invAb}	1898	AGAGAAUGAG AAGAUGCAAG GUU	2528	asGfsagaaUf gagaagAfuGf caaggsusu	3158
40783-1	3813	CUCUGAUCA CCCCAACCU CU{invAb}	1269	csuscugaUfcAfCfCfC fcaaccucusU{invAb}	1899	AAGAGGUUGG GGUGAUCAGA GUU	2529	asAfsgaggUf ugggguGfaU fcagagsusu	3159
40784-1	3820	CACCCCAAC CUCUCUCUG UC{invAb}	1270	csascccccAfaCfCfUfUfC fucucugucsU{invAb}	1900	AGACAGAGAG AGGUUGGGGU GUU	2530	asGfsacagAf gagaggUfuGf gggugsusu	3160
40785-1	3851	GCCAGCCUU GAUGGAGA CAA{invAb}	1271	gscscagcCfuUfGfAf UfggagacaasU{invAb}	1901	AUUGUCUCCA UCAAGGCUGG CUU	2531	asUfsugucUf ccaucaAfgGf cuggcsusu	3161

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40786-1	3853	CAGCCUUGA UGGAGACA AGC{invAb}	1272	csasgccuUfgAfUfGf Gfagacaagcs{invAb}	1902	AGCUUGUCUC CAUCAAGGCU GUU	2532	asGfscuugUf cuccauCfaAf ggcugsusu	3162
40787-1	3854	AGCCUUGA UGGAGACA AGCC{invAb}	1273	asgsccuuGfaUfGfGf Afgacaagccs{invAb}	1903	AGGCUUGUCU CCAUCAAGGC UUU	2533	asGfsgcuuGf ucuccaUfcAf aggcususu	3163
40788-1	3857	CUUGAUGG AGACAAGCC CUU{invAb}	1274	csusugauGfgAfGfAf Cfaagcccuus{invAb}	1904	AAAGGGCUUG UCUCCAUCAA GUU	2534	asAfsagggCf uugucuCfcAf ucaagsusu	3164
40789-1	3858	UUGAUGGA GACAAGCCC UUG{invAb}	1275	ususgaugGfaGfAfCf Afagcccuugs{invAb}	1905	UCAAGGGCUU GUCUCCAUCA AUU	2535	usCfsaaggGf cuugucUfcCf aucaasusu	3165
40790-1	3860	GAUGGAGA CAAGCCCUU GAG{invAb}	1276	gsasuggaGfaCfAfAf Gfcccuugags{invAb}	1906	UCUCAAGGGC UUGUCUCCCAU CUU	2536	usCfsucaaGf ggcuugUfcUf ccaucsusu	3166
40791-1	3862	UGGAGACA AGCCCUUGA GAC{invAb}	1277	usgsgagaCfaAfGfCf Cfcuugagacs{invAb}	1907	AGUCUCAAGG GCUUGUCUCC AUU	2537	asGfsucucAf agggcuUfgUf cuccasusu	3167
40792-1	3920	CAAGGUCA GUGUAAUA UGAC{invAb}	1278	csasagguCfaGfUfGf Ufaauaugacs{invAb}	1908	AGUCAUAUUA CACUGACCUU GUU	2538	asGfsucauAf uuacacUfgAf ccuugsusu	3168

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40793-1	3921	AAGGUCAG UGUAAUAU GACU{invAb}	1279	asasggucAfgUfGfUf Afauaugacus{invAb}	1909	AAGUCAUAUU ACACUGACCU UUU	2539	asAfsgucaUf auuacaCfuGf accuususu	3169
40794-1	3923	GGUCAGUG UAAUAUGA CUGA{invAb}	1280	gsgsucagUfgUfAfAf Ufaugacugas{invAb}	1910	AUCAGUCAUA UUACACUGAC CUU	2540	asUfscaguCf auauuaCfaCf ugaccsusu	3170
40795-1	3958	UUUUUUCU AUUUAUGC AUUU{invAb}	1281	ususuuuuCfuAfUfUf Ufaugcauuus{invAb}	1911	AAAAUGCAUA AAUAGAAAAA AUU	2541	asAfsaaugCf auaaauAfgAf aaaaasusu	3171
40796-1	4006	GUGUGCUC AAACUGUU AAAU{invAb}	1282	gsusgugcUfcAfAfAf Cfuguuaaaus{invAb}	1912	AAUUUAACAG UUUGAGCACA CUU	2542	asAfsuuuaAf caguuuGfaGf cacacsusu	3172
40797-1	4020	UUAAAUGU UGGAAAAG AAAG{invAb}	1283	ususaaaauGfuUfGfGf Afaaagaaags{invAb}	1913	UCUUUCUUUU CCAACAUUUA AUU	2543	usCfsuuucUf uuuccaAfcAf uuuaasusu	3173
40798-1	4095	CAGACAAA GCACUUGAC UGA{invAb}	1284	csasgacaAfaGfCfAfC fuugacugas{invAb}	1914	AUCAGUCAAG UGCUUUGUCU GUU	2544	asUfscaguCf aagugcUfuUf gucugsusu	3174
40799-1	4129	UAAAGGAA ACGGGUUC UAGG{invAb}	1285	usasaaggAfaAfCfGf Gfguucuaggs{invAb}	1915	ACCUAGAACC CGUUUCCUUU AUU	2545	asCfscuagAf acccguUfuCf cuuuasusu	3175

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40800-1	4130	AAAGGAAA CGGGUUCU AGGG{invAb}	1286	asasaggaAfaCfGfGf Gfuucuagggs{invAb}	1916	UCCCUAGAAC CCGUUUCCUU UUU	2546	usCfsccuaGf aacccgUfuUf ccuuususu	3176
40801-1	4132	AGGAAACG GGUUCUAG GGAC{invAb}	1287	asgsgaaaCfgGfGfUf Ufcuagggacs{invAb}	1917	UGUCCCUAGA ACCCGUUUCC UUU	2547	usGfsucccUf agaaccCfgUf uuccususu	3177
40802-1	4135	AAACGGGU UCUAGGGA CAAA{invAb}	1288	asasacggGfuUfCfUf Afgggacaaas{invAb}	1918	AUUUGUCCCU AGAACCCGUU UUU	2548	asUfsuuguCf ccuagaAfcCf cguuususu	3178
40803-1	4137	ACGGGUUC UAGGGACA AACU{invAb}	1289	ascsggguUfcUfAfGf Gfgacaaacus{invAb}	1919	AAGUUUGUCC CUAGAACCCG UUU	2549	asAfsguuuGf ucccuaGfaAf cccgususu	3179
40804-1	4138	CGGGUUCU AGGGACAA ACUC{invAb}	1290	csgsgguuCfuAfGfGf Gfacaaacucs{invAb}	1920	AGAGUUUGUC CCUAGAACCC GUU	2550	asGfsaguuUf gucccuAfgAf acccgsusu	3180
40805-1	4139	GGGUUCUA GGGACAAA CUCU{invAb}	1291	gsgsguucUfaGfGfGf Afcaaacucus{invAb}	1921	UAGAGUUUGU CCCUAGAACC CUU	2551	usAfsgaguUf ugucccUfaGf aacccsusu	3181
40806-1	4140	GGUUCUAG GGACAAAC UCUA{invAb}	1292	gsgsuucuAfgGfGfAf Cfaaacucuas{invAb}	1922	AUAGAGUUUG UCCCUAGAAC CUU	2552	asUfsagagUf uuguccCfuAf gaaccsusu	3182

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40807-1	4184	CCGUGAACU CUUUGAGA AAA{invAb}	1293	cscsgugaAfcUfcCfUf Ufugagaaaas{invAb}	1923	AUUUUCUCAA AGAGUUCACG GUU	2553	asUfsuuucUf caaagaGfuUf cacggsusu	3183
40808-1	4186	GUGAACUC UUUGAGAA AAGA{invAb}	1294	gsusgaacUfcUfUfUf Gfagaaaagas{invAb}	1924	AUCUUUUCUC AAAGAGUUCA CUU	2554	asUfscuuuUf cucaaaGfaGf uucacsusu	3184
40809-1	4191	CUCUUUGA GAAAAGAG GCUA{invAb}	1295	csuscuuuGfaGfAfAf Afagaggcuas{invAb}	1925	AUAGCCUCUU UUCUCAAAGA GUU	2555	asUfsagccUf cuuuucUfcAf aagagsusu	3185
40810-1	4193	CUUUGAGA AAAGAGGC UACU{invAb}	1296	csusuugaGfaAfAfAf Gfaggcuacus{invAb}	1926	AAGUAGCCUC UUUUCUCAAA GUU	2556	asAfsguagCf cucuuuUfcUf caaagsusu	3186
40811-1	4199	GAAAAGAG GCUACUUG UGAA{invAb}	1297	gsasaaagAfgGfCfUf Afcuugugaas{invAb}	1927	UUUCACAAGU AGCCUCUUUU CUU	2557	usUfsucacAf aguagcCfuCf uuuucsusu	3187
40812-1	4202	AAGAGGCU ACUUGUGA AAAU{invAb}	1298	asasgaggCfuAfCfUf Ufgugaaaaus{invAb}	1928	UAUUUUCACA AGUAGCCUCU UUU	2558	usAfsuuuuCf acaaguAfgCf cucuususu	3188
40813-1	4203	AGAGGCUA CUUGUGAA AAUA{invAb}	1299	asgsaggcUfaCfUfUf Gfugaaaauas{invAb}	1929	UUAUUUUCAC AAGUAGCCUC UUU	2559	usUfsauuuUf cacaagUfaGf ccucususu	3189

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40814-1	4251	GGGUUUGA ACCUGCCUU CUU{invAb}	1300	gsgsguuuGfaAfCfCf Ufgccuucuus{invAb}	1930	UAAGAAGGCA GGUUCAAACC CUU	2560	usAfsagaaGf gcagguUfcAf aacccsusu	3190
40815-1	4254	UUUGAACC UGCCUUCUU ACA{invAb}	1301	ususugaaCfcUfGfCf Cfuucuuacas{invAb}	1931	AUGUAAGAAG GCAGGUUCAA AUU	2561	asUfsguaaGf aaggcaGfgUf ucaaasusu	3191
40816-1	4259	ACCUGCCUU CUUACAUCU UG{invAb}	1302	ascscugcCfuUfCfUf Ufacaucuugs{invAb}	1932	UCAAGAUGUA AGAAGGCAGG UUU	2562	usCfsaagaUf guaagaAfgGf caggususu	3192
40817-1	4260	CCUGCCUUC UUACAUCU UGA{invAb}	1303	cscsugccUfuCfUfUf Afcaucuugas{invAb}	1933	AUCAAGAUGU AAGAAGGCAG GUU	2563	asUfscaagAf uguaagAfaGf gcaggsusu	3193
40818-1	4261	CUGCCUUCU UACAUCUU GAG{invAb}	1304	csusgccuUfcUfUfAf Cfaucuugags{invAb}	1934	ACUCAAGAUG UAAGAAGGCA GUU	2564	asCfsucaaGf auguaaGfaAf ggcagsusu	3194
40819-1	4262	UGCCUUCUU ACAUCUUG AGG{invAb}	1305	usgsccuuCfuUfAfCf Afucuugaggs{invAb}	1935	ACCUCAAGAU GUAAGAAGGC AUU	2565	asCfscucaAf gauguaAfgAf aggcasusu	3195
40862-1	4263	GCCUUCUUA CAUCUUGA GGG{invAb}	1306	gscscuucUfuAfCfAf Ufcuugagggs{invAb}	1936	ACCCUCAAGA UGUAAGAAGG CUU	2566	asCfsccucAf agauguAfaGf aaggcsusu	3196

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40863-1	4283	CUAAGUGA GUUCCCAAG GCC{invAb}	1307	csusaaguGfaGfUfUf Cfccaaggccs{invAb}	1937	AGGCCUUGGG AACUCACUUA GUU	2567	asGfsgccuUf gggaacUfcAf cuuagsusu	3197
40864-1	4286	AGUGAGUU CCCAAGGCC UCU{invAb}	1308	asgsugagUfuCfCfCf Afaggccucus{invAb}	1938	AAGAGGCCUU GGGAACUCAC UUU	2568	asAfsgaggCf cuugggAfaCf ucacususu	3198
40865-1	4289	GAGUUCCCA AGGCCUCUG UU{invAb}	1309	gsasguucCfcAfAfGf Gfccucuguus{invAb}	1939	AAACAGAGGC CUUGGGAACU CUU	2569	asAfsacagAf ggccuuGfgGf aacucsusu	3199
40866-1	4290	AGUUCCCAA GGCCUCUGU UC{invAb}	1310	asgsuuccCfaAfGfGf Cfcucuguucs{invAb}	1940	UGAACAGAGG CCUUGGGAAC UUU	2570	usGfsaacaGf aggccuUfgGf gaacususu	3200
40867-1	4291	GUUCCCAAG GCCUCUGUU CA{invAb}	1311	gsusucccAfaGfGfCf Cfucuguucas{invAb}	1941	AUGAACAGAG GCCUUGGGAA CUU	2571	asUfsgaacAf gaggccUfuGf ggaacsusu	3201
40868-1	4318	CUCCGUCAG UGAGCUCA GGU{invAb}	1312	csusccguCfaGfUfGf Afgcucaggus{invAb}	1942	AACCUGAGCU CACUGACGGA GUU	2572	asAfsccugAf gcucacUfgAf cggagsusu	3202
40869-1	4360	ACCCCCAAC CCCACCGGG UG{invAb}	1313	ascscccccAfaCfCfCfC faccgggugs{invAb}	1943	ACACCCGGUG GGGUUGGGGG UUU	2573	asCfsacccGf guggggUfuG fggggususu	3203

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40870-1	4361	CCCCCAACC CCACCGGGU GU{invAb}	1314	cscsccccaAfcCfCfCfA fccgggugus{invAb}	1944	AACACCCGGU GGGGUUGGGG GUU	2574	asAfscaccCf ggugggGfuU fgggggsusu	3204
40871-1	4362	CCCCAACCC CACCGGGUG UC{invAb}	1315	cscsccaaCfcCfCfAfC fcgggugucs{invAb}	1945	UGACACCCGG UGGGGUUGGG GUU	2575	usGfsacacCf cgggugGfgU fugggggsusu	3205
40872-1	4363	CCCAACCCC ACCGGGUG UCA{invAb}	1316	cscscaacCfcCfAfCfC fgggugucas{invAb}	1946	AUGACACCCG GUGGGGUUGG GUU	2576	asUfsgacaCf ccgggugGfgGf uugggsusu	3206
40873-1	4369	CCCACCGGG UGUCAGAG CAA{invAb}	1317	cscscaccGfgGfUfGf Ufcagagcaas{invAb}	1947	AUUGCUCUGA CACCCGGUGG GUU	2577	asUfsugcuCf ugacacCfcGf gugggsusu	3207
40874-1	4398	CCCCAUGGA GCUGGAAU GGG{invAb}	1318	cscsccauGfgAfGfCf Ufggaaugggs{invAb}	1948	ACCCAUUCCA GCUCCAUGGG GUU	2578	asCfsccauUf ccagcuCfcAf uggggsusu	3208
40875-1	4402	AUGGAGCU GGAAUGGG GUGG{invAb}	1319	asusggagCfuGfGfAf Afugggguggs{invAb}	1949	UCCACCCCAU UCCAGCUCCA UUU	2579	usCfscaccCfc auuccAfgCfu ccausususu	3209
40876-1	4403	UGGAGCUG GAAUGGGG UGGA{invAb}	1320	usgsgagcUfgGfAfAf Ufgggguggas{invAb}	1950	AUCCACCCCA UUCCAGCUCC AUU	2580	asUfsccacCfc cauucCfaGfc uccasusu	3210

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40877-1	4404	GGAGCUGG AAUGGGGU GGAG{invAb}	1321	gsgsagcuGfgAfAfUf Gfggguggags{invAb}	1951	ACUCCACCCCA UUCCAGCUCC UU	2581	asCfsuccaCfc ccauuCfcAfg cuccsusu	3211
40878-1	4484	AAGGAAAG UUACAAGU UUCU{invAb}	1322	asasggaaAfgUfUfAf Cfaaguuucus{invAb}	1952	AAGAAACUUG UAACUUUCCU UUU	2582	asAfsgaaaCf uuguaaCfuUf uccuususu	3212
40879-1	4487	GAAAGUUA CAAGUUUC UUUU{invAb}	1323	gsasaaguUfaCfAfAf Gfuuucuuuus{invAb}	1953	AAAAAGAAAC UUGUAACUUU CUU	2583	asAfsaaagAf aacuugUfaAf cuuucsusu	3213
40880-1	4488	AAAGUUAC AAGUUUCU UUUC{invAb}	1324	asasaguuAfcAfAfGf Ufuucuuuucs{invAb}	1954	AGAAAAGAAA CUUGUAACUU UUU	2584	asGfsaaaaGf aaacuuGfuAf acuuususu	3214
40881-1	4491	GUUACAAG UUUCUUUU CCCA{invAb}	1325	gsusuacaAfgUfUfUf Cfuuuucccas{invAb}	1955	UUGGGAAAAG AAACUUGUAA CUU	2585	usUfsgggaAf aagaaaCfuUf guaacsusu	3215
40882-1	4495	CAAGUUUC UUUUCCCAA GUU{invAb}	1326	csasaguuUfcUfUfUf Ufcccaaguus{invAb}	1956	AAACUUGGGA AAAGAAACUU GUU	2586	asAfsacuuGf ggaaaaGfaAf acuugsusu	3216
40883-1	4496	AAGUUUCU UUUCCCAAG UUU{invAb}	1327	asasguuuCfuUfUfUf Cfccaaguuus{invAb}	1957	AAAACUUGGG AAAAGAAACU UUU	2587	asAfsaacuUf gggaaaAfgAf aacuususu	3217

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40884-1	4500	UUCUUUUCC CAAGUUUCC CA{invAb}	1328	ususcuuuUfcCfCfAf Afguuucccas{invAb}	1958	AUGGGAAACU UGGGAAAAGA AUU	2588	asUfsgggaAf acuuggGfaAf aagaasusu	3218
40885-1	4543	ACGCCUUCG GUCAUUAG CAG{invAb}	1329	ascsgccuUfcGfGfUf Cfauuagcags{invAb}	1959	UCUGCUAAUG ACCGAAGGCG UUU	2589	usCfsugcuAf augaccGfaAf ggcgususu	3219
40886-1	4901	GCCCGGCCA ACAGUAUU UUC{invAb}	1330	gscsccggCfcAfAfCf Afguauuuucs{invAb}	1960	AGAAAAUACU GUUGGCCGGG CUU	2590	asGfsaaaaUf acuguuGfgCf cgggcsusu	3220
40887-1	4902	CCCGGCCAA CAGUAUUU UCU{invAb}	1331	cscscggcCfaAfCfAfG fuauuuucus{invAb}	1961	UAGAAAAUAC UGUUGGCCGG GUU	2591	usAfsgaaaAf uacuguUfgGf ccgggsusu	3221
40888-1	4903	CCGGCCAAC AGUAUUUU CUA{invAb}	1332	cscsggccAfaCfAfGf Ufauuuucuas{invAb}	1962	UUAGAAAAUA CUGUUGGCCG GUU	2592	usUfsagaaAf auacugUfuGf gccggsusu	3222
40889-1	4904	CGGCCAACA GUAUUUUC UAA{invAb}	1333	csgsgccaAfcAfGfUf Afuuuucuaas{invAb}	1963	AUUAGAAAAU ACUGUUGGCC GUU	2593	asUfsuagaAf aauacuGfuUf ggccgsusu	3223
40890-1	4905	GGCCAACAG UAUUUUCU AAU{invAb}	1334	gsgsccaaCfaGfUfAf Ufuuucuaaus{invAb}	1964	UAUUAGAAAA UACUGUUGGC CUU	2594	usAfsuuagAf aaauacUfgUf uggccsusu	3224

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40891-1	4906	GCCAACAGU AUUUUCUA AUA{invAb}	1335	gscscaacAfgUfAfUf Ufuucuaauas{invAb}	1965	UUAUUAGAAA AUACUGUUGG CUU	2595	usUfsauuaGf aaaauaCfuGf uuggcsusu	3225
40892-1	4957	GGUAUUGU GAUUGUUA UCAG{invAb}	1336	gsgsuauuGfuGfAfUf Ufguuaucags{invAb}	1966	ACUGAUAACA AUCACAAUAC CUU	2596	asCfsugauAf acaaucAfcAf auaccsusu	3226
40893-1	4958	GUAUUGUG AUUGUUAU CAGG{invAb}	1337	gsusauugUfgAfUfUf Gfuuaucaggs{invAb}	1967	UCCUGAUAAC AAUCACAAUA CUU	2597	usCfscugaUf aacaauCfaCf aauacsusu	3227
40894-1	4962	UGUGAUUG UUAUCAGG AAAA{invAb}	1338	usgsugauUfgUfUfAf Ufcaggaaaas{invAb}	1968	UUUUUCCUGA UAACAAUCAC AUU	2598	usUfsuuucCf ugauaaCfaAf ucacasusu	3228
40895-1	4963	GUGAUUGU UAUCAGGA AAAA{invAb}	1339	gsusgauuGfuUfAfUf Cfaggaaaaas{invAb}	1969	UUUUUUCCUG AUAACAAUCA CUU	2599	usUfsuuuuCf cugauuAfcAf aucacsusu	3229
40896-1	4965	GAUUGUUA UCAGGAAA AAAU{invAb}	1340	gsasuuguUfaUfCfAf Gfgaaaaaaus{invAb}	1970	UAUUUUUUCC UGAUAACAAU CUU	2600	usAfsuuuuUf uccugaUfaAf caaucsusu	3230
40897-1	4966	AUUGUUAU CAGGAAAA AAUA{invAb}	1341	asusuguuAfuCfAfGf Gfaaaaaauas{invAb}	1971	AUAUUUUUUC CUGAUAACAA UUU	2601	asUfsauuuUf uuccugAfuAf acaaususu	3231

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40898-1	4968	UGUUAUCA GGAAAAAA UAUA{invAb}	1342	usgsuuauCfaGfGfAf Afaaaauauas{invAb}	1972	AUAUAUUUUU UCCUGAUAAC AUU	2602	asUfsauauUf uuuuccUfgAf uaacasusu	3232
40899-1	5012	GGACGUAU UUUCUUUC UGCU{invAb}	1343	gsgsacguAfuUfUfUf Cfuuucugcus{invAb}	1973	AAGCAGAAAG AAAAUACGUC CUU	2603	asAfsgcagAf aagaaaAfuAf cguccsusu	3233
40900-1	5026	UCUGCUUU UAAAAAUU AUUC{invAb}	1344	uscsugcuUfuUfAfAf Afaauuauucs{invAb}	1974	UGAAUAAUUU UUAAAAGCAG AUU	2604	usGfsaauaAf uuuuuaAfaAf gcagasusu	3234
40901-1	5215	AUUAGUGG GUUGGCUG AGGC{invAb}	1345	asusuaguGfgGfUfUf Gfgcugaggcs{invAb}	1975	UGCCUCAGCC AACCCACUAA UUU	2605	usGfsccucAf gccaacCfcAf cuaaususu	3235
40902-1	5569	GUAUCAAG AUAAGGAA AUCA{invAb}	1346	gsusaucaAfgAfUfAf Afggaaaucas{invAb}	1976	AUGAUUUCCU UAUCUUGAUA CUU	2606	asUfsgauuUf ccuuauCfuUf gauacsusu	3236
40903-1	5571	AUCAAGAU AAGGAAAU CAGG{invAb}	1347	asuscaagAfuAfAfGf Gfaaaucaggs{invAb}	1977	UCCUGAUUUC CUUAUCUUGA UUU	2607	usCfscugaUf uuccuuAfuCf uugaususu	3237
40904-1	5575	AGAUAAGG AAAUCAGG AAGU{invAb}	1348	asgsauaaGfgAfAfAf Ufcaggaagus{invAb}	1978	AACUUCCUGA UUUCCUUAUC UUU	2608	asAfscuucCf ugauuuCfcUf uaucususu	3238

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40905-1	5576	GAUAAGGA AAUCAGGA AGUG{invAb}	1349	gsasuaagGfaAfAfUf Cfaggaagugs{invAb}	1979	ACACUUCCUG AUUUCCUUAU CUU	2609	asCfsacuuCf cugauuUfcCf uuaucsusu	3239
40906-1	5578	UAAGGAAA UCAGGAAG UGUA{invAb}	1350	usasaggaAfaUfCfAf Gfgaaguguas{invAb}	1980	UUACACUUCC UGAUUUCCUU AUU	2610	usUfsacacUf uccugaUfuUf ccuuasusu	3240
40907-1	5579	AAGGAAAU CAGGAAGU GUAA{invAb}	1351	asasggaaAfuCfAfGf Gfaaguguaas{invAb}	1981	AUUACACUUC CUGAUUUCCU UUU	2611	asUfsuacaCf uuccugAfuUf uccuususu	3241
40908-1	5600	AUUCUUAU AGAAAUGG CCAA{invAb}	1352	asusucuuAfuAfGfAf Afauggccaas{invAb}	1982	AUUGGCCAUU UCUAUAAGAA UUU	2612	asUfsuggcCf auuucuAfuAf agaaususu	3242
41030-1	5601	UUCUUAUA GAAAUGGC CAAG{invAb}	1353	ususcuuaUfaGfAfAf Afuggccaags{invAb}	1983	ACUUGGCCAU UUCUAUAAGA AUU	2613	asCfsuuggCf cauuucUfaUf aagaasusu	3243
41031-1	5640	CCUCAGAUG CUACCCAAU CC{invAb}	1354	cscsucagAfuGfCfUf Afcccaauccs{invAb}	1984	AGGAUUGGGU AGCAUCUGAG GUU	2614	asGfsgauuGf gguagcAfuCf ugaggsusu	3244
41032-1	5641	CUCAGAUGC UACCCAAUC CC{invAb}	1355	csuscagaUfgCfUfAf Cfccaaucccs{invAb}	1985	AGGGAUUGGG UAGCAUCUGA GUU	2615	asGfsggauUf ggguagCfaUf cugagsusu	3245

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41033-1	5668	CUGUCCCUC CAGAAGGC ACC{invAb}	1356	csusguccCfuCfCfAf Gfaaggcaccs{invAb}	1986	AGGUGCCUUC UGGAGGGACA GUU	2616	asGfsgugcCf uucuggAfgG fgacagsusu	3246
41034-1	5669	UGUCCCUCC AGAAGGCA CCC{invAb}	1357	usgsuccCUfcCfAfGf Afaggcaccs{invAb}	1987	AGGGUGCCUU CUGGAGGGAC AUU	2617	asGfsggugCf cuucugGfaGf ggacasusu	3247
41035-1	5670	GUCCCUCCA GAAGGCACC CU{invAb}	1358	gsuscccuCfcAfGfAf Afggcacccus{invAb}	1988	AAGGGUGCCU UCUGGAGGGA CUU	2618	asAfsggguGf ccuucuGfgAf gggacsusu	3248
41036-1	5671	UCCCUCCAG AAGGCACCC UU{invAb}	1359	uscsccucCfaGfAfAf Gfgcacccuus{invAb}	1989	AAAGGGUGCC UUCUGGAGGG AUU	2619	asAfsagggUf gccuucUfgGf agggasusu	3249
41037-1	5672	CCCUCCAGA AGGCACCCU UU{invAb}	1360	cscscuccAfgAfAfGf Gfcacccuuus{invAb}	1990	AAAAGGGUGC CUUCUGGAGG GUU	2620	asAfsaaggGf ugccuuCfuGf gagggsusu	3250
41038-1	5673	CCUCCAGAA GGCACCCUU UG{invAb}	1361	cscsuccaGfaAfGfGfC facccuuugs{invAb}	1991	ACAAAGGGUG CCUUCUGGAG GUU	2621	asCfsaaagGf gugccuUfcUf ggagggsusu	3251
41039-1	5674	CUCCAGAAG GCACCCUUU GC{invAb}	1362	csusccagAfaGfGfCf Afcccuuugcs{invAb}	1992	AGCAAAGGGU GCCUUCUGGA GUU	2622	asGfscaaaGf ggugccUfuCf uggagsusu	3252

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41040-1	5676	CCAGAAGGC ACCCUUUGC UU{invAb}	1363	cscsagaaGfgCfAfCfC fcuuugcuus{invAb}	1993	UAAGCAAAGG GUGCCUUCUG GUU	2623	usAfsagcaAf agggugCfcUf ucuggsusu	3253
41041-1	5679	GAAGGCACC CUUUGCUU AGG{invAb}	1364	gsasaggcAfcCfCfUf Ufugcuuaggs{invAb}	1994	ACCUAAGCAA AGGGUGCCUU CUU	2624	asCfscuaaGf caaaggGfuGf ccuucsusu	3254
41042-1	5680	AAGGCACCC UUUGCUUA GGC{invAb}	1365	asasggcaCfcCfUfUfU fgcuuaggcs{invAb}	1995	AGCCUAAGCA AAGGGUGCCU UUU	2625	asGfsccuaAf gcaaagGfgUf gccuususu	3255
41043-1	5681	AGGCACCCU UUGCUUAG GCC{invAb}	1366	asgsgcacCfcUfUfUf Gfcuuaggccs{invAb}	1996	AGGCCUAAGC AAAGGGUGCC UUU	2626	asGfsgccuAf agcaaaGfgGf ugccususu	3256
41044-1	5692	GCUUAGGCC UCCCUCUCU UC{invAb}	1367	gscsuuagGfcCfUfCf Cfcucucuucs{invAb}	1997	AGAAGAGAGG GAGGCCUAAG CUU	2627	asGfsaagaGf agggagGfcCf uaagcsusu	3257
41045-1	5705	UCUCUUCCU GAACCACCU CU{invAb}	1368	uscsucuuCfcUfGfAf Afccaccucus{invAb}	1998	AAGAGGUGGU UCAGGAAGAG AUU	2628	asAfsgaggUf gguucaGfgAf agagasusu	3258
41046-1	5736	AUUGGCCU AUGAAUGC AUUC{invAb}	1369	asusuggcCfuAfUfGf Afaugcauucs{invAb}	1999	AGAAUGCAUU CAUAGGCCAA UUU	2629	asGfsaaugCf auucauAfgGf ccaaususu	3259

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41047-1	5740	GCCUAUGA AUGCAUUC UUAU{invAb}	1370	gscscuauGfaAfUfGf Cfauucuuaus{invAb}	2000	AAUAAGAAUG CAUUCAUAGG CUU	2630	asAfsuaagAf augcauUfcAf uaggcsusu	3260
41048-1	5741	CCUAUGAA UGCAUUCU UAUU{invAb}	1371	cscsuaugAfaUfGfCf Afuucuuauus{invAb}	2001	AAAUAAGAAU GCAUUCAUAG GUU	2631	asAfsauaaGf aaugcaUfuCf auaggsusu	3261
41049-1	5967	GGGGUCAA GCCAUCUUC CCA{invAb}	1372	gsgsggucAfaGfCfCf Afucuucccas{invAb}	2002	AUGGGAAGAU GGCUUGACCC CUU	2632	asUfsgggaAf gauggcUfuGf acccsusu	3262
41050-1	6153	GCUACCAUG CCUGGUCCA AC{invAb}	1373	gscsuaccAfuGfCfCf Ufgguccaacs{invAb}	2003	UGUUGGACCA GGCAUGGUAG CUU	2633	usGfsuuggAf ccaggcAfuGf guagcsusu	3263
41051-1	6157	CCAUGCCUG GUCCAACAU UC{invAb}	1374	cscsaugcCfuGfGfUf Cfcaacauucs{invAb}	2004	AGAAUGUUGG ACCAGGCAUG GUU	2634	asGfsaaugUf uggaccAfgGf cauggsusu	3264
41052-1	6163	CUGGUCCAA CAUUCUUCA UU{invAb}	1375	csusggucCfaAfCfAf Ufucuucauus{invAb}	2005	AAAUGAAGAA UGUUGGACCA GUU	2635	asAfsaugaAf gaauguUfgGf accagsusu	3265
41053-1	6199	UUAGUGCA GAGUAUGA GCCU{invAb}	1376	ususagugCfaGfAfGf Ufaugagccus{invAb}	2006	AAGGCUCAUA CUCUGCACUA AUU	2636	asAfsggcuCf auacucUfgCf acuaasusu	3266

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41054-1	6201	AGUGCAGA GUAUGAGC CUGA{invAb}	1377	asgsugcaGfaGfUfAf Ufgagccugas{invAb}	2007	AUCAGGCUCA UACUCUGCAC UUU	2637	asUfscaggCf ucauacUfcUf gcacususu	3267
41055-1	6202	GUGCAGAG UAUGAGCC UGAU{invAb}	1378	gsusgcagAfgUfAfUf Gfagccugaus{invAb}	2008	AAUCAGGCUC AUACUCUGCA CUU	2638	asAfsucagGf cucauaCfuCf ugcacsusu	3268
41056-1	6243	UGUGGGUG UGUAUAUG UAUC{invAb}	1379	usgsugggUfgUfGfUf Afuauguaucs{invAb}	2009	AGAUACAUAU ACACACCCAC AUU	2639	asGfsauacAf uauacaCfaCf ccacasusu	3269
41057-1	6265	UGAGUGUA UAUAAAAA GACU{invAb}	1380	usgsagugUfaUfAfUf Afaaaagacus{invAb}	2010	AAGUCUUUUU AUAUACACUC AUU	2640	asAfsgucuUf uuuauaUfaCf acucasusu	3270
41058-1	6267	AGUGUAUA UAAAAAGA CUGA{invAb}	1381	asgsuguaUfaUfAfAf Afaagacugas{invAb}	2011	UUCAGUCUUU UUAUAUACAC UUU	2641	usUfscaguCf uuuuuaUfaUf acacususu	3271
41059-1	6268	GUGUAUAU AAAAAGAC UGAA{invAb}	1382	gsusguauAfuAfAfAf Afagacugaas{invAb}	2012	UUUCAGUCUU UUUAUAUACA CUU	2642	usUfsucagUf cuuuuuAfuA fuacacsusu	3272
41060-1	6271	UAUAUAAA AAGACUGA AAGA{invAb}	1383	usasuauaAfaAfAfGf Afcugaaagas{invAb}	2013	AUCUUUCAGU CUUUUUAUAU AUU	2643	asUfscuuuCf agucuuUfuUf auauasusu	3273

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41061-1	6279	AAGACUGA AAGAGGGC UGGG{invAb}	1384	asasgacuGfaAfAfGf Afgggcugggs{invAb}	2014	ACCCAGCCCUC UUUCAGUCUU UU	2644	asCfsccagCfc cucuuUfcAfg ucuususu	3274
41062-1	6280	AGACUGAA AGAGGGCU GGGC{invAb}	1385	asgsacugAfaAfGfAf Gfggcugggcs{invAb}	2015	UGCCCAGCCC UCUUUCAGUC UUU	2645	usGfscccaGf cccucuUfuCf agucususu	3275
41063-1	6503	UUGCAGUG ACCCGAGAU GCA{invAb}	1386	ususgcagUfgAfCfCf Cfgagaugcas{invAb}	2016	AUGCAUCUCG GGUCACUGCA AUU	2646	asUfsgcauCf ucggguCfaCf ugcaasusu	3276
41064-1	6568	UAAGGAUA UAUAUCAA AACC{invAb}	1387	usasaggaUfaUfAfUf Afucaaaaccs{invAb}	2017	AGGUUUUGAU AUAUAUCCUU AUU	2647	asGfsguuuUf gauauaUfaUf ccuuasusu	3277
41065-1	6571	GGAUAUAU AUCAAAACC CUU{invAb}	1388	gsgsauauAfuAfUfCf Afaaacccuus{invAb}	2018	UAAGGGUUUU GAUAUAUAUC CUU	2648	usAfsagggUf uuugauAfuA fuauccsusu	3278
41066-1	6573	AUAUAUAU CAAAACCCU UAU{invAb}	1389	asusauauAfuCfAfAf Afacccuuaus{invAb}	2019	AAUAAGGGUU UUGAUAUAUA UUU	2649	asAfsuaagGf guuuugAfuA fuauausususu	3279
41067-1	6574	UAUAUAUC AAAACCCUU AUG{invAb}	1390	usasuauaUfcAfAfAf Afcccuuaugs{invAb}	2020	ACAUAAGGGU UUUGAUAUAU AUU	2650	asCfsauaaGf gguuuuGfaU fauauasusu	3280

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41068-1	6575	AUAUAUCA AAACCCUUA UGG{invAb}	1391	asusauauuCfaAfAfAf Cfccuuauggs{invAb}	2021	ACCAUAAGGG UUUUGAUAUA UUU	2651	asCfscauuAf ggguuuUfgA fuauaususu	3281
41069-1	6576	UAUAUCAA AACCCUUAU GGC{invAb}	1392	usasuauuAfaAfAfAfCf Cfcuuauggcs{invAb}	2022	UGCCAUAAGG GUUUUGAUAU AUU	2652	usGfsccauAf aggguuUfuG fauauaususu	3282
41070-1	6594	GCAGACUG UUAUUUGU AAUU{invAb}	1393	gscsagacUfgUfUfAf Ufuuguaauus{invAb}	2023	AAAUUACAAA UAACAGUCUG CUU	2653	asAfsauuaCf aaauaaCfaGf ucugcsusu	3283
41140-1	138	CGAUUCCCG AUCCCGACC CA{invAb}	1394	csgsauuuCfcGfAfUf Cfccgacccas{invAb}	2024	AUGGGUCGGG AUCGGGAAUC GUU	2654	asUfsggguCf gggaucGfgGf aaucgsusu	3284
41141-1	143	CCCGAUCCC GACCCAGAU CC{invAb}	1395	cscscgauCfcCfGfAfC fccagauccs{invAb}	2025	AGGAUCUGGG UCGGGAUCGG GUU	2655	asGfsgaucUf gggucgGfgA fucgggsusu	3285
41142-1	266	GCGACCCGC UGCCUGAGC GA{invAb}	1396	gscsgaccCfgCfUfGfC fcugagcgas{invAb}	2026	AUCGCUCAGG CAGCGGGUCG CUU	2656	asUfscgcuCf aggcagCfgGf gucgcsusu	3286
41143-1	269	ACCCGCUGC CUGAGCGA GCA{invAb}	1397	ascscgcUfgCfCfUfG fagcgagcas{invAb}	2027	AUGCUCGCUC AGGCAGCGGG UUU	2657	asUfsgcucGf cucaggCfaGf cgggususu	3287

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41144-1	420	CCAGGAGUC GGAACAUU GGC{invAb}	1398	cscsaggaGfuCfGfGf Afacauuggcs{invAb}	2028	UGCCAAUGUU CCGACUCCUG GUU	2658	usGfsccaaUf guuccgAfcUf ccuggsusu	3288
41145-1	422	AGGAGUCG GAACAUUG GCAU{invAb}	1399	asgsgaguCfgGfAfAf Cfauuggcaus{invAb}	2029	AAUGCCAAUG UUCCGACUCC UUU	2659	asAfsugccAf auguucCfgAf cuccususu	3289
41146-1	423	GGAGUCGG AACAUUGG CAUC{invAb}	1400	gsgsagucGfgAfAfCf Afuuggcaucs{invAb}	2030	AGAUGCCAAU GUUCCGACUC CUU	2660	asGfsaugcCf aauguuCfcGf acuccsusu	3290
41147-1	424	GAGUCGGA ACAUUGGC AUCU{invAb}	1401	gsasgucgGfaAfCfAf Ufuggcaucus{invAb}	2031	AAGAUGCCAA UGUUCCGACU CUU	2661	asAfsgaugCf caauguUfcCf gacucsusu	3291
41148-1	586	CUUUCGGUC CAAAGACG AAG{invAb}	1402	csusuucgGfuCfCfAf Afagacgaags{invAb}	2032	ACUUCGUCUU UGGACCGAAA GUU	2662	asCfsuucgUf cuuuggAfcCf gaaagsusu	3292
41149-1	714	CCUUUCAUUG AUGCCAAA ACA{invAb}	1403	cscsuucaUfuGfAfUf Gfccaaaacas{invAb}	2033	UUGUUUUGGC AUCAAUGAAG GUU	2663	usUfsguuuUf ggcaucAfaUf gaaggsusu	3293
41150-1	715	CUUCAUUG AUGCCAAA ACAA{invAb}	1404	csusucauUfgAfUfGf Cfcaaaacaas{invAb}	2034	AUUGUUUUGG CAUCAAUGAA GUU	2664	asUfsuguuUf uggcauCfaAf ugaagsusu	3294

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41151-1	716	UUCAUUGA UGCCAAAAC AAC{invAb}	1405	ususcauuGfaUfGfCf Cfaaaacaacs{invAb}	2035	AGUUGUUUUG GCAUCAAUGA AUU	2665	asGfsuuguUf uuggcaUfcAf augaasusu	3295
41152-1	718	CAUUGAUG CCAAAACAA CCA{invAb}	1406	csasuugaUfgCfCfAf Afaacaaccas{invAb}	2036	AUGGUUGUUU UGGCAUCAAU GUU	2666	asUfsgguuGf uuuuggCfaUf caaugsusu	3296
41153-1	721	UGAUGCCA AAACAACCA UCA{invAb}	1407	usgsaugcCfaAfAfAf Cfaaccaucas{invAb}	2037	AUGAUGGUUG UUUUGGCAUC AUU	2667	asUfsgaugGf uuguuuUfgG fcaucasusu	3297
41154-1	722	GAUGCCAA AACAACCAU CAC{invAb}	1408	gsasugccAfaAfAfCf Afaccaucacs{invAb}	2038	AGUGAUGGUU GUUUUGGCAU CUU	2668	asGfsugauGf guuguuUfuG fgcaucsusu	3298
41155-1	723	AUGCCAAA ACAACCAUC ACC{invAb}	1409	asusgccaAfaAfCfAf Afccaucaccs{invAb}	2039	AGGUGAUGGU UGUUUUGGCA UUU	2669	asGfsugaUf gguuguUfuU fggcaususu	3299
41156-1	729	AAACAACCA UCACCGUGU CC{invAb}	1410	asasacaaCfcAfUfCfA fccgugucccs{invAb}	2040	AGGACACGGU GAUGGUUGUU UUU	2670	asGfsgacaCf ggugauGfgU fuguuususu	3300
41157-1	730	AACAACCAU CACCGUGUC CC{invAb}	1411	asascaacCfaUfCfAfC fcgugucccs{invAb}	2041	AGGGACACGG UGAUGGUUGU UUU	2671	asGfsggacAf cggugaUfgGf uuguususu	3301

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41158-1	1136	AGCAUCCUG GACACCCUC UC{invAb}	1412	asgscaucCfuGfGfAf Cfacccucucs{invAb}	2042	AGAGAGGGUG UCCAGGAUGC UUU	2672	asGfsagagGf gugucc AfgGf augcususu	3302
41159-1	1137	GCAUCCUGG ACACCCUCU CG{invAb}	1413	gscsauccUfgGfAfCf Afcccucucgs{invAb}	2043	ACGAGAGGGU GUCCAGGAUG CUU	2673	asCfsgagaGf ggugucCfaGf gaugcsusu	3303
41160-1	1162	GCUCGCUAC AGCACUGA GUG{invAb}	1414	gscsucgcUfaCfAfGf Cfacugagugs{invAb}	2044	UCACUCAGUG CUGUAGCGAG CUU	2674	usCfsacucAf gugcugUfaGf cgagcsusu	3304
41161-1	1858	CUGGUUGG GAAAUGAC ACCA{invAb}	1415	csusgguuGfgGfAfAf Afugacaccas{invAb}	2045	AUGGUGUCAU UUCCCAACCA GUU	2675	asUfsggugUf cauuucCfcAf accagsusu	3305
41162-1	1860	GGUUGGGA AAUGACACC AGG{invAb}	1416	gsgsuuggGfaAfAfUf Gfacaccaggs{invAb}	2046	UCCUGGUGUC AUUUCCCAAC CUU	2676	usCfscuggUf gucauuUfcCf caaccsusu	3306
41163-1	2187	UUAAUUUU AGAACACCU UUU{invAb}	1417	ususaauuUfuAfGfAf Afcaccuuuus{invAb}	2047	AAAAAGGUGU UCUAAAAUUA AUU	2677	asAfsaaagGf uguucuAfaAf auuaasusu	3307
41164-1	2189	AAUUUUAG AACACCUUU UUC{invAb}	1418	asasuuuuAfgAfAfCf Afccuuuuucs{invAb}	2048	UGAAAAAGGU GUUCUAAAAU UUU	2678	usGfsaaaaAf gguguuCfuA faaauususu	3308

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41165-1	2190	AUUUUAGA ACACCUUUU UCA{invAb}	1419	asusuuuaGfaAfCfAf Cfcuuuuucas{invAb}	2049	AUGAAAAAGG UGUUCUAAAA UUU	2679	asUfsgaaaAf agguguUfcUf aaaaususu	3309
41166-1	2191	UUUUAGAA CACCUUUUU CAC{invAb}	1420	ususuuagAfaCfAfCf Cfuuuuucacs{invAb}	2050	AGUGAAAAAG GUGUUCUAAA AUU	2680	asGfsugaaAf aaggugUfuCf uaaaasusu	3310
41167-1	2193	UUAGAACA CCUUUUUCA CCU{invAb}	1421	ususagaaCfaCfCfUfUf fuuucaccus{invAb}	2051	UAGGUGAAAA AGGUGUUCUA AUU	2681	usAfsggugAf aaaaggUfgUf ucuaasusu	3311
41168-1	2267	CUGUUGAA UUUUGUAU UAUG{invAb}	1422	csusguugAfaUfUfUf Ufguauuaugs{invAb}	2052	ACAUAAUACA AAAUUCAACA GUU	2682	asCfsauaaUf acaaaaUfuCf aacagsusu	3312
41169-1	2268	UGUUGAAU UUUGUAUU AUGU{invAb}	1423	usgsuugaAfuUfUfUf Gfuauuaugus{invAb}	2053	AACAUAAUAC AAAAUUCAAC AUU	2683	asAfscauaAf uacaaaAfuUf caacasusu	3313
41170-1	2269	GUUGAAUU UUGUAUUA UGUG{invAb}	1424	gsusugaaUfuUfUfUfGf Ufauuaugugs{invAb}	2054	UCACAUAAUA CAAAAUUCAA CUU	2684	usCfsacauAf auacaaAfaUf ucaacsusu	3314
41171-1	2273	AAUUUUGU AUUAUGUG AAUC{invAb}	1425	asasuuuuGfuAfUfUf Afugugaaucs{invAb}	2055	UGAUUCACAU AAUACAAAAU UUU	2685	usGfsauucAf cauaauAfcAf aaauususu	3315

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41172-1	2274	AUUUUGUA UUAUGUGA AUCA{invAb}	1426	asusuuugUfaUfUfAf Ufgugaaucas{invAb}	2056	AUGAUUCACA UAAUACAAAA UUU	2686	asUfsgauuCf acauaaUfaCf aaaaususu	3316
41173-1	2639	AAAAUAAU CUAGUGUG CAGG{invAb}	1427	asasaauaAfuCfUfAf Gfugugcaggs{invAb}	2057	ACCUGCACAC UAGAUUAUUU UUU	2687	asCfscugcAf cacuagAfuUf auuuususu	3317
41174-1	3893	UUUUCCCCCA GGUGUGAU AAU{invAb}	1428	ususuuccCfcAfGfGf Ufgugauaaus{invAb}	2058	AAUUAUCACA CCUGGGGAAA AUU	2688	asAfsuuauCf acaccuGfgGf gaaaasusu	3318
41175-1	4112	UGAGAAGA CAGACCCUU UAA{invAb}	1429	usgsagaaGfaCfAfGf Afcccuuuaas{invAb}	2059	UUUAAAGGGU CUGUCUUCUC AUU	2689	usUfsuaaaGf ggucugUfcUf ucucasusu	3319
41176-1	4113	GAGAAGAC AGACCCUUU AAA{invAb}	1430	gsasgaagAfcAfGfAf Cfccuuuaaas{invAb}	2060	AUUUAAAGGG UCUGUCUUCU CUU	2690	asUfsuuaaAf gggucuGfuCf uucucsusu	3320
41177-1	4115	GAAGACAG ACCCUUUAA AGG{invAb}	1431	gsasagacAfgAfCfCfC fuuuaaaggs{invAb}	2061	UCCUUUAAAG GGUCUGUCUU CUU	2691	usCfscuuuAf aaggguCfuGf ucuucsusu	3321
41178-1	4116	AAGACAGA CCCUUUAAA GGA{invAb}	1432	asasgacaGfaCfCfCfU fuuaaaggas{invAb}	2062	UUCCUUUAAA GGGUCUGUCU UUU	2692	usUfsccuuUf aaagggUfcUf gucuususu	3322

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41179-1	4117	AGACAGACC CUUUAAAG GAA{invAb}	1433	asgsacagAfcCfCfUfU fuaaaggaas{invAb}	2063	UUUCCUUUAA AGGGUCUGUC UUU	2693	usUfsuccuUf uaaaggGfuCf ugucususu	3323
41180-1	4118	GACAGACCC UUUAAAGG AAA{invAb}	1434	gsascagaCfcCfUfUfU faaaggaaas{invAb}	2064	AUUUCCUUUA AAGGGUCUGU CUU	2694	asUfsuccUf uuaaagGfgUf cugucsusu	3324
41280-1	6686	AGAAAAUA ACUCCUAAU AAA{invAb}	1435	asgsaaaaUfaAfCfUfC fcuaauaaas{invAb}	2065	AUUUAUUAGG AGUUAUUUUC UUU	2695	asUfsuuauUf aggaguUfaUf uuucususu	3325
41281-1	6685	GAGAAAAU AACUCCUAA UAA{invAb}	1436	gsasgaaaAfuAfAfCf Ufccuaauaas{invAb}	2066	UUUAUUAGGA GUUAUUUUCU CUU	2696	usUfsuauuAf ggaguuAfuU fuucucsusu	3326
41282-1	6684	UGAGAAAA UAACUCCUA AUA{invAb}	1437	usgsagaaAfaUfAfAf Cfuccuaauas{invAb}	2067	UUAUUAGGAG UUAUUUUCUC AUU	2697	usUfsauuaGf gaguuaUfuUf ucucasusu	3327
41283-1	6683	AUGAGAAA AUAACUCCU AAU{invAb}	1438	asusgagaAfaAfUfAf Afcuccuaaus{invAb}	2068	UAUUAGGAGU UAUUUUCUCA UUU	2698	usAfsuuagGf aguuauUfuUf cucaususu	3328
41284-1	6676	UUUCAGCA UGAGAAAA UAAC{invAb}	1439	ususucagCfaUfGfAf Gfaaauuaacs{invAb}	2069	AGUUAUUUUC UCAUGCUGAA AUU	2699	asGfsuuauUf uucucaUfgCf ugaaasusu	3329

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41285-1	6671	AUCACUUUC AGCAUGAG AAA{invAb}	1440	asuscacuUfuCfAfGf Cfaugagaaas{invAb}	2070	UUUUCUCAUG CUGAAAGUGA UUU	2700	usUfsuucuCf augcugAfaAf gugaususu	3330
41286-1	6670	CAUCACUUU CAGCAUGA GAA{invAb}	1441	csasucacUfuUfCfAf Gfcaugagaas{invAb}	2071	UUUCUCAUGC UGAAAGUGAU GUU	2701	usUfsucucAf ugcugaAfaGf ugaugsusu	3331
41287-1	6669	GCAUCACUU UCAGCAUG AGA{invAb}	1442	gscsaucaCfuUfUfCf Afgcaugagas{invAb}	2072	UUCUCAUGCU GAAAGUGAUG CUU	2702	usUfscucaUf gcugaaAfgUf gaugcsusu	3332
41288-1	6644	CCCAAGUUU CUAUGGUG AAC{invAb}	1443	cscscaagUfuUfCfUf Afuggugaacs{invAb}	2073	AGUUCACCAU AGAAACUUGG GUU	2703	asGfsuucaCf cauagaAfaCf uugggsusu	3333
41289-1	6643	GCCCAAGUU UCUAUGGU GAA{invAb}	1444	gscsccaaGfuUfUfCf Ufaugguaas{invAb}	2074	AUUCACCAUA GAAACUUGGG CUU	2704	asUfsucacCf auagaaAfcUf ugggcsusu	3334
41290-1	6641	UUGCCCAAG UUUCUAUG GUG{invAb}	1445	ususgcccAfaGfUfUf Ufcuauggugs{invAb}	2075	UCACCAUAGA AACUUGGGCA AUU	2705	usCfsaccaUf agaaacUfuGf ggcaasusu	3335
41291-1	6640	GUUGCCCAA GUUUCUAU GGU{invAb}	1446	gsusugccCfaAfGfUf Ufucuaugguus{invAb}	2076	AACCAUAGAA ACUUGGGCAA CUU	2706	asAfsccauAf gaaacuUfgGf gcaacsusu	3336

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41292-1	6638	GUGUUGCCC AAGUUUCU AUG{invAb}	1447	gsusguugCfcCfAfAf Gfuuucuaugs{invAb}	2077	ACAUAGAAAC UUGGGCAACA CUU	2707	asCfsauagAf aacuugGfgCf aacacsusu	3337
41293-1	6637	UGUGUUGC CCAAGUUUC UAU{invAb}	1448	usgsuguuGfcCfCfAf Afguuucuaus{invAb}	2078	AAUAGAAACU UGGGCAACAC AUU	2708	asAfsuagaAf acuuggGfcAf acacasusu	3338
41294-1	6636	AUGUGUUG CCCAAGUUU CUA{invAb}	1449	asusguguUfgCfCfCf Afaguuucuas{invAb}	2079	AUAGAAACUU GGGCAACACA UUU	2709	asUfsagaaAf cuugggCfaAf cacaususu	3339
41295-1	6635	UAUGUGUU GCCCAAGUU UCU{invAb}	1450	usasugugUfuGfCfCf Cfaaguuucus{invAb}	2080	UAGAAACUUG GGCAACACAU AUU	2710	usAfsgaaaCf uugggcAfaCf acauasusu	3340
41296-1	6614	GUAUUUUA UUUGUCGU GCUU{invAb}	1451	gsusauuuUfaUfUfUf Gfucgugcuus{invAb}	2081	UAAGCACGAC AAAUAAAAUA CUU	2711	usAfsagcaCf gacaaaUfaAf aauacsusu	3341
41297-1	6613	UGUAUUUU AUUUGUCG UGCU{invAb}	1452	usgsuauuUfuAfUfUf Ufgucgugcus{invAb}	2082	AAGCACGACA AAUAAAAUAC AUU	2712	asAfsgcacGf acaaauAfaAf auacasusu	3342
41298-1	6612	UUGUAUUU UAUUUGUC GUGC{invAb}	1453	ususguauUfuUfAfUf Ufugucgugcs{invAb}	2083	AGCACGACAA AUAAAAUACA AUU	2713	asGfscacgAf caaauaAfaAf uacaasusu	3343

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41299-1	6611	AUUGUAUU UUAUUUGU CGUG{invAb}	1454	asusuguaUfuUfUfAf Ufuugucgugs{invAb}	2084	ACACGACAAA UAAAAUACAA UUU	2714	asCfsacgaCfa aauaaAfaUfa caaususu	3344
41300-1	6610	AAUUGUAU UUUAUUUG UCGU{invAb}	1455	asasuuguAfuUfUfUf Afuuugucgus{invAb}	2085	AACGACAAAU AAAAUACAAU UUU	2715	asAfscgacAf aauaaaAfuAf caauususu	3345
41301-1	6162	CCUGGUCCA ACAUUCUUC AU{invAb}	1456	cscsuggguCfcAfAfCf Afuucuucaus{invAb}	2086	AAUGAAGAAU GUUGGACCAG GUU	2716	asAfsugaaGf aauguuGfgAf ccaggsusu	3346
41302-1	6158	CAUGCCUGG UCCAACAUU CU{invAb}	1457	csasugccUfgGfUfCf Cfaacauucus{invAb}	2087	AAGAAUGUUG GACCAGGCAU GUU	2717	asAfsgaauGf uuggacCfaGf gcaugsusu	3347
41303-1	6154	CUACCAUGC CUGGUCCAA CA{invAb}	1458	csusaccaUfgCfCfUfG fguccaacas{invAb}	2088	AUGUUGGACC AGGCAUGGUA GUU	2718	asUfsguugGf accaggCfaUf gguagsusu	3348
41304-1	5691	UGCUUAGG CCUCCCUCU CUU{invAb}	1459	usgscuuaGfgCfCfUf Cfccucucuus{invAb}	2089	AAAGAGAGGG AGGCCUAAGC AUU	2719	asAfsagagAf gggaggCfcUf aagcasusu	3349
41305-1	5642	UCAGAUGC UACCCAAUC CCG{invAb}	1460	uscsagauGfcUfAfCf Cfcaaucccgs{invAb}	2090	ACGGGAUUGG GUAGCAUCUG AUU	2720	asCfsgggaUf uggguaGfcAf ucugasusu	3350

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41306-1	4097	GACAAAGC ACUUGACU GAGA{invAb}	1461	gsascaaaGfcAfCfUfUfU fgacugagas{invAb}	2091	UUCUCAGUCA AGUGCUUUGU CUU	2721	usUfscucaGf ucaaguGfcUf uugucsusu	3351
41307-1	4046	CCCUUACCC AUAUUGUG UAA{invAb}	1462	cscscuuaCfcCfAfUfA fuuguguaas{invAb}	2092	AUUACACAAU AUGGGUAAGG GUU	2722	asUfsuacaCf aauaugGfgUf aagggsusu	3352
41308-1	4008	GUGCUCAA ACUGUUAA AUGU{invAb}	1463	gsusgcucAfaAfCfUf Gfuuaaaugus{invAb}	2093	AACAUUUAAC AGUUUGAGCA CUU	2723	asAfscauuUf aacaguUfuGf agcacsusu	3353
41309-1	3773	UCUGGUCU GCGUUCUU UUUU{invAb}	1464	uscsugguCfuGfCfGf Ufucuuuuuus{invAb}	2094	AAAAAAAGAA CGCAGACCAG AUU	2724	asAfsaaaaAf gaacgcAfgAf ccagasusu	3354
41408-1	6601	GUUAUUUG UAAUUGUA UUUU{invAb}	1465	gsusuauuUfgUfAfAf Ufuguauuuus{invAb}	2095	UAAAAUACAA UUACAAAUAA CUU	2725	usAfsaaauAf caauuaCfaAf auaacsusu	3355
41409-1	5857	AGGCGGCA ACAUUCUU UUUU{invAb}	1466	asgsgcggCfaAfCfAf Ufucuuuuuus{invAb}	2096	AAAAAAAGAA UGUUGCCGCC UUU	2726	asAfsaaaaAf gaauguUfgCf cgccususu	3356
41410-1	5824	CAGGAAUA AUCAGUAU GUAG{invAb}	1467	csasggaaUfaAfUfCf Afguauguags{invAb}	2097	ACUACAUACU GAUUAUUCCU GUU	2727	asCfsuacaUf acugauUfaUf uccugsusu	3357

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41411-1	5823	UCAGGAAU AAUCAGUA UGUA{invAb}	1468	uscsaggaAfuAfAfUf Cfaguauguas{invAb}	2098	AUACAUACUG AUUAUUCCUG AUU	2728	asUfsacauAf cugauuAfuUf ccugasusu	3358
41412-1	5822	CUCAGGAA UAAUCAGU AUGU{invAb}	1469	csuscaggAfaUfAfAf Ufcaguaugus{invAb}	2099	UACAUACUGA UUAUUCCUGA GUU	2729	usAfscauaCf ugauuaUfuCf cugagsusu	3359
41413-1	5820	CUCUCAGGA AUAAUCAG UAU{invAb}	1470	csuscucaGfgAfAfUf Afaucaguaus{invAb}	2100	AAUACUGAUU AUUCCUGAGA GUU	2730	asAfsuacuGf auuauuCfcUf gagagsusu	3360
41414-1	5819	ACUCUCAGG AAUAAUCA GUA{invAb}	1471	ascsucucAfgGfAfAf Ufaaucaguas{invAb}	2101	AUACUGAUUA UUCCUGAGAG UUU	2731	asUfsacugAf uuauucCfuGf agagususu	3361
41415-1	5774	UAAAGCCU UCCCUUUAA UUU{invAb}	1472	usasaagcCfuUfCfCfC fuuuaauuus{invAb}	2102	UAAAUUAAAG GGAAGGCUUU AUU	2732	usAfsaauuAf aagggaAfgGf cuuuasusu	3362
41416-1	5773	AUAAAGCC UUCCCUUUA AUU{invAb}	1473	asusaaagCfcUfUfCfC fcuuuaauus{invAb}	2103	AAAUUAAAGG GAAGGCUUUA UUU	2733	asAfsauuaAf agggaaGfgCf uuuaususu	3363
41417-1	5772	AAUAAAGC CUUCCCUUU AAU{invAb}	1474	asasuaaaGfcCfUfUfC fccuuuaaus{invAb}	2104	AAUUAAAGGG AAGGCUUUAU UUU	2734	asAfsuuaaAf gggaagGfcUf uuauususu	3364

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41418-1	5771	AAAUAAAG CCUUCCCUU UAA{invAb}	1475	asasauaaAfgCfCfUfUfU fcccuuuaas{invAb}	2105	AUUAAAGGGA AGGCUUUAUU UUU	2735	asUfsuaaaGf ggaaggCfuUf uauuususu	3365
41419-1	5770	CAAAUAAA GCCUUCCCU UUA{invAb}	1476	csasaauaAfaGfCfCfU fucccuuuas{invAb}	2106	UUAAAGGGAA GGCUUUAUUU GUU	2736	usUfsaaagGf gaaggcUfuUf auuugsusu	3366
41420-1	5707	UCUUCCUGA ACCACCUCU GG{invAb}	1477	uscsuuccUfgAfAfCf Cfaccucuggs{invAb}	2107	UCCAGAGGUG GUUCAGGAAG AUU	2737	usCfscagaGf gugguuCfaGf gaagasusu	3367
41421-1	4983	AUAUAUUA AAUGGCUG AUAG{invAb}	1478	asusauauUfaAfAfUf Gfgcugauags{invAb}	2108	ACUAUCAGCC AUUUAAUAUA UUU	2738	asCfsuaucAf gccauuUfaAf uauaususu	3368
41422-1	4441	CCACGUGGC CUCCUUGUG AC{invAb}	1479	cscsacguGfgCfCfUfUfC fcuugugacs{invAb}	2109	AGUCACAAGG AGGCCACGUG GUU	2739	asGfsucacAf aggaggCfcAf cguggsusu	3369
41423-1	4160	CGUGGGCCU GUUCUCUU GAU{invAb}	1480	csgsugggCfcUfGfUf Ufcucuugaus{invAb}	2110	UAUCAAGAGA ACAGGGCCCAC GUU	2740	usAfsucaaGf agaacaGfgCf ccacgsusu	3370
41424-1	4119	ACAGACCCU UUAAAGGA AAC{invAb}	1481	ascsagacCfcUfUfUfA faaggaaacs{invAb}	2111	AGUUUCCUUU AAAGGGUCUG UUU	2741	asGfsuuucCf uuuaaaGfgGf ucugususu	3371

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41425-1	262	CGGGGCGACCCGCUGCCUGA{invAb}	1482	csgsgggcGfaCfCfCfGfcugccugas{invAb}	2112	AUCAGGCAGCGGGUCGCCCCGUU	2742	asUfscaggCfagcgggUfcGfccccgsusu	3372
41426-1	258	ACGUCGGGGCGACCCGCUGC{invAb}	1483	ascsgucgGfgGfCfGfAfcccgcugcs{invAb}	2113	AGCAGCGGGUCGCCCCGACGUUU	2743	asGfscagcGfggucgcCfcCfgacgususu	3373
41427-1	257	CACGUCGGGGCGACCCGCUG{invAb}	1484	csascgucGfgGfGfCfGfacccgcugs{invAb}	2114	ACAGCGGGUCGCCCCGACGUGUU	2744	asCfsagcgGfgucgccCfcGfacgugsusu	3374
41428-1	142	UCCCGAUCCCGACCCAGAUC{invAb}	1485	uscscCfgaUfcCfCfGfAfcccagaucs{invAb}	2115	AGAUCUGGGUCGGGAUCGGGAUU	2745	asGfsaucuGfggucggGfaUfcgggasusu	3375
41429-1	22	UGGUCCGAGGGGGGCGGGC{invAb}	1486	usgsguccGfaGfGfGfGfGfgcgggggcs{invAb}	2116	AGCCCCCGCCCCCCUCGGACCAUU	2746	asGfsccccGfccccccUfcGfgaccasusu	3376
41430-1	21	AUGGUCCGAGGGGGGCGGGG{invAb}	1487	asusgguccCfgAfGfGfGfGfgfgggcgggggs{invAb}	2117	ACCCCCGCCCCCCCUCGGACCAUUU	2747	asCfscccgCfcccccuCfgGfaccaususu	3377
41908-1	360	UCCUCUCCGGUAUCCCGCUG{invAb}	1488	uscscucuCfcGfGfUfAfuccccgcugs{invAb}	2118	ACAGCGGGAUACCGGAGAGGAUU	2748	asCfsagcgGfgauaccGfgAfggagasusu	3378

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41909-1	490	CAAAUGCCU CCCGGCCAA UG{invAb}	1489	csasaaugCfcUfCfCfC fggccaaugs{invAb}	2119	ACAUUGGCCG GGAGGCAUUU GUU	2749	asCfsauugGf ccgggaGfgCf auuugsusu	3379
41910-1	510	UCCACCAGC UCAUCUCCG GC{invAb}	1490	uscscaccAfgCfUfCfA fucuccggcs{invAb}	2120	UGCCGGAGAU GAGCUGGUGG AUU	2750	usGfsccggAf gaugagCfuGf guggasusu	3380
41911-1	511	CCACCAGCU CAUCUCCGG CA{invAb}	1491	cscsaccaGfcUfCfAfU fcuccggcas{invAb}	2121	UUGCCGGAGA UGAGCUGGUG GUU	2751	usUfsgccgGf agaugaGfcUf gguggsusu	3381
41912-1	512	CACCAGCUC AUCUCCGGC AA{invAb}	1492	csasccagCfuCfAfUfC fuccggcaas{invAb}	2122	UUUGCCGGAG AUGAGGCUGG GUU	2752	usUfsugccGf gagaugAfgCf uggugsusu	3382
41913-1	513	ACCAGCUCA UCUCCGGCA AA{invAb}	1493	ascscagcUfcAfUfCfU fccggcaaas{invAb}	2123	UUUUGCCGGA GAUGAGCUGG UUU	2753	usUfsuugcCf ggagauGfaGf cuggususu	3383
41914-1	514	CCAGCUCAU CUCCGGCAA AA{invAb}	1494	cscsagcuCfaUfCfUfC fcggcaaaas{invAb}	2124	AUUUUGCCGG AGAUGAGCUG GUU	2754	asUfsuuugCf cggagaUfgAf gcuggsusu	3384
41915-1	515	CAGCUCAUC UCCGGCAAA AU{invAb}	1495	csasgcucAfuCfUfCfC fggcaaaaus{invAb}	2125	UAUUUUGCCG GAGAUGAGCU GUU	2755	usAfsuuuuGf ccggagAfuGf agcugsusu	3385

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41916-1	538	CAUCUCUCU UACCAGAG UGU{invAb}	1496	csasucucUfcUfUfAf Cfcagagugus{invAb}	2126	AACACUCUGG UAAGAGAGAU GUU	2756	asAfscacuCf ugguaaGfaGf agaugsusu	3386
41917-1	540	UCUCUCUUA CCAGAGUG UCU{invAb}	1497	uscsucucUfuAfCfCf Afgagugucus{invAb}	2127	AAGACACUCU GGUAAGAGAG AUU	2757	asAfsgacaCf ucugguAfaGf agagasusu	3387
41918-1	542	UCUCUUACC AGAGUGUC UGA{invAb}	1498	uscsucuuAfcCfAfGf Afgugucugas{invAb}	2128	AUCAGACACU CUGGUAAGAG AUU	2758	asUfscagaCf acucugGfuAf agagasusu	3388
41919-1	572	GUUCUGGU GUCUGACU UUCG{invAb}	1499	gsusucugGfuGfUfCf Ufgacuuucgs{invAb}	2129	ACGAAAGUCA GACACCAGAA CUU	2759	asCfsgaaaGf ucagacAfcCf agaacsusu	3389
41920-1	573	UUCUGGUG UCUGACUU UCGG{invAb}	1500	ususcuggUfgUfCfUf Gfacuuucggs{invAb}	2130	ACCGAAAGUC AGACACCAGA AUU	2760	asCfscgaaAf gucagaCfaCf cagaasusu	3390
41921-1	574	UCUGGUGU CUGACUUU GGU{invAb}	1501	uscsugguGfuCfUfGf Afcuuucggus{invAb}	2131	AACCGAAAGU CAGACACCAG AUU	2761	asAfsccgaAf agucagAfcAf ccagasusu	3391
41922-1	576	UGGUGUCU GACUUUCG GUCC{invAb}	1502	usgsguguCfuGfAfCf Ufuucgguccs{invAb}	2132	UGGACCGAAA GUCAGACACC AUU	2762	usGfsgaccGf aaagucAfgAf caccasusu	3392

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41923-1	583	UGACUUUC GGUCCAAA GACG{invAb}	1503	usgsacuuUfcGfGfUf Cfcaaagacgs{invAb}	2133	UCGUCUUUGG ACCGAAAGUC AUU	2763	usCfsgucuUf uggaccGfaAf agucasusu	3393
41924-1	584	GACUUUCG GUCCAAAG ACGA{invAb}	1504	gsascuuuCfgGfUfCf Cfaaagacgas{invAb}	2134	UUCGUCUUUG GACCGAAAGU CUU	2764	usUfscgucUf uuggacCfgAf aagucsusu	3394
41925-1	585	ACUUUCGG UCCAAAGAC GAA{invAb}	1505	ascsuuucGfgUfCfCf Afaagacgaas{invAb}	2135	AUUCGUCUUU GGACCGAAAG UUU	2765	asUfsucguCf uuuggaCfcGf aaagususu	3395
41926-1	603	AAGUCGUG GAUGCCUU GGUA{invAb}	1506	asasgucgUfgGfAfUf Gfccuugguas{invAb}	2136	AUACCAAGGC AUCCACGACU UUU	2766	asUfsaccaAf ggcaucCfaCf gacuususu	3396
41927-1	604	AGUCGUGG AUGCCUUG GUAU{invAb}	1507	asgsucguGfgAfUfGf Cfcuugguaus{invAb}	2137	AAUACCAAGG CAUCCACGAC UUU	2767	asAfsuaccAf aggcauCfcAf cgacususu	3397
41928-1	605	GUCGUGGA UGCCUUGG UAUG{invAb}	1508	gsuscgugGfaUfGfCf Cfuugguaugs{invAb}	2138	ACAUACCAAG GCAUCCACGA CUU	2768	asCfsauacCfa aggcaUfcCfa cgacsusu	3398
41929-1	615	CCUUGGUA UGUCCUGC UUC{invAb}	1509	cscsuuggUfaUfGfUf Ufccugcuucs{invAb}	2139	UGAAGCAGGA ACAUACCAAG GUU	2769	usGfsaagcAf ggaacaUfaCf caaggsusu	3399

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41930-1	688	GGAUGGAG GAGUGAGU GACA{invAb}	1510	gsgsauggAfgGfAfGf UfgagugacasAfgGfAfGf{invAb}	2140	UUGUCACUCA CUCCUCCAUCC UU	2770	usUfsgucaCf ucacucCfuCf cauccsusu	3400
41931-1	691	UGGAGGAG UGAGUGAC AACG{invAb}	1511	usgsgaggAfgUfGfAf GfugacaacgsAfgUfGfAf{invAb}	2141	ACGUUGUCAC UCACUCCUCC AUU	2771	asCfsguugUf cacucaCfuCf cuccasusu	3401
41932-1	692	GGAGGAGU GAGUGACA ACGU{invAb}	1512	gsgsaggaGfuGfAfGf UfgacaacgusAfgUfGfAf{invAb}	2142	UACGUUGUCA CUCACUCCUCC UU	2772	usAfscguuGf ucacucAfcUf ccuccsusu	3402
41933-1	693	GAGGAGUG AGUGACAA CGUA{invAb}	1513	gsasggagUfgAfGfUf GfacaacguasAfgUfGfAf{invAb}	2143	AUACGUUGUC ACUCACUCCU CUU	2773	asUfsacguUf gucacuCfaCf uccucsusu	3403
41934-1	694	AGGAGUGA GUGACAAC GUAC{invAb}	1514	asgsgaguGfaGfUfGf AfcaacguacsAfgUfGfAf{invAb}	2144	AGUACGUUGU CACUCACUCC UUU	2774	asGfsuacgUf ugucacUfcAf cuccususu	3404
41935-1	776	CCUAAAGUC AAGUCCACG AA{invAb}	1515	cscsuaaaGfuCfAfAf GfuccacgaasAfgUfGfAf{invAb}	2145	AUUCGUGGAC UUGACUUUAG GUU	2775	asUfsucguGf gacuugAfcUf uuaggsusu	3405
41936-1	777	CUAAAGUC AAGUCCACG AAC{invAb}	1516	csusaaagUfcAfAfGf UfccacgaacsAfgUfGfAf{invAb}	2146	AGUUCGUGGA CUUGACUUUA GUU	2776	asGfsuucgUf ggacuuGfaCf uuuagsusu	3406

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41937-1	778	UAAAGUCA AGUCCACGA ACU{invAb}	1517	usasaaguCfaAfGfUf Cfcacgaacus{invAb}	2147	AAGUUCGUGG ACUUGACUUU AUU	2777	asAfsguucGf uggacuUfgAf cuuuasusu	3407
41938-1	781	AGUCAAGU CCACGAACU UUC{invAb}	1518	asgsucaaGfuCfCfAfC fgaacuuucs{invAb}	2148	AGAAAGUUCG UGGACUUGAC UUU	2778	asGfsaaagUf ucguggAfcUf ugacususu	3408
41939-1	786	AGUCCACGA ACUUUCUUC AU{invAb}	1519	asgsuccaCfgAfAfCf Ufuucuucaus{invAb}	2149	AAUGAAGAAA GUUCGUGGAC UUU	2779	asAfsugaaGf aaaguuCfgUf ggacususu	3409
41940-1	788	UCCACGAAC UUUCUUCA UGU{invAb}	1520	uscscacgAfaCfUfUf Ufcuucaugus{invAb}	2150	AACAUGAAGA AAGUUCGUGG AUU	2780	asAfscaugAf agaaagUfuCf guggasusu	3410
41941-1	807	UGGACAUC ACCAAGCUC AGU{invAb}	1521	usgsgacaUfcAfCfCf Afagcucagus{invAb}	2151	AACUGAGCUU GGUGAUGUCC AUU	2781	asAfscugaGf cuugguGfaUf guccasusu	3411
41942-1	811	CAUCACCAA GCUCAGUCU AC{invAb}	1522	csasucacCfaAfGfCfU fcagucuacs{invAb}	2152	AGUAGACUGA GCUUGGUGAU GUU	2782	asGfsuagaCf ugagcuUfgGf ugaugsusu	3412
41943-1	813	UCACCAAGC UCAGUCUAC GC{invAb}	1523	uscsaccaAfgCfUfCfA fgucuacgcs{invAb}	2153	AGCGUAGACU GAGCUUGGUG AUU	2783	asGfscguaGf acugagCfuUf ggugasusu	3413

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41944-1	814	CACCAAGCU CAGUCUACG CC{invAb}	1524	csasccaaGfcUfCfAfG fucuacgccs{invAb}	2154	AGGCGUAGAC UGAGCUUGGU GUU	2784	asGfsgcguAf gacugaGfcUf uggugsusu	3414
41945-1	817	CAAGCUCAG UCUACGCCU CU{invAb}	1525	csasagcuCfaGfUfCfU facgccucus{invAb}	2155	AAGAGGCGUA GACUGAGCUU GUU	2785	asAfsgaggCf guagacUfgAf gcuugsusu	3415
41946-1	844	GAACCUCUA CCUUCUCUC GA{invAb}	1526	gsasaccuCfuAfCfCfU fucucucgas{invAb}	2156	AUCGAGAGAA GGUAGAGGUU CUU	2786	asUfscgagAf gaagguAfgAf gguucsusu	3416
41947-1	845	AACCUCUAC CUUCUCUCG AG{invAb}	1527	asasccucUfaCfCfUfU fcucucgags{invAb}	2157	UCUCGAGAGA AGGUAGAGGU UUU	2787	usCfsucgaGf agaaggUfaGf agguususu	3417
41948-1	848	CUCUACCUU CUCUCGAGA GC{invAb}	1528	csuscuacCfuUfCfUfC fucgagagcs{invAb}	2158	AGCUCUCGAG AGAAGGUAGA GUU	2788	asGfscucuCf gagagaAfgGf uagagsusu	3418
41949-1	853	CCUUCUCUC GAGAGCUU UUG{invAb}	1529	cscsuucuCfuCfGfAf Gfagcuuuugs{invAb}	2159	ACAAAAGCUC UCGAGAGAAG GUU	2789	asCfsaaaaGfc ucucgAfgAfg aaggsusu	3419
41950-1	854	CUUCUCUCG AGAGCUUU UGU{invAb}	1530	csusucucUfcGfAfGf Afgcuuuugus{invAb}	2160	AACAAAAGCU CUCGAGAGAA GUU	2790	asAfscaaaAf gcucucGfaGf agaagsusu	3420

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41951-1	855	UUCUCUCCGA GAGCUUUU GUC{invAb}	1531	ususcucuCfgAfGfAf Gfcuuuugucs{invAb}	2161	AGACAAAAGC UCUCGAGAGA AUU	2791	asGfsacaaAf agcucuCfgAf gagaasusu	3421
41952-1	856	UCUCUCGAG AGCUUUUG UCC{invAb}	1532	uscsucucGfaGfAfGf Cfuuuugucs{invAb}	2162	AGGACAAAAG CUCUCGAGAG AUU	2792	asGfsgacaAf aagcucUfcGf agagasusu	3422
41953-1	906	GCCUUCGAG GAUAUUUG GAU{invAb}	1533	gscscuucGfaGfGfAf Ufauuuggaus{invAb}	2163	AAUCCAAAUA UCCUCGAAGG CUU	2793	asAfsuccaAf auauccUfcGf aaggcsusu	3423
41954-1	907	CCUUCGAGG AUAUUUGG AUG{invAb}	1534	cscsuucgAfgGfAfUf Afuuuggaugs{invAb}	2164	ACAUCCAAAU AUCCUCGAAG GUU	2794	asCfsauccAf aauaucCfuCf gaaggsusu	3424
41955-1	909	UUCGAGGA UAUUUGGA UGCA{invAb}	1535	ususcgagGfaUfAfUf Ufuggaugcas{invAb}	2165	AUGCAUCCAA AUAUCCUCGA AUU	2795	asUfsgcauCf caaauaUfcCf ucgaasusu	3425
41956-1	912	GAGGAUAU UUGGAUGC AUUC{invAb}	1536	gsasggauAfuUfUfGf Gfaugcauucs{invAb}	2166	UGAAUGCAUC CAAAUAUCCU CUU	2796	usGfsaaugCf auccaaAfuAf uccucsusu	3426
41957-1	916	AUAUUUGG AUGCAUUC AGGU{invAb}	1537	asusauuuGfgAfUfGf Cfauucaggus{invAb}	2167	AACCUGAAUG CAUCCAAAUA UUU	2797	asAfsccugAf augcauCfcAf aauaususu	3427

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41958-1	918	AUUUGGAU GCAUUCAG GUUC{invAb}	1538	asusuuggAfuGfCfAf Ufucagguucs{invAb}	2168	AGAACCUGAA UGCAUCCAAA UUU	2798	asGfsaaccUf gaaugcAfuCf caaaususu	3428
41959-1	919	UUUGGAUG CAUUCAGG UUCU{invAb}	1539	ususuggaUfgCfAfUf Ufcagguucus{invAb}	2169	AAGAACCUGA AUGCAUCCAA AUU	2799	asAfsgaacCf ugaaugCfaUf ccaaasusu	3429
41960-1	923	GAUGCAUU CAGGUUCU UGGA{invAb}	1540	gsasugcaUfuCfAfGf Gfuucuuggas{invAb}	2170	UUCCAAGAAC CUGAAUGCAU CUU	2800	usUfsccaaGf aaccugAfaUf gcaucsusu	3430
42053-1	985	AUCCUCAGA AGGGAUGG AUC{invAb}	1541	asusccucAfgAfAfGf Gfgauggaucs{invAb}	2171	AGAUCCAUCC CUUCUGAGGA UUU	2801	asGfsauccAf ucccuuCfuGf aggaususu	3431
42054-1	989	UCAGAAGG GAUGGAUC CUGA{invAb}	1542	uscsagaaGfgGfAfUf Gfgauccugas{invAb}	2172	AUCAGGAUCC AUCCCUUCUG AUU	2802	asUfscaggAf uccaucCfcUf ucugasusu	3432
42055-1	992	GAAGGGAU GGAUCCUG AGGU{invAb}	1543	gsasagggAfuGfGfAf Ufccugaggus{invAb}	2173	AACCUCAGGA UCCAUCCCUU CUU	2803	asAfsccucAf ggauccAfuCf ccuucsusu	3433
42056-1	995	GGGAUGGA UCCUGAGG UCGC{invAb}	1544	gsgsgaugGfaUfCfCf Ufgaggucgcs{invAb}	2174	AGCGACCUCA GGAUCCAUCC CUU	2804	asGfscgacCf ucaggaUfcCf aucccsusu	3434

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
42057-1	1009	GGUCGCCAUGCCCAGCUGGG{invAb}	1545	gsgsucgcCfaUfGfCfCfCfagcuggggs{invAb}	2175	ACCCAGCUGGGCAUGGCGACCUU	2805	asCfsccagCfugggcaUfgGfcgaccsusu	3435
42058-1	1040	CUGGAUUCUUCCCCGGAGUC{invAb}	1546	csusggauUfcUfUfUfCfCfccggagucs{invAb}	2176	AGACUCCGGGGAAGAAUCCAGUU	2806	asGfsacucCfgggaaGfaAfuccagsusu	3436
42059-1	1044	AUUCUUCCCCGGAGUCGGCU{invAb}	1547	asusucuuCfcCfCfCfGfGfagucggcus{invAb}	2177	AAGCCGACUCCGGGGAAGAAUUU	2807	asAfsgccgAfcuccggGfgAfagaaususu	3437
42060-1	1229	CUACCCAUUAGGAUAAUGUC{invAb}	1548	csusacccAfuUfAfGfGfGfauaaugucs{invAb}	2178	AGACAUUAUCCUAAUGGGUAGUU	2808	asGfsacauUfauccuaAfuGfgguagsusu	3438
42061-1	1230	UACCCAUUAGGAUAAUGUCU{invAb}	1549	usascccaUfuAfGfGfGfAfuaaugucus{invAb}	2179	AAGACAUUAUCCUAAUGGGUAUU	2809	asAfsgacaUfuauccuAfaUfggguasusu	3439
42062-1	1236	UUAGGAUAAUGUCUUAUGUA{invAb}	1550	ususaggaUfaAfUfUfGfUfcuuauguas{invAb}	2180	UUACAUAAGACAUUAUCCUAAUU	2810	usUfsacauAfagacauUfaUfccuaasusu	3440
42063-1	1237	UAGGAUAAUGUCUUAUGUAA{invAb}	1551	usasggauAfaUfGfUfCfUfuuauguaas{invAb}	2181	AUUACAUAAGACAUUAUCCUAUU	2811	asUfsuacaUfaagacaUfuAfuccuasusu	3441

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
42064-1	1240	GAUAAUGU CUUAUGUA AUGC{invAb}	1552	gsasuaauGfuCfUfUf Afuguaaugcs{invAb}	2182	AGCAUUACAU AAGACAUUAU CUU	2812	asGfscauuAf cauaagAfcAf uuaucsusu	3442
42065-1	1250	UAUGUAAU GCUGCCCUG UAC{invAb}	1553	usasuguaAfuGfCfUf Gfcccuguacs{invAb}	2183	AGUACAGGGC AGCAUUACAU AUU	2813	asGfsuacaGf ggcagcAfuUf acauasusu	3443
42066-1	1266	GUACCCUGC CUGUGGAA UCU{invAb}	1554	gsusacccUfgCfCfUf Gfuggaaucus{invAb}	2184	AAGAUUCCAC AGGCAGGGUA CUU	2814	asAfsgauuCf cacaggCfaGf gguacsusu	3444
42067-1	1268	ACCCUGCCU GUGGAAUC UGC{invAb}	1555	ascscccugCfcUfGfUf Gfgaaucugcs{invAb}	2185	AGCAGAUUCC ACAGGCAGGG UUU	2815	asGfscagaUf uccacaGfgCf agggususu	3445
42068-1	1269	CCCUGCCUG UGGAAUCU GCC{invAb}	1556	cscscugcCfuGfUfGf Gfaaucugccs{invAb}	2186	UGGCAGAUUC CACAGGCAGG GUU	2816	usGfsgcagAf uuccacAfgGf cagggsusu	3446
42069-1	1324	AGAUAUGC CCGACGAUG UCC{invAb}	1557	asgsauauGfcCfCfGf Afcgauguccs{invAb}	2187	AGGACAUCGU CGGGCAUAUC UUU	2817	asGfsgacaUf cgucggGfcAf uaucususu	3447
42034-1	1371	UGUUCACUC GAGUGCUG AUG{invAb}	1558	usgsuucaCfuCfGfAf Gfugcugaugs{invAb}	2188	ACAUCAGCAC UCGAGUGAAC AUU	2818	asCfsaucaGf cacucgAfgUf gaacasusu	3448

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
42035-1	1376	ACUCGAGU GCUGAUGU GUCU{invAb}	1559	ascsucgaGfuGfCfUf Gfaugugucus{invAb}	2189	AAGACACAUC AGCACUCGAG UUU	2819	asAfsgacaCf aucagcAfcUf cgagususu	3449
42036-1	1417	AAUGCCAG UGAGCAGCC AAC{invAb}	1560	asasugccAfgUfGfAf Gfcagccaacs{invAb}	2190	UGUUGGCUGC UCACUGGCAU UUU	2820	usGfsuuggCf ugcucaCfuGf gcauususu	3450
42037-1	1445	CCAUGCACA CCUGAGCAG GA{invAb}	1561	cscsaugcAfcAfCfCfU fgagcaggas{invAb}	2191	AUCCUGCUCA GGUGUGCAUG GUU	2821	asUfsccugCf ucagguGfuGf cauggsusu	3451
42038-1	1450	CACACCUGA GCAGGACU GGC{invAb}	1562	csascaccUfgAfGfCfA fggacuggcs{invAb}	2192	AGCCAGUCCU GCUCAGGUGU GUU	2822	asGfsccagUf ccugcuCfaGf gugugsusu	3452
42039-1	1504	AGCAGAGA CCAAAGCAG AGG{invAb}	1563	asgscagaGfaCfCfAfA fagcagaggs{invAb}	2193	ACCUCUGCUU UGGUCUCUGC UUU	2823	asCfscucuGf cuuuggUfcUf cugcususu	3453
42040-1	1516	AGCAGAGG CCACCCCGC GGU{invAb}	1564	asgscagaGfgCfCfAfC fcccgcggus{invAb}	2194	AACCGCGGGG UGGCCUCUGC UUU	2824	asAfsccgcGf ggguggCfcUf cugcususu	3454
42041-1	1517	GCAGAGGCC ACCCCGCGG UC{invAb}	1565	gscsagagGfcCfAfCfC fccgcggucs{invAb}	2195	AGACCGCGGG GUGGCCUCUG CUU	2825	asGfsaccgCf ggggugGfcCf ucugcsusu	3455

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
42042-1	1553	CUGAACUUC UUCUUGGG CAA{invAb}	1566	csusgaacUfuCfUfUf Cfuugggcaas{invAb}	2196	AUUGCCCAAG AAGAAGUUCA GUU	2826	asUfsugccCf aagaagAfaGf uucagsusu	3456
42043-1	1554	UGAACUUC UUCUUGGG CAAU{invAb}	1567	usgsaacuUfcUfUfCf Ufugggcaaus{invAb}	2197	UAUUGCCCAA GAAGAAGUUC AUU	2827	usAfsuugcCf caagaaGfaAf guucasusu	3457
42044-1	1556	AACUUCUUC UUGGGCAA UAA{invAb}	1568	asascuucUfuCfUfUf Gfggcaauaas{invAb}	2198	UUUAUUGCCC AAGAAGAAGU UUU	2828	usUfsuauuGf cccaagAfaGf aaguususu	3458
42045-1	1557	ACUUCUUCU UGGGCAAU AAA{invAb}	1569	ascsuucuUfcUfUfGf Gfgcaauaaas{invAb}	2199	AUUUAUUGCC CAAGAAGAAG UUU	2829	asUfsuuauUf gcccaaGfaAf gaagususu	3459
42046-1	1558	CUUCUUCUU GGGCAAUA AAG{invAb}	1570	csusucuuCfuUfGfGf Gfcaauaaags{invAb}	2200	ACUUUAUUGC CCAAGAAGAA GUU	2830	asCfsuuuaUf ugcccaAfgAf agaagsusu	3460
42047-1	1560	UCUUCUUG GGCAAUAA AGUA{invAb}	1571	uscsuucuUfgGfGfCf Afauaaaguas{invAb}	2201	AUACUUUAUU GCCCAAGAAG AUU	2831	asUfsacuuUf auugccCfaAf gaagasusu	3461
42048-1	1561	CUUCUUGG GCAAUAAA GUAC{invAb}	1572	csusucuuGfgGfCfAf Afuaaaguacs{invAb}	2202	AGUACUUUAU UGCCCAAGAA GUU	2832	asGfsuacuUf uauugcCfcAf agaagsusu	3462

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
42049-1	1607	UUUCCCAGU UUUUCACU AGA{invAb}	1573	ususucccAfgUfUfUfUf Ufucacuagas{invAb}	2203	AUCUAGUGAA AAACUGGGAA AUU	2833	asUfscuagUf gaaaaaCfuGf ggaaasusu	3463
42050-1	1612	CAGUUUUU CACUAGAG AAGA{invAb}	1574	csasguuuUfuCfAfCf Ufagagaagas{invAb}	2204	AUCUUCUCUA GUGAAAAACU GUU	2834	asUfscuucUf cuagugAfaAf aacugsusu	3464
42051-1	1614	GUUUUUCA CUAGAGAA GAGU{invAb}	1575	gsusuuuuCfaCfUfAf Gfagaagagus{invAb}	2205	AACUCUUCUC UAGUGAAAAA CUU	2835	asAfscucuUf cucuagUfgAf aaaacsusu	3465
42052-1	1618	UUCACUAG AGAAGAGU CUGU{invAb}	1576	ususcacuAfgAfGfAf Afgagucugus{invAb}	2206	AACAGACUCU UCUCUAGUGA AUU	2836	asAfscagaCf ucuucuCfuAf gugaasusu	3466
44903-1	312	CGCGCAUGU UGUUCGGC GCU{invAb}	1577	csgscgcaUfgUfUfUfGf Ufucggcgcus{invAb}	2207	AAGCGCCGAA CAACAUGCGC GUU	2837	asAfsgcgcCf gaacaaCfaUf gcgcgsusu	3467
44904-1	774	GCCCUAAAG UCAAGUCCA CG{invAb}	1578	gscsccuaAfaGfUfCf Afaguccacgs{invAb}	2208	UCGUGGACUU GACUUUAGGG CUU	2838	usCfsguggAf cuugacUfuUf agggcsusu	3468
44905-1	812	AUCACCAAG CUCAGUCUA CG{invAb}	1579	asuscaccAfaGfCfUfC fagucuacgs{invAb}	2209	ACGUAGACUG AGCUUGGUGA UUU	2839	asCfsguagAf cugagcUfuGf gugaususu	3469

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44906-1	353	GUCGGCGUCCUCUCCGGUAU{invAb}	1580	gsuscggcGfuCfCfUfCfuccgguaus{invAb}	2210	AAUACCGGAGAGGACGCCGACUU	2840	asAfsuaccGfgagaggAfcGfccgacsusu	3470
44907-1	357	GCGUCCUCUCCCGGUAUCCCG{invAb}	1581	gscsguccUfcUfCfUfCfGfguaucccgs{invAb}	2211	ACGGGAUACCGGAGAGGACGCUU	2841	asCfsgggaUfaccggaGfaGfgacgcsusu	3471
44908-1	396	UCCUCUCAGAUCUUGUGCGG{invAb}	1582	uscscucuCfaGfAfUfCfuugugcggs{invAb}	2212	UCCGCACAAGAUCUGAGAGGAUU	2842	usCfscgcaCfaagaucUfgAfgaggasusu	3472
44909-1	397	CCUCUCAGAUCUUGUGCGGA{invAb}	1583	cscsucucAfgAfUfCfUfugugcggas{invAb}	2213	UUCCGCACAAGAUCUGAGAGGUU	2843	usUfsccgcAfcaagauCfuGfagaggsusu	3473
44910-1	442	CUUCCAUCCAUCCUUCAACU{invAb}	1584	csusuccaUfcCfAfUfUfCfcuucaacus{invAb}	2214	AAGUUGAAGGAUGGAUGGAAGUU	2844	asAfsguugAfaggaugGfaUfggaagsusu	3474
44911-1	445	CCAUCCAUCCUUCAACUUAA{invAb}	1585	cscsauccAfuCfCfUfUfUfcaacuuaas{invAb}	2215	AUUAAGUUGAAGGAUGGAUGUU	2845	asUfsuaagUfugaaggAfuGfgauggsusu	3475
44912-1	449	CCAUCCUUCAACUUAAGCAA{invAb}	1586	cscsauccUfuCfAfAfAfCfuuaagcaas{invAb}	2216	AUUGCUUAAGUUGAAGGAUGGUU	2846	asUfsugcuUfaagugAfaGfgauggsusu	3476

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44913-1	450	CAUCCUUCA ACUUAAGC AAG{invAb}	1587	csasuccuUfcAfAfCf Ufuaagcaags{invAb}	2217	ACUUGCUUAA GUUGAAGGAU GUU	2847	asCfsuugcUf uaaguuGfaAf ggaugsusu	3477
44914-1	459	ACUUAAGC AAGUUCCUC CGA{invAb}	1588	ascsuuaaGfcAfAfGf Ufuccuccgas{invAb}	2218	AUCGGAGGAA CUUGCUUAAG UUU	2848	asUfscggaGf gaacuuGfcUf uaagususu	3478
44915-1	1328	AUGCCCGAC GAUGUCCU GUG{invAb}	1589	asusgcccGfaCfGfAf Ufguccugugs{invAb}	2219	ACACAGGACA UCGUCGGGCA UUU	2849	asCfsacagGf acaucgUfcGf ggcaususu	3479
44916-1	1329	UGCCCGACG AUGUCCUG UGG{invAb}	1590	usgscccgAfcGfAfUf Gfuccuguggs{invAb}	2220	ACCACAGGAC AUCGUCGGGC AUU	2850	asCfscacaGf gacaucGfuCf gggcasusu	3480
44917-1	1332	CCGACGAUG UCCUGUGG UUG{invAb}	1591	cscsgacgAfuGfUfCf Cfugugguugs{invAb}	2221	ACAACCACAG GACAUCGUCG GUU	2851	asCfsaaccAfc aggacAfuCfg ucggsusu	3481
44918-1	1334	GACGAUGU CCUGUGGU UGCA{invAb}	1592	gsascgauGfuCfCfUf Gfugguugcas{invAb}	2222	AUGCAACCAC AGGACAUCGU CUU	2852	asUfsgcaaCf cacaggAfcAf ucgucsusu	3482
44919-1	1344	UGUGGUUG CAGUGGGU GACC{invAb}	1593	usgsuggu UfgCfAfGf Ufggugaccs{invAb}	2223	AGGUCACCCA CUGCAACCAC AUU	2853	asGfsgucaCf ccacugCfaAf ccacasusu	3483

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44920-1	1356	GGGUGACC UCACAGGU GUUC{invAb}	1594	gsgsgugaCfcUfCfCfAf Cfagguguucs{invAb}	2224	UGAACACCUG UGAGGUCACC CUU	2854	usGfsaacaCf cugugaGfgUf cacccsusu	3484
44921-1	1358	GUGACCUCA CAGGUGUU CAC{invAb}	1595	gsusgaccUfcAfCfAf Gfguguucacs{invAb}	2225	AGUGAACACC UGUGAGGUCA CUU	2855	asGfsugaaCf accuguGfaGf gucacsusu	3485
44922-1	1359	UGACCUCAC AGGUGUUC ACU{invAb}	1596	usgsaccuCfaCfAfGf Gfuguucacus{invAb}	2226	AAGUGAACAC CUGUGAGGUC AUU	2856	asAfsgugaAf caccugUfgAf ggucasusu	3486
44923-1	1361	ACCUCACAG GUGUUCAC UCG{invAb}	1597	ascscucaCfaGfGfUfG fuucacucgs{invAb}	2227	UCGAGUGAAC ACCUGUGAGG UUU	2857	usCfsgaguGf aacaccUfgUf gaggususu	3487
44924-1	1363	CUCACAGGU GUUCACUCG AG{invAb}	1598	csuscacaGfgUfGfUf Ufcacucgags{invAb}	2228	ACUCGAGUGA ACACCUGUGA GUU	2858	asCfsucgaGf ugaacaCfcUf gugagsusu	3488
44925-1	1364	UCACAGGU GUUCACUCG AGU{invAb}	1599	uscsacagGfuGfUfUf Cfacucgagus{invAb}	2229	AACUCGAGUG AACACCUGUG AUU	2859	asAfscucgAf gugaacAfcCf ugugasusu	3489
44926-1	1365	CACAGGUG UUCACUCGA GUG{invAb}	1600	csascaggUfgUfUfCf Afcucgagugs{invAb}	2230	ACACUCGAGU GAACACCUGU GUU	2860	asCfsacucGf agugaaCfaCf cugugsusu	3490

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44927-1	1366	ACAGGUGU UCACUCGAG UGC{invAb}	1601	ascsagguGfuUfCfAf CfucgagugcsUinvAb}	2231	AGCACUCGAG UGAACACCUG UUU	2861	asGfscacuCf gagugaAfcAf ccugususu	3491
44928-1	1367	CAGGUGUU CACUCGAGU GCU{invAb}	1602	csasggugUfuCfAfCf UfcgagugcusUinvAb}	2232	AAGCACUCGA GUGAACACCU GUU	2862	asAfsgcacUf cgagugAfaCf accugsusu	3492
44929-1	1373	UUCACUCGA GUGCUGAU GUG{invAb}	1603	ususcacuCfgAfGfUf GfcugaugugsUinvAb}	2233	ACACAUCAGC ACUCGAGUGA AUU	2863	asCfsacauCfa gcacuCfgAfg ugaasusu	3493
44930-1	1416	AAAUGCCA GUGAGCAG CCAA{invAb}	1604	asasaugcCfaGfUfGf AfgcagccaasUinvAb}	2234	AUUGGCUGCU CACUGGCAUU UUU	2864	asUfsuggcUf gcucacUfgGf cauuususu	3494
44931-1	1435	ACAGGCCUC CCCAUGCAC AC{invAb}	1605	ascsaggcCfuCfCfCfC faugcacacsUinvAb}	2235	AGUGUGCAUG GGGAGGCCUG UUU	2865	asGfsugugCf auggggAfgG fccugususu	3495
44932-1	1446	CAUGCACAC CUGAGCAG GAC{invAb}	1606	csasugcaCfaCfCfUfUfG fagcaggacsUinvAb}	2236	AGUCCUGCUC AGGUGUGCAU GUU	2866	asGfsuccuGf cucaggUfgUf gcaugsusu	3496
44933-1	1451	ACACCUGAG CAGGACUG GCC{invAb}	1607	ascsaccuGfaGfCfAfG fgacuggccsUinvAb}	2237	AGGCCAGUCC UGCUCAGGUG UUU	2867	asGfsgccaGf uccugcUfcAf ggugususu	3497

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44934-1	1497	GCUGUCCAG CAGAGACCA AA{invAb}	1608	gscsugucCfaGfCfAf Gfagaccaaas{invAb}	2238	AUUUGGUCUC UGCUGGACAG CUU	2868	asUfsuuggUf cucugcUfgGf acagcsusu	3498
44935-1	1500	GUCCAGCAG AGACCAAA GCA{invAb}	1609	gsusccagCfaGfAfGf Afccaaagcas{invAb}	2239	AUGCUUUGGU CUCUGCUGGA CUU	2869	asUfsgcuuUf ggucucUfgCf uggacsusu	3499
44936-1	1520	GAGGCCACC CCGCGGUCC AU{invAb}	1610	gsasggccAfcCfCfCfCfG fcgguccaus{invAb}	2240	AAUGGACCGC GGGGUGGCCU CUU	2870	asAfsuggaCf cgcgggGfuGf gccucsusu	3500
44937-1	966	CCCAGCCAG GCCUGAAG UCA{invAb}	1611	cscscagcCfaGfGfCfC fugaagucas{invAb}	2241	AUGACUUCAG GCCUGGCUGG GUU	2871	asUfsgacuUf caggccUfgGf cugggsusu	3501
44938-1	967	CCAGCCAGG CCUGAAGUC AU{invAb}	1612	cscsagccAfgGfCfCfU fgaagucaus{invAb}	2242	AAUGACUUCA GGCCUGGCUG GUU	2872	asAfsugacUf ucaggcCfuGf gcuggsusu	3502
44939-1	991	AGAAGGGA UGGAUCCU GAGG{invAb}	1613	asgsaaggGfaUfGfGf Afuccugaggs{invAb}	2243	ACCUCAGGAU CCAUCCCUUC UUU	2873	asCfscucaGf gauccaUfcCf cuucususu	3503
44940-1	994	AGGGAUGG AUCCUGAG GUCG{invAb}	1614	asgsggauGfgAfUfCf Cfugaggucgs{invAb}	2244	ACGACCUCAG GAUCCAUCCC UUU	2874	asCfsgaccUf caggauCfcAf ucccususu	3504

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44941-1	1003	UCCUGAGG UCGCCAUGC CCA{invAb}	1615	uscscugaGfgUfCfGf Cfcaugcccas{invAb}	2245	AUGGGCAUGG CGACCUCAGG AUU	2875	asUfsgggcAf uggcgaCfcUf caggasusu	3505
44942-1	1010	GUCGCCAUG CCCAGCUGG GC{invAb}	1616	gsuscgccAfuGfCfCf Cfagcugggcs{invAb}	2246	UGCCCAGCUG GGCAUGGCGA CUU	2876	usGfscccaGf cugggcAfuGf gcgacsusu	3506
44943-1	1020	CCAGCUGGG CAAACAUG AGU{invAb}	1617	cscsagcuGfgGfCfAf Afacaugagus{invAb}	2247	AACUCAUGUU UGCCCAGCUG GUU	2877	asAfscucaUf guuugcCfcAf gcuggsusu	3507
44944-1	1021	CAGCUGGGC AAACAUGA GUC{invAb}	1618	csasgcugGfgCfAfAf Afcaugagucs{invAb}	2248	AGACUCAUGU UUGCCCAGCU GUU	2878	asGfsacucAf uguuugCfcCf agcugsusu	3508
44945-1	1022	AGCUGGGC AAACAUGA GUCU{invAb}	1619	asgscuggGfcAfAfAf Cfaugagucus{invAb}	2249	AAGACUCAUG UUUGCCCAGC UUU	2879	asAfsgacuCf auguuuGfcCf cagcususu	3509
44946-1	1024	CUGGGCAA ACAUGAGU CUGG{invAb}	1620	csusgggcAfaAfCfAf Ufgagucuggs{invAb}	2250	UCCAGACUCA UGUUUGCCCA GUU	2880	usCfscagaCf ucauguUfuGf cccagsusu	3510
44947-1	1027	GGCAAACA UGAGUCUG GAUU{invAb}	1621	gsgscaaaCfaUfGfAf Gfucuggauus{invAb}	2251	AAAUCCAGAC UCAUGUUUGC CUU	2881	asAfsauccAf gacucaUfgUf uugccsusu	3511

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44948-1	1028	GCAAACAU GAGUCUGG AUUC{invAb}	1622	gscsaaacAfuGfAfGf Ufcuggauucs{invAb}	2252	AGAAUCCAGA CUCAUGUUUG CUU	2882	asGfsaaucCf agacucAfuGf uuugcsusu	3512
44949-1	1029	CAAACAUG AGUCUGGA UUCU{invAb}	1623	csasaacaUfgAfGfUfC fuggauucus{invAb}	2253	AAGAAUCCAG ACUCAUGUUU GUU	2883	asAfsgaauCf cagacuCfaUf guuugsusu	3513
44950-1	1042	GGAUUCUU CCCCGGAGU CGG{invAb}	1624	gsgsauucUfuCfCfCf Cfggagucggs{invAb}	2254	ACCGACUCCG GGGAAGAAUC CUU	2884	asCfscgacUf ccggggAfaGf aauccsusu	3514
44951-1	1051	CCCGGAGUC GGCUGCCUU GG{invAb}	1625	cscscggaGfuCfGfGf Cfugccuuggs{invAb}	2255	ACCAAGGCAG CCGACUCCGG GUU	2885	asCfscaagGf cagccgAfcUf ccgggsusu	3515
44952-1	1148	ACCCUCUCG CCCAGGCUC GC{invAb}	1626	ascsccucUfcGfCfCfC faggcucgcs{invAb}	2256	AGCGAGCCUG GGCGAGAGGG UUU	2886	asGfscgagCf cugggcGfaGf agggususu	3516
44953-1	1149	CCCUCUCGC CCAGGCUCG CU{invAb}	1627	cscscucuCfgCfCfCfA fggcucgcus{invAb}	2257	UAGCGAGCCU GGGCGAGAGG GUU	2887	usAfsgcgaGf ccugggCfgAf gagggsusu	3517
44954-1	1152	UCUCGCCCA GGCUCGCUA CA{invAb}	1628	uscsucgcCfcAfGfGf Cfucgcuacas{invAb}	2258	AUGUAGCGAG CCUGGGCGAG AUU	2888	asUfsguagCf gagccuGfgGf cgagasusu	3518

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
44955-1	1168	UACAGCACU GAGUGAAG AAA{invAb}	1629	usascagcAfcUfGfAf Gfugaagaaas{invAb}	2259	AUUUCUUCAC UCAGUGCUGU AUU	2889	asUfsuucuUf cacucaGfuGf cuguasusu	3519
44956-1	1233	CCAUUAGG AUAAUGUC UUAU{invAb}	1630	cscsauuaGfgAfUfAf Afugucuuaus{invAb}	2260	AAUAAGACAU UAUCCUAAUG GUU	2890	asAfsuaagAf cauuauCfcUf aauggsusu	3520
44957-1	1234	CAUUAGGA UAAUGUCU UAUG{invAb}	1631	csasuuagGfaUfAfAf Ufgucuuaugs{invAb}	2261	ACAUAAGACA UUAUCCUAAU GUU	2891	asCfsauaaGf acauuaUfcCf uaaugsusu	3521
45199-1	695	GGAGUGAG UGACAACG UACC{invAb}	1632	gsgsagugAfgUfGfAf Cfaacguaccs{invAb}	2262	AGGUACGUUG UCACUCACUC CUU	2892	asGfsguacGf uugucaCfuCf acuccsusu	3522
45200-1	696	GAGUGAGU GACAACGU ACCC{invAb}	1633	gsasgugaGfuGfAfCf Afacguacccs{invAb}	2263	AGGGUACGUU GUCACUCACU CUU	2893	asGfsgguaCf guugucAfcUf cacucsusu	3523
45201-1	1562	UUCUUGGG CAAUAAAG UACC{invAb}	1634	ususcuugGfgCfAfAf Ufaaaguaccs{invAb}	2264	AGGUACUUUA UUGCCCAAGA AUU	2894	asGfsguacUf uuauugCfcCf aagaasusu	3524
45202-1	493	AUGCCUCCC GGCCAAUG UCC{invAb}	1635	asusgccuCfcCfGfGfC fcaaugucc{invAb}	2265	UGGACAUUGG CCGGGAGGCA UUU	2895	usGfsgacaUf uggccgGfgAf ggcaususu	3525

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45203-1	822	UCAGUCUAC GCCUCUGCA CA{invAb}	1636	uscsaguc UfaCfGfCfC fucugcacas{invAb}	2266	AUGUGCAGAG GCGUAGACUG AUU	2896	asUfsgugcAf gaggcgUfaGf acugasusu	3526
45204-1	460	CUUAAGCA AGUUCCUCC GAC{invAb}	1637	csusuaagCfaAfGfUf Ufccuccgacs{invAb}	2267	UGUCGGAGGA ACUUGCUUAA GUU	2897	usGfsucggAf ggaacuUfgCf uuaagsusu	3527
45205-1	491	AAAUGCCUC CCGGCCAAU GU{invAb}	1638	asasaugcCfuCfCfCfG fgccaaugus{invAb}	2268	AACAUUGGCC GGGAGGCAUU UUU	2898	asAfscauuGf gccgggAfgGf cauuususu	3528
45206-1	492	AAUGCCUCC CGGCCAAUG UC{invAb}	1639	asasugccUfcCfCfGfG fccaaugucs{invAb}	2269	AGACAUUGGC CGGGAGGCAU UUU	2899	asGfsacauUf ggccggGfaGf gcauususu	3529
45207-1	1564	CUUGGGCA AUAAAGUA CCUG{invAb}	1640	csusugggCfaAfUfAf Afaguaccugs{invAb}	2270	ACAGGUACUU UAUUGCCCAA GUU	2900	asCfsagguAf cuuuauUfgCf ccaagsusu	3530
45208-1	327	GCGCUUUCGG CCGGGGCGU UG{invAb}	1641	gscsgcuuCfgGfCfCf Gfgggcguugs{invAb}	2271	ACAACGCCCC GGCCGAAGCG CUU	2901	asCfsaacgCfc ccggcCfgAfa gcgcsusu	3531
45209-1	1038	GUCUGGAU UCUUCCCCG GAG{invAb}	1642	gsuscuggAfuUfCfUf Ufccccggags{invAb}	2272	ACUCCGGGGA AGAAUCCAGA CUU	2902	asCfsuccgGf ggaagaAfuCf cagacsusu	3532

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45210-1	546	UUACCAGA GUGUCUGA UGGG{invAb}	1643	ususaccaGfaGfUfGf Ufcugaugggs{invAb}	2273	ACCCAUCAGA CACUCUGGUA AUU	2903	asCfsccauCfa gacacUfcUfg guaasusu	3533
45211-1	1347	GGUUGCAG UGGGUGAC CUCA{invAb}	1644	gsgsuugcAfgUfGfGf Gfugaccucas{invAb}	2274	AUGAGGUCAC CCACUGCAAC CUU	2904	asUfsgaggUf cacccaCfuGf caaccsusu	3534
45212-1	571	CGUUCUGG UGUCUGAC UUUC{invAb}	1645	csgsuucuGfgUfGfUf Cfugacuuucs{invAb}	2275	AGAAAGUCAG ACACCAGAAC GUU	2905	asGfsaaagUf cagacaCfcAf gaacgsusu	3535
45213-1	1081	GGAGGGAG AUGAGCUG CUAG{invAb}	1646	ggsgagggAfgAfUfGf Afgcugcuags{invAb}	2276	UCUAGCAGCU CAUCUCCCUCC UU	2906	usCfsuagcAf gcucauCfuCf ccuccsusu	3536
45214-1	792	CGAACUUUC UUCAUGUG GAC{invAb}	1647	csgsaacuUfuCfUfUf Cfauguggacs{invAb}	2277	UGUCCACAUG AAGAAAGUUC GUU	2907	usGfsuccaCf augaagAfaAf guucgsusu	3537
45215-1	1413	CCCAAAUGC CAGUGAGC AGC{invAb}	1648	cscscaaaUfgCfCfAfG fugagcagcs{invAb}	2278	AGCUGCUCAC UGGCAUUUGG GUU	2908	asGfscugcUf cacuggCfaUf uugggsusu	3538
45216-1	842	GGGAACCUC UACCUUUCUC UC{invAb}	1649	gsgsgaacCfuCfUfAf Cfcuucucucs{invAb}	2279	AGAGAGAAGG UAGAGGUUCC CUU	2909	asGfsagagAf agguagAfgGf uucccsusu	3539

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45217-1	790	CACGAACUU UCUUCAUG UGG{invAb}	1650	csascgaaCfuUfUfCfU fucauguggs{invAb}	2280	UCCACAUGAA GAAAGUUCGU GUU	2910	usCfscacaUf gaagaaAfgUf ucgugsusu	3540
45218-1	1184	GAAAUGAA AGACAAAG GUGG{invAb}	1651	gsasaaugAfaAfGfAf Cfaaagguggs{invAb}	2281	UCCACCUUUG UCUUUCAUUU CUU	2911	usCfscaccUf uugucuUfuCf auuucsusu	3541
45219-1	1262	CCCUGUACC CUGCCUGUG GA{invAb}	1652	cscscuguAfcCfCfUf Gfccuguggas{invAb}	2282	UUCCCACAGGC AGGGUACAGG GUU	2912	usUfsccacAf ggcaggGfuAf cagggsusu	3542
45220-1	1185	AAAUGAAA GACAAAGG UGGA{invAb}	1653	asasaugaAfaGfAfCf Afaagguggas{invAb}	2283	AUCCACCUUU GUCUUUCAUU UUU	2913	asUfsccacCf uuugucUfuU fcauuususu	3543
45221-1	1379	CGAGUGCU GAUGUGUC UGCU{invAb}	1654	csgsagugCfuGfAfUf Gfugucugcus{invAb}	2284	AAGCAGACAC AUCAGCACUC GUU	2914	asAfsgcagAf cacaucAfgCf acucgsusu	3544
45222-1	194	AUGUACGA CGCAGAGCG CGG{invAb}	1655	asusguacGfaCfGfCf Afgagcgcggs{invAb}	2285	ACCGCGCUCU GCGUCGUACA UUU	2915	asCfscgcgCf ucugcgUfcGf uacaususu	3545
45334-1	451	AUCCUUCAA CUUAAGCA AGU{invAb}	1656	asusccuuCfaAfCfUf Ufaagcaagus{invAb}	2286	AACUUGCUUA AGUUGAAGGA UUU	2916	asAfscuugCf uuaaguUfgAf aggaususu	3546

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45223-1	452	UCCUUCAACUUAAGCAAGUU{invAb}	1657	uscscuucAfaCfUfUfAfagcaaguus{invAb}	2287	AAACUUGCUUAAGUUGAAGGAUU	2917	asAfsacuuGfcuuaagUfuGfaaggasusu	3547
45224-1	489	GCAAAUGCCUCCCGGCCAAU{invAb}	1658	gscsaaauGfcCfUfCfCfCfcggccaaus{invAb}	2288	AAUUGGCCGGGAGGCAUUUGCUU	2918	asAfsuuggCfcgggagGfcAfuuugcsusu	3548
45225-1	1333	CGACGAUGUCCUGUGGUUGC{invAb}	1659	csgsacgaUfgUfCfCfUfgugguugcs{invAb}	2289	UGCAACCACAGGACAUCGUCGUU	2919	usGfscaacCfacaggaCfaUfcgucgsusu	3549
45226-1	317	AUGUUGUUCGGCGCUUCGGC{invAb}	1660	asusguugUfuCfGfGfCfgcuucggcs{invAb}	2290	AGCCGAAGCGCCGAACAACAUUU	2920	asGfsccgaAfgcgccgAfaCfaacaususu	3550
45227-1	321	UGUUCGGCGCUUCGGCGGG{invAb}	1661	usgsuucgGfcGfCfUfUfcggccgggs{invAb}	2291	ACCCGGCCGAAGCGCCGAACAUU	2921	asCfsccggCfcgaagcGfcCfgaacasusu	3551
45228-1	601	CGAAGUCGUGGAUGCCUUGG{invAb}	1662	csgsaaguCfgUfGfGfAfugccuuggs{invAb}	2292	ACCAAGGCAUCCACGACUUCGUU	2922	asCfscaagGfcauccaCfgAfcuucgsusu	3552
45229-1	782	GUCAAGUCCACGAACUUUCU{invAb}	1663	gsuscaagUfcCfAfCfGfaacuuucus{invAb}	2293	AAGAAAGUUCGUGGACUUGACUU	2923	asAfsgaaaGfuucgugGfaCfuugacsusu	3553

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45230-1	783	UCAAGUCCA CGAACUUUC UU{invAb}	1664	uscsaaguCfcAfCfGf Afacuuucuus{invAb}	2294	AAAGAAAGUU CGUGGACUUG AUU	2924	asAfsagaaAf guucguGfgA fcuugasusu	3554
45231-1	843	GGAACCUCU ACCUUCUCU CG{invAb}	1665	gsgsaaccUfcUfAfCfC fuucucucgs{invAb}	2295	UCGAGAGAAG GUAGAGGUUC CUU	2925	usCfsgagaGf aagguaGfaGf guuccsusu	3555
45232-1	857	CUCUCGAGA GCUUUUGU CCC{invAb}	1666	csuscucgAfgAfGfCf Ufuuugucccs{invAb}	2296	AGGGACAAAA GCUCUCGAGA GUU	2926	asGfsggacAf aaagcuCfuCf gagagsusu	3556
45233-1	354	UCGGCGUCC UCUCCGGUA UC{invAb}	1667	uscsggcgUfcCfUfCf Ufccgguaucs{invAb}	2297	AGAUACCGGA GAGGACGCCG AUU	2927	asGfsauacCf ggagagGfaCf gccgasusu	3557
45234-1	355	CGGCGUCCU CUCCGGUAU CC{invAb}	1668	csgsgcguCfcUfCfUf Cfcgguauccs{invAb}	2298	AGGAUACCGG AGAGGACGCC GUU	2928	asGfsgauaCf cggagaGfgAf cgccgsusu	3558
45235-1	364	CUCCGGUAU CCCGCUGGA GC{invAb}	1669	csusccggUfaUfCfCfC fgcuggagcs{invAb}	2299	UGCUCCAGCG GGAUACCGGA GUU	2929	usGfscuccAf gcgggaUfaCf cggagsusu	3559
45236-1	402	CAGAUCUU GUGCGGAA GGCC{invAb}	1670	csasgaucUfuGfUfGf Cfggaaggccs{invAb}	2300	UGGCCUUCCG CACAAGAUCU GUU	2930	usGfsgccuUf ccgcacAfaGf aucugsusu	3560

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45237-1	448	UCCAUCCUU CAACUUAA GCA{invAb}	1671	uscscaucCfuUfCfAf AfcuuaagcasAf{invAb}	2301	UUGCUUAAGU UGAAGGAUGG AUU	2931	usUfsgcuuAf aguugaAfgGf auggasusu	3561
45238-1	1501	UCCAGCAGA GACCAAAGC AG{invAb}	1672	uscscagcAfgAfGfAf CfcaaagcagsAf{invAb}	2302	UCUGCUUUGG UCUCUGCUGG AUU	2932	usCfsugcuUf uggucuCfuGf cuggasusu	3562
45239-1	988	CUCAGAAG GGAUGGAU CCUG{invAb}	1673	csuscagaAfgGfGfAf UfggauccugsAf{invAb}	2303	UCAGGAUCCA UCCCUUCUGA GUU	2933	usCfsaggaUf ccauccCfuUf cugagsusu	3563
45240-1	1006	UGAGGUCG CCAUGCCCA GCU{invAb}	1674	usgsagguCfgCfCfAf UfgcccagcusAf{invAb}	2304	AAGCUGGGCA UGGCGACCUC AUU	2934	asAfsgcugGf gcauggCfgAf ccucasusu	3564
45241-1	1013	GCCAUGCCC AGCUGGGC AAA{invAb}	1675	gscscaugCfcCfAfGfC fugggcaaasAf{invAb}	2305	AUUUGCCCAG CUGGGCAUGG CUU	2935	asUfsuugcCf cagcugGfgCf auggcsusu	3565
45242-1	1235	AUUAGGAU AAUGUCUU AUGU{invAb}	1676	asusuaggAfuAfAfUf GfucuuaugusAf{invAb}	2306	UACAUAAGAC AUUAUCCUAA UUU	2936	usAfscauaAf gacauuAfuCf cuaaususu	3566
45243-1	1239	GGAUAAUG UCUUAUGU AAUG{invAb}	1677	gsgsauaaUfgUfCfUf UfauguaaugsAf{invAb}	2307	ACAUUACAUA AGACAUUAUC CUU	2937	asCfsauuaCf auaagaCfaUf uauccsusu	3567

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45244-1	1248	CUUAUGUA AUGCUGCCC UGU{invAb}	1678	csusuaugUfaAfUfGf Cfugcccugus{invAb}	2308	UACAGGGCAG CAUUACAUAA GUU	2938	usAfscaggGf cagcauUfaCf auaagsusu	3568
45245-1	1264	CUGUACCCU GCCUGUGG AAU{invAb}	1679	csusguacCfcUfGfCfC fuguggaaus{invAb}	2309	AAUUCCACAG GCAGGGUACA GUU	2939	asAfsuuccAf caggcaGfgGf uacagsusu	3569
45246-1	1277	GUGGAAUC UGCCAUUGC GAU{invAb}	1680	gsusggaaUfcUfGfCf Cfauugcgaus{invAb}	2310	AAUCGCAAUG GCAGAUUCCA CUU	2940	asAfsucgcAf auggcaGfaUf uccacsusu	3570
45247-1	1494	AGGGCUGU CCAGCAGAG ACC{invAb}	1681	asgsggcuGfuCfCfAf Gfcagagaccs{invAb}	2311	UGGUCUCUGC UGGACAGCCC UUU	2941	usGfsgucuCf ugcuggAfcAf gcccususu	3571
45248-1	1439	GCCUCCCCCA UGCACACCU GA{invAb}	1682	gscscuccCfcAfUfGfC facaccugas{invAb}	2312	AUCAGGUGUG CAUGGGGAGG CUU	2942	asUfscaggUf gugcauGfgGf gaggcsusu	3572
45249-1	1039	UCUGGAUU CUUCCCCGG AGU{invAb}	1683	uscsuggaUfuCfUfUf Cfcccggagus{invAb}	2313	AACUCCGGGG AAGAAUCCAG AUU	2943	asAfscuccGf gggaagAfaUf ccagasusu	3573
45250-1	1357	GGUGACCUC ACAGGUGU UCA{invAb}	1684	gsgsugacCfuCfAfCf Afgguguucas{invAb}	2314	AUGAACACCU GUGAGGUCAC CUU	2944	asUfsgaacAf ccugugAfgGf ucaccsusu	3574

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45251-1	1354	GUGGGUGA CCUCACAGG UGU{invAb}	1685	gsusggguGfaCfCfUf Cfacaggugus{invAb}	2315	AACACCUGUG AGGUCACCCA CUU	2945	asAfscaccUf gugaggUfcAf cccacsusu	3575
45252-1	446	CAUCCAUCC UUCAACUU AAG{invAb}	1686	csasuccaUfcCfUfUfC faacuuaags{invAb}	2316	ACUUAAGUUG AAGGAUGGAU GUU	2946	asCfsuuaaGf uugaagGfaUf ggaugsusu	3576
45253-1	395	GUCCUCUCA GAUCUUGU GCG{invAb}	1687	gsusccucUfcAfGfAf Ufcuugugcgs{invAb}	2317	ACGCACAAGA UCUGAGAGGA CUU	2947	asCfsgcacAf agaucuGfaGf aggacsusu	3577
45254-1	358	CGUCCUCUC CGGUAUCCC GC{invAb}	1688	csgsuccuCfuCfCfGf Gfuaucccgcs{invAb}	2318	AGCGGGAUAC CGGAGAGGAC GUU	2948	asGfscgggAf uaccggAfgAf ggacgsusu	3578
45255-1	356	GGCGUCCUC UCCGGUAUC CC{invAb}	1689	gsgscgucCfuCfUfCf Cfgguaucccs{invAb}	2319	AGGGAUACCG GAGAGGACGC CUU	2949	asGfsggauAf ccggagAfgGf acgccsusu	3579
45256-1	352	CGUCGGCGU CCUCUCCGG UA{invAb}	1690	csgsucggCfgUfCfCf Ufcuccgguas{invAb}	2320	AUACCGGAGA GGACGCCGAC GUU	2950	asUfsaccgGf agaggaCfgCf cgacgsusu	3580
45257-1	608	GUGGAUGC CUUGGUAU GUUC{invAb}	1691	gsusggauGfcCfUfUf Gfguauguucs{invAb}	2321	AGAACAUACC AAGGCAUCCA CUU	2951	asGfsaacaUf accaagGfcAf uccacsusu	3581

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45258-1	606	UCGUGGAU GCCUUGGU AUGU{invAb}	1692	uscsguggAfuGfCfCf Ufugguaugus{invAb}	2322	AACAUACCAA GGCAUCCACG AUU	2952	asAfscauaCf caaggcAfuCf cacgasusu	3582
45259-1	351	GCGUCGGCG UCCUCUCCG GU{invAb}	1693	gscsgucgGfcGfUfCf Cfucuccggus{invAb}	2323	UACCGGAGAG GACGCCGACG CUU	2953	usAfsccggAf gaggacGfcCf gacgcsusu	3583
45260-1	318	UGUUGUUC GGCGCUUCG GCC{invAb}	1694	usgsuuguUfcGfGfCf Gfcuucggccs{invAb}	2324	AGGCCGAAGC GCCGAACAAC AUU	2954	asGfsgccgAf agcgccGfaAf caacasusu	3584
45261-1	467	AAGUUCCUC CGACAGGG UCU{invAb}	1695	asasguucCfuCfCfGf Afcagggucus{invAb}	2325	AAGACCCUGU CGGAGGAACU UUU	2955	asAfsgaccCf ugucggAfgG faacuusu	3585
45262-1	315	GCAUGUUG UUCGGCGCU UCG{invAb}	1696	gscsauguUfgUfUfCf Gfgcgcuucgs{invAb}	2326	ACGAAGCGCC GAACAACAUG CUU	2956	asCfsgaagCf gccgaaCfaAf caugcsusu	3586
45263-1	458	AACUUAAG CAAGUUCCU CCG{invAb}	1697	asascuuaAfgCfAfAf Gfuuccucccgs{invAb}	2327	UCGGAGGAAC UUGCUUAAGU UUU	2957	usCfsggagGf aacuugCfuUf aaguususu	3587
45264-1	197	UACGACGCA GAGCGCGGC UG{invAb}	1698	usascgacGfcAfGfAf Gfcgcggcugs{invAb}	2328	ACAGCCGCGC UCUGCGUCGU AUU	2958	asCfsagccGf cgcucuGfcGf ucguasusu	3588

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
39193-1	650	GGCCUUAUCCCUC CUUCCUUA	61	{sGalNAc3}ggcc uuAfuCfCfCfucc uuccuusa	313	UAAGGAAGG AGGGAUAAG GCCAC	565	usAfsaggAfaGfGfa gggAfuAfagccsas c	817
40430-1	768	ACAUCUGCCCUAA AGUCAAG{invAb}	62	{sGalNAc3}acau cuGfcCfCfUfAfa agucaags{invAb}	314	ACUUGACUUU AGGGCAGAUG UUU	566	asCfsuugaCfuuuag gGfcAfgaugususu	818
40624-1	832	CCUCUGCACAGGG AACCUCU{invAb}	63	{sGalNAc3}ccuc ugCfaCfAfGfGfg aaccucus{invAb}	315	UAGAGGUUCC CUGUGCAGAG GUU	567	usAfsgaggUfucccu gUfgCfagaggsusu	819
40625-1	220	CUUGUCCUUCGCG GGCUGCG{invAb}	64	{sGalNAc3}cuug ucCfuUfCfGfCfg ggcugcgs{invAb }	316	ACGCAGCCCG CGAAGGACAA GUU	568	asCfsgcagCfccgcga AfgGfacaagsusu	820
40626-1	1092	AGCUGCUAGACCA CCUGCGU{invAb}	65	{sGalNAc3}agcu gcUfaGfArCfCfa ccugcgus{invAb}	317	AACGCAGGUG GUCUAGCAGC UUU	569	asAfscgcaGfguggu cUfaGfcagcususu	821
40627-1	905	UGCCUUCGAGGAU AUUUGGA{invAb}	66	{sGalNAc3}ugcc uuCfgAfGfGfAf uauuuggas{invA b}	318	AUCCAAAUAU CCUCGAAGGC AUU	570	asUfsccaaAfuauccu CfgAfaggcasusu	822
40627-2	905	UGCCUUCGAGGAU AUUUGGA{invAb}	67	{sGalNAc3}ugcc uuCfgAfGfGfAf uauuuggas{invA b}	319	AUCCAAAUAU CCUCGAAGGC AUU	571	asUfsccaaAfuauccu CfgAfaggcasusu	823
40628-1	767	GACAUCUGCCCUA AAGUCAA{invAb}	68	{sGalNAc3}gaca ucUfgCfCfCfUfa aagucaas{invAb}	320	AUUGACUUUA GGGCAGAUGU CUU	572	asUfsugacUfuuagg gCfaGfaugucsusu	824

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40633-1	766	CGACAUCUGCCCU AAAGUCA{invAb}	69	{sGalNAc3}cgac auCfuGfCfCfCfu aaagucas{invAb}	321	UUGACUUUAG GGCAGAUGUC GUU	573	usUfsgacuUfuaggg cAfgAfugucgsusu	825
40634-1	897	GAGAGAUAUGCC UUCGAGGA{invAb}	70	{sGalNAc3}gaga gaUfaUfGfCfCfu ucgaggas{invAb}	322	AUCCUCGAAG GCAUAUCUCU CUU	574	asUfsccucGfaaggca UfaUfcucucsusu	826
40635-1	1217	AUUUGCAACUUGC UACCCAU{invAb}	71	{sGalNAc3}auuu gcAfaCfUfUfGfc uacccaus{invAb}	323	AAUGGGUAGC AAGUUGCAAA UUU	575	asAfsugggUfagcaa gUfuGfcaaaususu	827
40636-1	309	ACGCGCGCAUGUU GUUCGGC{invAb}	72	{sGalNAc3}acgc gcGfcAfUfGfUfu guucggcs{invAb }	324	AGCCGAACAA CAUGCGCGCG UUU	576	asGfsccgaAfcaacau GfcGfcgcgususu	828
40637-1	1220	UGCAACUUGCUAC CCAUUAG{invAb}	73	{sGalNAc3}ugca acUfuGfCfUfAfc ccauuags{invAb}	325	ACUAAUGGGU AGCAAGUUGC AUU	577	asCfsuaauGfgguag cAfaGfuugcasusu	829
40640-1	902	AUAUGCCUUCGAG GAUAUUU{invAb}	74	{sGalNAc3}auau gcCfuUfCfGfAfg gauauuus{invAb }	326	AAAAUAUCCU CGAAGGCAUA UUU	578	asAfsaauaUfccucga AfgGfcauaususu	830
40641-1	211	CGGCUGGAGCUUG UCCUUCG{invAb}	75	{sGalNAc3}cggc ugGfaGfCfUfUfg uccuucgs{invAb}	327	ACGAAGGACA AGCUCCAGCC GUU	579	asCfsgaagGfacaagc UfcCfagccgsusu	831
40642-1	899	GAGAUAUGCCUUC GAGGAUA{invAb}	76	{sGalNAc3}gaga uaUfgCfCfUfUfc gaggauas{invAb}	328	AUAUCCUCGA AGGCAUAUCU CUU	580	asUfsauccUfcgaagg CfaUfaucucsusu	832
40643-1	764	UACGACAUCUGCC CUAAAGU{invAb}	77	{sGalNAc3}uacg acAfuCfUfGfCfc cuaaagus{invAb}	329	AACUUUAGGG CAGAUGUCGU AUU	581	asAfscuuuAfgggca gAfuGfucguasusu	833

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
40644-1	1189	GAAAGACAAAGG UGGAUACA{invAb}	78	{sGalNAc3}gaaa gaCfaAfAfGfGfu ggauacas{invAb}	330	AUGUAUCCAC CUUUGUCUUU CUU	582	asUfsguauCfcaccuu UfgUfcuuucsusu	834
41310-1	895	GGGAGAGAUAUG CCUUCGAG{invAb}	79	{sGalNAc3}ggga gaGfaUfAfUfGfc cuucgags{invAb}	331	ACUCGAAGGC AUAUCUCUCC CUU	583	asCfsucgaAfggcaua UfcUfcucccsusu	835
41311-1	894	UGGGAGAGAUAU GCCUUCGA{invAb}	80	{sGalNAc3}uggg agAfgAfUfAfUf gccuucgas{invAb}	332	AUCGAAGGCA UAUCUCUCCC AUU	584	asUfscgaaGfgcauau CfuCfucccasusu	836
41312-1	1219	UUGCAACUUGCUA CCCAUUA{invAb}	81	{sGalNAc3}uugc aaCfuUfGfCfUfa cccauuas{invAb}	333	AUAAUGGGU AGCAAGUUGC AAUU	585	asUfsaaugGfguagc aAfgUfugcaasusu	837
41313-1	893	CUGGGAGAGAUA UGCCUUCG{invAb}	82	{sGalNAc3}cugg gaGfaGfAfUfAfu gccuucgs{invAb}	334	UCGAAGGCAU AUCUCUCCCA GUU	586	usCfsgaagGfcauauc UfcUfcccagsusu	838
41314-1	1213	CAAGAUUUGCAAC UUGCUAC{invAb}	83	{sGalNAc3}caag auUfuGfCfAfAfc uugcuacs{invAb}	335	AGUAGCAAGU UGCAAAUCUU GUU	587	asGfsuagcAfaguug cAfaAfucuugsusu	839
41315-1	1201	UGGAUACAUGAG CAAGAUUU{invAb}	84	{sGalNAc3}ugga uaCfaUfGfAfGfc aagauuus{invAb}	336	AAAAUCUUGC UCAUGUAUCC AUU	588	asAfsaaucUfugcuca UfgUfauccasusu	840
41316-1	878	CCGGAUCUCAAGG UGCUGGG{invAb}	85	{sGalNAc3}ccgg auCfuCfAfAfGfg ugcugggs{invAb}	337	UCCCAGCACC UUGAGAUCCG GUU	589	usCfsccagCfaccuug AfgAfuccggsusu	841
41317-1	347	CACUGCGUCGGCG UCCUCUC{invAb}	86	{sGalNAc3}cacu gcGfuCfGfGfCfg uccucucs{invAb}	338	AGAGAGGACG CCGACGCAGU GUU	590	asGfsagagGfacgccg AfcGfcagugsusu	842

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41318-1	1224	ACUUGCUACCCAU UAGGAUA{invAb}	87	{sGalNAc3}acuu gcUfaCfCfCfAfu uaggauas{invAb}	339	UUAUCCUAAU GGGUAGCAAG UUU	591	usUfsauccUfaaugg gUfaGfcaagususu	843
41319-1	1223	AACUUGCUACCCA UUAGGAU{invAb}	88	{sGalNAc3}aacu ugCfuAfCfCfCfa uuaggaus{invAb }	340	UAUCCUAAUG GGUAGCAAGU UUU	592	usAfsuccuAfauggg uAfgCfaaguususu	844
41320-1	756	AUGGGGAGUACG ACAUCUGC{invAb}	89	{sGalNAc3}augg ggAfgUfAfCfGfa caucugcs{invAb}	341	AGCAGAUGUC GUACUCCCCA UUU	593	asGfscagaUfgucgu aCfuCfcccaususu	845
41321-1	706	CAACGUACCCUUC AUUGAUG{invAb}	90	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb }	342	ACAUCAAUGA AGGGUACGUU GUU	594	asCfsaucaAfugaagg GfuAfcguugsusu	846
41321-2	706	CAACGUACCCUUC AUUGAUG{invAb}	91	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb }	343	ACAUCAAUGA AGGGUACGUU GU	595	asCfsaucaAfugaagg GfuAfcguugsus	847
41322-1	705	ACAACGUACCCUU CAUUGAU{invAb}	92	{sGalNAc3}acaa cgUfaCfCfCfUfu cauugaus{invAb}	344	AAUCAAUGAA GGGUACGUUG UUU	596	asAfsucaaUfgaagg gUfaCfguugususu	848
41323-1	662	CCUUCCUUCAGAG GCGUGCG{invAb}	93	{sGalNAc3}ccuu ccUfuCfAfGfAfg gcgugcgs{invAb }	345	UCGCACGCCU CUGAAGGAAG GUU	597	usCfsgcacGfccucug AfaGfgaaggsusu	849
41324-1	704	GACAACGUACCCU UCAUUGA{invAb}	94	{sGalNAc3}gaca acGfuAfCfCfCfu ucauugas{invAb}	346	AUCAAUGAAG GGUACGUUGU CUU	598	asUfscaauGfaaggg uAfcGfuugucsusu	850

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41325-1	641	UUCUACAGUGGCC UUAUCCC{invAb}	95	{sGalNAc3}uucu acAfgUfGfGfCfc uuaucccs{invAb}	347	AGGGAUAAG GCCACUGUAG AAUU	599	asGfsggauAfaggcc aCfuGfuagaasusu	851
41326-1	593	UCCAAAGACGAAG UCGUGGA{invAb}	96	{sGalNAc3}ucca aaGfaCfGfAfAfg ucguggas{invAb}	348	AUCCACGACU UCGUCUUUGG AUU	600	asUfsccacGfacuucg UfcUfuuggasusu	852
41327-1	392	CAGGUCCUCUCAG AUCUUGU{invAb}	97	{sGalNAc3}cagg ucCfuCfUfCfAfg aucuugus{invAb}	349	AACAAGAUCU GAGAGGACCU GUU	601	asAfscaagAfucuga gAfgGfaccugsusu	853
41327-2	392	CAGGUCCUCUCAG AUCUUGU{invAb}	98	{sGalNAc3}cagg ucCfuCfUfCfAfg aucuugus{invAb}	350	AACAAGAUCU GAGAGGACCU GUU	602	asAfscaagAfucuga gAfgGfaccugsusu	854
41328-1	391	GCAGGUCCUCUCA GAUCUUG{invAb}	99	{sGalNAc3}gcag guCfcUfCfUfUfCfa gaucuugs{invAb}	351	ACAAGAUCUG AGAGGACCUG CUU	603	asCfsaagaUfcugaga GfgAfccugcsusu	855
41329-1	1603	CACCUUUCCCAGU UUUUCAC{invAb}	100	{sGalNAc3}cacc uuUfcCfCfAfGfu uuuucacs{invAb}	352	AGUGAAAAAC UGGGAAAGG UGUU	604	asGfsugaaAfaacug gGfaAfagggusu	856
41330-1	1602	CCACCUUUCCCAG UUUUUCA{invAb}	101	{sGalNAc3}ccac cuUfuCfCfCfAfg uuuuucas{invAb}	353	AUGAAAAACU GGGAAAGGU GGUU	605	asUfsgaaaAfacugg gAfaAfgguggsusu	857
41331-1	701	AGUGACAACGUAC CCUUCAU{invAb}	102	{sGalNAc3}agug acAfaCfGfUfAfc ccuucaus{invAb}	354	AAUGAAGGG UACGUUGUCA CUUU	606	asAfsugaaGfgguac gUfuGfucacususu	858

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41332-1	698	GUGAGUGACAAC GUACCCUU{invAb}	103	{sGalNAc3}guga guGfaCfAfAfAfCfg uacccuus{invAb}	355	AAAGGGUACG UUGUCACUCA CUU	607	asAfsagggUfacguu gUfcAfcucacsusu	859
41332-2	698	GUGAGUGACAAC GUACCCUU{invAb}	104	{sGalNAc3}guga guGfaCfAfAfAfCfg uacccuus{invAb}	356	AAAGGGUACG UUGUCACUCA CUU	608	asAfsagggUfacguu gUfcAfcucacsusu	860
41333-1	590	CGGUCCAAAGACG AAGUCGU{invAb}	105	{sGalNAc3}cggu ccAfaAfGfAfCfg aagucgus{invAb}	357	AACGACUUCG UCUUUGGACC GUU	609	asAfscgacUfucguc uUfuGfgaccgsusu	861
41334-1	568	AAACGUUCUGGU GUCUGACU{invAb}	106	{sGalNAc3}aaac guUfcUfGfGfUf gucugacus{invA b}	358	AAGUCAGACA CCAGAACGUU UUU	610	asAfsgucaGfacacca GfaAfcguuususu	862
41335-1	1300	CCAGAGACUGGUG ACAUGGC{invAb}	107	{sGalNAc3}ccag agAfcUfGfGfUfg acauggcs{invAb}	359	AGCCAUGUCA CCAGUCUCUG GUU	611	asGfsccauGfucacca GfuCfucuggsusu	863
41336-1	671	AGAGGCGUGCGA UAUGUGGA{invAb}	108	{sGalNAc3}agag gcGfuGfCfGfAfu auguggas{invAb }	360	AUCCACAUAU CGCACGCCUC UUU	612	asUfsccacAfuaucgc AfcGfccucususu	864
41337-1	563	GGGGAAAACGUU CUGGUGUC{invAb}	109	{sGalNAc3}gggg aaAfaCfGfUfUfc uggugucs{invAb }	361	AGACACCAGA ACGUUUUCCC CUU	613	asGfsacacCfagaacg UfuUfucccсsusu	865
41338-1	562	UGGGGAAAACGU UCUGGUGU{invAb}	110	{sGalNAc3}uggg gaAfaAfCfGfUfu cuggugus{invAb }	362	AACACCAGAA CGUUUUCCCC AUU	614	asAfscaccAfgaacgu UfuUfccccasusu	866

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41338-2	562	UGGGGAAAACGU UCUGGUGU{invAb}	111	{sGalNAc3}uggg gaAfaAfCfGfUfu cuggugus{invAb }	363	AACACCAGAA CGUUUUCCCC AU	615	asAfscaccAfgaacgu UfuUfcccasus	867
41339-1	1322	CCAGAUAUGCCCG ACGAUGU{invAb}	112	{sGalNAc3}ccag auAfuGfCfCfCfg acgaugus{invAb}	364	AACAUCGUCG GGCAUAUCUG GUU	616	asAfscaucGfucggg cAfuAfucuggsusu	868
41340-1	1280	GAAUCUGCCAUUG CGAUUGU{invAb}	113	{sGalNAc3}gaau cuGfcCfAfUfUfg cgauugus{invAb }	365	AACAAUCGCA AUGGCAGAUU CUU	617	asAfscaauCfgcaaug GfcAfgauucsusu	869
41341-1	1226	UUGCUACCCAUUA GGAUAAU{invAb}	114	{sGalNAc3}uugc uaCfcCfAfUfUfa ggauaaus{invAb}	366	AAUUAUCCUA AUGGGUAGCA AUU	618	asAfsuuauCfcuaau gGfgUfagcaasusu	870
41344-1	2197	AACACCUUUUUCA CCUAACU{invAb}	115	{sGalNAc3}aaca ccUfuUfUfUfCfa ccuaacus{invAb}	367	UAGUUAGGU GAAAAAGGU GUUUU	619	usAfsguuaGfgugaa aAfaGfguguususu	871
41345-1	1760	UCUGAGCUGAGU UGGUUUUA{invAb}	116	{sGalNAc3}ucug agCfuGfAfGfUfu gguuuuas{invAb }	368	AUAAAACCAA CUCAGCUCAG AUU	620	asUfsaaaaCfcaacuc AfgCfucagasusu	872
41346-1	1763	GAGCUGAGUUGG UUUUAUGA{invAb}	117	{sGalNAc3}gagc ugAfgUfUfGfGf uuuuaugas{invA b}	369	UUCAUAAAAC CAACUCAGCU CUU	621	usUfscauuAfaaccaa CfuCfagcucsusu	873
41347-1	1764	AGCUGAGUUGGU UUUAUGAA{invAb}	118	{sGalNAc3}agcu gaGfuUfGfGfUf uuuaugaas{invA b}	370	UUUCAUAAAA CCAACUCAGC UUU	622	usUfsucauAfaaacca AfcUfcagcususu	874

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
41348-1	1771	UUGGUUUUAUGA AAAGCUAG{invAb}	119	{sGalNAc3}uugg uuUfuAfUfGfAf aaagcuags{invAb}	371	ACUAGCUUUU CAUAAAACCA AUU	623	asCfsuagcUfuuuca uAfaAfaccaasusu	875
41349-1	1890	CAGAGGGUCCCUU ACUGACU{invAb}	120	{sGalNAc3}caga ggGfuCfCfCfUfu acugacus{invAb}	372	AAGUCAGUAA GGGACCCUCU GUU	624	asAfsgucaGfuaagg gAfcCfcucugsusu	876
41350-1	2198	ACACCUUUUUCAC CUAACUA{invAb}	121	{sGalNAc3}acac cuUfuUfUfCfAfc cuaacuas{invAb}	373	UUAGUUAGG UGAAAAAGG UGUUU	625	usUfsaguuAfgguga aAfaAfgggugsusu	877
41351-1	2199	CACCUUUUUCACC UAACUAA{invAb}	122	{sGalNAc3}cacc uuUfuUfCfAfCfc uaacuaas{invAb}	374	UUUAGUUAG GUGAAAAAG GUGUU	626	usUfsuaguUfaggug aAfaAfagggugsusu	878
41352-1	2200	ACCUUUUUCACCU AACUAAA{invAb}	123	{sGalNAc3}accu uuUfuCfAfCfCfu aacuaaas{invAb}	375	UUUUAGUUA GGUGAAAAA GGUUU	627	usUfsuuagUfuaggu gAfaAfaaggugsusu	879
41353-1	2201	CCUUUUUCACCUA ACUAAAA{invAb}	124	{sGalNAc3}ccuu uuUfcAfCfCfCfUfa acuaaaas{invAb}	376	AUUUUAGUU AGGUGAAAA AGGUU	628	asUfsuuuaGfuuagg uGfaAfaaaggsusu	880
41354-1	2202	CUUUUUCACCUAA CUAAAAU{invAb}	125	{sGalNAc3}cuuu uuCfaCfCfUfUfAfa cuaaaaus{invAb}	377	UAUUUUAGU UAGGUGAAA AAGUU	629	usAfsuuuuAfguuag gUfgAfaaaagsusu	881
41355-1	2204	UUUUCACCUAACU AAAAUAA{invAb}	126	{sGalNAc3}uuuu caCfcUfAfAfCfu aaaauaas{invAb}	378	AUUAUUUUA GUUAGGUGA AAAUU	630	asUfsuauuUfuaguu aGfgUfgaaaasusu	882
43781-1	767	GACAUCUGCCCUA AAGUCAA{invAb}	127	{sGalNAc3}gaca ucUfgCfCfCfUfa aagucaas{invAb}	379	AUUGACUUUA GGGCAGAUGU C	631	asUfsugacUfuuagg gCfaGfaugsusc	883

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
43782-1	1280	GAAUCUGCCAUUG CGAUUGU{invAb}	128	{sGalNAc3}gaau cuGfcCfAfUfUfg cgauugus{invAb}	380	AACAAUCGCA AUGGCAGAUU C	632	asAfscaauCfgcaaug GfcAfgaususc	884
43782-2	1280	GAAUCUGCCAUUG CGAUUGU{invAb}	129	{sGalNAc3}gaau cuGfcCfAfUfUfg cgauugus{invAb}	381	AACAAUCGCA AUGGCAGAUU C	633	asAfscaauCfgcaaug GfcAfgaususc	885
43783-1	706	CAACGUACCCUUC AUUGAUG{invAb}	130	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb}	382	ACAUCAAUGA AGGGUACGUU G	634	asCfsaucaAfugaagg GfuAfcgususg	886
43783-2	706	CAACGUACCCUUC AUUGAUG{invAb}	131	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb}	383	ACAUCAAUGA AGGGUACGUU G	635	asCfsaucaAfugaagg GfuAfcgususg	887
43784-1	704	GACAACGUACCCU UCAUUGA{invAb}	132	{sGalNAc3}gaca acGfuAfCfCfCfu ucauugas{invAb}	384	AUCAAUGAAG GGUACGUUGU C	636	asUfscaauGfaaggg uAfcGfuugsusc	888
43785-1	211	CGGCUGGAGCUUG UCCUUCG{invAb}	133	{sGalNAc3}cggc ugGfaGfCfUfUfg uccuucgs{invAb}	385	ACGAAGGACA AGCUCCAGCC G	637	asCfsgaagGfacaagc UfcCfagcscsg	889
43787-1	767	CAUCUGCCCUAAA GUCAAUU{invAb}	134	{sGalNAc3}cauc UfgCfCfCfUfaaa gucaausus{invAb}	386	AUUGACUUUA GGGCAGAUGU U	638	asUfsugacUfuuagg gCfaGfaugsusu	890
43788-1	1280	GUCUGCCAUUGCG AUUGUUU{invAb}	135	{sGalNAc3}gucu GfcCfAfUfUfgcg auugususs{invAb}	387	AACAAUCGCA AUGGCAGACU U	639	asAfscaauCfgcaaug GfcAfgacsusu	891

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
43789-1	706	GCGUACCCUUCAU UGAUGUU{invAb}	136	{sGalNAc3}gcgu AfcCfCfUfUfcau ugaugusus{invA b}	388	ACAUCAAUGA AGGGUACGCU U	640	asCfsaucaAfugaagg GfuAfcgcsusu	892
43790-1	704	CAACGUACCCUUC AUUGAUU{invAb}	137	{sGalNAc3}caac GfuAfCfCfCfuuc auugausus{invAb }	389	AUCAAUGAAG GGUACGUUGU U	641	asUfscaauGfaaggg uAfcGfuugsusu	893
43791-1	211	GCUGGAGCUUGUC CUUCGUU{invAb}	138	{sGalNAc3}gcug GfaGfCfUfUfguc cuucgusus{invAb }	390	ACGAAGGACA AGCUCCAGCU U	642	asCfsgaagGfacaagc UfcCfagcsusu	894
43793-1	767	GACAUCUGCCCUA AAGUCAA{invAb}	139	{sGalNAc3}gaca ucUfgCfCfCfUfa aagucaas{invAb}	391	AUUGACUUUA GGGCAGAUGU CUU	643	asUfsugacUfuuagG fgCfaGfaugucsusu	895
43794-1	1280	GAAUCUGCCAUUG CGAUUGU{invAb}	140	{sGalNAc3}gaau cuGfcCfAfUfUfg cgauugus{invAb }	392	AACAAUCGCA AUGGCAGAUU CUU	644	asAfscaauCfgcaaUf gGfcAfgaucsusu	896
43795-1	706	CAACGUACCCUUC AUUGAUG{invAb}	141	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb }	393	ACAUCAAUGA AGGGUACGUU GUU	645	asCfsaucaAfugaaG fgGfuAfcguugsusu	897
43796-1	704	GACAACGUACCCU UCAUUGA{invAb}	142	{sGalNAc3}gaca acGfuAfCfCfCfu ucauugas{invAb}	394	AUCAAUGAAG GGUACGUUGU CUU	646	asUfscaauGfaaggG fuAfcGfuugucsusu	898
43797-1	211	CGGCUGGAGCUUG UCCUUCG{invAb}	143	{sGalNAc3}cggc ugGfaGfCfUfUfg uccuucgs{invAb}	395	ACGAAGGACA AGCUCCAGCC GUU	647	asCfsgaagGfacaaGf cUfcCfagccgsusu	899

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
43798-1	767	GACAUCUGCCCUAAAGUCAA{invAb}	144	{sGalNAc3}gacaucugCfcCfUfAfAfagucaas{invAb}	396	AUUGACUUUAGGGCAGAUGUCUU	648	asUfsugacUfuuagGfgCfagaugucsusu	900
43799-1	1280	GAAUCUGCCAUUGCGAUUGU{invAb}	145	{sGalNAc3}gaaucugcCfaUfUfGfCfgauugus{invAb}	397	AACAAUCGCAAUGGCAGAUUCUU	649	asAfscaauCfgcaaUfgGfcagauucsusu	901
43800-1	704	GACAACGUACCCUUCAUUGA{invAb}	146	{sGalNAc3}gacaacguAfcCfCfUfUfcauugas{invAb}	398	AUCAAUGAAGGGUACGUUGUCUU	650	asUfscaauGfaaggGfuAfcguugucsusu	902
43801-2	211	CGGCUGGAGCUUGUCCUUCG{invAb}	147	{sGalNAc3}cggcuggaGfcUfUfGfUfccuucgs{invAb}	399	ACGAAGGACAAGCUCCAGCCGUU	651	asCfsgaagGfacaaGfcUfccagccgsusu	903
43803-1	767	CAUCUGCCCUAAAGUCAAUU{invAb}	148	{sGalNAc3}caucUfgCfCfCfUfaaagucaausus{invAb}	400	AUUGACUUUAGGGCAGAUGUU	652	asUfsugacUfuuagGfgCfaGfaugsusu	904
43804-1	1280	GUCUGCCAUUGCGAUUGUUU{invAb}	149	{sGalNAc3}gucuGfcCfAfUfUfgcgauuguusus{invAb}	401	AACAAUCGCAAUGGCAGACUU	653	asAfscaauCfgcaaUfgGfcAfgacsusu	905
43805-1	706	GCGUACCCUUCAUUGAUGUU{invAb}	150	{sGalNAc3}gcguAfcCfCfUfUfcaugaugusus{invAb}	402	ACAUCAAUGAAGGGUACGCUU	654	asCfsaucaAfugaaGfgGfuAfcgcsusu	906
43806-1	704	CAACGUACCCUUCAUUGAUU{invAb}	151	{sGalNAc3}caacGfuAfCfCfCfuucauugausus{invAb}	403	AUCAAUGAAGGGUACGUUGUU	655	asUfscaauGfaaggGfuAfcGfuugsusu	907

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
43806-2	704	CAACGUACCCUUC AUUGAUU{invAb}	152	{sGalNAc3}caac GfuAfCfCfCfuuc auugausus{invAb}	404	AUCAAUGAAG GGUACGUUGU	656	asUfscaauGfaaggG fuAfcGfuugsus	908
43807-2	211	GCUGGAGCUUGUC CUUCGUU{invAb}	153	{sGalNAc3}gcug GfaGfCfUfUfguc cuucgusus{invAb}	405	ACGAAGGACA AGCUCCAGCU U	657	asCfsgaagGfacaaGf cUfcCfagcsusu	909
43808-1	767	GACAUCUGCCCUA AAGUCAA{invAb}	154	{sGalNAc3}gaca ucUfgCfCfCfUfa aagucaas{invAb}	406	AUUGACUUUA GGGCAGAUGU C	658	asUfsugacUfuuagG fgCfaGfaugsusc	910
43808-2	767	GACAUCUGCCCUA AAGUCAA{invAb}	155	{sGalNAc3}gaca ucUfgCfCfCfUfa aagucaas{invAb}	407	AUUGACUUUA GGGCAGAUGU C	659	asUfsugacUfuuagG fgCfaGfaugsusc	911
43809-1	1280	GAAUCUGCCAUUG CGAUUGU{invAb}	156	{sGalNAc3}gaau cuGfcCfAfUfUfg cgauugus{invAb}	408	AACAAUCGCA AUGGCAGAUU C	660	asAfscaauCfgcaaUf gGfcAfgaususc	912
43810-1	706	CAACGUACCCUUC AUUGAUG{invAb}	157	{sGalNAc3}caac guAfcCfCfUfUfc auugaugs{invAb}	409	ACAUCAAUGA AGGGUACGUU G	661	asCfsaucaAfugaaG fgGfuAfcgususg	913
43811-1	704	GACAACGUACCCU UCAUUGA{invAb}	158	{sGalNAc3}gaca acGfuAfCfCfCfu ucauugas{invAb}	410	AUCAAUGAAG GGUACGUUGU C	662	asUfscaauGfaaggG fuAfcGfuugsusc	914
43812-2	211	CGGCUGGAGCUUG UCCUUCG{invAb}	159	{sGalNAc3}cggc ugGfaGfCfUfUfg uccuucgs{invAb}	411	ACGAAGGACA AGCUCCAGCC	663	asCfsgaagGfacaaGf cUfcCfagcscs	915

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
46275-1	704	CAACGUACCCUUC AUUGA{invAb}	160	{sGalNAc3}caac GfuAfCfCfCfCfuuc auugas{invAb}	412	AUCAAUGAAG GGUACGUUGU U	664	asUfscaauGfaaggG fuAfcGfuugsusu	916
46275-2	704	CAACGUACCCUUC AUUGA{invAb}	161	{sGalNAc3}caac GfuAfCfCfCfCfuuc auugas{invAb}	413	AUCAAUGAAG GGUACGUUGU	665	asUfscaauGfaaggG fuAfcGfuugsus	917
46276-1	1379	CGAGUGCUGAUG UGUCUGCU{invAb}	162	{sGalNAc3}cgag ugCfuGfAfUfGf ugucugcus{invA b}	414	AAGCAGACAC AUCAGCACUC GUU	666	asAfsgcagAfcacauc AfgCfacucgsusu	918
46277-1	1185	AAAUGAAAGACA AAGGUGGA{invAb}	163	{sGalNAc3}aaau gaAfaGfAfCfAfa agguggas{invAb }	415	AUCCACCUUU GUCUUUCAUU UUU	667	asUfsccacCfuuuguc UfuUfcauuususu	919
46278-1	1184	GAAAUGAAAGAC AAAGGUGG{invAb}	164	{sGalNAc3}gaaa ugAfaAfGfAfCfa aagguggs{invAb }	416	UCCACCUUUG UCUUUCAUUU CUU	668	usCfscaccUfuuguc uUfuCfauuucsusu	920
46279-1	790	CACGAACUUUCUU CAUGUGG{invAb}	165	{sGalNAc3}cacg aaCfuUfUfCfUfu cauguggs{invAb }	417	UCCACAUGAA GAAAGUUCGU GUU	669	usCfscacaUfgaagaa AfgUfucgugsusu	921
46280-1	1562	UUCUUGGGCAAU AAAGUACC{invAb}	166	{sGalNAc3}uucu ugGfgCfAfAfUfa aaguaccs{invAb}	418	AGGUACUUUA UUGCCCAAGA AUU	670	asGfsguacUfuuauu gCfcCfaagaasusu	922
46280-2	1562	UUCUUGGGCAAU AAAGUACC{invAb}	167	{sGalNAc3}uucu ugGfgCfAfAfUfa aaguaccs{invAb}	419	AGGUACUUUA UUGCCCAAGA AU	671	asGfsguacUfuuauu gCfcCfaagaasus	923

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
46280-3	1562	UUCUUGGGCAAU AAAGUACC{invAb}	168	{sGalNAc3}uucu ugGfgCfAfAfUfa aaguaccs{invAb}	420	AGGUACUUUA UUGCCCAAGA AU	672	asGfsguacUfuuauu gCfcCfaagaasus	924
46281-1	842	GGGAACCUCUACC UUCUCUC{invAb}	169	{sGalNAc3}ggga acCfuCfUfAfCfc uucucucs{invAb}	421	AGAGAGAAG GUAGAGGUUC CCUU	673	asGfsagagAfaggua gAfgGfuucccsusu	925
46282-1	696	GAGUGAGUGACA ACGUACCC{invAb}	170	{sGalNAc3}gagu gaGfuGfAfCfAfa cguacccs{invAb}	422	AGGGUACGUU GUCACUCACU CUU	674	asGfsgguaCfguugu cAfcUfcacucsusu	926
46283-1	571	CGUUCUGGUGUCU GACUUUC{invAb}	171	{sGalNAc3}cguu cuGfgUfGfUfCfu gacuuucs{invAb}	423	AGAAAGUCAG ACACCAGAAC GUU	675	asGfsaaagUfcagaca CfcAfgaacgsusu	927
46284-1	695	GGAGUGAGUGAC AACGUACC{invAb}	172	{sGalNAc3}ggag ugAfgUfGfAfCfa acguaccs{invAb}	424	AGGUACGUUG UCACUCACUC CUU	676	asGfsguacGfuuguc aCfuCfacuccsusu	928
46285-1	1564	CUUGGGCAAUAA AGUACCUG{invAb}	173	{sGalNAc3}cuug ggCfaAfUfAfAfa guaccugs{invAb}	425	ACAGGUACUU UAUUGCCCAA GUU	677	asCfsagguAfcuuua uUfgCfccaagsusu	929
46287-1	6576	UAUAUCAAAACCC UUAUGGC{invAb}	174	{sGalNAc3}uaua ucAfaAfAfAfCfCfc uuauggcs{invAb}	426	UGCCAUAAGG GUUUUGAUA UAUU	678	usGfsccauAfagggu uUfuGfauauasusu	930
46288-1	2273	AAUUUUGUAUUA UGUGAAUC{invAb}	175	{sGalNAc3}aauu uuGfuAfUfUfAf ugugaaucs{invAb}	427	UGAUUCACAU AAUACAAAAU UUU	679	usGfsauucAfcauaa uAfcAfaaauususu	931
46289-1	2268	UGUUGAAUUUUG UAUUAUGU{invAb}	176	{sGalNAc3}uguu gaAfuUfUfUfGf uauuaugus{invAb}	428	AACAUAAUAC AAAAUUCAAC AUU	680	asAfscauaAfuacaaa AfuUfcaacasusu	932

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
46290-1	6676	UUUCAGCAUGAG AAAAUAAC{invAb}	177	{sGalNAc3}uuuc agCfaUfGfAfGfa aaauaacs{invAb}	429	AGUUAUUUUC UCAUGCUGAA AUU	681	asGfsuuauUfuucuc aUfgCfugaaasusu	933
46291-1	4119	ACAGACCCUUUAA AGGAAAC{invAb}	178	{sGalNAc3}acag acCfcUfUfUfAfa aggaaacs{invAb}	430	AGUUUCCUUU AAAGGGUCUG UUU	682	asGfsuuucCfuuuaa aGfgGfucugususu	934
46292-1	1860	GGUUGGGAAAUG ACACCAGG{invAb}	179	{sGalNAc3}gguu ggGfaAfAfUfGfa caccaggs{invAb}	431	UCCUGGUGUC AUUUCCCAAC CUU	683	usCfscuggUfgucau uUfcCfcaaccsusu	935
46293-1	1858	CUGGUUGGGAAA UGACACCA{invAb}	180	{sGalNAc3}cugg uuGfgGfAfAfAf ugacaccas{invAb }	432	AUGGUGUCAU UUCCCAACCA GUU	684	asUfsggugUfcauuu cCfcAfaccagsusu	936
46294-1	6154	CUACCAUGCCUGG UCCAACA{invAb}	181	{sGalNAc3}cuac caUfgCfCfUfGfg uccaacas{invAb}	433	AUGUUGGACC AGGCAUGGUA GUU	685	asUfsguugGfaccag gCfaUfgguagsusu	937
46295-1	5707	UCUUCCUGAACCA CCUCUGG{invAb}	182	{sGalNAc3}ucuu ccUfgAfAfCfCfa ccucuggs{invAb}	434	UCCAGAGGUG GUUCAGGAAG AUU	686	usCfscagaGfguggu uCfaGfgaagasusu	938
46296-1	6635	UAUGUGUUGCCCA AGUUUCU{invAb}	183	{sGalNAc3}uaug ugUfuGfCfCfCfa aguuucus{invAb }	435	UAGAAACUUG GGCAACACAU AUU	687	usAfsgaaaCfuuggg cAfaCfacauasusu	939
46297-1	4113	GAGAAGACAGACC CUUUAAA{invAb}	184	{sGalNAc3}gaga agAfcAfGfAfCfc cuuuaaas{invAb}	436	AUUUAAAGG GUCUGUCUUC UCUU	688	asUfsuuaaAfggguc uGfuCfuucucsusu	940
46298-1	6637	UGUGUUGCCCAAG UUUCUAU{invAb}	185	{sGalNAc3}ugug uuGfcCfCfAfAfg uuucuaus{invAb }	437	AAUAGAAACU UGGGCAACAC AUU	689	asAfsuagaAfacuug gGfcAfacacasusu	941

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
46299-1	5819	ACUCUCAGGAAUA AUCAGUA{invAb}	186	{sGalNAc3}acuc ucAfgGfAfAfUfa aucaguas{invAb}	438	AUACUGAUUA UUCCUGAGAG UUU	690	asUfsacugAfuuauu cCfuGfagagususu	942
46300-1	5736	AUUGGCCUAUGA AUGCAUUC{invAb}	187	{sGalNAc3}auug gcCfuAfUfGfAfa ugcauucs{invAb}	439	AGAAUGCAUU CAUAGGCCAA UUU	691	asGfsaaugCfauucau AfgGfccaaususu	943
46301-1	4963	GUGAUUGUUAUC AGGAAAAA{invAb}	188	{sGalNAc3}guga uuGfuUfAfUfCfa ggaaaaas{invAb}	440	UUUUUUCCUG AUAACAAUCA CUU	692	usUfsuuuuCfcugau aAfcAfaucacsusu	944
46302-1	5579	AAGGAAAUCAGG AAGUGUAA{invAb}	189	{sGalNAc3}aagg aaAfuCfAfGfGfa aguguaas{invAb}	441	AUUACACUUC CUGAUUUCCU UUU	693	asUfsuacaCfuuccug AfuUfuccuususu	945
46303-1	4286	AGUGAGUUCCCAA GGCCUCU{invAb}	190	{sGalNAc3}agug agUfuCfCfCfAfa ggccucus{invAb}	442	AAGAGGCCUU GGGAACUCAC UUU	694	asAfsgaggCfcuugg gAfaCfucacususu	946
46304-1	4140	GGUUCUAGGGAC AAACUCUA{invAb}	191	{sGalNAc3}gguu cuAfgGfGfAfCfa aacucuas{invAb}	443	AUAGAGUUU GUCCCUAGAA CCUU	695	asUfsagagUfuuguc cCfuAfgaaccsusu	947
46304-2	4140	GGUUCUAGGGAC AAACUCUA{invAb}	192	{sGalNAc3}gguu cuAfgGfGfAfCfa aacucuas{invAb}	444	AUAGAGUUU GUCCCUAGAA CCU	696	asUfsagagUfuuguc cCfuAfgaaccsus	948
46305-1	4495	CAAGUUUCUUUUC CCAAGUU{invAb}	193	{sGalNAc3}caag uuUfcUfUfUfUfc ccaaguus{invAb}	445	AAACUUGGGA AAAGAAACUU GUU	697	asAfsacuuGfggaaaa GfaAfacuugsusu	949
46306-1	4132	AGGAAACGGGUU CUAGGGAC{invAb}	194	{sGalNAc3}agga aaCfgGfGfUfUfc uagggacs{invAb}	446	UGUCCCUAGA ACCCGUUUCC UUU	698	usGfsucccUfagaacc CfgUfuuccususu	950
46307-1	6163	CUGGUCCAACAUU CUUCAUU{invAb}	195	{sGalNAc3}cugg ucCfaAfCfAfUfu cuucauus{invAb}	447	AAAUGAAGA AUGUUGGACC AGUU	699	asAfsaugaAfgaaug uUfgGfaccagsusu	951

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
46308-1	3794	CUCCUUGCAUCUU CUCAUUC{invAb}	196	{sGalNAc3}cucc uuGfcAfUfCfUfu cucauucs{invAb}	448	AGAAUGAGA AGAUGCAAGG AGUU	700	asGfsaaugAfgaaga uGfcAfaggagsusu	952
46309-1	1917	GGCCCUAUUAAUG GUCAGAC{invAb}	197	{sGalNAc3}ggcc cuAfuUfAfAfUf ggucagacs{invAb}	449	AGUCUGACCA UUAAUAGGGCC CUU	701	asGfsucugAfccauu aAfuAfgggccsusu	953
46310-1	1666	AUUCUUUCAGAG GUGCUAAA{invAb}	198	{sGalNAc3}auuc uuUfcAfGfAfGf gugcuaaas{invAb}	450	AUUUAGCACC UCUGAAAGAA UUU	702	asUfsuuagCfaccucu GfaAfagaaususu	954
51579-1	1379	AGUGCUGAUGUG UCUGCUUU{invAb}	199	{sGalNAc3}agug cuGfaUfGfUfGfu cugcuusus{invAb}	451	AAGCAGACAC AUCAGCACUU U	703	asAfsgcagAfcacauc AfgCfacususu	955
51580-1	1184	AAUGAAAGACAA AGGUGGAU{invAb}	200	{sGalNAc3}aaug aaAfgAfCfAfAfa gguggasus{invAb}	452	UCCACCUUUG UCUUUCAUUU U	704	usCfscaccUfuuguc uUfuCfauususu	956
51581-1	1562	CUUGGGCAAUAA AGUACCUU{invAb}	201	{sGalNAc3}cuug ggCfaAfUfAfAfa guaccusus{invAb}	453	AGGUACUUUA UUGCCCAAGU U	705	asGfsguacUfuuauu gCfcCfaagsusu	957
51582-1	695	AGUGAGUGACAA CGUACCUU{invAb}	202	{sGalNAc3}agug agUfgAfCfAfAfc guaccusus{invAb}	454	AGGUACGUUG UCACUCACUU U	706	asGfsguacGfuuguc aCfuCfacususu	958
51583-1	1379	AGUGCUGAUGUG UCUGCUUU{invAb}	203	{sGalNAc3}agug CfuGfAfUfGfug	455	AAGCAGACAC AUCAGCACUU U	707	asAfsgcagAfcacauc AfgCfacususu	959

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
				ucugcuusus{invAb}					
51584-1	1184	AAUGAAAGACAAAGGUGGAU{invAb}	204	{sGalNAc3}aaugAfaAfGfAfCfaaagguggasus{invAb}	456	UCCACCUUUGUCUUUCAUUUU	708	usCfscaccUfuugucuUfuCfauususu	960
51585-1	1562	CUUGGGCAAUAAAGUACCUU{invAb}	205	{sGalNAc3}cuugGfgCfAfAfUfaaaguaccusus{invAb}	457	AGGUACUUUAUUGCCCAAGUU	709	asGfsguacUfuuauugCfcCfaagsusu	961
51586-1	695	AGUGAGUGACAACGUACCUU{invAb}	206	{sGalNAc3}agugAfgUfGfAfCfaacguaccusus{invAb}	458	AGGUACGUUGUCACUCACUUU	710	asGfsguacGfuuguccaCfuCfacususu	962
51587-1	1379	CGAGUGCUGAUGUGUCUGCU{invAb}	207	{sGalNAc3}cgagugCfuGfAfUfGfugucugcus{invAb}	459	AAGCAGACACAUCAGCACUCGUU	711	asAfsgcagAfcacaUfcAfgCfacucgsusu	963
51588-1	1184	GAAAUGAAAGACAAAGGUGG{invAb}	208	{sGalNAc3}gaaaugAfaAfGfAfCfaaagguggs{invAb}	460	UCCACCUUUGUCUUUCAUUUCUU	712	usCfscaccUfuuguCfuUfuCfauuucsusu	964
51589-1	1562	UUCUUGGGCAAUAAAGUACC{invAb}	209	{sGalNAc3}uucuugGfgCfAfAfUfaaaguaccs{invAb}	461	AGGUACUUUAUUGCCCAAGAAUU	713	asGfsguacUfuuauUfgCfcCfaagaasusu	965
51590-1	695	GGAGUGAGUGACAACGUACC{invAb}	210	{sGalNAc3}ggagugAfgUfGfAfCfaacguaccs{invAb}	462	AGGUACGUUGUCACUCACUCCUU	714	asGfsguacGfuuguCfaCfuCfacuccsusu	966

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
51591-1	1379	CGAGUGCUGAUG UGUCUGCU{invAb}	211	{sGalNAc3}cgag ugcuGfaUfGfUf Gfucugcus{invA b}	463	AAGCAGACAC AUCAGCACUC GUU	715	asAfsgcagAfcacaU fcAfgcacucgsusu	967
51592-1	1184	GAAAUGAAAGAC AAAGGUGG{invAb}	212	{sGalNAc3}gaaa ugaaAfgAfCfAf Afagguggs{invA b}	464	UCCACCUUUG UCUUUCAUUU CUU	716	usCfscaccUfuuguC fuUfucauuucsusu	968
51593-1	1562	UUCUUGGGCAAU AAAGUACC{invAb}	213	{sGalNAc3}uucu ugggCfaAfUfAf Afaguaccs{invAb }	465	AGGUACUUUA UUGCCCAAGA AUU	717	asGfsguacUfuuauU fgCfccaagaasusu	969
51594-1	695	GGAGUGAGUGAC AACGUACC{invAb}	214	{sGalNAc3}ggag ugagUfgAfCfAf Afcguaccs{invAb }	466	AGGUACGUUG UCACUCACUC CUU	718	asGfsguacGfuuguC faCfucacuccsusu	970
51595-1	1379	AGUGCUGAUGUG UCUGCUUU{invAb}	215	{sGalNAc3}agug CfuGfAfUfGfug ucugcuusus{invA b}	467	AAGCAGACAC AUCAGCACUU U	719	asAfsgcagAfcacaU fcAfgCfacususu	971
51596-1	1184	AAUGAAAGACAA AGGUGGAU{invAb}	216	{sGalNAc3}aaug AfaAfGfAfCfaaa gguggasus{invA b}	468	UCCACCUUUG UCUUUCAUUU U	720	usCfscaccUfuuguC fuUfuCfauususu	972
51597-1	1562	CUUGGGCAAUAA AGUACCUU{invAb}	217	{sGalNAc3}cuug GfgCfAfAfUfaaa guaccusus{invAb }	469	AGGUACUUUA UUGCCCAAGU U	721	asGfsguacUfuuauU fgCfcCfaagsusu	973

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
51598-1	695	AGUGAGUGACAA CGUACCUU{invAb}	218	{sGalNAc3}agug AfgUfGfAfCfaac guaccusus{invAb }	470	AGGUACGUUG UCACUCACUU U	722	asGfsguacGfuuguC faCfuCfacususu	974
51599-1	1379	AGUGCUGAUGUG UCUGCUUU{invAb}	219	{sGalNAc3}agug cuGfaUfGfUfGfu cugcuuus{invAb }	471	AAGCAGACAC AUCAGCACUU U	723	asAfsgcagAfcacaU fcAfgCfacususu	975
51600-1	1184	AAUGAAAGACAA AGGUGGAU{invAb}	220	{sGalNAc3}aaug aaAfgAfCfAfAfa gguggaus{invAb }	472	UCCACCUUUG UCUUUCAUUU U	724	usCfscaccUfuuguC fuUfuCfauususu	976
51601-1	1562	CUUGGGCAAUAA AGUACCUU{invAb}	221	{sGalNAc3}cuug ggCfaAfUfAfAfa guaccuus{invAb}	473	AGGUACUUUA UUGCCCAAGU U	725	asGfsguacUfuuauU fgCfcCfaagsusu	977
51602-1	695	AGUGAGUGACAA CGUACCUU{invAb}	222	{sGalNAc3}agug agUfgAfCfAfAfc guaccuus{invAb}	474	AGGUACGUUG UCACUCACUU U	726	asGfsguacGfuuguC faCfuCfacususu	978
52280-1	6594	GCAGACUGUUAU UUGUAAUU{invAb}	223	{sGalNAc3}gcag acUfgUfUfAfUfu uguaauus{invAb }	475	AAAUUACAAA UAACAGUCUG CUU	727	asAfsauuaCfaaauaa CfaGfucugcsusu	979
52281-1	2269	GUUGAAUUUUGU AUUAUGUG{invAb}	224	{sGalNAc3}guug aaUfuUfUfGfUfa uuaugugs{invAb }	476	UCACAUAAUA CAAAAUUCAA CUU	728	usCfsacauAfauacaa AfaUfucaacsusu	980
52282-1	6644	CCCAAGUUUCUAU GGUGAAC{invAb}	225	{sGalNAc3}ccca agUfuUfCfUfAfu ggugaacs{invAb}	477	AGUUCACCAU AGAAACUUGG GUU	729	asGfsuucaCfcauaga AfaCfuugggsusu	981

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52283-1	2187	UUAAUUUUAGAACACCUUUU{invAb}	226	{sGalNAc3}uuaauuUfuAfGfAfAfcaccuuuus{invAb}	478	AAAAAGGUGUUCUAAAAUUAAUU	730	asAfsaaagGfuguucuAfaAfauuaasusu	982
52284-1	4117	AGACAGACCCUUUAAAGGAA{invAb}	227	{sGalNAc3}agacagAfcCfCfUfUfuaaaggaas{invAb}	479	UUUCCUUUAAAGGGUCUGUCUUU	731	usUfsuccuUfuaaaggGfuCfugucususu	983
52285-1	4116	AAGACAGACCCUUUAAAGGA{invAb}	228	{sGalNAc3}aagacaGfaCfCfCfUfuuaaaggas{invAb}	480	UUCCUUUAAAGGGUCUGUCUUUU	732	usUfsccuuUfaaagggUfcUfgucuususu	984
52286-1	4112	UGAGAAGACAGACCCUUUAA{invAb}	229	{sGalNAc3}ugagaaGfaCfAfGfAfccuuuaas{invAb}	481	UUUAAAGGGUCUGUCUUCUCAUU	733	usUfsuaaaGfggucugUfcUfucucasusu	985
52287-1	3893	UUUUCCCCAGGUGUGAUAAU{invAb}	230	{sGalNAc3}uuuuccCfcAfGfGfUfgugauaaus{invAb}	482	AAUUAUCACACCUGGGGAAAAUU	734	asAfsuuauCfacaccuGfgGfgaaaasusu	986
52288-1	5012	GGACGUAUUUUCUUUCUGCU{invAb}	231	{sGalNAc3}ggacguAfuUfUfUfCfuuucugcus{invAb}	483	AAGCAGAAAGAAAAUACGUCCUU	735	asAfsgcagAfaagaaaAfuAfcguccsusu	987
52288-2	5012	GGACGUAUUUUCUUUCUGCU{invAb}	232	{sGalNAc3}ggacguAfuUfUfUfCfuuucugcus{invAb}	484	AAGCAGAAAGAAAAUACGUCCU	736	asAfsgcagAfaagaaaAfuAfcguccsus	988
52289-1	4260	CCUGCCUUCUUACAUCUUGA{invAb}	233	{sGalNAc3}ccugccUfuCfUfUfAfcaucuugas{invAb}	485	AUCAAGAUGUAAGAAGGCAGGUU	737	asUfscaagAfuguaagAfaGfgcaggsusu	989
52290-1	5680	AAGGCACCCUUUGCUUAGGC{invAb}	234	{sGalNAc3}aaggcaCfcCfUfUfUfgcuuaggcs{invAb}	486	AGCCUAAGCAAAGGGUGCCUUUU	738	asGfsccuaAfgcaaagGfgUfgccuususu	990

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52291-1	4193	CUUUGAGAAAAG AGGCUACU{invAb}	235	{sGalNAc3}cuuu gaGfaAfAfAfGfa ggcuacus{invAb}	487	AAGUAGCCUC UUUUCUCAAA GUU	739	asAfsguagCfcucuu uUfcUfcaaagsusu	991
52292-1	3858	UUGAUGGAGACA AGCCCUUG{invAb}	236	{sGalNAc3}uuga ugGfaGfAfCfAfa gcccuugs{invAb}	488	UCAAGGGCUU GUCUCCAUCA AUU	740	usCfsaaggGfcuugu cUfcCfaucaasusu	992
52292-2	3858	UUGAUGGAGACA AGCCCUUG{invAb}	237	{sGalNAc3}uuga ugGfaGfAfCfAfa gcccuugs{invAb}	489	UCAAGGGCUU GUCUCCAUCA AU	741	usCfsaaggGfcuugu cUfcCfaucaasus	993
52293-1	3857	CUUGAUGGAGAC AAGCCCUU{invAb}	238	{sGalNAc3}cuug auGfgAfGfAfCfa agcccuus{invAb}	490	AAAGGGCUUG UCUCCAUCAA GUU	742	asAfsagggCfuuguc uCfcAfucaagsusu	994
52293-2	3857	CUUGAUGGAGAC AAGCCCUU{invAb}	239	{sGalNAc3}cuug auGfgAfGfAfCfa agcccuus{invAb}	491	AAAGGGCUUG UCUCCAUCAA GU	743	asAfsagggCfuuguc uCfcAfucaagsus	995
52294-1	4500	UUCUUUUCCCAAG UUUCCCA{invAb}	240	{sGalNAc3}uucu uuUfcCfCfAfAfg uuucccas{invAb}	492	AUGGGAAACU UGGGAAAAG AAUU	744	asUfsgggaAfacuug gGfaAfaagaasusu	996
52295-1	4290	AGUUCCCAAGGCC UCUGUUC{invAb}	241	{sGalNAc3}aguu ccCfaAfGfGfCfc ucuguucs{invAb}	493	UGAACAGAGG CCUUGGGAAC UUU	745	usGfsaacaGfaggccu UfgGfgaacususu	997
52296-1	5578	UAAGGAAAUCAG GAAGUGUA{invAb}	242	{sGalNAc3}uaag gaAfaUfCfAfGfg aaguguas{invAb}	494	UUACACUUCC UGAUUUCCUU AUU	746	usUfsacacUfuccuga UfuUfccuuasusu	998
52297-1	3813	CUCUGAUCACCCC AACCUCU{invAb}	243	{sGalNAc3}cucu gaUfcAfCfCfCfc aaccucus{invAb}	495	AAGAGGUUG GGGUGAUCAG AGUU	747	asAfsgaggUfugggg uGfaUfcagagsusu	999

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52298-1	5674	CUCCAGAAGGCAC CCUUUGC{invAb}	244	{sGalNAc3}cucc agAfaGfGfCfAfc ccuuugcs{invAb}	496	AGCAAAGGGU GCCUUCUGGA GUU	748	asGfscaaaGfggugcc UfuCfuggagsusu	1000
52299-1	6199	UUAGUGCAGAGU AUGAGCCU{invAb}	245	{sGalNAc3}uuag ugCfaGfAfGfUfa ugagccus{invAb}	497	AAGGCUCAUA CUCUGCACUA AUU	749	asAfsggcuCfauacuc UfgCfacuaasusu	1001
52300-1	5640	CCUCAGAUGCUAC CCAAUCC{invAb}	246	{sGalNAc3}ccuc agAfuGfCfUfAfc ccaauccs{invAb}	498	AGGAUUGGG UAGCAUCUGA GGUU	750	asGfsgauuGfgguag cAfuCfugaggsusu	1002
52301-1	5741	CCUAUGAAUGCAU UCUUAUU{invAb}	247	{sGalNAc3}ccua ugAfaUfGfCfAfu ucuuauus{invAb }	499	AAAUAAGAA UGCAUUCAUA GGUU	751	asAfsauaaGfaaugca UfuCfauaggsusu	1003
52302-1	1855	CAGCUGGUUGGG AAAUGACA{invAb}	248	{sGalNAc3}cagc ugGfuUfGfGfGf aaaugacas{invAb }	500	AUGUCAUUUC CCAACCAGCU GUU	752	asUfsgucaUfuuccca AfcCfagcugsusu	1004
52303-1	1852	AUUCAGCUGGUU GGGAAAUG{invAb}	249	{sGalNAc3}auuc agCfuGfGfUfUfg ggaaaugs{invAb}	501	UCAUUUCCCA ACCAGCUGAA UUU	753	usCfsauuuCfccaacc AfgCfugaaususu	1005
52304-1	776	CCUAAAGUCAAGU CCACGAA{invAb}	250	{sGalNAc3}ccua aaGfuCfAfAfGfu ccacgaas{invAb}	502	AUUCGUGGAC UUGACUUUAG GUU	754	asUfsucguGfgacuu gAfcUfuuaggsusu	1006
52305-1	909	UUCGAGGAUAUU UGGAUGCA{invAb}	251	{sGalNAc3}uucg agGfaUfAfUfUfu ggaugcas{invAb}	503	AUGCAUCCAA AUAUCCUCGA AUU	755	asUfsgcauCfcaaaua UfcCfucgaasusu	1007
52306-1	844	GAACCUCUACCUU CUCUCGA{invAb}	252	{sGalNAc3}gaac cuCfuAfCfCfUfu cucucgas{invAb}	504	AUCGAGAGAA GGUAGAGGU UCUU	756	asUfscgagAfgaagg uAfgAfgguucsusu	1008

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52307-1	1240	GAUAAUGUCUUA UGUAAUGC{invAb}	253	{sGalNAc3}gaua auGfuCfUfUfAfu guaaugcs{invAb}	505	AGCAUUACAU AAGACAUUAU CUU	757	asGfscauuAfcauaag AfcAfuuaucsusu	1009
52308-1	572	GUUCUGGUGUCU GACUUUCG{invAb}	254	{sGalNAc3}guuc ugGfuGfUfCfUf gacuuucgs{invA b}	506	ACGAAAGUCA GACACCAGAA CUU	758	asCfsgaaaGfucagac AfcCfagaacsusu	1010
52309-1	574	UCUGGUGUCUGAC UUUCGGU{invAb}	255	{sGalNAc3}ucug guGfuCfUfGfAfc uuucggus{invAb }	507	AACCGAAAGU CAGACACCAG AUU	759	asAfsccgaAfagucag AfcAfccagasusu	1011
52310-1	853	CCUUCUCUCGAGA GCUUUUG{invAb}	256	{sGalNAc3}ccuu cuCfuCfGfAfGfa gcuuuugs{invAb }	508	ACAAAAGCUC UCGAGAGAAG GUU	760	asCfsaaaaGfcucucg AfgAfgaaggsusu	1012
52311-1	692	GGAGGAGUGAGU GACAACGU{invAb}	257	{sGalNAc3}ggag gaGfuGfAfGfUf gacaacgus{invAb }	509	UACGUUGUCA CUCACUCCUC CUU	761	usAfscguuGfucacu cAfcUfccuccsusu	1013
52312-1	442	CUUCCAUCCAUCC UUCAACU{invAb}	258	{sGalNAc3}cuuc caUfcCfAfUfCfc uucaacus{invAb}	510	AAGUUGAAG GAUGGAUGG AAGUU	762	asAfsguugAfaggau gGfaUfggaagsusu	1014
52313-1	445	CCAUCCAUCCUUC AACUUAA{invAb}	259	{sGalNAc3}ccau ccAfuCfCfUfUfc aacuuaas{invAb}	511	AUUAAGUUG AAGGAUGGA UGGUU	763	asUfsuaagUfugaag gAfuGfgauggsusu	1015
52314-1	1168	UACAGCACUGAGU GAAGAAA{invAb}	260	{sGalNAc3}uaca gcAfcUfGfAfGfu gaagaaas{invAb}	512	AUUUCUUCAC UCAGUGCUGU AUU	764	asUfsuucuUfcacuca GfuGfcuguasusu	1016

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52315-1	449	CCAUCCUUCAACU UAAGCAA{invAb}	261	{sGalNAc3}ccau ccUfuCfAfAfCfu uaagcaas{invAb}	513	AUUGCUUAAG UUGAAGGAU GGUU	765	asUfsugcuUfaaguu gAfaGfgauggsusu	1017
52316-1	1233	CCAUUAGGAUAA UGUCUUAU{invAb}	262	{sGalNAc3}ccau uaGfgAfUfAfAf ugucuuaus{invA b}	514	AAUAAGACAU UAUCCUAAUG GUU	766	asAfsuaagAfcauua uCfcUfaauggsusu	1018
52317-1	1234	CAUUAGGAUAAU GUCUUAUG{invAb}	263	{sGalNAc3}cauu agGfaUfAfAfUfg ucuuaugs{invAb }	515	ACAUAAGACA UUAUCCUAAU GUU	767	asCfsauaaGfacauua UfcCfuaaugsusu	1019
52317-2	1234	CAUUAGGAUAAU GUCUUAUG{invAb}	264	{sGalNAc3}cauu agGfaUfAfAfUfg ucuuaugs{invAb }	516	ACAUAAGACA UUAUCCUAAU GU	768	asCfsauaaGfacauua UfcCfuaaugsus	1020
52318-1	991	AGAAGGGAUGGA UCCUGAGG{invAb}	265	{sGalNAc3}agaa ggGfaUfGfGfAf uccugaggs{invA b}	517	ACCUCAGGAU CCAUCCCUUC UUU	769	asCfscucaGfgaucca UfcCfcuucususu	1021
52319-1	994	AGGGAUGGAUCC UGAGGUCG{invAb}	266	{sGalNAc3}aggg auGfgAfUfCfCfu gaggucgs{invAb }	518	ACGACCUCAG GAUCCAUCCC UUU	770	asCfsgaccUfcaggau CfcAfucccususu	1022
52320-1	1359	UGACCUCACAGGU GUUCACU{invAb}	267	{sGalNAc3}ugac cuCfaCfAfGfGfu guucacus{invAb}	519	AAGUGAACAC CUGUGAGGUC AUU	771	asAfsgugaAfcaccu gUfgAfggucasusu	1023
52321-1	1328	AUGCCCGACGAUG UCCUGUG{invAb}	268	{sGalNAc3}augc ccGfaCfGfAfUfg uccugugs{invAb }	520	ACACAGGACA UCGUCGGGCA UUU	772	asCfsacagGfacaucg UfcGfggcaususu	1024

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
52322-1	1367	CAGGUGUUCACUC GAGUGCU{invAb}	269	{sGalNAc3}cagg ugUfuCfAfCfUfc gagugcus{invAb}	521	AAGCACUCGA GUGAACACCU GUU	773	asAfsgcacUfcgagu gAfaCfaccugsusu	1025
52323-1	1024	CUGGGCAAACAUG AGUCUGG{invAb}	270	{sGalNAc3}cugg gcAfaAfCfAfUfg agucuggs{invAb}	522	UCCAGACUCA UGUUUGCCCA GUU	774	usCfscagaCfucaugu UfuGfcccagsusu	1026
52324-1	1029	CAAACAUGAGUCU GGAUUCU{invAb}	271	{sGalNAc3}caaa caUfgAfGfUfCfu ggauucus{invAb}	523	AAGAAUCCAG ACUCAUGUUU GUU	775	asAfsgaauCfcagacu CfaUfguuugsusu	1027
52325-1	396	UCCUCUCAGAUCU UGUGCGG{invAb}	272	{sGalNAc3}uccu cuCfaGfAfUfCfu ugugcggs{invAb}	524	UCCGCACAAG AUCUGAGAGG AUU	776	usCfscgcaCfaagauc UfgAfgaggasusu	1028
52326-1	397	CCUCUCAGAUCUU GUGCGGA{invAb}	273	{sGalNAc3}ccuc ucAfgAfUfCfUfu gugcggas{invAb}	525	UUCCGCACAA GAUCUGAGAG GUU	777	usUfsccgcAfcaagau CfuGfagaggsusu	1029
52327-1	1236	UUAGGAUAAUGU CUUAUGUA{invAb}	274	{sGalNAc3}uuag gaUfaAfUfGfUfc uuauguas{invAb}	526	UUACAUAAGA CAUUAUCCUA AUU	778	usUfsacauAfagacau UfaUfccuaasusu	1030
57799-1	5012	ACGUAUUUUCUU UCUGCUUU{invAb}	275	{sGalNAc3}acgu auUfuUfCfUfUfu cugcuusus{invAb}	527	AAGCAGAAAG AAAAUACGUU	779	asAfsgcagAfaagaaa AfuAfcgusus	1031
57800-1	5012	ACGUAUUUUCUU UCUGCUUU{invAb}	276	{sGalNAc3}acgu AfuUfUfUfCfuu	528	AAGCAGAAAG AAAAUACGUU	780	asAfsgcagAfaagaA faAfuAfcgusus	1032

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
				ucugcuusus{invAb}					
57801-1	5012	GGACGUAUUUUC UUUCUGCU{invAb}	277	{sGalNAc3}ggac guauUfuUfcUf Ufucugcus{invAb}	529	AAGCAGAAAG AAAAUACGUC CU	781	asAfsgcagAfaagaA faAfuacguccsus	1033
57802-1	3858	GAUGGAGACAAG CCCUUGAU{invAb}	278	{sGalNAc3}gaug gaGfaCfAfAfGfc ccuugasus{invAb}	530	UCAAGGGCUU GUCUCCAUCU	782	usCfsaaggGfcuugu cUfcCfaucsus	1034
57803-1	3858	GAUGGAGACAAG CCCUUGAU{invAb}	279	{sGalNAc3}gaug GfaGfAfCfAfagc ccuugasus{invAb}	531	UCAAGGGCUU GUCUCCAUCU	783	usCfsaaggGfcuugU fcUfcCfaucsus	1035
57804-1	3858	UUGAUGGAGACA AGCCCUUG{invAb}	280	{sGalNAc3}uuga uggaGfaCfAfAf Gfcccuugs{invA b}	532	UCAAGGGCUU GUCUCCAUCA AU	784	usCfsaaggGfcuugU fcUfccaucaasus	1036
57805-1	3857	UGAUGGAGACAA GCCCUUUU{invAb}	281	{sGalNAc3}ugau ggAfgAfCfAfAf gcccuuusus{invA b}	533	AAAGGGCUUG UCUCCAUCAU	785	asAfsagggCfuuguc uCfcAfucasus	1037
57806-1	3857	UGAUGGAGACAA GCCCUUUU{invAb}	282	{sGalNAc3}ugau GfgAfGfAfCfaag cccuuusus{invAb}	534	AAAGGGCUUG UCUCCAUCAU	786	asAfsagggCfuuguC fuCfcAfucasus	1038
57807-1	3857	CUUGAUGGAGAC AAGCCCUU{invAb}	283	{sGalNAc3}cuug auggAfgAfCfAf Afgcccuus{invA b}	535	AAAGGGCUUG UCUCCAUCAA GU	787	asAfsagggCfuuguC fuCfcaucaagsus	1039

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
57808-1	4140	UUCUAGGGACAA ACUCUAUU{invAb}	284	{sGalNAc3}uucu agGfgAfCfAfAfa cucuausus{invAb}	536	AUAGAGUUU GUCCCUAGAA U	788	asUfsagagUfuuguc cCfuAfgaasus	1040
57809-1	4140	UUCUAGGGACAA ACUCUAUU{invAb}	285	{sGalNAc3}uucu AfgGfGfAfCfaaa cucuausus{invAb}	537	AUAGAGUUU GUCCCUAGAA U	789	asUfsagagUfuuguC fcCfuAfgaasus	1041
57810-1	4140	GGUUCUAGGGAC AAACUCUA{invAb}	286	{sGalNAc3}gguu cuagGfgAfCfAf Afacucuas{invAb}	538	AUAGAGUUU GUCCCUAGAA CCU	790	asUfsagagUfuuguC fcCfuagaaccsus	1042
57811-1	1366	ACAGGUGUUCACU CGAGUGC{invAb}	287	{sGalNAc3}acag guGfuUfCfAfCfu cgagugcs{invAb}	539	AGCACUCGAG UGAACACCUG UU	791	asGfscacuCfgaguga AfcAfccugusus	1043
57812-1	1334	GACGAUGUCCUGU GGUUGCA{invAb}	288	{sGalNAc3}gacg auGfuCfCfUfGfu gguugcas{invAb}	540	AUGCAACCAC AGGACAUCGU CU	792	asUfsgcaaCfcacagg AfcAfucgucsus	1044
57813-1	1361	ACCUCACAGGUGU UCACUCG{invAb}	289	{sGalNAc3}accu caCfaGfGfUfGfu ucacucgs{invAb}	541	UCGAGUGAAC ACCUGUGAGG UU	793	usCfsgaguGfaacacc UfgUfgaggusus	1045
57814-1	459	ACUUAAGCAAGU UCCUCCGA{invAb}	290	{sGalNAc3}acuu aaGfcAfAfGfUfu ccuccgas{invAb}	542	AUCGGAGGAA CUUGCUUAAG UU	794	asUfscggaGfgaacu uGfcUfuaagusus	1046
57815-1	812	AUCACCAAGCUCA GUCUACG{invAb}	291	{sGalNAc3}auca ccAfaGfCfUfCfa gucuacgs{invAb}	543	ACGUAGACUG AGCUUGGUGA UU	795	asCfsguagAfcugag cUfuGfgugausus	1047

Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
57816-1	1042	GGAUUCUUCCCCGGAGUCGG{invAb}	292	{sGalNAc3}ggauucUfuCfCfCfCfggagucggs{invAb}	544	ACCGACUCCGGGGAAGAAUCCU	796	asCfscgacUfccggggAfaGfaauccsus	1048
57817-1	1266	GUACCCUGCCUGUGGAAUCU{invAb}	293	{sGalNAc3}guaccUfgCfCfUfGfuggaaucus{invAb}	545	AAGAUUCCACAGGCAGGGUACU	797	asAfsgauuCfcacaggCfaGfgguacsus	1049
57818-1	1240	GAUAAUGUCUUAUGUAAUGC{invAb}	294	{sGalNAc3}gauaauguCfuUfAfUfGfuaaugcs{invAb}	546	AGCAUUACAUAAGACAUUAUCU	798	asGfscauuAfcauaAfgAfcauuaucsus	1050
57819-1	1240	GAUAAUGUCUUAUGUAAUGC{invAb}	295	{sGalNAc3}gauaauguCfuUfAfUfGfuaaugcs{invAb}	547	AGCAUUACAUAAGACAUUAUCU	799	asGfscauuAfcauaagAfcAfuuaucsus	1051
57820-1	1240	GAUAAUGUCUUAUGUAAUGC{invAb}	296	{sGalNAc3}gauaauguCfUfUfAfuguaaugcs{invAb}	548	AGCAUUACAUAAGACAUUAUCU	800	asGfscauuacauaAfgAfcAfuuaucsus	1052
7498-2	706	CAACGUACCCUUCAUUGAUG{invAb}	297	{sGalNAc3}caacguacCfcUfUfCfAfuugaugs{invAb}	549	ACAUCAAUGAAGGGUACGUUGUU	801	asCfsaucaAfugaaGfgGfuacguugsusu	1053
NA	1240	GAUAAUGUCUUAUGUAAUGC{invAb}	298	{sGalNAc3}gauaauGfuCfUfUfAfuguaaugcs{invAb}	550	AGCAUUACAUAAGACAUUAUCU	802	asGfscauuAfcauaagAfcAfuuaucsus	1054
NA	1313	ACAUGGCUUCCAGAUAUGCC{invAb}	299	{sGalNAc3}acauggCfuUfCfCfAfgauaugccs{invAb}	551	AGGCAUAUCUGGAAGCCAUGUU	803	asGfsgcauAfucuggaAfgCfcaugusus	1055
41321-3	706	CAACGUACCCUUCAUUGAUG{invAb}	300	{sGalNAc3}caacguAfcCfCfUfUfc	552	ACAUCAAUGAAGGGUACGUUGU	804	asCfsaucaAfugaaggGfuAfcguugsus	1056

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
				auugaugs{invAb}					
41321-4	706	CAACGUACCCUUC AUUGAUG{invAb}	301	{sGalNAc3}caac guAfcCfCfUfUfUfc auugaugs{invAb}	553	ACAUCAAUGA AGGGUACGUU GU	805	asCfsaucaAfugaagg GfuAfcgugugsus	1057
43783-3	706	CAACGUACCCUUC AUUGAUG{invAb}	302	{sGalNAc3}caac guAfcCfCfUfUfUfc auugaugs{invAb}	554	ACAUCAAUGA AGGGUACGUU G	806	asCfsaucaAfugaagg GfuAfcgususg	1058
43806-3	704	CAACGUACCCUUC AUUGAUU{invAb}	303	{sGalNAc3}caac GfuAfCfCfCfuuc auugausus{invAb}	555	AUCAAUGAAG GGUACGUUGU	807	asUfscaauGfaaggG fuAfcGfuugsus	1059
43806-4	704	CAACGUACCCUUC AUUGAUU{invAb}	304	{sGalNAc3}caac GfuAfCfCfCfuuc auugausus{invAb}	556	AUCAAUGAAG GGUACGUUGU	808	asUfscaauGfaaggG fuAfcGfuugsus	1060
45567-1	706	CAACGUACCCUUC AUUGAUG{invAb}	305	{sGalNAc3}caac guAfcCfCfUfUfUfc auugaugs{invAb}	557	ACAUCAAUGA AGGGUACGUU GUU	809	asCfsaucAfAfugaa ggGfuAfcgugugsusu	1061
45569-1	706	CAACGUACCCUUC AUUGAUG{invAb}	306	{sGalNAc3}caac guAfcCfCfUfUfUfc auugaugs{invAb}	558	ACAUCAAUGA AGGGUACGUU GUU	810	asCfsaucaAfugaaG fgGfuacgugugsusu	1062
45571-1	706	CAACGUACCCUUC AUUGAUG{invAb}	307	{sGalNAc3}caac guAfcCfcUfucau ugaugs{invAb}	559	ACAUCAAUGA AGGGUACGUU GUU	811	asCfsaucAfAfugaa ggGfuAfcgugugsusu	1063

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Figure 2

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
45572-1	706	CAACGUACCCUUCAUUGAUG{invAb}	308	{sGalNAc3}caacguAfcCfcUfucaugaugs{invAb}	560	ACAUCAAUGAAGGGUACGUUGUU	812	asCfsaucaAfugaaGfgGfuAfcguugsusu	1064
45574-1	706	ACGUACCCUUCAUUGAUGUU{invAb}	309	{sGalNAc3}acguacccUfuCfAfUfUfgauguus{invAb}	561	ACAUCAAUGAAGGGUACGUUU	813	asCfsaucaAfugaaggGfuAfcgususu	1065
45564-1	706	ACGUACCCUUCAUUGAUGUU{invAb}	310	{sGalNAc3}acguacCfcUfUfCfAfuugauguus{invAb}	562	ACAUCAAUGAAGGGUACGUUU	814	asCfsaucaAfugaaggGfuAfcgususu	1066
45566-1	706	CAACGUACCCUUCAUUGAUG{invAb}	311	{sGalNAc3}caacguAfcCfcUfucaugaugs{invAb}	563	ACAUCAAUGAAGGGUACGUUGUU	815	asCfsaucaaugaaGfgGfuAfcguugsusu	1067
46286-1	1313	ACAUGGCUUCCAGAUAUGCC{invAb}	312	{sGalNAc3}acauggCfuUfCfCfAfgauaugccs{invAb}	564	AGGCAUAUCUGGAAGCCAUGUUU	816	asGfsgcauAfucuggaAfgCfcaugususu	1068

Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
768	40430-1	PNPLA3-T768_M867_3G3-5'	1	4	-16.4	34.6
832	40624-1	PNPLA3-T832_M867_3G3-5'	1	4	6.9	42.1
220	40625-1	PNPLA3-T220-g.1c>a_M867_3G3-5'	1	4	-40.6	20.8
1092	40626-1	PNPLA3-T1092-g.1g>a_M867_3G3-5'	1	4	-46.5	9.5

Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
905	40627-1	PNPLA3-T905_M867_3G3-5'	1	4	-53.2	23.5
767	40628-1	PNPLA3-T767-g.1c>a_M867_3G3-5'	1	4	-80.1	5.0
766	40633-1	PNPLA3-T766_M867_3G3-5'	1	4	-78.5	9.6
897	40634-1	PNPLA3-T897_M867_3G3-5'	1	4	-68.8	6.2
1217	40635-1	PNPLA3-T1217_M867_3G3-5'	1	4	-21.8	13.6
309	40636-1	PNPLA3-T309-g.1c>a_M867_3G3-5'	1	4	-50.8	3.5
1220	40637-1	PNPLA3-T1220-g.1c>a_M867_3G3-5'	1	3	-61.5	9.1
902	40640-1	PNPLA3-T902-g.1c>a_M867_3G3-5'	1	4	-53.1	4.4
211	40641-1	PNPLA3-T211-g.1g>a_M867_3G3-5'	1	4	-60.5	15.8
899	40642-1	PNPLA3-T899_M867_3G3-5'	1	4	-39.3	70.8
764	40643-1	PNPLA3-T764-g.1g>a_M867_3G3-5'	1	4	-31.6	11.2
1189	40644-1	PNPLA3-T1189_M867_3G3-5'	1	4	-59.1	12.8
895	41310-1	PNPLA3-T895-g.1c>a_M867_3G3-5'	1	4	-48.7	26.0
894	41311-1	PNPLA3-T894-g.1c>a_M867_3G3-5'	1	4	-61.1	10.4
1219	41312-1	PNPLA3-T1219-g.1c>a_M867_3G3-5'	1	4	-55.8	16.0
893	41313-1	PNPLA3-T893_M867_3G3-5'	1	4	-74.3	8.4
1213	41314-1	PNPLA3-T1213-g.1g>a_M867_3G3-5'	1	4	-68.8	25.7
1201	41315-1	PNPLA3-T1201-g.1c>a_M867_3G3-5'	1	4	-28.9	32.1
878	41316-1	PNPLA3-T878_M867_3G3-5'	1	4	-15.8	22.5
347	41317-1	PNPLA3-T347-g.1g>a_M867_3G3-5'	1	4	-29.8	29.0
1224	41318-1	PNPLA3-T1224_M867_3G3-5'	1	3	-12.9	15.2
1223	41319-1	PNPLA3-T1223_M867_3G3-5'	1	4	-79.7	2.0
756	41320-1	PNPLA3-T756-g.1g>a_M867_3G3-5'	1	4	6.3	46.5
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	1	4	-79.7	5.0
705	41322-1	PNPLA3-T705-g.1c>a_M867_3G3-5'	1	4	-70.3	8.6

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
662	41323-1	PNPLA3-T662_M867_3G3-5'	1	4	-6.8	10.2
704	41324-1	PNPLA3-T704_M867_3G3-5'	1	4	-82.8	2.9
641	41325-1	PNPLA3-T641_M867_3G3-5'	1	4	-33.0	45.4
593	41326-1	PNPLA3-T593_M867_3G3-5'	1	4	-27.1	5.8
392	41327-1	PNPLA3-T392-g.1c>a_M867_3G3-5'	1	4	-71.5	11.4
391	41328-1	PNPLA3-T391_M867_3G3-5'	1	4	-44.1	13.2
1603	41329-1	PNPLA3-T1603_M867_3G3-5'	1	4	-40.8	3.6
1602	41330-1	PNPLA3-T1602-g.1g>a_M867_3G3-5'	1	4	-65.4	14.9
701	41331-1	PNPLA3-T701_M867_3G3-5'	1	4	1.8	26.7
698	41332-1	PNPLA3-T698-g.1g>a_M867_3G3-5'	1	4	-40.5	38.6
590	41333-1	PNPLA3-T590-g.1c>a_M867_3G3-5'	1	4	-48.4	10.6
568	41334-1	PNPLA3-T568_M867_3G3-5'	1	4	-39.2	29.5
1300	41335-1	PNPLA3-T1300_M867_3G3-5'	1	4	-49.7	7.7
671	41336-1	PNPLA3-T671_M867_3G3-5'	1	4	-50.8	3.5
563	41337-1	PNPLA3-T563_M867_3G3-5'	1	4	-48.6	4.9
562	41338-1	PNPLA3-T562-g.1g>a_M867_3G3-5'	1	4	-75.1	9.7
1322	41339-1	PNPLA3-T1322-g.1g>a_M867_3G3-5'	1	4	-66.3	12.0
1280	41340-1	PNPLA3-T1280-g.1g>a_M867_3G3-5'	1	4	-69.9	9.6
1226	41341-1	PNPLA3-T1226-g.1c>a_M867_3G3-5'	1	4	-60.5	15.8
1280	43782-1	PNPLA3-T1280-g.1g>a_M622_3G3-5'	0.5	4	-54.8	12.2
1280	43788-1	PNPLA3-T1280-g.1g>a,g.19u>c_M1281_3G3-5'	0.5	4	-29.8	9.5
1280	43794-1	PNPLA3-T1280-g.1g>a_M1170_3G3-5'	0.5	4	3.3	16.3
1280	43799-1	PNPLA3-T1280-g.1g>a_M242_3G3-5'	0.5	4	-18.5	26.9
1280	43804-1	PNPLA3-T1280-g.1g>a,g.19u>c_M1282_3G3-5'	0.5	4	-43.3	14.3
1280	43809-1	PNPLA3-T1280-g.1g>a_M941_3G3-5'	0.5	4	-44.0	18.3

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
211	43785-1	PNPLA3-T211-g.1g>a_M622_3G3-5'	0.5	4	-56.5	14.4
211	43791-1	PNPLA3-T211-g.1g>a_M1281_3G3-5'	0.5	4	-45.8	10.8
211	43797-1	PNPLA3-T211-g.1g>a_M1170_3G3-5'	0.5	4	-35.5	11.5
704	43784-1	PNPLA3-T704_M622_3G3-5'	0.5	4	-62.8	11.0
704	43790-1	PNPLA3-T704_M1281_3G3-5'	0.5	4	-76.5	10.7
704	43796-1	PNPLA3-T704_M1170_3G3-5'	0.5	4	-75.0	19.0
704	43800-1	PNPLA3-T704_M242_3G3-5'	0.5	4	-57.0	16.9
704	43806-1	PNPLA3-T704_M1282_3G3-5'	0.5	4	-72.3	7.7
704	43811-1	PNPLA3-T704_M941_3G3-5'	0.5	4	-70.8	2.1
706	43783-1	PNPLA3-T706-g.1g>a_M622_3G3-5'	0.5	4	-74.3	1.9
706	43789-1	PNPLA3-T706-g.1g>a,g.19u>c_M1281_3G3-5'	0.5	4	-54.5	11.8
706	43795-1	PNPLA3-T706-g.1g>a_M1170_3G3-5'	0.5	4	-61.0	17.8
706	7498-2	PNPLA3-T706-g.1g>a_M242_3G3-5'	0.5	4	-50.5	12.1
706	43805-1	PNPLA3-T706-g.1g>a,g.19u>c_M1282_3G3-5'	0.5	4	-36.0	20.2
706	43810-1	PNPLA3-T706-g.1g>a_M941_3G3-5'	0.5	4	-52.5	8.8
767	43781-1	PNPLA3-T767-g.1c>a_M622_3G3-5'	0.5	4	-52.3	5.5
T767	43787-1	PNPLA3-T767-g.1c>a_M1281_3G3-5'	0.5	4	-46.5	9.7
T767	43793-1	PNPLA3-T767-g.1c>a_M1170_3G3-5'	0.5	4	-46.3	12.5
T767	43798-1	PNPLA3-T767-g.1c>a_M242_3G3-5'	0.5	4	-43.0	10.8
T767	43803-1	PNPLA3-T767-g.1c>a_M1282_3G3-5'	0.5	4	-53.0	9.5
T767	43808-1	PNPLA3-T767-g.1c>a_M941_3G3-5'	0.5	4	-55.5	4.8
211	40641-1	PNPLA3-T211-g.1g>a_M867_3G3-5'	3	4	-91.0	5.3
704	41324-1	PNPLA3-T704_M867_3G3-5'	3	4	-94.0	3.7
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	3	4	-88.0	5.4
767	40628-1	PNPLA3-T767-g.1c>a_M867_3G3-5'	3	4	-94.5	1.3

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
1280	41340-1	PNPLA3-T1280-g.1g>a_M867_3G3-5'	3	4	-74.5	16.8
562	41338-1	PNPLA3-T562-g.1g>a_M867_3G3-5'	3	4	-89.5	3.4
766	40633-1	PNPLA3-T766_M867_3G3-5'	3	4	-93.5	2.6
211	40641-1	PNPLA3-T211-g.1g>a_M867_3G3-5'	1	4	-74.0	16.6
704	41324-1	PNPLA3-T704_M867_3G3-5'	1	4	-81.5	7.9
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	1	4	-67.3	17.7
767	40628-1	PNPLA3-T767-g.1c>a_M867_3G3-5'	1	3	-84.7	4.5
1280	41340-1	PNPLA3-T1280-g.1g>a_M867_3G3-5'	1	4	-77.0	18.2
562	41338-1	PNPLA3-T562-g.1g>a_M867_3G3-5'	1	4	-69.8	9.4
766	40633-1	PNPLA3-T766_M867_3G3-5'	1	4	-66.0	6.1
211	40641-1	PNPLA3-T211-g.1g>a_M867_3G3-5'	0.5	4	-46.3	3.3
704	41324-1	PNPLA3-T704_M867_3G3-5'	0.5	4	-51.8	3.1
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	0.5	4	-0.3	7.0
767	40628-1	PNPLA3-T767-g.1c>a_M867_3G3-5'	0.5	4	-54.8	12.2
1280	41340-1	PNPLA3-T1280-g.1g>a_M867_3G3-5'	0.5	4	-46.3	15.6
562	41338-1	PNPLA3-T562-g.1g>a_M867_3G3-5'	0.5	4	-66.8	21.1
766	40633-1	PNPLA3-T766_M867_3G3-5'	0.5	4	-63.3	16.3
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	0.5	4	-34.8	21.1
706	43783-1	PNPLA3-T706-g.1g>a_M622_3G3-5'	0.5	4	-53.9	24.0
706	45564-1	PNPLA3-T706-g.1g>a_M622_3G3-5'	0.5	4	18.2	48.0
706	45566-1	PNPLA3-T706-g.1g>a_M695_3G3-5'	0.5	4	-0.9	38.7
706	45567-1	PNPLA3-T706-g.1g>a_M1167_3G3-5'	0.5	4	-42.8	24.7
706	45569-1	PNPLA3-T706-g.1g>a_M1210_3G3-5'	0.5	4	-16.3	20.6
706	45571-1	PNPLA3-T706-g.1g>a_M1213_3G3-5'	0.5	4	-19.1	26.7
706	45572-1	PNPLA3-T706-g.1g>a_M1215_3G3-5'	0.5	4	-13.7	27.2

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
706	45574-1	PNPLA3-T706-g.1g>a_M1294_3G3-5'	0.5	4	-42.7	29.4
211	43801-2	PNPLA3-T211-g.1g>a_M242_3G3-5'	0.5	4	-32.0	40.8
211	43807-2	PNPLA3-T211-g.1g>a_M1282_3G3-5'	0.5	4	-21.3	5.9
211	43812-2	PNPLA3-T211-g.1g>a_M941_3G3-5'	0.5	4	-52.2	19.0
704	46275-1	PNPLA3-T704_M1297_3G3-5'	0.5	4	-73.7	11.1
1379	46276-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1379-g.1g>a_M867_3G3-5'	0.5	4	-32.0	28.9
1185	46277-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1185_M867_3G3-5'	0.5	4	3.2	42.1
1184	46278-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1184_M867_3G3-5'	0.5	4	-42.4	19.9
790	46279-1	PNPLA3(Hu-Only/NHP 15-17mers)-T790_M867_3G3-5'	0.5	4	-18.2	27.1
1562	46280-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	0.5	4	-58.2	4.2
842	46281-1	PNPLA3(Hu-Only/NHP 15-17mers)-T842-g.1c>a_M867_3G3-5'	0.5	4	10.4	37.6
696	46282-1	PNPLA3(Hu-Only/NHP 15-17mers)-T696_M867_3G3-5'	0.5	4	0.8	38.3
571	46283-1	PNPLA3(Hu-Only/NHP 15-17mers)-T571-g.1c>a_M867_3G3-5'	0.5	4	-11.1	14.6
695	46284-1	PNPLA3(Hu-Only/NHP 15-17mers)-T695-g.1g>a_M867_3G3-5'	0.5	4	-43.4	18.8
1564	46285-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1564-g.1g>a_M867_3G3-5'	0.5	4	-19.1	39.6
1313	46286-1	PNPLA3-T1313_M867_M867_3G3-5'	0.5	4	19.0	28.9
706	43783-1	PNPLA3-T706-g.1g}a_M622_3G3-5'	3	4	-91.0	3.0
706	43783-1	PNPLA3-T706-g.1g}a_M622_3G3-5'	1	4	-66.8	10.1
706	43783-1	PNPLA3-T706-g.1g}a_M622_3G3-5'	0.5	4	-63.5	26.2
704	43806-1	PNPLA3-T704_M1282_3G3-5'	3	4	-92.8	2.2
704	43806-1	PNPLA3-T704_M1282_3G3-5'	1	4	-80.7	5.2
704	43806-1	PNPLA3-T704_M1282_3G3-5'	0.5	4	-40.5	9.7
704	46275-1	PNPLA3-T704_M1297_3G3-5'	3	4	-91.6	2.9
704	46275-1	PNPLA3-T704_M1297_3G3-5'	1	4	-71.2	6.5
704	46275-1	PNPLA3-T704_M1297_3G3-5'	0.5	4	-55.7	11.6

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
1562	46280-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	3	4	-82.3	4.6
1562	46280-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	1	4	-42.2	11.9
1562	46280-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	0.5	4	-41.5	16.0
1562	51581-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M1250_3G3-5'	0.5	4	-45.8	40.2
1562	51589-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M1170_3G3-5'	0.5	4	-37.6	42.6
1562	51593-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M242_3G3-5'	0.5	4	-64.2	24.7
1562	51597-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M1282_3G3-5'	0.5	4	-28.6	12.9
1184	46278-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1184_M867_3G3-5'	0.5	4	-22.6	34.1
1184	51580-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1184_M1250_3G3-5'	0.5	4	-23.9	29.7
1184	51588-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1184_M1170_3G3-5'	0.5	4	-37.3	21.1
1184	51592-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1184_M242_3G3-5'	0.5	4	-42.7	36.2
695	46284-1	PNPLA3(Hu-Only/NHP 15-17mers)-T695-g.1g>a_M867_3G3-5'	0.5	4	-53.4	20.3
695	51582-1	PNPLA3(Hu-Only/NHP 15-17mers)-T695-g.1g>a_M1250_3G3-5'	0.5	4	-0.2	9.0
695	51590-1	PNPLA3(Hu-Only/NHP 15-17mers)-T695-g.1g>a_M1170_3G3-5'	0.5	4	5.2	23.5
695	51594-1	PNPLA3(Hu-Only/NHP 15-17mers)-T695-g.1g>a_M242_3G3-5'	0.5	4	-42.6	12.3
1379	46276-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1379-g.1g>a_M867_3G3-5'	0.5	4	-52.2	25.0
1379	51579-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1379-g.1g>a_M1250_3G3-5'	0.5	4	-19.8	22.3
1379	51587-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1379-g.1g>a_M1170_3G3-5'	0.5	4	-25.3	26.2
1379	51591-1	PNPLA3(Hu-Only/NHP 15-17mers)-T1379-g.1g>a_M242_3G3-5'	0.5	4	-18.1	31.3
776	52304-1	PNPLA3(Human-Only)-T776-g.1g}a_M867_3G3-5'	1	4	-34.9	11.5
909	52305-1	PNPLA3(Human-Only)-T909_M867_3G3-5'	1	4	-60.0	9.4
844	52306-1	PNPLA3(Human-Only)-T844-g.1c}a_M867_3G3-5'	1	4	-58.0	22.0
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	1	4	-89.7	3.4
572	52308-1	PNPLA3(Human-Only)-T572-g.1c}a_M867_3G3-5'	1	4	-70.6	13.6
574	52309-1	PNPLA3(Human-Only)-T574-g.1g}a_M867_3G3-5'	1	4	-3.1	8.8

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
853	52310-1	PNPLA3(Human-Only)-T853_M867_3G3-5'	1	4	-62.2	7.0
692	52311-1	PNPLA3(Human-Only)-T692_M867_3G3-5'	1	4	-56.1	12.1
442	52312-1	PNPLA3(Human-Only)-T442_M867_3G3-5'	1	4	-22.9	18.0
445	52313-1	PNPLA3(Human-Only)-T445-g.1c>a_M867_3G3-5'	1	4	-74.0	7.3
1168	52314-1	PNPLA3(Human-Only)-T1168_M867_3G3-5'	1	4	8.7	24.7
449	52315-1	PNPLA3(Human-Only)-T449-g.1c>a_M867_3G3-5'	1	4	-45.8	14.2
1233	52316-1	PNPLA3(Human-Only)-T1233-g.1c>a_M867_3G3-5'	1	4	-70.0	9.6
1234	52317-1	PNPLA3(Human-Only)-T1234_M867_3G3-5'	1	4	-90.4	6.5
991	52318-1	PNPLA3(Human-Only)-T991_M867_3G3-5'	1	4	-0.9	16.2
994	52319-1	PNPLA3(Human-Only)-T994-g.1g>a_M867_3G3-5'	1	4	-65.3	3.2
1359	52320-1	PNPLA3(Human-Only)-T1359-g.1g>a_M867_3G3-5'	1	4	-8.1	14.3
1328	52321-1	PNPLA3(Human-Only)-T1328-g.1c>a_M867_3G3-5'	1	4	-32.5	30.0
1367	52322-1	PNPLA3(Human-Only)-T1367-g.1c>a_M867_3G3-5'	1	4	-70.5	10.9
1024	52323-1	PNPLA3(Human-Only)-T1024_M867_3G3-5'	1	4	-74.2	16.2
1029	52324-1	PNPLA3(Human-Only)-T1029_M867_3G3-5'	1	4	-35.9	10.9
396	52325-1	PNPLA3(Human-Only)-T396_M867_3G3-5'	1	4	-52.6	26.6
397	52326-1	PNPLA3(Human-Only)-T397_M867_3G3-5'	1	4	-68.8	6.7
1236	52327-1	PNPLA3(Human-Only)-T1236_M867_3G3-5'	1	4	-66.5	10.0
1562	46280-3	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	0.5	4	-39.8	18.5
1562	46280-3	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	1	4	-41.6	9.8
1562	46280-3	PNPLA3(Hu-Only/NHP 15-17mers)-T1562_M867_3G3-5'	3	4	-78.7	2.8
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	0.5	4	-55.8	2.1
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	1	4	-77.2	4.6
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	3	4	-94.3	0.4
1234	52317-2	PNPLA3(Human-Only)-T1234_M867_3G3-5'	0.5	4	-65.9	0.9

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
1234	52317-2	PNPLA3(Human-Only)-T1234_M867_3G3-5'	1	4	-70.1	2.8
1234	52317-2	PNPLA3(Human-Only)-T1234_M867_3G3-5'	3	4	-89.8	4.2
622	43783-3	PNPLA3-T706-g.1g}a_M622_3G3-5'	0.5	4	-47.8	9.8
622	43783-3	PNPLA3-T706-g.1g}a_M622_3G3-5'	1	4	-64.9	13.2
622	43783-3	PNPLA3-T706-g.1g}a_M622_3G3-5'	3	4	-92.0	3.1
1282	43806-4	PNPLA3-T704_M1282_3G3-5'	0.5	4	-50.7	12.4
1282	43806-4	PNPLA3-T704_M1282_3G3-5'	1	4	-72.2	7.1
1282	43806-4	PNPLA3-T704_M1282_3G3-5'	3	4	-91.4	4.3
706	41321-4	PNPLA3-T706-g.1g>a_M867_3G3-5'	0.5	4	-31.5	5.9
706	41321-4	PNPLA3-T706-g.1g>a_M867_3G3-5'	1	4	-62.3	13.7
706	41321-4	PNPLA3-T706-g.1g>a_M867_3G3-5'	3	4	-84.1	4.8
562	41338-2	PNPLA3-T562-g.1g}a_M867_	0.5	4	-29.7	12.6
562	41338-2	PNPLA3-T562-g.1g}a_M867_	1	4	-69.5	12.8
562	41338-2	PNPLA3-T562-g.1g}a_M867_	3	4	-69.3	8.5
767	43808-2	PNPLA3-T767-g.1c}a_M941_3G3-5'	0.5	4	-35.5	13.0
767	43808-2	PNPLA3-T767-g.1c}a_M941_3G3-5'	1	4	-68.2	16.1
767	43808-2	PNPLA3-T767-g.1c}a_M941_3G3-5'	3	4	-82.4	5.3
1297	46275-2	PNPLA3-T704_M1297_3G3-5'	0.5	4	-54.0	7.3
1297	46275-2	PNPLA3-T704_M1297_3G3-5'	1	4	-70.0	9.9
1297	46275-2	PNPLA3-T704_M1297_3G3-5'	3	4	-88.8	4.6
1280	43782-2	PNPLA3-T1280-g.1g}a_M622_3G3-5'	0.5	4	-29.7	12.6
1280	43782-2	PNPLA3-T1280-g.1g}a_M622_3G3-5'	1	4	-59.5	6.1
1280	43782-2	PNPLA3-T1280-g.1g}a_M622_3G3-5'	3	4	-75.1	1.6
1240	57818-1	PNPLA3(Human-Only)-T1240_M242_3G3-5'	0.5	4	-59.9	3.4
1240	57819-1	PNPLA3(Human-Only)-T1240_M1207_3G3-5'	0.5	4	-59.3	5.0

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Figure 3

					qPCR	
					huPNPLA3 mRNA	
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL %KD	SD
1240	57820-1	PNPLA3(Human-Only)-T1240_M1394_3G3-5'	0.5	4	-49.2	17.2

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Figure 4

				qPCR						WES		
				GFP1		GFP2		BghpA		GFP protein		
Duplex No.	Name	DOSE (MPK)	N	REL% KD	SD	REL% KD	SD	REL% KD	SD	REL% KD	SD	Analysis
41344-1	PNPLA3-T2197_M867_3G3-5'	1	4			-21.3	44.7			-41.2	37.2	qPCR/WES
41345-1	PNPLA3-T1760_M867_3G3-5'	1	4			-19.8	32.1			-27.8	27.7	qPCR/WES
41346-1	PNPLA3-T1763_M867_3G3-5'	1	4			-37.5	10.3			-32.9	26.3	qPCR/WES
41347-1	PNPLA3-T1764_M867_3G3-5'	1	4			27.6	83.7			-71.5	8.2	qPCR/WES
41348-1	PNPLA3-T1771-g.1c>a_M867_3G3-5'	1	4			-51.5	15.5			-67.5	15.6	qPCR/WES
41349-1	PNPLA3-T1890-g.1c>a_M867_3G3-5'	1	4			-10.0	44.2			-70.2	8.7	qPCR/WES
41350-1	PNPLA3-T2198_M867_M1224_3G3-5'	1	4			-55.0	29.4			-83.3	14.5	qPCR/WES
41351-1	PNPLA3-T2199_M867_M1224_3G3-5'	1	4			18.5	26.6			-75.8	5.5	qPCR/WES
41352-1	PNPLA3-T2200_M867_M1224_3G3-5'	1	4			-11.0	23.1			-75.8	5.5	qPCR/WES
41353-1	PNPLA3-T2201_M867_M1224_3G3-5'	1	4			-25.5	14.2			-67.4	8.4	qPCR/WES
41354-1	PNPLA3-T2202_M867_M1224_3G3-5'	1	4			-6.4	31.6			-47.3	18.5	qPCR/WES
41355-1	PNPLA3-T2204_M867_M1224_3G3-5'	1	4			-3.8	14.9			-47.3	18.5	qPCR/WES
52281-1	PNPLA3-T2269_M867_3G3-5'	1	4	-9.9	48.9	-16.2	44.8	-19.1	46.8	-75.6	10.0	qPCR/WES
52283-1	PNPLA3-T2187_M867_3G3-5'	1	4	50.9	68.0	38.5	65.3	30.0	69.2	-47.0	28.2	qPCR/WES
52302-1	PNPLA3-T1855-g.1g>a_M867_3G3-5'	1	4	54.7	52.1	49.3	57.6	18.7	32.0			qPCR
52303-1	PNPLA3-T1852_M867_3G3-5'	1	4	13.9	38.9	14.8	41.7	0.5	29.9			qPCR
46288-1	PNPLA3-T2273_M867_3G3-5'	1	4	-22.0	19.6	-20.9	26.0	-27.2	15.6			qPCR
46289-1	PNPLA3-T2268-g.1c}a_M867_3G3-5'	1	4	-15.0	38.9	-33.3	32.7	-23.2	31.7			qPCR
46292-1	PNPLA3-T1860_M867_3G3-5'	1	4	-42.1	29.4	-49.7	31.0	-40.8	20.6			qPCR
46293-1	PNPLA3-T1858-g.1c}a_M867_3G3-5'	1	4	-3.6	34.9	-13.0	34.2	-18.1	26.5	-52.7	7.0	qPCR/WES
46309-1	PNPLA3-T1917_M867_3G3-5'	1	4	-57.4	13.7	-61.3	13.2	-61.1	7.9	-69.5	16.3	qPCR/WES
46310-1	PNPLA3-T1666-g.1c}a_M867_3G3-5'	1	4	-16.5	35.6	-32.0	21.0	-25.4	25.2	-11.5	26.9	qPCR/WES
52284-1	PNPLA3-T4117_M867_3G3-5'	1	4	-32.7	3.1	-29.3	8.7	-37.9	5.7			qPCR

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Figure 4

				qPCR						WES		
				GFP1		GFP2		BghpA		GFP protein		
Duplex No.	Name	DOSE (MPK)	N	REL% KD	SD	REL% KD	SD	REL% KD	SD	REL% KD	SD	Analysis
52285-1	PNPLA3-T4116_M867_3G3-5'	1	4	-21.8	2.9	-15.5	8.9	-28.5	8.0			qPCR
52286-1	PNPLA3-T4112_M867_3G3-5'	1	4	-42.7	27.9	-40.4	29.0	-43.2	29.3	-72.0	13.5	qPCR/WES
52287-1	PNPLA3-T3893-g.1g}a_M867_3G3-5'	1	4	-20.7	20.2	-15.3	18.7	-21.6	17.9			qPCR
52288-1	PNPLA3-T5012_M867_3G3-5'	1	4	-80.1	14.2	-81.1	14.7	-82.2	12.6	-91.1	6.8	qPCR/WES
52289-1	PNPLA3-T4260-g.1c}a_M867_3G3-5'	1	4	-38.2	22.8	-34.5	26.2	-33.6	22.9			qPCR
52291-1	PNPLA3-T4193_M867_3G3-5'	1	4	-54.4	17.6	-50.1	19.9	-57.8	16.6			qPCR
52292-1	PNPLA3-T3858_M867_3G3-5'	1	4	-86.4	7.8	-85.0	8.9	-88.3	6.3	-95.2	5.3	qPCR/WES
52293-1	PNPLA3-T3857-g.1c}a_M867_3G3-5'	1	4	-71.2	22.1	-69.5	24.4	-73.0	21.3	-79.1	21.6	qPCR/WES
52294-1	PNPLA3-T4500-g.1c}a_M867_3G3-5'	1	4	-52.7	24.1	-51.9	22.6	-57.4	21.4			qPCR
52295-1	PNPLA3-T4290_M867_3G3-5'	1	4	-48.7	40.2	-54.7	23.2	-62.0	14.4			qPCR
52297-1	PNPLA3-T3813-g.1g}a_M867_3G3-5'	1	4	-36.6	17.9	-30.0	18.5	-35.6	23.9			qPCR
46291-1	PNPLA3-T4119-g.1c}a_M867_3G3-5'	1	4	28.3	42.0	46.8	60.0	26.8	48.4			qPCR
46297-1	PNPLA3-T4113-g.1c}a_M867_3G3-5'	1	4	74.3	18.1	84.2	30.6	81.2	21.7			qPCR
46301-1	PNPLA3-T4963_M867_3G3-5'	1	4	-22.9	8.4	-13.1	16.2	-30.7	6.0			qPCR
46303-1	PNPLA3-T4286-g.1c}a_M867_3G3-5'	1	4	24.8	21.0	34.0	28.1	11.0	28.4			qPCR
46304-1	PNPLA3-T4140-g.1g}a_M867_3G3-5'	1	4	-53.9	35.4	-50.3	37.5	-55.1	30.9	-45.1	42.7	qPCR/WES
46305-1	PNPLA3-T4495_M867_3G3-5'	1	4	-37.9	26.4	-36.0	28.3	-36.6	28.9			qPCR
46306-1	PNPLA3-T4132_M867_3G3-5'	1	4	4.2	36.7	12.0	21.6	7.5	19.6	23.8	34.4	qPCR/WES
46308-1	PNPLA3-T3794_M867_3G3-5'	1	4	-5.3	33.4	-5.5	46.0	-11.4	34.7			qPCR
52280-1	PNPLA3-T6594-g.1c}a_M867_3G3-5'	1	4	-2.9	19.2	-8.6	18.7	-2.1	18.0			qPCR
52282-1	PNPLA3-T6644-g.1c}a_M867_3G3-5'	1	4	-3.1	27.9	-3.1	21.3	-12.1	31.3			qPCR
52290-1	PNPLA3-T5680-g.1g}a_M867_3G3-5'	1	4	-26.4	24.7	-32.1	21.1	-34.6	16.0			qPCR
52296-1	PNPLA3-T5578_M867_3G3-5'	1	4	-33.7	18.1	-31.1	18.1	-25.5	22.3			qPCR
52298-1	PNPLA3-T5674_M867_3G3-5'	1	4	-37.2	23.8	-36.4	23.5	-28.2	26.1			qPCR
52299-1	PNPLA3-T6199-g.1c}a_M867_3G3-5'	1	4	-19.3	29.4	-18.2	31.5	-18.5	28.1			qPCR

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Figure 4

				qPCR						WES		
				GFP1		GFP2		BghpA		GFP protein		
Duplex No.	Name	DOSE (MPK)	N	REL% KD	SD	REL% KD	SD	REL% KD	SD	REL% KD	SD	Analysis
52300-1	PNPLA3-T5640-g.1g}a_M867_3G3-5'	1	4	-28.4	39.2	-30.0	36.6	-28.0	37.4			qPCR
52301-1	PNPLA3-T5741_M867_3G3-5'	1	4	-17.2	31.5	-18.1	31.0	-15.7	29.2			qPCR
46287-1	PNPLA3-T6576_M867_3G3-5'	1	4	9.3	22.8	15.0	26.8	12.7	21.9			qPCR
46290-1	PNPLA3-T6676_M867_3G3-5'	1	4	-5.6	6.9	-9.5	7.4	-11.6	13.6			qPCR
46294-1	PNPLA3-T6154_M867_3G3-5'	1	4	10.0	16.4	26.4	29.5	3.4	12.3			qPCR
46295-1	PNPLA3-T5707_M867_3G3-5'	1	4	-16.7	13.8	-5.2	6.7	-21.5	6.6			qPCR
46296-1	PNPLA3-T6635_M867_3G3-5'	1	4	1.8	12.7	6.0	20.6	-7.6	14.3			qPCR
46298-1	PNPLA3-T6637-g.1c}a_M867_3G3-5'	1	4	3.3	39.0	5.6	42.7	-2.3	40.0			qPCR
46299-1	PNPLA3-T5819_M867_3G3-5'	1	4	20.5	10.0	16.5	5.3	19.8	8.5			qPCR
46300-1	PNPLA3-T5736_M867_3G3-5'	1	4	1.6	26.2	3.0	29.3	2.0	26.1			qPCR
46302-1	PNPLA3-T5579_M867_3G3-5'	1	4	-1.2	8.5	-2.1	17.5	-5.0	14.7			qPCR
46307-1	PNPLA3-T6163_M867_3G3-5'	1	4	1.8	45.1	7.2	54.3	-14.1	37.1			qPCR

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Figure 5

					dPCR				
					huPNPLA3 mRNA		PNPLA3 protein		
PNPLA3 Transcript location	**Duplex No.**	**Name**	**DOSE (MPK)**	**N**	**REL%KD**	**SD**	**REL% KD**	**SD**	**Analysis**
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211	40641-1	PNPLA3-T211-g.1g}a_M867_	3	6	-89.9	7.4			dPCR
893	41313-1	PNPLA3-T893_M867_	3	6	-91.1	6.2			dPCR
706	41321-1	PNPLA3-T706-g.1g}a_M867_	3	6	-95.4	4.3			dPCR
704	41324-1	PNPLA3-T704_M867_	3	6	-94.1	4.2			dPCR
562	41338-1	PNPLA3-T562-g.1g}a_M867_	3	6	-88.6	8.9			dPCR
1280	41340-1	PNPLA3-T1280-g.1g}a_M867_	3	6	-92.3	4.2			dPCR
704	43790-1	PNPLA3-T704_M1281_3G3-5'	1	5	-85.1	6.7			dPCR
706	43783-1	PNPLA3-T706-g.1g}a_M622_3G3-5'	1	6	-88.3	8.7			dPCR
704	43806-1	PNPLA3-T704_M1282_3G3-5'	1	5	-92.7	3.5			dPCR
704	43811-1	PNPLA3-T704_M941_3G3-5'	1	6	-92.0	5.5			dPCR
562	41338-1	PNPLA3-T562-g.1g}a_M867_	1	6	-94.4	3.0			dPCR
766	40633-1	PNPLA3-T766_M867_	1	5	-88.7	9.4			dPCR
211	43785-1	PNPLA3-T211-g.1g}a_M622_3G3-5'	1	5	-81.5	12.3			dPCR
767	43808-1	PNPLA3-T767-g.1c}a_M941_3G3-5'	1	5	-91.7	5.0			dPCR
767	40628-1	PNPLA3-T767-g.1c}a_M867_	1	5	-88.0	8.3			dPCR
1280	43782-1	PNPLA3-T1280-g.1g}a_M622_3G3-5'	1	5	-89.5	8.6			dPCR
706	41321-1	PNPLA3-T706-g.1g}a_M867_	1	5	-97.6	0.8			dPCR
706	43795-1	PNPLA3-T706-g.1g}a_M1170_3G3-5'	1	5	-82.8	10.0			dPCR
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	1	6	-86.0	10.2	-83.2	9.9	dPCR
1240	52307-1	PNPLA3(Human-Only)-T1240_M867_3G3-5'	3	6	-88.1	12.1	-92.8	11.9	dPCR
1234	52317-1	PNPLA3(Human-Only)-T1234_M867_3G3-5'	1	6	-81.5	10.3	-86.7	7.3	dPCR
1234	52317-1	PNPLA3(Human-Only)-T1234_M867_3G3-5'	3	6	-93.6	1.8	-97.1	1.6	dPCR

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Figure 5

					dPCR		PNPLA3 protein		
					huPNPLA3 mRNA				
PNPLA3 Transcript location	Duplex No.	Name	DOSE (MPK)	N	REL%KD	SD	REL% KD	SD	Analysis
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1282	43806-1	PNPLA3-T704_M1282_3G3-5'	3	6	-92.6	4.5	-97.1	1.3	dPCR
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	1	6	-90.8	3.9	-81.5	8.9	dPCR
706	41321-1	PNPLA3-T706-g.1g>a_M867_3G3-5'	3	6	-88.7	3.7	-89.6	6.9	dPCR

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