



(51) International Patent Classification:
C12N 15/113 (2010.01)

(21) International Application Number:

PCT/US2024/048763

(22) International Filing Date:

27 September 2024 (27.09.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/587,235 02 October 2023 (02.10.2023) US

(71) Applicant: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors: **BRISKEY, Sarah Ashley**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **BUQUER, Selene Hernandez**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **MILES, Rebecca R.**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **PERKINS, Douglas Raymond**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

ana 46206-6288 (US). **SAMMS, Ricardo J.**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

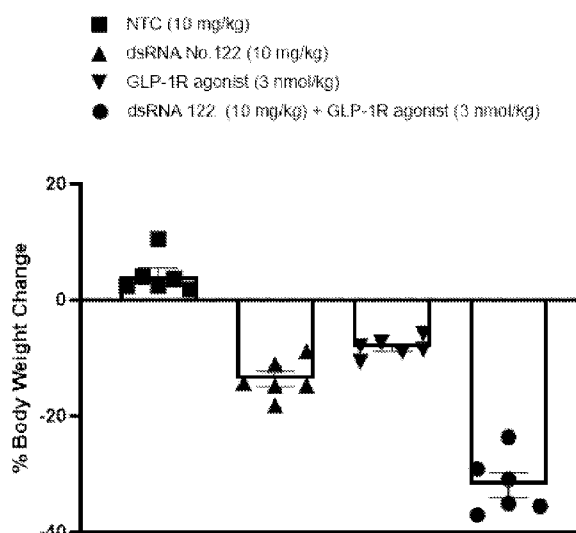
(74) Agent: **GAO, Xiaoguang Michelle** et al.; c/o Eli Lilly and Company, P.O. Box 6288, INDIANAPOLIS, Indiana 46206-6288 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ,

(54) Title: PPP1R15B RNA INTERFERENCE AGENTS

Figure 1



(57) Abstract: Provided herein are PPP1R15B RNAi agents and compositions comprising a PPP1R15B RNAi agent. Also provided herein are methods of using the PPP1R15B RNAi agents or compositions comprising a PPP1R15B RNAi agent for reducing PPP1R15B expression, and/or treating PPP1R15B associated metabolic disorder in a subject.

RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

PPP1R15B RNA INTERFERENCE AGENTS**SEQUENCE LISTING**

[0001] The present application is being filed along with a Sequence Listing in ST.26 XML format. The Sequence Listing is provided as a file titled 30554_WO.xml created September 10, 2024, and is 2.26 megabytes in size. The Sequence Listing information in the ST.26 XML format is incorporated herein by reference in its entirety.

BACKGROUND

[0002] PPP1R15B gene encodes the protein phosphatase 1 regulatory subunit 15B (also known as constitutive repressor of eIF2 α phosphorylation or CReP), which is a critical subunit of the phosphatase complex that promotes the dephosphorylation of eukaryotic translation initiation factor 2A (eIF2 α). eIF2 α is a central component of the integrated stress response (ISR), an evolutionarily conserved intracellular signaling system that helps the cell, tissue, organism to adapt to different environmental and pathological conditions and restore balance (Mauro Costa-Mattioli and Peter Walter, *Science*. 2020;368(6489): eaat5314). PPP1R15B /CReP ablation causes constitutive eIF2 α phosphorylation in the liver, which leads to activation of the activation transcription factor 4 (ATF4) transcriptional program (Xu, et al., *Hepatology*. 2018; 68(6): 2167–2181).

[0003] ISR activation has been observed in metabolic diseases including diabetes, hepatic steatosis, steatohepatitis and obesity. It has been reported that PPP1R15B /CReP ablation causes constitutive eIF2 α phosphorylation in the liver, which leads to activation of the ATF4 transcriptional program (Xu, et al., *Hepatology*. 2018; 68(6): 2167–2181). Liver-specific PPP1R15B /CReP knockout mice exhibited marked browning of white adipose tissue, increased energy expenditure and insulin sensitivity (Xu, et al., *Hepatology*. 2018; 68(6): 2167–2181).

[0004] RNA interference (RNAi) is a highly conserved regulatory mechanism in which RNA molecules are involved in sequence-specific suppression of gene expression by double-stranded RNA molecules (dsRNA) (Fire et al., *Nature* 391:806-811, 1998).

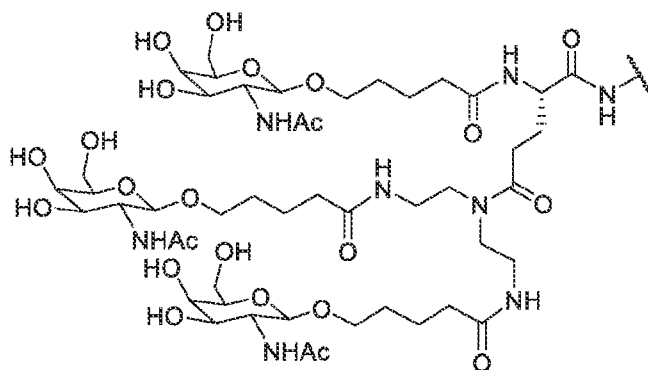
[0005] There remains a need for therapeutic agents that can inhibit or adjust the expression of PPP1R15B/CReP for treating PPP1R15B associated metabolic disorders, e.g., by utilizing RNAi.

SUMMARY OF INVENTION

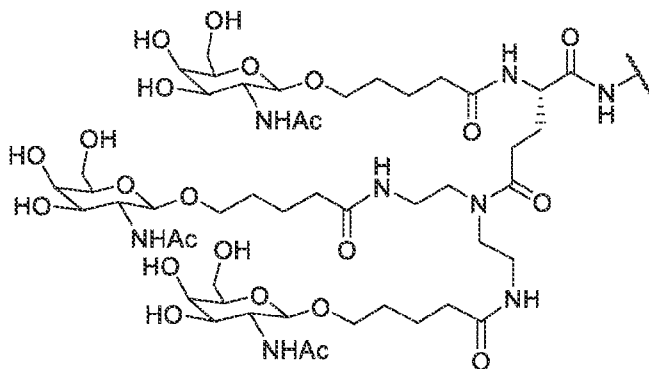
[0006] Provided herein are PPP1R15B RNAi agents and compositions comprising a PPP1R15B RNAi agent. Also provided herein are methods of using the PPP1R15B RNAi agents or compositions comprising a PPP1R15B RNAi agent for treating PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes (T2D), or nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome in a subject.

[0007] In one aspect, provided herein are PPP1R15B RNAi agent comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the antisense strand is complementary to a region of PPP1R15B mRNA. In some embodiments, provided herein are PPP1R15B RNAi agent comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[0008] In some embodiments, the sense strand is linked to a delivery moiety, e.g., a lipid or a carbohydrate. In some embodiments, the delivery moiety is linked to the 3' end of the sense strand, optionally via a linker (L). In some embodiments, the delivery moiety comprises a GalNAc (N-acetylgalactosamine) moiety. In some embodiments, the delivery moiety comprises Formula (II) (Ac means acetyl):



[0009] In another aspect, provided herein are PPP1R15B RNAi agent comprising Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to PPP1R15B mRNA, wherein L is a linker, or optionally absent, and wherein D is a delivery moiety comprising Formula (II):



[00010] Exemplary sense strand and antisense strand sequences of the dsRNA of PPP1R15B RNAi agent are provided in Tables 1 and 2. In some embodiments, the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 2-80, wherein optionally one or more nucleotides of the sense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand are modified internucleotide linkages. In some embodiments, the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00011] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 1-79, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00012] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 93, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 172;

- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 123, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 202;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 125, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 204;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 129, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 208;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 132, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 211;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 136, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 215; and
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 157, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 236,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00013] The PPP1R15B RNAi agents described herein may include modifications. The modifications can be made to one or more nucleotides of the sense strand and/or antisense strand or to the internucleotide linkages. In some embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, 2' deoxy nucleotide (DNA), or 2'-O-alkyl modified nucleotide.

[00014] In some embodiments, the sense strand has four 2'-fluoro modified nucleotides, e.g., at positions 7, 9, 10, 11 from the 5' end of the sense strand. In some embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has four 2'-fluoro modified nucleotides, e.g., at positions 2, 6, 14, 16 from the 5' end of the antisense strand. In some embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00015] In some embodiments, the sense strand has three 2'-fluoro modified nucleotides, e.g., at positions 9, 10, 11 from the 5' end of the sense strand. In some embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 7, 14, 16 from the 5' end of the antisense strand. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 8, 14, 16 from the 5' end of the antisense strand. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 3, 7, 14, 16 from the 5' end of the antisense strand. In some embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00016] In some embodiments, the 5' end of the antisense strand has 5' phosphate or 5' vinylphosphonate (5'-VP).

[00017] In some embodiments, the sense strand or the antisense strand comprises an abasic moiety or inverted abasic moiety.

[00018] In some embodiments, the sense strand and the antisense strand have one or more modified internucleotide linkages. In some embodiments, the modified internucleotide linkage is phosphorothioate linkage. In some embodiments, the sense strand has four or five phosphorothioate linkages. In some embodiments, the antisense strand has four or five phosphorothioate linkages. In some embodiments, the sense strand and the antisense strand each has four or five phosphorothioate linkages. In some embodiments, the sense strand has four phosphorothioate linkages and the antisense strand has five phosphorothioate linkages.

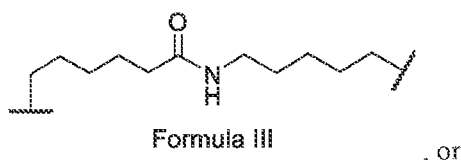
[00019] Exemplary modified sense strand and antisense strand nucleic acid sequences of PPP1R15B RNAi agent are provided in Table 3. In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 80-186.

[00020] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

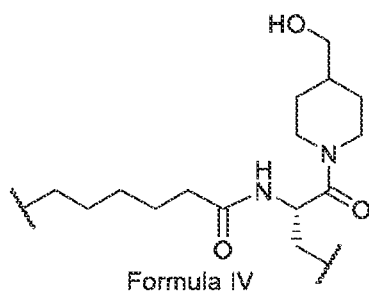
- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 251, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 340;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 281, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 370;

- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 283, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 372;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 287, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 376;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 290, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 379;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 294, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 383; and
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 315, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 404.

[00021] In some embodiments, L (linker) is present and comprises Formula (III) or Formula (IV):



, or



[00022] In another aspect, provided herein are pharmaceutical compositions comprising an PPP1R15B RNAi agent described herein and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising a means for reducing PPP1R15B expression in a cell and a pharmaceutically acceptable carrier.

[00023] In another aspect, provided herein are methods of treating a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome in a patient in need thereof, and such method comprises administering to the patient an effective amount of a PPP1R15B RNAi agent or a pharmaceutical composition described herein. In some

embodiments, the PPP1R15B RNAi agent or the pharmaceutical composition is administered to the patient intravenously or subcutaneously. In some embodiments, such methods further comprise administering a second therapeutic agent (e.g., an incretin) to the patient.

[00024] Also provided herein are methods of reducing PPP1R15B expression in a cell, such methods comprising: introducing a PPP1R15B RNAi agent described herein into the cell; and incubating the cell for a time sufficient for degradation of PPP1R15B mRNA, thereby reducing PPP1R15B expression in the cell.

[00025] In another aspect, provided herein are PPP1R15B RNAi agents or the pharmaceutical composition comprising an PPP1R15B RNAi agent for use in a therapy. Also provided are PPP1R15B RNAi agents or pharmaceutical compositions comprising a PPP1R15B RNAi agent for use in the treatment of a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome. Also provided herein are uses of PPP1R15B RNAi agents in the manufacture of a medicament for the treatment of a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

[00026] Figure 1 is a bar graph showing the percent body weight change in diet-induced obese (DIO) mice up to day 11 after a single dose of a PPP1R15B RNAi agent (dsRNA No. 122), a daily GLP-1R agonist, or a combination of the PPP1R15B RNAi agent (dsRNA No. 122) and daily GLP-1R agonist.

[00027] Figure 2 is a line graph illustrating energy expenditure in DIO mice up to day 10 after a single dose of a PPP1R15B RNAi agent (dsRNA No. 122) as compared with vehicle.

DETAILED DESCRIPTION

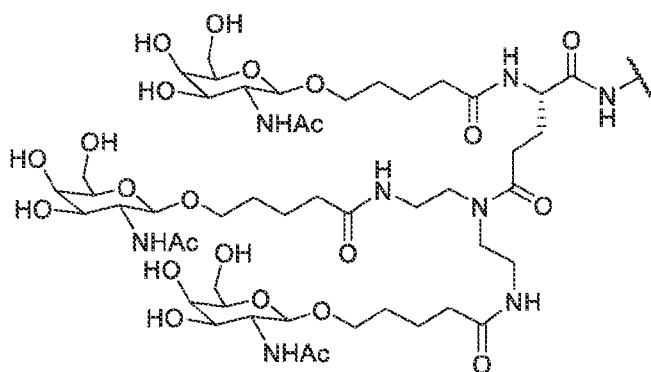
[00028] Provided herein are PPP1R15B RNAi agents and compositions comprising a PPP1R15B RNAi agent. Also provided herein are methods of using the PPP1R15B RNAi agents or compositions comprising a PPP1R15B RNAi agent for treating PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome, in a subject.

[00029] In one aspect, provided herein are PPP1R15B RNAi agent comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, and wherein the antisense strand is complementary to a region of PPP1R15B mRNA. In some embodiments, the sense strand and the antisense strand are each 15-30 nucleotides in length, e.g., 20-25 nucleotides in length. In some embodiments, provided herein are PPP1R15B RNAi agents comprising a sense strand of 21 nucleotides and an antisense strand of 23 nucleotides. In some embodiments, the sense strand and antisense strand of the PPP1R15B RNAi agent may have overhangs at either the 5' end or the 3' end (i.e., 5' overhang or 3' overhang). For example, the sense strand and the antisense strand may have 5' or 3' overhangs of 1 to 5 nucleotides.

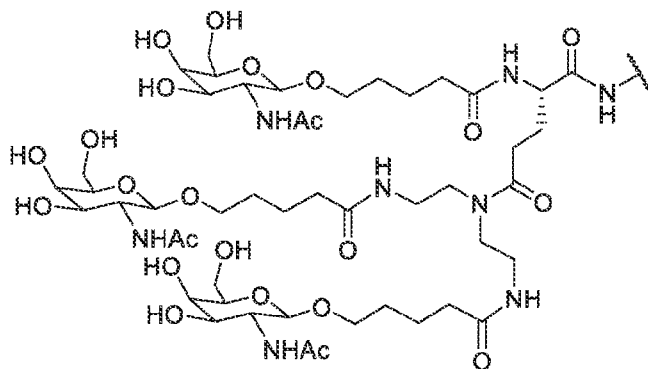
[00030] Exemplary sense strand and antisense strand sequences of PPP1R15B RNAi agent are provided in Tables 1 and 2.

[00031] In some embodiments, provided herein are PPP1R15B RNAi agent comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00032] In some embodiments, the sense strand is linked to a delivery moiety, e.g., a lipid or a carbohydrate. The delivery moiety can facilitate the entry of RNAi agent into the cells. In some embodiments, the delivery moiety is linked to the 3' end of the sense strand, optionally via a linker. In some embodiments, the delivery moiety comprises a GalNAc (N-acetylgalactosamine) moiety. In some embodiments, the delivery moiety comprises Formula (II) (Ac means acetyl):



[00033] In another aspect, provided herein are PPP1R15B RNAi agent comprising Formula (I): R-L-D, wherein R is a double stranded RNA (dsRNA) comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to PPP1R15B mRNA, wherein L is a linker, or optionally absent, and wherein D is a delivery moiety comprising Formula (II):



[00034] Exemplary sense strand and antisense strand sequences of the dsRNA of PPP1R15B RNAi agent are provided in Tables 1 and 2. In some embodiments, the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 2-80, wherein optionally one or more nucleotides of the sense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand are modified internucleotide linkages. In some embodiments, the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00035] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 1-79, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00036] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 93, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 172;
- (b) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 123, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 202;
- (c) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 125, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 204;
- (d) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 129, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 208;
- (e) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 132, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 211;
- (f) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 136, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 215; and
- (g) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 157, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 236,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00037] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 93, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 172;

- (b) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 123, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 202;
- (c) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 125, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 204;
- (d) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 129, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 208;
- (e) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 132, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 211;
- (f) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 136, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 215; and
- (g) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 157, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 236,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00038] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 93, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 172;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 123, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 202;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 125, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 204;
- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 129, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 208;

(e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 132, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 211;

(f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 136, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 215; and

(g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 157, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 236,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

Table 1: Exemplary sense strand sequences of PPP1R15B RNAi agents

SEQ ID NO	Sense Strand (5' to 3')	Start position of target region on human PPP1R15B transcript NM_032833.5 (SEQ ID NO: 1)	Start position of target region on mouse PPP1R15B transcript NM_133819.3 (SEQ ID NO: 425)
2	UACGUGUAACGUGGAGAU	N/A	5477
3	GAUGAAGCAGAGAAUCUU	2048	2172
4	UGUAUAUAAUUAUUAACU	N/A	5515
5	GGCACACACCAUUAUGCC	N/A	4079
6	AGCAGUCUGUUUUGUGAA	N/A	1683
7	GAAGUUGCCAUUGGCUAC	N/A	2568
8	UAAUGGGCUUUAUGGGUU	N/A	3499
9	GGUGUCCCCUGCUGCAGA	N/A	1598
10	UCUGAAUCAGACGUGGAA	N/A	1923
11	UUAUAUUUUGGGAGGCGC	1687	1814
12	GUUUGGCUUGCACAUGGC	N/A	3937
13	GACUGGGAAAGCGGGGUU	N/A	4046
14	AGAAACGAAUUCAAGAAA	2424	2548
15	AAGAUAAUGGCUAUCUA	N/A	1513
16	GCUAACAAGGGCAAGAG	N/A	1479
17	CGGUCGCCACCGCUUGCG	N/A	365
18	GGAAACGCCGCCGUCGUC	N/A	252
19	CGAUCGCACGCCUGCUCU	N/A	660
20	AUGGACCCACAACAUUGC	N/A	1560
21	CUUCUGGAGGCAGGGGCU	N/A	3084
22	UACUAAUCUGUAAAUUG	5210	5528

23	UCCGCCUCUCGGGAGGCA	N/A	44
24	CGGGAGGAAUCUGCCGCU	N/A	897
25	AACUAGGGGGUAUUUGGG	N/A	4266
26	UCUUUUUAAGAUAUUUCC	N/A	3991
27	GAGAAGCAAAGCAGAAAG	N/A	4478
28	AACGCACAGGGCCCGGAA	N/A	593
29	CGCACGCCUGCUCUUCGG	N/A	664
30	GCGGCCAUUUUGAGCUUC	632	161
31	GAACUCCGCUCUGCCCGA	N/A	716
32	UGGACAUGUUUUUAAAAGA	N/A	2750
33	ACCAUAGUUCGCGGGAGG	2007	2131
34	CGGAGCCACUGAGAAAA	N/A	1621
35	GCCGUUGCGGGCAGAGAU	N/A	1367
36	GCCUCUUCUGAGGCUACA	N/A	2298
37	CGCCUCUCUCUACAGAAG	N/A	1411
38	GCAAACUGUCCAUUUGGA	N/A	4134
39	GUGAGGCAAGUCCGCCUC	N/A	34
40	UCUCUGUAGCUUUAAGA	N/A	4188
41	ACCAGAUGGCUAGAUUUU	686	843
42	CUUACUUUCUUGUAAGGC	2215	2339
43	UCACCUUUGGAACUCUUU	1831	1958
44	GAAACGAAUUAAGAAAC	2425	2549
45	UUUGCACUUUCAAACGU	2850	3064
46	UAUUUAUAAGUGGUGAU	2354	2478
47	UAAGUGGUGAUGAGGAUC	2361	2485
48	CAACAAACUGAUAGAUUA	1672	1799
49	AUGGAUGCAGGUUCCAGA	2409	2533
50	GAGUAUUUAUAAGUGGU	2351	2475
51	GCAGGUUCCAGAAACGAA	2415	2539
52	ACUACCUCAGUUUAUAAU	3980	4706
53	ACGAAUUAAGAAACAGA	2428	2552
54	GAUAGAUUAUUAUUUGGG	1681	1808
55	UAUAUAAGUGGUGAUGAG	2357	2481
56	AGGUUCCAGAAACGAAU	2417	2541
57	CAGGUUCCAGAAACGAAU	2416	2540
58	UACCUCAGUUUAUAAUCU	3982	4708
59	UAGCAACAAACUGAUAGA	1669	1796
60	CCAUUUUGAGCUUCGCUU	636	165
61	AGGGAUGGAUGCAGGUUC	2405	2529
62	CACCCCUGACCAAGAUAA	1348	1502
63	UUAAGGCUCCUUUUAAC	2118	2242

64	AUUCAGACGGCUGCCAGA	1892	2019
65	AACGAAUUAAGAAACAG	2427	2551
66	GAUGAGGAUCGCAAAGGA	2369	2493
67	UGAUAGAUUAUUAUUUGG	1680	1807
68	AAGGCCUUCACCUUUGGA	1824	1951
69	AUUAUAUUUUGGGAGGCG	1686	1813
70	GAUGGAUGCAGGUUCCAG	2408	2532
71	CAUACCUUACUUUCUUGU	2210	2334
72	GCAACAAACUGAUAGAUU	1671	1798
73	UAUCCAGGUUUGUUGUGU	3626	4445
74	GGCCAUUUUGAGCUUCGC	634	163
75	AGAUUAUUAUUUGGGAGG	1684	1811
76	CCAGAUGGCUAGAUUUUG	687	844
77	AAAAAAUGUUUAAUAGAC	2484	2608
78	UGAUGAGGAUCGCAAAGG	2368	2492
79	UUGAUUGGCUAGAGGAGG	825	982
80	UGAUUGGCUAGAGGAGGG	826	983

Table 2: Unmodified sense strand and antisense strand sequences of PPP1R15B RNAi agents

dsRNA No.	Sense Strand (5' to 3')	SEQ ID NO	Antisense Strand (5' to 3')	SEQ ID NO	Start position of target region on human PPP1R15B transcript NM_03283 3.5 (SEQ ID NO: 1)	Start position of target region on mouse PPP1R15B transcript NM_1338 19.3 (SEQ ID NO: 425)
1	UUUACGUGUAACG UGGAGAUU	81	UAUCUCCACGUUAC ACGUAAAAU	160	N/A	5477
2	CAGAUGAAGCAGA GAAUCUUA	82	UAAGAUUCUCUGCU UCAUCUGCA	161	2048	2172
3	UUUGUAUAUAAUU AUUAACUA	83	UAGUUAUAAUUAU AUACAAAUA	162	N/A	5515
4	AAGGCACACACCA UUAUGCCA	84	UGGCAUAAUGGUGU GUGCCUUUG	163	N/A	4079
5	GAAGCAGUCUGUU UUGUGAAA	85	UUUCACAAAACAGA CUGCUUCCC	164	N/A	1683
6	CAGAAGUUGCCAU UGGCUACA	86	UGUAGCCAAUGGCA ACUUCUGUU	165	N/A	2568

7	AUUAUAUGGGCUUU AUGGGUUA	87	UAACCCAUAAGGCC CAUUAUUUU	166	N/A	3499
8	GCGGUGUCCCCUG CUGCAGAA	88	UUCUGCAGCAGGGG ACACCGCCU	167	N/A	1598
9	UGUCUGAAUCAGA CGUGGAAA	89	UUUCCACGUCUGAU UCAGACAGG	168	N/A	1923
10	GAUUAUAUUUUGG GAGGCGCA	90	UGCGCCUCCCCAAA UAUAAUCUA	169	1687	1814
11	UUGUUUGGCUUGC ACAUGGCA	91	UGCCAUGUGCAAGC CAAACAAGA	170	N/A	3937
12	UUGACUGGGAAAG CGGGGUUA	92	UAACCCCGCUUUC CAGUCAAGA	171	N/A	4046
13	CCAGAAACGAAUU CAAGAAAA	93	UUUUCUUGAAUUCG UUUCUGGAA	172	2424	2548
14	CCAAGAUAAUGGC UAUCAUAA	94	UUAUGAUAGCCAUU AUCUUGGUC	173	N/A	1513
15	AGGCUAACAAAGG GCAAGAGA	95	UCUCUUGCCCUUG UUAGCCUGG	174	N/A	1479
16	CGCGGUCGCCACC GCUUGCGA	96	UCGCAAGCGGUGGC GACCGCGGU	175	N/A	365
17	CCGGAACGCCCGC CGUCGUCA	97	UGACGACGGCGGCG UUUCCGGUG	176	N/A	252
18	GGCGAUCGCACGC CUGCUCUA	98	UAGAGCAGGCGUGC GAUCGCCGA	177	N/A	660
19	GGAUGGACCCACA ACAUUGCA	99	UGCAAUGUUGUGGG UCCAUCCGG	178	N/A	1560
20	UUCUUCUGGAGGC AGGGGCUA	100	UAGCCCCUGCCUCC AGAAGAAAC	179	N/A	3084
21	AUUAACUAAUCUG UAAAUUGA	101	UCAAUUUACAGAUU AGUUAUAA	180	5210	5528
22	AGUCCGCCUCUCG GGAGGCAA	102	UUGCCUCCCGAGAG GCGGACUUG	181	N/A	44
23	GACGGGAGGAAUC UGCCGCUA	103	UAGCGGCAGAUUCC UCCCGUCCU	182	N/A	897
24	UUAACUAGGGGGU AUUUGGGA	104	UCCCAAAUACCCCC UAGUAAAAA	183	N/A	4266
25	GGUCUUUUUAAGA UAUUUCCA	105	UGGAAAUAUUCUAA AAAGACCUA	184	N/A	3991
26	GAGAGAAGCAAAG CAGAAAGA	106	UCUUUCUGCUUUGC UUCUCUCUA	185	N/A	4478
27	GGAACGCACAGGG CCCGGAAA	107	UUUCCGGGCCUGU GCGUUCUG	186	N/A	593
28	AUCGCACGCCUGC UCUUCGGA	108	UCCGAAGAGCAGGC GUGCGAUCC	187	N/A	664
29	CUGCGGCCAUUUU GAGCUUCA	109	UGAAGCUCAAAAUG GCCGCAGCC	188	632	161
30	GGGAACUCCGCUC UGCCCGAA	110	UUCGGGCAGAGCGG AGUUCCCGG	189	N/A	716
31	CUUGGACAUGUUU UUAAGAA	111	UUCUUUAAAAACAU GUCCAAGGA	190	N/A	2750

32	CGACCAUAGUUC GGGGAGGA	112	UCCUCCCCGGAACU AUGGUCGGG	191	2007	2131
33	GCCGGAGCCCACU GAGAAAAA	113	UUUUUCUCAGUGGG CUCCGGCCU	192	N/A	1621
34	CAGCCGUUGCGGG CAGAGUA	114	UAUCUCUGCCCGCA ACGGCUGAG	193	N/A	1367
35	AGGCCUCUUCUGA GGCUACAA	115	UUGUAGCCUCAGAA GAGGCCUUU	194	N/A	2298
36	UCCGCCUCUCUCU ACAGAAGA	116	UCUUCUGUAGAGAG AGGCGGACA	195	N/A	1411
37	GUGCAAACUGUCC AUUUGGAA	117	UUCAAAUGGACAG UUUGCACAG	196	N/A	4134
38	GGGUGAGGCAAGU CCGCCUCA	118	UGAGGCGGACUUGC CUCACCCUC	197	N/A	34
39	GCUCUCUGUAGCU UUCAAGAA	119	UUCUUGAAAGCUAC AGAGAGCCA	198	N/A	4188
40	CUACCAGAUGGCU AGAUUUUA	120	UAAAAUCUAGCCA CUGGUAGGA	199	686	843
41	ACCUUACUUUCUU GUAAGGCA	121	UGCCUUACAAGAAA GUAAGGUAAU	200	2215	2339
42	CUUCACCUUUGGA ACUCUUUA	122	UAAAGAGUUCCAAA GGUGAAGGC	201	1831	1958
43	CAGAAACGAAUUC AAGAAACA	123	UGUUUCUUGAAUUC GUUUCUGGA	202	2425	2549
44	AUUUUGCACUUUC AAAACGUA	124	UACGUUUUGAAAGU GCAAAAUUA	203	2850	3064
45	AGUAUUUAUAAG UGGUGUA	125	UAUACCACUUAUA UAAUACUCA	204	2354	2478
46	UAUAAGUGGUGAU GAGGAUCA	126	UGAUCCUCAUACC ACUUAUAUA	205	2361	2485
47	AGCAACAAACUGA UAGAUUAA	127	UUAUUCUAUCAGUU UGUUGCUAC	206	1672	1799
48	GGAUGGAUGCAGG UCCAGAA	128	UUCUGGAACCUGCA UCCAUCCCU	207	2409	2533
49	CUGAGUAUUAUAU AAGUGGUA	129	UACCACUUAUAUA UACUCAGUA	208	2351	2475
50	AUGCAGGUUCCAG AAACGAAA	130	UUUCGUUUCUGGAA CCUGCAUCC	209	2415	2539
51	AAACUACCUCAGU UUAUAAUA	131	UAUUAUAAACUGAG GUAGUUUAC	210	3980	4706
52	AAACGAAUUCAG AAACAGAA	132	UUCUGUUUCUUGAA UUCGUUUUCU	211	2428	2552
53	CUGAUAGAUUAUA UUUUGGGA	133	UCCCAAAAUUAUU CUAUCAGUU	212	1681	1808
54	AUUAUAUAAGUGG UGAUGAGA	134	UCUCAUACCACUU AUUAUAUAC	213	2357	2481
55	GCAGGUUCCAGAA ACGAAUUA	135	UAAUUCGUUUCUGG AACCUGCAU	214	2417	2541
56	UGCAGGUUCCAGA AACGAAUA	136	UAUUCGUUUCUGGA ACCUGCAUC	215	2416	2540

57	ACUACCUCAGUUU AUAUUCUA	137	UAGAUUAUAAACUG AGGUAGUUU	216	3982	4708
58	UGUAGCAACAAAC UGAUAGAA	138	UUCUAUCAGUUUGU UGCUACAAA	217	1669	1796
59	GGCCAUUUUGAGC UUCGCUUA	139	UAAGCGAAGCUCAA AAUGGCCCGC	218	636	165
60	CAAGGGAUGGAUG CAGGUUCA	140	UGAACCUGCAUCCA UCCCUUGCA	219	2405	2529
61	CCCACCCUGACCA AGAUAAA	141	UUUAUCUUGGUCAG GGGUGGGUA	220	1348	1502
62	UUUUAAGGCUCU UUUCAACA	142	UGUUGAAAAGGAGC CUUAAAAAU	221	2118	2242
63	CGAUUCAGACGGC UGCCAGAA	143	UUCUGGCAGCCGUC UGAAUCGUG	222	1892	2019
64	GAAACGAAUUCAA GAAACAGA	144	UCUGUUUCUUGAAU UCGUUUCUG	223	2427	2551
65	GUGAUGAGGAUCG CAAAGGAA	145	UUCCUUUGCGAUCC UCAUCACCA	224	2369	2493
66	ACUGAUAGAUUAU AUUUUGGA	146	UCCAAAAUAUAAUC UAUCAGUUU	225	1680	1807
67	GGAAGGCCUUCAC CUUUGGAA	147	UUCCAAAGGUGAAG GCCUUCCGA	226	1824	1951
68	AGAUUAUAUUUUG GGAGGCGA	148	UCGCCUCCCAAAAU AUAUUCUAU	227	1686	1813
69	GGGAUGGAUGCAG GUUCCAGA	149	UCUGGAACCUGCAU CCAUCCCUU	228	2408	2532
70	AUCAUACCUUACU UUCUUGUA	150	UACAAGAAAGUAAG GUAUGAUGG	229	2210	2334
71	UAGCAACAAACUG AUAGAUUA	151	UAAUCUAUCAGUUU GUUGCACA	230	1671	1798
72	AAUAUCCAGGUUU GUUGUGUA	152	UACACAACAAACCU GGAUAUUGA	231	3626	4445
73	GCGGCCAUUUUGA GCUUCGCA	153	UGCGAAGCUCAAAA UGGCCGCGAG	232	634	163
74	AUAGAUUAUAUUU UGGGAGGA	154	UCCUCCCAAAAUAU AAUCUAUCA	233	1684	1811
75	UACCAGAUGGCUA GAUUUUGA	155	UCAAAAUCUAGCCA UCUGGUAGG	234	687	844
76	AGAAAAAUGUUU AAUAGACA	156	UGUCUAUUAACAUA UUUUUCUCU	235	2484	2608
77	GGUGAUGAGGAUC GCAAAGGA	157	UCCUUUGCGAUCCU CAUACCAC	236	2368	2492
78	UCUUGAUUGGCUA GAGGAGGA	158	UCCUCCUCUAGCCA AUCAAGAGA	237	825	982
79	CUUGAUUGGCUAG AGGAGGGA	159	UCCCUCCUCUAGCC AAUCAAGAG	238	826	983

[00039] The PPP1R15B RNAi agents described herein may include modifications. The modifications can be made to one or more nucleotides of the sense strand and/or antisense strand or to the internucleotide linkages. In some embodiments, one or more nucleotides of the sense strand are modified nucleotides. In some embodiments, each nucleotide of the sense strand is a modified nucleotide. In some embodiments, one or more nucleotides of the antisense strand are modified nucleotides. In some embodiments, each nucleotide of the antisense strand is a modified nucleotide. In some embodiments, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, 2' deoxy nucleotide (DNA), or 2'-O-alkyl modified nucleotide.

[00040] In some embodiments, the sense strand has four 2'-fluoro modified nucleotides, e.g., at positions 7, 9, 10, 11 from the 5' end of the sense strand. In some embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has four 2'-fluoro modified nucleotides, e.g., at positions 2, 6, 14, 16 from the 5' end of the antisense strand. In some embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00041] In some embodiments, the sense strand has three 2'-fluoro modified nucleotides, e.g., at positions 9, 10, 11 from the 5' end of the sense strand. In some embodiments, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 7, 14, 16 from the 5' end of the antisense strand. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 8, 14, 16 from the 5' end of the antisense strand. In some embodiments, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 3, 7, 14, 16 from the 5' end of the antisense strand. In some embodiments, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00042] In some embodiments, the 5' end of the antisense strand has 5' phosphate or 5' vinylphosphonate (5'-VP).

[00043] In some embodiments, the sense strand or the antisense strand comprises an abasic moiety or inverted abasic moiety, e.g., a moiety in Table 4.

[00044] In some embodiments, the sense strand and the antisense strand have one or more modified internucleotide linkages. In some embodiments, the modified internucleotide linkage is phosphorothioate linkage. In some embodiments, the sense strand has four or five

phosphorothioate linkages. In some embodiments, the antisense strand has four or five phosphorothioate linkages. In some embodiments, the sense strand and the antisense strand each has four or five phosphorothioate linkages. In some embodiments, the sense strand has four phosphorothioate linkages and the antisense strand has five phosphorothioate linkages.

[00045] Exemplary modified sense strand and antisense strand nucleic acid sequences of PPP1R15B RNAi agent are provided in Table 3. In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 80-186.

[00046] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 251, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 340;
- (b) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 281, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 370;
- (c) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 283, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 372;
- (d) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 287, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 376;
- (e) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 290, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 379;
- (f) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 294, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 383; and
- (g) the sense strand comprises a first nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 315, and the antisense strand comprises a second nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 404.

[00047] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 251, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 340;
- (b) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 281, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 370;
- (c) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 283, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 372;
- (d) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 287, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 376;
- (e) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 290, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 379;
- (f) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 294, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 383; and
- (g) the sense strand comprises a first nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 315, and the antisense strand comprises a second nucleic acid sequence having at least 95% sequence identity to SEQ ID NO: 404.

[00048] In some embodiments, the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 251, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 340;
- (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 281, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 370;
- (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 283, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 372;

- (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 287, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 376;
- (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 290, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 379;
- (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 294, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 383; and
- (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 315, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 404.

Table 3a: Modified sense strand and antisense strand sequences of PPP1R15B RNAi agents

dsRNA No.	Oligo Sequence (5' to 3')	SEQ ID NO
80	mU*mU*mUmAmCmGmUmGfUfAfAmCmGmUmGmGmAmGmA*mU*mA	239
	PmU*fA*mUmCfUmCfCmAmCmGmUmUmAfCmAfCmGmUmAmAmA*mA*mU	328
81	mC*mA*mGmAmUmGmAmAfGfCfAmGmAmGmAmAmUmCmU*mU*mA	240
	PmU*fA*mAmGfAmUfUmCmUmCmUmGmCfUmUfCmAmUmCmUmG*mC*mA	329
82	mU*mU*mUmGmUmAmUmAfUfAfAmUmUmAmUmUmAmAmC*mU*mA	241
	PmU*fA*mGmUfUmAfAmUmAmAmUmUmAfUmAfUmAmCmAmAmA*mU*mA	330
83	mA*mA*mGmGmCmAmCmAfCfAfCmCmAmUmUmAmUmGmC*mC*mA	242
	PmU*fG*mGmCfAmUfAmAmUmGmGmUmGfUmGfUmGmCmCmUmU*mU*mG	331
84	mG*mA*mAmGmCmAmGmUfCfUfGmUmUmUmUmGmUmGmA*mA*mA	243
	PmU*fU*mUmCfAmCfAmAmAmAmCmAmGfAmCfUmGmCmUmUmC*mC*mC	332
85	mC*mA*mGmAmAmGmUmUfGfCfCmAmUmUmGmGmCmUmA*mC*mA	244
	PmU*fG*mUmAfGmCfCmAmAmUmGmGmCfAmAfCmUmUmCmUmG*mU*mU	333
86	mA*mU*mUmAmAmUmGmGfGfCfUmUmUmAmUmGmGmGmU*mU*mA	245
	PmU*fA*mAmCfCmCfAmUmAmAmAmGmCfCmCfAmUmUmAmAmU*mU*mU	334
87	mG*mC*mGmGmUmGmUmCfCfCfCmUmGmCmUmGmCmAmG*mA*mA	246
	PmU*fU*mCmUfGmCfAmGmCmAmGmGmGfGmAfCmAmCmCmGmC*mC*mU	335
88	mU*mG*mUmCmUmGmAmAfUfCfAmGmAmCmGmUmGmGmA*mA*mA	247
	PmU*fU*mUmCfCmAfCmGmUmCmUmGmAfUmUfCmAmGmAmCmA*mG*mG	336
89	mG*mA*mUmUmAmUmAmUfUfUfUmGmGmGmAmGmGmCmG*mC*mA	248
	PmU*fG*mCmGfCmCfUmCmCmCmAmAmAfAmUfAmUmAmAmUmC*mU*mA	337
90	mU*mU*mGmUmUmUmGmGfCfUfUmGmCmAmCmAmUmGmG*mC*mA	249
	PmU*fG*mCmCfAmUfGmUmGmCmAmAmGfCmCfAmAmAmCmAmA*mG*mA	338
91	mU*mU*mGmAmCmUmGmGfGfAfAmAmGmCmGmGmGmU*mU*mA	250

	PmU*fA*mAmCfCmCfCmGmCmUmUmUmCfCmCfAmGmUmCmAmA*mG*mA	339
92	mC*mC*mAmGmAmAmAmCfGfAfAmUmUmCmAmAmGmAmA*mA*mA	251
	PmU*fU*mUmUfCmUfUmGmAmAmUmUmCfGmUfUmUmCmUmGmG*mA*mA	340
93	mC*mC*mAmAmGmAmUmAfAfUfGmGmCmUmAmUmCmAmU*mA*mA	252
	PmU*fU*mAmUfGmAfUmAmGmCmCmAmUfUmAfUmCmUmUmGmG*mU*mC	341
94	mA*mG*mGmCmUmAmAmCfAfAfAmGmGmGmCmAmAmGmA*mG*mA	253
	PmU*fC*mUmCfUmUfGmCmCmCmUmUmUfGmUfUmAmGmCmCmU*mG*mG	342
95	mC*mG*mCmGmGmUmCmGfCfCfAmCmCmGmCmUmUmGmC*mG*mA	254
	PmU*fC*mGmCfAmAfGmCmGmGmUmGmGfCmGfAmCmCmGmCmG*mG*mU	343
96	mC*mC*mGmGmAmAmAmCfGfCfCmGmCmCmGmUmCmGmU*mC*mA	255
	PmU*fG*mAmCfGmAfCmGmGmCmGmGmCfGmUfUmUmCmCmGmG*mU*mG	344
97	mG*mG*mCmGmAmUmCmGfCfAfCmGmCmCmUmGmCmUmC*mU*mA	256
	PmU*fA*mGmAfGmCfAmGmGmCmGmUmGfCmGfAmUmCmGmCmC*mG*mA	345
98	mG*mG*mAmUmGmGmAmCfCfCfAmCmAmAmCmAmUmUmG*mC*mA	257
	PmU*fG*mCmAfAmUfGmUmUmGmUmGmGfGmUfCmCmAmUmCmC*mG*mG	346
99	mU*mU*mCmUmUmCmUmGfGfAfGmGmCmAmGmGmGmC*mU*mA	258
	PmU*fA*mGmCfCmCfCmUmGmCmCmUmCfCmAfGmAmAmGmAmA*mA*mC	347
100	mA*mU*mUmAmAmCmUmAfAfUfCmUmGmUmAmAmAmUmU*mG*mA	259
	PmU*fC*mAmAfUmUfUmAmCmAmGmAmUfUmAfGmUmUmAmAmU*mA*mA	348
101	mA*mG*mUmCmCmGmCmCfUfCfUmCmGmGmGmAmGmGmC*mA*mA	260
	PmU*fU*mGmCfCmUfCmCmCmGmAmGmAfGmGfCmGmGmAmCmU*mU*mG	349
102	mG*mA*mCmGmGmGmAmGfGfAfAmUmCmUmGmCmCmGmC*mU*mA	261
	PmU*fA*mGmCfGmGfCmAmGmAmUmUmCfCmUfCmCmCmGmUmC*mC*mU	350
103	mU*mU*mAmAmCmUmAmGfGfGfGmGmUmAmUmUmUmGmG*mG*mA	262
	PmU*fC*mCmCfAmAfAmUmAmCmCmCmCfCmUfAmGmUmUmAmA*mA*mA	351
104	mG*mG*mUmCmUmUmUmUfUfAfAmGmAmUmAmUmUmUmC*mC*mA	263
	PmU*fG*mGmAfAmAfUmAmUmCmUmUmAfAmAfAmAmGmAmCmC*mU*mA	352
105	mG*mA*mGmAmGmAmAmGfCfAfAmAmGmCmAmGmAmAmA*mG*mA	264
	PmU*fC*mUmUfUmCfUmGmCmUmUmUmGfCmUfUmCmUmCmU*mU*mA	353
106	mG*mG*mAmAmCmGmCmAfCfAfGmGmGmCmCmCmGmGmA*mA*mA	265
	PmU*fU*mUmCfCmGfGmGmCmCmCmUmGfUmGfCmGmUmUmCmC*mU*mG	354
107	mA*mU*mCmGmCmAmCmGfCfCfUmGmCmUmCmUmUmCmG*mG*mA	266
	PmU*fC*mCmGfAmAfGmAmGmCmAmGmGfCmGfUmGmCmGmAmU*mC*mG	355
108	mC*mU*mGmCmGmGmCmCfAfUfUmUmUmGmAmGmCmUmU*mC*mA	267
	PmU*fG*mAmAfGmCfUmCmAmAmAmAmUfGmGfCmCmGmCmAmG*mC*mC	356
109	mG*mG*mGmAmAmCmUmCfCfGfCmUmCmUmGmCmCmCmG*mA*mA	268
	PmU*fU*mCmGfGmGfCmAmGmAmGmCmGfGmAfGmUmUmCmCmC*mG*mG	357
110	mC*mU*mUmGmGmAmCmAfUfGfUmUmUmUmUmAmAmAmG*mA*mA	269
	PmU*fU*mCmUfUmUfAmAmAmAmAmCmAfUmGfUmCmCmAmAmG*mG*mA	358
111	mC*mG*mAmCmCmAmUmAfGfUfUmCmCmGmGmGmGmAmG*mG*mA	270
	PmU*fC*mCmUfCmCfCmCmGmGmAmAmCfUmAfUmGmGmUmCmG*mG*mG	359

112	mG*mC*mCmGmGmAmGmCfCfCfAmCmUmGmAmGmAmAmA*mA*mA	271
	PmU*fU*mUmUfUmCfUmCmAmGmUmGmGfGmCfUmCmCmGmGmC*mC*mU	360
113	mC*mA*mGmCmCmGmUmUfGfCfGmGmGmCmAmGmAmGmA*mU*mA	272
	PmU*fA*mUmCfUmCfUmGmCmCmCmGmCfAmAfCmGmGmCmUmG*mA*mG	361
114	mA*mG*mGmCmCmUmCmUfUfCfUmGmAmGmGmCmUmAmC*mA*mA	273
	PmU*fU*mGmUfAmGfCmCmUmCmAmGmAfAmGfAmGmGmCmCmU*mU*mU	362
115	mU*mC*mCmGmCmCmUmCfUfCfUmCmUmAmCmAmGmAmA*mG*mA	274
	PmU*fC*mUmUfCmUfGmUmAmGmAmGmAfGmAfGmGmCmGmGmA*mC*mA	363
116	mG*mU*mGmCmAmAmAmCfUfGfUmCmCmAmUmUmUmGmG*mA*mA	275
	PmU*fU*mCmCfAmAfAmUmGmGmAmCmAfGmUfUmUmGmCmAmC*mA*mG	364
117	mG*mG*mGmUmGmAmGmGfCfAfAmGmUmCmCmGmCmCmU*mC*mA	276
	PmU*fG*mAmGfGmCfGmGmAmCmUmUmGfCmCfUmCmAmCmCmC*mU*mC	365
118	mG*mC*mUmCmUmCmUmGfUfAfGmCmUmUmUmCmAmAmG*mA*mA	277
	PmU*fU*mCmUfUmGfAmAmAmGmCmUmAfCmAfGmAmGmAmGmC*mC*mA	366
119	mC*mU*mAmCmCmAmGmAfUfGfGmCmUmAmGmAmUmUmU*mU*mA	278
	PmU*fA*mAmAfAmUfCmUmAmGmCmCmAfUmCfUmGmGmUmAmG*mG*mA	367
120	mA*mC*mCmUmUmAmCmUfUfUfCmUmUmGmUmAmAmGmG*mC*mA	279
	PmU*fG*mCmCfUmUfAmCmAmAmGmAmAfAmGfUmAmAmGmGmU*mA*mU	368
121	mC*mU*mUmCmAmCmCmUfUfUfGmGmAmAmCmUmCmUmU*mU*mA	280
	PmU*fA*mAmAfGmAfGmUmUmCmCmAmAfAmGfGmUmGmAmAmG*mG*mC	369
122	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGmAmAmUmUfCmGfUmUmUmCmUmG*mG*mA	370
123	mA*mU*mUmUmUmGmCmAfCfUfUmUmCmAmAmAmAmCmG*mU*mA	282
	PmU*fA*mCmGfUmUfUmUmGmAmAmAmGfUmGfCmAmAmAmAmU*mU*mA	371
124	mA*mG*mUmAmUmUmAmUfAfUfAmAmGmUmGmGmUmGmA*mU*mA	283
	PmU*fA*mUmCfAmCfCmAmCmUmUmAmUfAmUfAmAmUmAmCmU*mC*mA	372
125	mU*mA*mUmAmAmGmUmGfGfUfGmAmUmGmAmGmGmAmU*mC*mA	284
	PmU*fG*mAmUfCmCfUmCmAmUmCmAmCfCmAfCmUmUmAmUmA*mU*mA	373
126	mA*mG*mCmAmAmCmAmAfAfCfUmGmAmUmAmGmAmUmU*mA*mA	285
	PmU*fU*mAmAfUmCfUmAmUmCmAmGmUfUmUfGmUmUmGmCmU*mA*mC	374
127	mG*mG*mAmUmGmGmAmUfGfCfAmGmGmUmUmCmCmAmG*mA*mA	286
	PmU*fU*mCmUfGmGfAmAmCmCmUmGmCfAmUfCmCmAmUmCmC*mC*mU	375
128	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAmUmAmUmAfAmUfAmCmUmCmAmG*mU*mA	376
129	mA*mU*mGmCmAmGmGmUfUfCfCmAmGmAmAmAmCmGmA*mA*mA	288
	PmU*fU*mUmCfGmUfUmUmCmUmGmGmAfAmCfCmUmGmCmAmU*mC*mC	377
130	mA*mA*mAmCmUmAmCmCfUfCfAmGmUmUmUmAmUmAmA*mU*mA	289
	PmU*fA*mUmUfAmUfAmAmAmCmUmGmAfGmGfUmAmGmUmUmU*mA*mC	378
131	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCmUmUmGmAfAmUfUmCmGmUmUmU*mC*mU	379
132	mC*mU*mGmAmUmAmGmAfUfUfAmUmAmUmUmUmUmGmG*mG*mA	291

	PmU*fC*mCmCfAmAfAmAmUmAmUmAmAfUmCfUmAmUmCmAmG*mU*mU	380
133	mA*mU*mUmAmUmAmUmAfAfGfUmGmGmUmGmAmUmGmA*mG*mA	292
	PmU*fC*mUmCfAmUfCmAmCmCmAmCmUfUmAfUmAmUmAmAmU*mA*mC	381
134	mG*mC*mAmGmGmUmUmCfCfAfGmAmAmAmCmGmAmAmU*mU*mA	293
	PmU*fA*mAmUfUmCfGmUmUmUmCmUmGfGmAfAmCmCmUmGmC*mA*mU	382
135	mU*mG*mCmAmGmGmUmUfCfCfAmGmAmAmAmCmGmAmAmU*mU*mA	294
	PmU*fA*mUmUfCmGfUmUmUmCmUmGmGfAmAfCmCmUmGmCmA*mU*mC	383
136	mA*mC*mUmAmCmCmUmCfAfGfUmUmUmAmUmAmAmUmC*mU*mA	295
	PmU*fA*mGmAfUmUfAmUmAmAmAmCmUfGmAfGmGmUmAmGmU*mU*mU	384
137	mU*mG*mUmAmGmCmAmAfCfAfAmAmCmUmGmAmUmAmG*mA*mA	296
	PmU*fU*mCmUfAmUfCmAmGmUmUmUmGfUmUfGmCmUmAmCmA*mA*mA	385
138	mG*mG*mCmCmAmUmUmUfUfGfAmGmCmUmUmCmGmCmU*mU*mA	297
	PmU*fA*mAmGfCmGfAmAmGmCmUmCmAfAmAfAmUmGmGmCmC*mG*mC	386
139	mC*mA*mAmGmGmGmAmUfGfGfAmUmGmCmAmGmGmUmU*mC*mA	298
	PmU*fG*mAmAfCmCfUmGmCmAmUmCmCfAmUfCmCmCmUmUmG*mC*mA	387
140	mC*mC*mCmAmCmCmCmCfUfGfAmCmCmAmAmGmAmUmA*mA*mA	299
	PmU*fU*mUmAfUmCfUmUmGmGmUmCmAfGmGfGmGmUmGmGmG*mU*mA	388
141	mU*mU*mUmUmAmAmGmGfCfUfCmCmUmUmUmUmCmAmA*mC*mA	300
	PmU*fG*mUmUfGmAfAmAmAmGmGmAmGfCmCfUmUmAmAmAmA*mU*mU	389
142	mC*mG*mAmUmUmCmAmGfAfCfGmGmCmUmGmCmCmAmG*mA*mA	301
	PmU*fU*mCmUfGmGfCmAmGmCmCmGmUfCmUfGmAmAmUmCmG*mU*mG	390
143	mG*mA*mAmAmCmGmAmAfUfUfCmAmAmGmAmAmAmCmA*mG*mA	302
	PmU*fC*mUmGfUmUfUmCmUmUmGmAmAfUmUfCmGmUmUmUmC*mU*mG	391
144	mG*mU*mGmAmUmGmAmGfGfAfUmCmGmCmAmAmAmGmG*mA*mA	303
	PmU*fU*mCmCfUmUfUmGmCmGmAmUmCfCmUfCmAmUmCmAmC*mC*mA	392
145	mA*mC*mUmGmAmUmAmGfAfUfUmAmUmAmUmUmUmUmG*mG*mA	304
	PmU*fC*mCmAfAmAfAmUmAmUmAmAmUfCmUfAmUmCmAmGmU*mU*mU	393
146	mG*mG*mAmAmGmGmCmCfUfUfCmAmCmCmUmUmUmGmG*mA*mA	305
	PmU*fU*mCmCfAmAfAmGmGmUmGmAmAfGmGfCmCmUmUmCmC*mG*mA	394
147	mA*mG*mAmUmUmAmUmAfUfUfUmUmGmGmGmAmGmGmC*mG*mA	306
	PmU*fC*mGmCfCmUfCmCmAmAmAmAfUmAfUmAmAmUmCmU*mA*mU	395
148	mG*mG*mGmAmUmGmGmAfUfGfCmAmGmGmUmUmCmCmA*mG*mA	307
	PmU*fC*mUmGfGmAfAmCmCmUmGmCmAfUmCfCmAmUmCmCmC*mU*mU	396
149	mA*mU*mCmAmUmAmCmCfUfUfAmCmUmUmUmCmUmUmG*mU*mA	308
	PmU*fA*mCmAfAmGfAmAmAmGmUmAmAfGmGfUmAmUmGmAmU*mG*mG	397
150	mU*mA*mGmCmAmAmCmAfAfAfCmUmGmAmUmAmGmAmU*mU*mA	309
	PmU*fA*mAmUfCmUfAmUmCmAmGmUmUfUmGfUmUmGmCmUmA*mC*mA	398
151	mA*mA*mUmAmUmCmCmAfGfGfUmUmUmGmUmUmGmUmG*mU*mA	310
	PmU*fA*mCmAfCmAfAmCmAmAmAmCmCfUmGfGmAmUmAmUmU*mG*mA	399
152	mG*mC*mGmGmCmCmAfUfUfUfUmGmAmGmCmUmUmCmG*mC*mA	311
	PmU*fG*mCmGfAmAfGmCmUmCmAmAmAfAmUfGmGmCmCmGmC*mA*mG	400

153	mA*mU*mAmGmAmUmUmAfUfAfUmUmUmUmGmGmGmAmG*mG*mA	312
	PmU*fC*mCmUfCmCfCmAmAmAmAmUmAfUmAfAmUmCmUmAmU*mC*mA	401
154	mU*mA*mCmCmAmGmAmUfGfGfCmUmAmGmAmUmUmUmU*mG*mA	313
	PmU*fC*mAmAfAmAfUmCmUmAmGmCmCfAmUfCmUmGmGmUmA*mG*mG	402
155	mA*mG*mAmAmAmAmAmAfUfGfUmUmUmAmAmUmAmGmA*mC*mA	314
	PmU*fG*mUmCfUmAfUmUmAmAmAmCmAfUmUfUmUmUmUmCmU*mC*mU	403
156	mG*mG*mUmGmAmUmGmAfGfGfAmUmCmGmCmAmAmAmG*mG*mA	315
	PmU*fC*mCmUfUmUfGmCmGmAmUmCmCfUmCfAmUmCmAmCmC*mA*mC	404
157	mU*mC*mUmUmGmAmUmUfGfGfCmUmAmGmAmGmGmAmG*mG*mA	316
	PmU*fC*mCmUfCmCfUmCmUmAmGmCmCfAmAfUmCmAmAmGmA*mG*mA	405
158	mC*mU*mUmGmAmUmUmGfGfCfUmAmGmAmGmGmAmGmG*mG*mA	317
	PmU*fC*mCmCfUmCfCmUmCmUmAmGmCfCmAfAmUmCmAmAmG*mA*mG	406
159	mU*mU*mUmAmCmGfUmGfUfAfAmCmGmUmGmGmAmGmA*mU*mA	318
	PmU*fA*mUmCfUmCfCmAmCmGmUmUmAfCmAfCmGmUmAmAmA*mA*mU	328
160	mC*mA*mGmAmUmGfAmAfGfCfAmGmAmGmAmAmUmCmU*mU*mA	319
	PmU*fA*mAmGfAmUfUmCmUmCmUmGmCfUmUfCmAmUmCmUmG*mC*mA	329
161	mU*mU*mUmGmUmAfUmAfUfAfAmUmUmAmUmUmAmAmC*mU*mA	320
	PmU*fA*mGmUfUmAfAmUmAmAmUmUmAfUmAfUmAmCmAmAmA*mU*mA	330
162	mA*mA*mGmGmCmAfCmAfCfAfCmCmAmUmUmAmUmGmC*mC*mA	321
	PmU*fG*mGmCfAmUfAmAmUmGmGmUmGfUmGfUmGmCmCmUmU*mU*mG	331
163	mG*mA*mAmGmCmAfGmUfCfUfGmUmUmUmUmGmUmGmA*mA*mA	322
	PmU*fU*mUmCfAmCfAmAmAmAmCmAmGfAmCfUmGmCmUmUmC*mC*mC	332
164	mC*mA*mGmAmAmGfUmUfGfCfCmAmUmUmGmGmCmUmA*mC*mA	323
	PmU*fG*mUmAfGmCfCmAmAmUmGmGmCfAmAfCmUmUmCmUmG*mU*mU	333
165	mA*mU*mUmAmAmUfGmGfGfCfUmUmUmAmUmGmGmGmU*mU*mA	324
	PmU*fA*mAmCfCmCfAmUmAmAmAmGmCfCmCfAmUmUmAmAmU*mU*mU	334
166	mG*mC*mGmGmUmGfUmCfCfCfCmUmGmCmUmGmCmAmG*mA*mA	325
	PmU*fU*mCmUfGmCfAmGmCmAmGmGmGfGmAfCmAmCmCmGmC*mC*mU	335
167	mU*mG*mUmCmUmGfAmAfUfCfAmGmAmCmGmUmGmGmA*mA*mA	326
	PmU*fU*mUmCfCmAfCmGmUmCmUmGmAfUmUfCmAmGmAmCmA*mG*mG	336
168	mG*mA*mUmUmAmUfAmUfUfUfUmGmGmGmAmGmGmCmG*mC*mA	327
	PmU*fG*mCmGfCmCfUmCmCmCmAmAmAfAmUfAmUmAmAmUmC*mU*mA	337

Abbreviations – “m” indicates 2’-OMe; “f” indicates 2’-fluoro; “*” indicates phosphorothioate linkage; “P” indicates 5’-phosphate; “S” means the sense strand; “AS” means the antisense strand.

Table 3b: Modified sense strand and antisense strand sequences of PPP1R15B RNAi agents

dsRNA No.	Oligo Sequence with (5’ to 3’)	SEQ ID NO
122	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGmAmAmUmUfCmGfUmUmUmCmUmG*mG*mA	370

169	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUfUmGmAmAmUmUfCmGmUmUmUmCmUmG*mG*mA	407
170	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUfGmAmAmUmUfCmGmUmUmUmCmUmG*mG*mA	408
171	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGfAmAmUmUfCmGmUmUmUmCmUmG*mG*mA	409
172	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGmAfAmUmUfCmGmUmUmUmCmUmG*mG*mA	410
173	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGmAmAfUmUfCmGmUmUmUmCmUmG*mG*mA	411
174	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA	281
	PmU*fG*mUmUfUmCfUmUmGmAmAmUfUfCmGmUmUmUmCmUmG*mG*mA	412
128	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAmUmAmUmAfAmUfAmCmUmCmAmG*mU*mA	376
175	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUfUmAmUmAmUmAfAmUmAmCmUmCmAmG*mU*mA	413
176	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUfAmUmAmUmAfAmUmAmCmUmCmAmG*mU*mA	414
177	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAfUmAmUmAfAmUmAmCmUmCmAmG*mU*mA	415
178	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAmUfAmUmAfAmUmAmCmUmCmAmG*mU*mA	416
179	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAmUmAfUmAfAmUmAmCmUmCmAmG*mU*mA	417
180	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA	287
	PmU*fA*mCmCfAmCfUmUmAmUmAmUfAfAmUmAmCmUmCmAmG*mU*mA	418
131	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCmUmUmGmAfAmUfUmCmGmUmUmU*mC*mU	379
181	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUfUmCmUmUmGmAfAmUmUmCmGmUmUmU*mC*mU	419
182	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUfCmUmUmGmAfAmUmUmCmGmUmUmU*mC*mU	420
183	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCfUmUmGmAfAmUmUmCmGmUmUmU*mC*mU	421
184	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCmUfUmGmAfAmUmUmCmGmUmUmU*mC*mU	422
185	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCmUmUfGmAfAmUmUmCmGmUmUmU*mC*mU	423
186	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA	290
	PmU*fU*mCmUfGmUfUmUmCmUmUmGfAfAmUmUmCmGmUmUmU*mC*mU	424

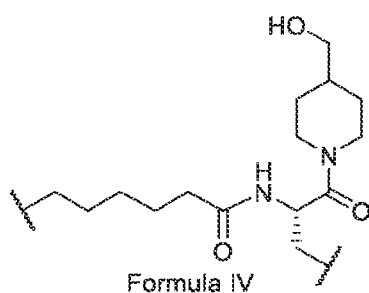
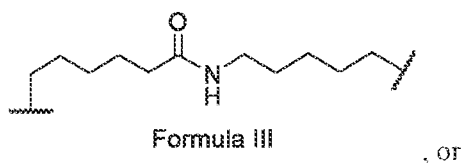
Abbreviations – “m” indicates 2'-OMe; “f” indicates 2'-fluoro; “*” indicates phosphorothioate linkage; “P” indicates 5'-phosphate; “S” means the sense strand; “AS” means the antisense strand.

Table 4. Abasic and inverted abasic (iAb) moieties

	Structure
1 (abasic)	
2 (iAb)	

"5'" and "3'" indicate the 5' to 3' direction of the sequences.

[00049] In some embodiments, the delivery moiety (D) is conjugated to the 3' end of the sense stand via a linker (L). Suitable linkers are known in the art. In some embodiments, linker (L) comprises Formula (III) or Formula (IV):



[00050] The sense strand and antisense strand of PPP1R15B RNAi agent can be synthesized using any nucleic acid polymerization methods known in the art, for example, solid-phase synthesis by employing phosphoramidite chemistry methodology (e.g., Current Protocols in Nucleic Acid Chemistry, Beaucage, S.L. et al. (Edrs.), John Wiley & Sons, Inc., New York,

NY, USA), H-phosphonate, phosphotriester chemistry, or enzymatic synthesis. Automated commercial synthesizers can be used, for example, MerMade™ 12 from LGC Biosearch Technologies, or other synthesizers from BioAutomation or Applied Biosystems.

Phosphorothioate linkages can be introduced using a sulfurizing reagent such as phenylacetyl disulfide or DDTT (((dimethylaminomethylidene) amino)-3H-1,2,4-dithiazaoline-3-thione). It is well known to use similar techniques and commercially available modified amidites and controlled-pore glass (CPG) products to synthesize modified oligonucleotides or conjugated oligonucleotides.

[00051] Purification methods can be used to exclude the unwanted impurities from the final oligonucleotide product. Commonly used purification techniques for single stranded oligonucleotides include reverse-phase ion pair high performance liquid chromatography (RP-IP-HPLC), capillary gel electrophoresis (CGE), anion exchange HPLC (AX-HPLC), and size exclusion chromatography (SEC). After purification, oligonucleotides can be analyzed by mass spectrometry and quantified by spectrophotometry at a wavelength of 260 nm. The sense strand and antisense strand can then be annealed to form a duplex.

[00052] In another aspect, provided herein are pharmaceutical compositions comprising an PPP1R15B RNAi agent described herein and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising a means for reducing PPP1R15B expression in a cell and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can also comprise one or more pharmaceutically acceptable excipient, diluent, or carrier. Pharmaceutical compositions can be prepared by methods well known in the art (e.g., Remington: The Science and Practice of Pharmacy, 23rd edition (2020), A. Loyd et al., Academic Press).

[00053] In a further aspect, provided herein are methods of reducing PPP1R15B expression in a cell, such methods can include introducing a PPP1R15B RNAi agent described herein into the cell; and incubating the cell for a time sufficient for degradation of PPP1R15B mRNA, thereby reducing PPP1R15B expression in the cell. The PPP1R15B RNAi agent can be introduced into the cell using a method known in the art, e.g., transfection, electroporation, microinjection, or uptake by the cell via natural transport mechanisms.

[00054] In another aspect, provided herein are methods of treating a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH),

nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome in a patient in need thereof, and such method comprises administering to the patient an effective amount of a PPP1R15B RNAi agent or a pharmaceutical composition described herein. In some embodiments, the PPP1R15B RNAi agent or the pharmaceutical composition is administered to the patient intravenously or subcutaneously.

[00055] In some embodiments, such methods further comprise administering a second therapeutic agent to the patient. The PPP1R15B RNAi agent described herein may be used in simultaneous, separate, and sequential combinations with a second therapeutic agent selected from incretin, metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor, a growth differentiation factor 15 modulator (“GDF15”), a peptide tyrosine tyrosine modulator (“PYY”), a modified insulin, amylin, a dual amylin calcitonin receptor agonist, or oxyntomodulin agonist (“OXM”) for the treatment of a condition selected from the group consisting of T2D, obesity, NASH, NAFLD, dyslipidemia, and metabolic syndrome.

[00056] In some embodiments, such methods comprise administering a PPP1R15B RNAi agent and an incretin to the patient in simultaneous, separate, and sequential combinations. Examples of incretin include glucagon like peptide-1 (GLP-1) or GLP-1 analogs, glucose-dependent insulintropic polypeptide (GIP) or GIP analogs, oxyntomodulin or oxyntomodulin analogs; dual GIP and GLP-1 receptor agonists; GCG, and GIP receptor agonist and GLP-1 receptor tri-agonists. In certain embodiments, the incretin may be selected from semaglutide, dulaglutide, tirzepatide, exenatide, liraglutide, albiglutide, lixisenatide, or retatrutide.

[00057] In some embodiments, a PPP1R15B RNAi agent described here is for use in simultaneous, separate and sequential combinations with a second therapeutic agent selected from incretin, metformin, a thiazolidinedione, a sulfonylurea, a dipeptidyl peptidase 4 inhibitor, a sodium glucose co-transporter, a SGLT-2 inhibitor, GDF15, PYY, a modified insulin, amylin, a dual amylin calcitonin receptor agonist, OXM, a glucagon like peptide-1 (GLP-1) or GLP-1 analog, a glucose-dependent insulintropic polypeptide (GIP) or GIP analog, oxyntomodulin or an oxyntomodulin analog, a dual GIP and GLP-1 receptor agonist; a GCG, and GIP receptor agonist and GLP-1 receptor tri-agonists; semaglutide, dulaglutide, tirzepatide, exenatide, liraglutide, albiglutide, lixisenatide, and retatrutide in the treatment of a condition selected from the group consisting of T2D, NASH, obesity, NAFLD, dyslipidemia, and metabolic syndrome.

[00058] RNAi dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

[00059] Dosage values may vary with the type and severity of the condition to be alleviated. It is further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[00060] In another aspect, provided herein are PPP1R15B RNAi agents or the pharmaceutical composition comprising an PPP1R15B RNAi agent for use in a therapy. Also provided are PPP1R15B RNAi agents or pharmaceutical compositions comprising a PPP1R15B RNAi agent for use in the treatment of a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome. Also provided herein are uses of PPP1R15B RNAi agents in the manufacture of a medicament for the treatment of a PPP1R15B associated metabolic disorder, such as obesity, Type 2 diabetes, or nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome.

[00061] As used herein, the terms “a,” “an,” “the,” and similar terms used in the context of the present disclosure (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

[00062] As used herein, the term “alkyl” means saturated linear or branched-chain monovalent hydrocarbon radical, containing the indicated number of carbon atoms. For example, “C₁-C₂₀ alkyl” means a radical having 1-20 carbon atoms in a linear or branched arrangement.

[00063] As used herein, “antisense strand” means a single-stranded oligonucleotide that is complementary to a region of a target sequence. Likewise, and as used herein, “sense strand” means a single-stranded oligonucleotide that is complementary to a region of an antisense strand.

[00064] As used herein, “complementary” means a structural relationship between two nucleotides (e.g., on two opposing nucleic acids or on opposing regions of a single nucleic acid strand, e.g., a hairpin) that permits the two nucleotides to form base pairs with one another. For

example, a purine nucleotide of one nucleic acid that is complementary to a pyrimidine nucleotide of an opposing nucleic acid may base pair together by forming hydrogen bonds with one another. Complementary nucleotides can base pair in the Watson-Crick manner or in any other manner that allows for the formation of stable duplexes. Likewise, two nucleic acids may have regions of multiple nucleotides that are complementary with each other to form regions of complementarity, as described herein.

[00065] As used herein, a “delivery moiety” refers to a chemical moiety that facilitates the entry of an oligonucleotide or RNAi agent into a cell. The delivery moiety can be lipid, cholesterol, vitamin E, carbohydrate (e.g., GalNAc), amino sugar, or polypeptide.

[00066] As used herein, “duplex,” in reference to nucleic acids or oligonucleotides, means a structure formed through complementary base pairing of two antiparallel sequences of nucleotides (i.e., in opposite directions), whether formed by two separate nucleic acid strands or by a single, folded strand (e.g., via a hairpin).

[00067] An “effective amount” refers to an amount necessary (for periods of time and for the means of administration) to achieve the desired therapeutic result. An effective amount of a RNAi agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the RNAi agent to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the RNAi agent are outweighed by the therapeutically beneficial effects.

[00068] The term “knockdown” or “expression knockdown” refers to reduced mRNA or protein expression of a gene after treatment of a reagent, e.g., a RNAi agent.

[00069] As used herein, “modified internucleotide linkage” means an internucleotide linkage having one or more chemical modifications when compared with a reference internucleotide linkage having a phosphodiester bond. A modified internucleotide linkage can be a non-naturally occurring linkage. In some embodiments, the modified internucleotide linkage is phosphorothioate linkage.

[00070] As used herein, “modified nucleotide” refers to a nucleotide having one or more chemical modifications when compared with a corresponding reference nucleotide selected from: adenine ribonucleotide, guanine ribonucleotide, cytosine ribonucleotide, uracil ribonucleotide, adenine deoxyribonucleotide, guanine deoxyribonucleotide, cytosine deoxyribonucleotide, and thymidine deoxyribonucleotide. A modified nucleotide can have, for

example, one or more chemical modification in its sugar, nucleobase, and/or phosphate group. Additionally, or alternatively, a modified nucleotide can have one or more chemical moieties conjugated to a corresponding reference nucleotide.

[00071] As used herein, “nucleotide” means an organic compound having a nucleoside (a nucleobase, e.g., adenine, cytosine, guanine, thymine, or uracil, and a pentose sugar, e.g., ribose or 2'-deoxyribose) linked to a phosphate group. A “nucleotide” can serve as a monomeric unit of nucleic acid polymers such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

[00072] As used herein, “oligonucleotide” means a polymer of linked nucleotides, each of which can be modified or unmodified. An oligonucleotide is typically less than about 100 nucleotides in length.

[00073] As used herein, “overhang” means the unpaired nucleotide or nucleotides that protrude from the duplex structure of a double stranded oligonucleotide. An overhang may include one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a double stranded oligonucleotide. The overhang can be a 3' or 5' overhang on the antisense strand or sense strand of a double stranded oligonucleotide.

[00074] The term “patient”, as used herein, refers to a human patient.

[00075] As used herein, “phosphate analog” means a chemical moiety that mimics the electrostatic and/or steric properties of a phosphate group. In some embodiments, a phosphate analog is positioned at the 5' terminal nucleotide of an oligonucleotide in place of a 5'-phosphate, which is often susceptible to enzymatic removal. A 5' phosphate analog can include a phosphatase-resistant linkage. Examples of phosphate analogs include 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). In some embodiments, the phosphate analog is 5'-VP.

[00076] The term “% sequence identity” or “percentage sequence identity” with respect to a reference nucleic acid sequence is defined as the percentage of nucleotides, nucleosides, or nucleobases in a candidate sequence that are identical with the nucleotides, nucleosides, or nucleobases in the reference nucleic acid sequence, after optimally aligning the sequences and introducing gaps or overhangs, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software programs, for example, those described in Current Protocols in Molecular

Biology (Ausubel *et al.*, eds., 1987, Supp. 30, section 7.7.18, Table 7.7.1), and including BLAST, BLAST-2, ALIGN, Megalign (DNASTAR), Clustal W2.0 or Clustal X2.0 software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. Percentage of “sequence identity” can be determined by comparing two optimally aligned sequences over a comparison window, where the fragment of the nucleic acid sequence in the comparison window may comprise additions or deletions (e.g., gaps or overhangs) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage can be calculated by determining the number of positions at which the identical nucleotide, nucleoside, or nucleobase occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison, and multiplying the result by 100 to yield the percentage of sequence identity. The output is the percent identity of the subject sequence with respect to the query sequence.

[00077] As used herein, “RNAi,” “RNAi agent,” “iRNA,” “iRNA agent,” and “RNA interference agent” means an agent that mediates sequence-specific degradation of a target mRNA by RNA interference, e.g., via RNA-induced silencing complex (RISC) pathway. In some embodiments, the RNAi agent has a sense strand and an antisense strand, and the sense strand and the antisense strand form a duplex (e.g., a double stranded RNA). In some embodiments, the sense strand has a delivery moiety conjugated to the 3’ end of the sense strand or a nucleotide of the sense strand.

[00078] As used herein, “strand” refers to a single, contiguous sequence of nucleotides linked together through internucleotide linkages (e.g., phosphodiester linkages or phosphorothioate linkages). A strand can have two free ends (e.g., a 5’ end and a 3’ end).

[00079] As used herein, PPP1R15B refers to a PPP1R15B mRNA transcript. The nucleic acid sequence of human PPP1R15B mRNA can be found at NM_032833.5 (SEQ ID NO: 1). The amino acid sequence of human PPP1R15B protein can be found at NP_116222.4. The nucleic acid sequence of mouse PPP1R15B mRNA can be found at NM_133819.3 (SEQ ID NO: 425). The amino acid sequence of mouse PPP1R15B protein can be found at NP_598580.1.

[00080] As used herein, “PPP1R15B associated metabolic disorder” means a metabolic disorder associated with abnormal PPP1R15B expression, activity, or function.

[00081] As used herein, “subject” means a mammal, including cat, dog, mouse, rat, chimpanzee, ape, monkey, and human. Preferably the subject is human.

[00082] As used herein, “treatment” or “treating” refers to all processes wherein there may be a slowing, controlling, delaying, or stopping of the progression of the disorders or disease disclosed herein, or ameliorating disorder or disease symptoms, but does not necessarily indicate a total elimination of all disorder or disease symptoms. Treatment includes administration of a protein or nucleic acid or vector or composition for treatment of a disease or condition in a patient, particularly in a human.

EXAMPLES

Example 1. Synthesis of PPP1R15B RNAi Agents

[00083] Single strands (sense and antisense) of the dsRNA were typically synthesized on solid support via a MerMade™ 12 (LGC Biosearch Technologies) or a similar automated oligonucleotide synthesizer. The sequences of the sense and antisense strands were shown in Tables 2 and 3. The sense strands were synthesized using an appropriate CPG such as 3'-Cholesterol-TEG CNA CPG 500 (LGC Biosearch Technologies) or phthalamido amino C6 lcaa CPG 500 Å (Chemgenes) whereas the antisense strands used standard support (LGC Biosearch Technologies). The oligonucleotides were synthesized via phosphoramidite chemistry at an appropriate scale for in-vitro or in-vivo experimentation.

[00084] Standard reagents were used in the oligo synthesis (Table 5), where 0.1M xanthane hydride in pyridine was used as the sulfurization reagent and 20% DEA in ACN was used as an auxiliary wash post synthesis. All monomers (Table 6) were made at 0.1M in ACN and contained a molecular sieves trap bag. The structure of linked cholesterol is shown in Table 7.

[00085] The antisense strands were typically cleaved and deprotected (C/D) at 45 °C for 16-24 hours. The sense strands were typically cleaved and deprotected from the CPG using cold 50% (methylamine/ammonia hydroxide 28-30%) at RT for 2-3 hrs, whereas 3% DEA in ammonia hydroxide (28-30%, cold) was typically used for the antisense strands. C/D was determined complete by IP-RP LCMS when the resulting mass data confirmed the identity of sequence. RNA hydroxy desilylation may be carried out using triethylamine trihydrofluoride in DMSO. Dependent on scale, the CPG was filtered via 0.45 µm PVDF syringeless filter, 0.22 µm PVDF Steriflip® vacuum filtration or 0.22 µm PVDF Stericup® Quick release. The CPG was

typically back washed/rinsed with either 30% EtOH/RNase free water then filtered through the same filtering device and combined with the first filtrate. This was repeated twice. The material was then divided evenly into conical centrifuge tubes to remove organics via Genevac™. After concentration, the crude oligonucleotides were diluted back to synthesized scale with RNase free water and filtered either by 0.45 µm PVDF syringeless filter, 0.22 µm PVDF Steriflip® vacuum filtration or 0.22 µm PVDF Stericup® Quick release.

[00086] The crude oligonucleotides were purified via AKTA™ Pure purification system using anion-exchange (AEX) or reverse-phase (RP) chromatography. For AEX, an ES Industry Source™ 15Q column with MPA: 20mM NaH₂PO₄, 15% ACN, pH 7.4 and MPB: 20 mM NaH₂PO₄, 1M NaBr, 15% ACN, pH 7.4. For RP, an ES Industry Source™ 15RPC with MPA: 50mM sodium acetate, 10% ACN and MPB: 80% ACN. Fractions which contained a mass purity greater than 85% without impurities >5% were combined.

[00087] The purified oligonucleotides were desalted using 15 mL 3K MWCO centrifugal spin tubes at 3500xg for ~30 min. The oligonucleotides were rinsed with RNase free water until the eluent conductivity reached < 100 usemi/cm. After desalting was complete, 2-3 mL of RNase free water was added then aspirated 10x, the retainment was transferred to a 50 mL falcon tube, this was repeated until complete transfer of oligo by measuring concentration of compound on filter via nanodrop. The final oligonucleotide was then nano filtered 2x via 15 mL 100K MWCO centrifugal spin tubes at 3500xg for 2 min. Cholesterol-linked oligonucleotides were annealed at this stage to give cholesterol conjugated dsRNA by mixing equimolar aliquots of sense and antisense strands at room temperature for 30 minutes. The final desalted oligonucleotides were analyzed for concentration (nano drop at A260), characterized by IP-RP LC/MS for mass purity and UPLC for UV-purity.

[00088] RNAi agents comprising a GalNAc moiety, e.g., Formula (II), can be synthesized according to the methods described in WO2022/271806.

Table 5 - Oligonucleotide Synthesis Reagents

Reagents
Activator Solution (0.5M ETT in ACN)
Cap A (Acetic Anhydride, Pyridine in THF, 1:1:8)

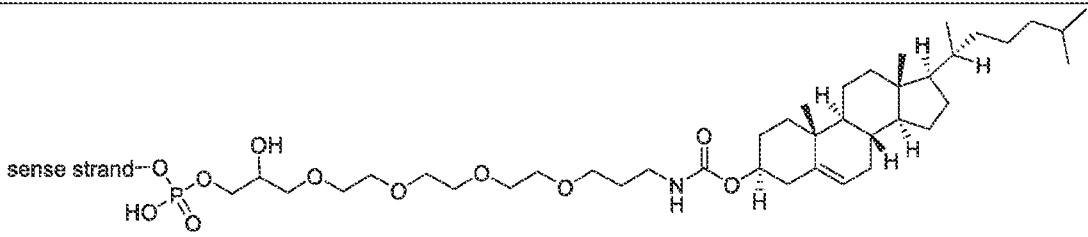
Cap B (1-Methylimidazole in THF, 16:84)
Oxidation Solution (0.02M Iodine in THF/Pyridine/Water, 70:20:10)
Deblock Solution, 3% TCA in DCM (w/v)
Acetonitrile (Anhydrosolv, Water max. 10 ppm)
Xanthane Hydride (0.1M in Pyridine)
Diethylamine (20% in Acetonitrile)

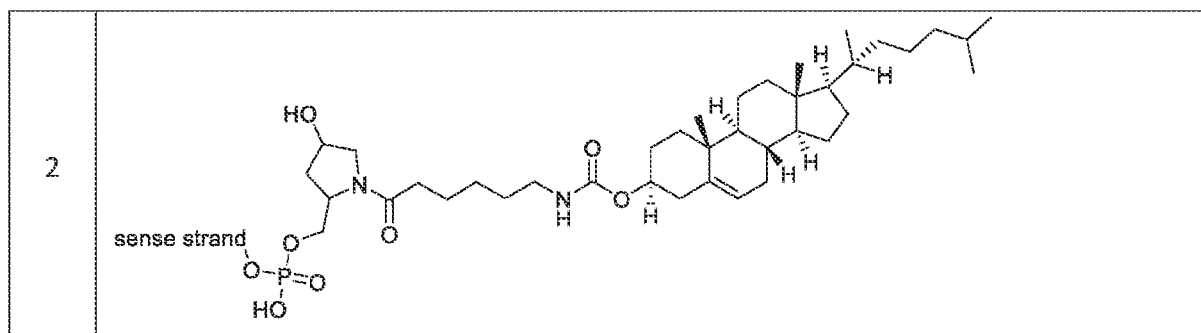
Table 6 - Phosphoramidites

Phosphoramidite	Abbreviation	Supplier	Catalog #	CAS
DMT-2'-F-A(Bz)-CE Phosphoamidite	fA	Hongene	PD1-001	136834-22-5
DMT-2'-F-C(Ac)-CE Phosphoamidite	fC	Hongene	PD3-001	159414-99-0
DMT-2'-F-G(iBu)-CE Phosphoamidite	fG	Hongene	PD2-002	144089-97-4
DMT-2'-F-U-CE Phosphoamidite	fU	Hongene	PD5-001	146954-75-8
DMT-2'-O-Me-A(Bz)- CE Phosphoamidite	mA	Hongene	PR1-001	110782-31-5
DMT-2'-O-Me-C(Ac)- CE Phosphoamidite	mC	Hongene	PR3-001	199593-09-4
DMT-2'-O-Me-G(iBu)- CE Phosphoamidite	mG	Hongene	PR2-002	150780-67-9

DMT-2'-O-Me-U-CE Phosphoamidite	mU	Hongene	PR5-001	110764-79-9
DMT-2'O-TBDMS- rA(bz) Phosphoramidite	A	Hongene	PR1-008	104992-55-4
DMT-dC(Ac) Phosphoramidite	dC	Chemgenes	ANP-5560	154110-40-4
5'bis(POM) vinyl phosphate-2'-Ome- U3'CE phosphoroamidite	POM-VPmU	Hongene	PR5-032	BVPMUP23B2A1
Reverse Abasic phosphoroamidite	iAb	Chemgenes	ANP-1422	401813-16-9
Abasic phosphoroamidite	Aba	Chemgenes	ANP-7058	129821-76-7

Table 7. Linked Cholesterol Structures

	Structure
1	



Example 2. *In vitro* Characterization of PPP1R15B RNAi Agents

[00089] Selected PPP1R15B RNAi agents were tested *in vitro* for PPP1R15B knock down in cultured cells. Knockdown of PPP1R15B expression by these RNAi agents is assayed using the following procedure: human Hep3b cells were plated and each RNAi agent was added directly to an individual well. The RNAi agents were added at concentrations of 500 nM and 50 nM, in duplicate. Treated cells were lysed and an analysis of changes in gene expression in RNAi agent treated cells was measured using Cells-to-CT Kits following the manufacturer's protocol (ThermoFisher A35377). Predesigned gene expression assays (supplied as 20X mixtures) were selected from Applied Bio-systems (Foster City, CA, USA). The efficiencies of these assays (ThermoFisher Hs03044848_m1 PPP1R15B and ThermoFisher Hs99999905_m1 GAPDH) were characterized with a dilution series of cDNA. RT-QPCR was performed in MicroAmp Optical 384-well reaction plates using QuantStudio 7 Flex system. The delta-delta CT method of normalizing to the housekeeping gene GAPDH was used to determine relative amounts of gene expression. GraphPad Prism was used to determine IC₅₀ with a three-parameter logistic fit. Select siRNA agents were further tested at multiple concentrations: 1000, 200, 40, 8, 1.6, 0.32, 0.064, and 0.0128 nM of cholesterol conjugated siRNA was used. Results are shown as percent knockdown (%KD) of the PPP1R15B transcript.

[00090] Knockdown of PPP1R15B expression by top 7 RNAi agents at 1000, 200, 40, 8, 1.6, 0.32, 0.064, and 0.0128 nM was assayed in Hepa1C1C7 (mouse) cells using the same procedure described in Hep3b cells. Predesigned gene expression assays (supplied as 20X mixtures) were selected from Applied Bio-systems (Foster City, CA, USA). The efficiencies of these assays (ThermoFisher Mm00551747_m1 PPP1R15B and ThermoFisher 4352341E beta-actin) were

characterized with a dilution series of cDNA. RT-QPCR was performed in MicroAmp Optical 384-well reaction plates using QuantStudio 7 Flex system. The delta-delta CT method of normalizing to the housekeeping gene beta-actin was used to determine relative amounts of gene expression. GraphPad Prism was used to determine IC50 with a three-parameter logistic fit. Results are shown as percent knockdown (%KD) of the PPP1R15B transcript.

Results

[00091] Table 8 shows the percentage knockdown of PPP1R15B mRNA in human Hep3b cells by the tested PPP1R15B RNAi agents. Table 9 shows the percentage knockdown of PPP1R15B in human Hep3b cells by selected PPP1R15B RNAi agents at different concentrations. Table 10 shows the percentage knockdown of PPP1R15B in mouse Hepa1C1C7 cells by selected PPP1R15B RNAi agents.

Table 8: *In vitro* knock down of PPP1R15B mRNA in human Hep3b cells by PPP1R15B RNAi agents.

dsRNA No.	Average % PPP1R15B KD - 500 nM treatment	Standard Error for % PPP1R15B KD - 500 nM treatment	Average % PPP1R15B KD - 50 nM treatment	Standard Error for % PPP1R15B KD - 50 nM treatment
80	-0.46	0.27	60.65	1.77
81	22.33	2.48	60.54	3.57
82	15.06	3.49	55.42	6.79
83	17.37	0.80	54.95	1.24
84	3.93	7.79	52.99	0.92
85	2.29	5.79	47.77	4.15
86	-6.58	1.42	46.37	0.29
87	-21.08	12.50	45.90	1.63
88	7.85	1.19	38.42	0.76
89	34.81	2.51	37.21	0.33
90	18.82	11.01	31.13	2.12
91	27.22	3.07	30.02	7.18
92	65.48	0.29	29.38	5.71
93	20.77	2.31	28.57	10.25
94	4.16	6.59	28.38	2.19
95	0.07	2.27	28.11	2.44
96	-8.98	14.18	26.76	10.55
97	6.94	6.23	26.26	7.95

98	2.29	1.30	25.96	3.25
99	24.20	1.49	24.87	5.69
100	33.87	6.41	24.69	6.38
101	11.00	0.06	23.70	1.91
102	-15.45	2.60	21.85	4.60
103	-19.22	4.18	21.83	5.19
104	5.62	9.00	21.71	5.30
105	17.12	3.33	21.56	3.38
106	14.92	2.19	21.52	0.70
107	22.67	2.38	21.35	1.24
108	12.90	5.40	21.21	14.91
109	0.14	3.27	20.14	3.74
110	-18.08	2.36	19.61	3.46
111	-30.03	3.07	18.29	4.46
112	-8.79	9.43	17.96	4.12
113	3.21	2.65	17.75	2.05
114	6.10	3.70	17.72	12.96
115	14.86	3.64	17.57	7.41
116	9.84	2.69	17.49	9.59
117	4.41	1.38	16.74	4.25
118	-3.61	0.95	15.97	3.27
119	-1.57	5.61	14.90	29.88
120	2.58	6.78	13.92	3.65
121	25.07	0.80	13.70	3.39
122	65.16	2.88	13.67	6.30
123	50.69	3.45	13.33	5.29
124	70.18	3.73	13.00	0.69
125	26.24	8.21	12.90	3.82
126	44.11	0.91	12.28	21.80
127	10.97	3.67	12.05	14.29
128	73.32	2.34	10.44	2.22
129	58.78	5.06	10.16	2.72
130	7.42	0.10	9.55	1.50
131	68.09	1.43	9.50	2.65
132	50.67	2.31	8.09	7.74
133	59.31	0.84	7.76	0.92
134	65.01	2.36	7.25	2.81
135	54.92	3.58	6.99	3.53
136	11.69	5.60	6.03	42.65
137	31.24	2.44	5.31	6.73
138	-2.48	7.05	4.89	0.91

139	57.44	0.96	4.73	2.02
140	6.19	18.62	4.45	2.55
141	49.66	8.28	3.44	0.61
142	1.80	5.47	2.86	2.90
143	45.87	7.25	2.40	11.17
144	43.09	2.93	1.99	6.09
145	18.58	4.70	1.34	3.93
146	13.13	14.65	1.18	0.35
147	46.12	7.83	0.55	26.92
148	41.25	0.61	0.09	9.23
149	13.81	13.91	-0.09	1.57
150	38.59	10.07	-0.65	1.89
151	34.31	7.58	-1.21	7.61
152	-22.67	2.30	-1.98	0.92
153	25.60	2.96	-5.27	10.87
154	57.06	2.02	-5.49	6.80
155	52.67	3.00	-5.63	2.09
156	59.68	3.48	-6.54	45.79
157	-6.20	3.64	-7.76	15.86
158	-7.97	0.61	-8.40	5.32
159	-33.30	8.16	-8.60	27.59
160	19.38	18.33	-9.54	15.78
161	-6.77	12.15	-10.14	3.28
162	-1.65	32.85	-15.67	14.89
163	9.79	16.01	-17.27	23.66
164	-5.18	23.75	-17.37	16.74
165	2.88	11.88	-32.89	42.03
166	20.94	1.82	-38.76	23.80
167	5.22	7.40	-41.21	18.60
168	61.65	1.11	-600.05	623.10

Table 9: *In vitro* knock down of PPP1R15B in human Hep3b cells by PPP1R15B RNAi agents

dsRNA No.	% PPP1R15B KD Hep3b (human) cells								PPP1R15B IC50 (nM) Human
	1000 nM	200 nM	40 nM	8 nM	1.6 nM	0.32 nM	0.064 nM	0.0128 nM	
92	75.93	61.06	37.46	31.80	16.60	20.94	16.17	17.78	3 parameter fit

122	71.69	63.12	46.96	22.39	21.39	17.13	7.52	14.22	34.08
124	79.34	61.07	40.10	21.42	17.13	15.47	12.91	10.21	70.83
128	81.78	67.98	43.83	17.69	24.22	15.65	11.37	16.29	66.43
129	66.81	41.14	24.55	16.81	17.43	11.28	13.05	16.37	287.60
131	70.63	61.13	40.08	18.54	15.91	22.37	-9.58	21.50	48.47
132	52.61	36.84	14.30	15.91	13.41	19.37	11.08	18.66	333.00
133	72.93	47.70	25.02	24.26	12.54	11.87	7.87	5.01	167.10
134	71.10	58.21	31.38	9.93	9.50	24.09	20.61	7.96	110.60
135	66.83	54.54	29.51	15.96	12.66	0.93	1.51	-15.40	40.31
139	64.91	40.59	22.68	12.08	7.83	13.08	-4.83	0.08	139.30
144	66.79	42.14	22.20	23.55	14.33	1.85	12.71	-17.96	114.50
145	30.99	23.42	14.80	-15.35	15.52	13.58	-4.64	4.49	135.20
146	12.80	3.05	13.07	10.28	6.78	17.17	16.37	-7.15	>500
147	31.42	37.41	10.04	2.12	3.21	4.79	1.17	-3.60	64.72
148	56.16	31.08	3.13	16.88	9.55	-11.65	7.78	-0.06	352.60
150	48.52	33.40	7.34	5.86	-6.12	-12.13	-17.01	-12.72	76.19
154	70.49	59.04	19.22	23.46	16.64	-0.77	4.47	-39.05	50.29
156	70.08	76.54	59.57	53.38	9.00	12.08	-19.98	12.87	4.58
168	47.18	23.20	10.44	15.14	28.62	-3.08	-8.07	-24.92	0.26
Non-targeting control	8.83	-5.11	-12.21	-0.20	-1.20	-21.94	13.20	-6.50	

Table 10: *In vitro* knock down of PPP1R15B in mouse Hepa1C1C7 cells by PPP1R15B RNAi agents.

	% PPP1R15B KD in mouse Hepa1C1C7 cells								PPP1R15B IC50 (nM) Mouse
dsRNA No.	1000 nM	200 nM	40 nM	8 nM	1.6 nM	0.32 nM	0.064 nM	0.0128 nM	3 parameter fit
92	63.28	39.37	18.40	9.88	5.56	4.16	-10.91	-2.84	124.90
122	54.91	45.75	25.74	12.77	-0.24	4.01	-8.16	-11.23	30.72
124	59.98	42.23	21.56	13.28	4.37	0.35	5.10	-1.08	91.70
128	56.63	34.52	14.04	2.23	-0.06	-0.03	-5.72	-5.16	141.30
131	65.61	46.65	25.18	14.62	2.68	7.41	-0.51	-1.65	78.90
135	29.85	26.90	17.27	8.47	3.09	3.20	-0.74	-4.40	23.78
156	42.47	29.51	17.96	10.22	8.92	6.85	10.09	-2.66	108.00

Non-targeting control	-16.83	-19.10	-11.07	1.76	-2.10	5.18	-2.65	0.71	
-----------------------	--------	--------	--------	------	-------	------	-------	------	--

Example 3. *In vivo* Characterization of Selected PPP1R15B RNAi Agents in Mice

[00092] The efficacy of selected PPP1R15B RNAi agents was studied in mice.

PPP1R15B RNAi potency study

[00093] Animals were individually housed in a temperature-controlled facility with 12h/12h light/dark cycle and fed a standard chow diet (TD2014; Teklad Diets). Animal protocols were approved by the Eli Lilly and Co., Animal Use and Care Committee (Protocol No. 20-025). C57BL/6 male mice were dosed subcutaneously with vehicle control (PBS) or an RNAi agent (5 mg/kg), n=6 per group. Animals were sacrificed 14 days post dose and livers were harvested. RNA was isolated from liver tissue using TRIzol reagent (Invitrogen) and the PureLink Pro 96 Total RNA purification kit (Invitrogen). RNA was transcribed into cDNA using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Taqman assays for RPLP0 (Mm01974474_gH, Applied Biosystems), PPP1R15B (Mm00551747_m1, Applied Biosystems) were used to measure gene expression using QuanStudio 7 Flex and normalized to RPLP0 mRNA.

[00094] The results from this study are shown in Table 11 as the percent knockdown (%KD) of PPP1R15B relative to vehicle group.

Table 11: *In vivo* knockdown of PPP1R15B in mouse liver by GalNAc conjugated PPP1R15B RNAi agents

<u>dsRNA No.</u>	<u>Ave %KD</u>	<u>StdError (n of 6)</u>
Vehicle	1.0	0.1
92	79.1	1.0
122	86.4	0.9
124	71.2	1.5

128	81.3	1.0
131	83.2	1.5
135	63.0	2.3
156	65.4	1.1

Efficacy of PPP1R15B RNAi agent in diet induced obese (DIO) mice

[00095] Animals were individually housed at thermoneutrality with 12h/12h light/dark cycle and fed 60% high-fat diet (D12492; Research Diets). C57Bl/6J male mice (Jax 380050, The Jackson Laboratory) were treated with RNAi agent or vehicle (PBS, Invitrogen) control subcutaneously at 10 mg/kg (n=4 for vehicle, n=6 for siRNA group). Animals were euthanized 14 or 28 days post dose and livers were harvested for confirmation of gene knockdown. RNA isolation and gene expression were tested as described above.

[00096] The results from this study are shown in Table 12 as the percent knockdown (%KD) of PPP1R15B relative to vehicle group.

Table 12: Knockdown of PPP1R15B in liver samples collected from DIO mice after PPP1R15B RNAi agent treatment.

	Day 14 post dose		Day 28 post dose		
dsRNA No.	Average %KD	StdError	Average %KD	StdError	n
Vehicle	1.0	0.1	1.0	0.1	4.0
122	69.2	4.0	49.5	5.8	6.0

Example 4. PPP1R15B RNAi agent enhances GLP-1R agonist induced body weight loss in DIO mice

[00097] Animals were individually housed at thermoneutrality with 12h/12h light/dark cycle and fed 60% high-fat diet (D12492; Research Diets). C57Bl/6J male mice (Jax 380050, The Jackson Laboratory) were dosed subcutaneously with a non-targeting control (NTC, 10 mg/kg), PPP1R15B RNAi agent (10 mg/kg), GLP-1R agonist (3 nmol/kg/day), or a combination of PPP1R15B RNAi agent and GLP-1R agonist (n=6 for each agent). Animals were monitored daily for body weight, food intake and were euthanized 18 days post dose when livers were

harvested for confirmation of gene knockdown. RNA was isolated from liver tissue using TRIzol reagent (Invitrogen) and the RNeasy Plus mini kit (Qiagen). RNA was transcribed into cDNA using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Taqman assays for RPLP0 (Mm01974474_gH, Applied Biosystems), PPP1R15B (Mm00551747_m1, Applied Biosystems) were used to measure gene expression using QuanStudio 7 Flex and normalized to RPLP0 mRNA.

[00098] Results from this study showed that a single dose of RNAi agent or daily dosing with GLP-1R agonist reduced body weight by 13% and 8% respectively after 11 days, while the combination treatment led to ~32% body weight loss (Figure 1).

Example 5. PPP1R15B RNAi agent enhances energy expenditure in DIO mice

[00099] To investigate the effect of the PPP1R15B RNAi agent on whole-body metabolic rate, animals were individually housed in metabolic cages (Sable Systems) at thermoneutrality with 12h/12h light/dark cycle and fed 60% high-fat diet (HFD, D12492; Research Diets). Animals had ad libitum access to water and HFD when in metabolic cages. Energy expenditure was determined in obese mice treated with vehicle (n = 6) or the PPP1R15B RNAi agent (dsRNA No. 122; 10 mg/kg, n = 6) using an open respirometer system (Sable Systems). Energy expenditure was calculated by standard methods using oxygen consumption (VO_2 , mL/kg/h) and carbon dioxide production (VCO_2 , mL/kg/h) to arrive at the energy expenditure in kilocalories (kcal) per day ($1.440 (3.9 \text{ VO}_2 + 1.1 \text{ VCO}_2)$, Weir, 1949, J. Physiol. 109:1-9).

[000100] As shown in Figure 2, mice given PPP1R15B RNAi agent showed increased daily energy expenditure when compared to the vehicle control group in statistically significant fashion starting on day 2 and continuing throughout the 10-day treatment period.

SEQUENCE LISTING

SEQ ID NO	Sequence (5' to 3')
1	ATTTTGGGCT TCGCTTCCAC CGCACCAGCC GGCCTACCCA GTCCTTCCGG TATCGCGTTG CTCAGGGGCT TTTCAACCCT CTGTCAGTCG GAAAACCATC GCCGAGGCCG TGGGGGGACT CCTATCCATG GTGTTGAAGC GTCGAGCCGA CTAGGGAACC TCCTTCCCCG CCAGGATGGA AGTCGCATCA GTCGCCGCCT ATTGCGCGGG CTGTTCTTCC CTGTGTTCTG CCGCCCGCTG CCGCATTCCG TGCCCTCTGT GGCTTTTCTG CTGGCTCGAA GATCGGCCTG GAGCAGCGAC GCCACCGCTG GGCAAGGCCG AGACTCTGTA GGCTTCCTCC GAATCCCGTC GACCTCCAGC CGCTGAGCGC CGCGGCCCTA CCTGAGAGAC TGTCAAGAAA AAGGAGATGG AGCCGGGGAC AGGCGGATCG CGGAAACGGC TTGGCCCTCG GGCGGGCTTC CGGTTCTGGC CACCCTTTT CCCTCGGCGA TCGCAAGCAG GCTCTTCTAA GTTCCCGACG CCTCTTGCC CGGAAAATC CGGGAACCCC AACTGCTTT CCTCTGCCCA GCCCGAGACT CGGGTCAGTT ACTGGACGAA ACTGCTCTCC CAGCTCCTTG CGCCGCTCCC CGGATTGCTT CAGAAGGTGC TAATTTGGAG CCAACTTTT GGTGGAATGT TTCCGACCAG ATGGCTAGAT TTGCTGGAG TCTACAGCGC CCTGAGAGCC CTGAAGGGAC GGGAGAAACC AGCCGCCCCC ACAGCGCAGA AATCTTTGAG TTCGCTGCAG CTCGACTCCT CAGACCCCTC GGTCACCAGT CCCCTTGATT GGCTAGAGGA GGGGATCCAC TGGCAATACT CGCCCCCAGA CCTAAAATTG GAGCTTAAGG CCAAGGGAAG TGCTTTGGAC CCTGCAGCAC AGGCTTTTCT CTTAGAGCAG CAGCTGTGGG GAGTGGAGCT GTTGCCAGT AGCCTTCAAT CCCGTCTGTA CTCTAACCGG GAACTTGGCT CTTCGCCCTC TGGGCCTCTA AACATTCAAC GCATAGACAA TTTCAGTGTG GTATCCTATT TGCTGAACCC TTCCTACCTG GACTGCTTTC CTAGGCTAGA AGTCAGCTAT CAGAACAGTG ATGGAAATAG CGAGGTAGTC GGCTTCCAGA CACTAACCCC AGAGAGCAGC TGCCTGAGAG AGGACCATTG TCATCCCCAG CCGCTGAGTG CAGAACTCAT TCCGGCCTCG TGGCAGGGAT GTCCACCTCT TTCTACGGAA GGCCTACCAG AAATTCACCA TCTTCGCATG AAACGGCTGG AATTCCTTCA ACAGGCTAGC AAGGGGCAAG ATTTACCCAC CCCTGACCAG GATAATGGCT ACCACAGCCT GGAGGAGGAA CACAGCCTTC TCCGGATGGA TCCAAAACAC TGCAGAGATA ACCCAACACA GTTTGTTCCT GCTGCTGGAG ACATTCTTGG AAACACCCAG GAATCCACTG AAGAAAAAAT AGAATTATTA ACTACAGAGG TTCCACTTGC TTTGGAAGAA GAGAGCCCTT CTGAGGGCTG TCCATCTAGT GAGATACCTA TGGAAAAGGA GCCTGGAGAG GGCCGAATAA GTGTAGTTGA TTAATCATAC CTAGAAGGTG ACCTTCCCAT TTCTGCCAGA CCAGCTTGTA GTAACAAACT GATAGATTAT ATTTTGGGAG GTGCATCCAG TGACCTGGAA ACAAGTTCTG ATCCAGAAGG TGAGGATTGG GATGAGGAAG CTGAGGATGA TGGTTTTGAT AGTGATAGCT CACTGTCAGA CTCAGACCTT GAACAAGACC CTGAAGGGCT TCACCTTTGG AACTCTTTCT GCAGTGTAGA TCCTTATAAT CCCAGAACT TTACAGCAAC AATTCAGACT GCTGCCAGAA TTGTTCTGA AGAGCCTTCT GATTAGAGA AGGATTGTG TGGCAAGTCT GATCTAGAGA ATTCCTCCA GTCTGGAAGC CTTCTGAGA CCCCTGAGCA TAGTTCTGGG GAGGAAGATG ACTGGGAATC TAGTGCAGAT GAAGCAGAGA GTCTCAAACCT GTGGAACCTA TTCTGTAATT CTGATGACCC CTACAACCCT TTAATTTTA AGGCTCCTT TCAAACATCA GGGGAAAATG AGAAAGGCTG TCGTGACTCA AAGACCCCAT CTGAGTCCAT TGTGGCCATT

TCTGAGTGTG ACACCTTACT TTCTTGTAAG GTGCAGCTGT TGGGGAGCCA
 AGAAAGTGAA TGTCCAGACT CCGTACAGCG TGACGTTCTT TCTGGAGGAA
 GACACACACA TGTCAAAAGA AAAAAGGTAA CCTTCCTTGA AGAAGTTACT
 GAGTATTATA TAAGTGGTGA TGAGGATCGC AAAGGACCAT GGGGAAGAATT
 TGCAAGGGAT GGATGCAGGT TCCAGAAACG AATTCAAGAA ACAGAAGATG
 CTATTGGATA TTGCTTGACA TTTGAACACA GAGAAAGAAT GTTTAATAGA
 CTCCAGGGAA CATGCTTCAA AGGACTTAAT GTTCTCAAGC AATGTTGAGT
 TGGCAGCCTG TAGTCCTAGC TAGCATAAC TACCTCTTAC CTGAGAGGTG
 TCTTTTAAAA ACAAATCTTG GCAGCTGTCC TTTGACATTT TTTTTTTT
 AGGAAATGTA ACTTGGATCT AGTTTAATTT TTTTTTTTGC AACATATCCC
 ACTCAGAAAC ATTCAGGTTT GAAGCCAGCC CTGATAATGA AGGATGAACT
 AGTGTGATTT CTAATCCTCC CTTTTTTGAT TTAGTTGGAT GTGCTTTTAA
 ATGTCCTTTG CCTGCATGAG GTGGAAAGGG GACCTTTTGT AGTTGTCATT
 TTGCACCTTC AAAACTTATT TTCTTGGAAA ACAATATTTA TAGGGCTTAA
 AGCCCATTTT CATTTCTAAT CTAAATTATG TGTGCCTATC TGAAAACCTT
 GGGCTCTTTC TTGTTTCTTT CCAAAAATTC AGAAGTTAAT GGGCTTTTAT
 GTTTTTCTAT ATTTTTTTT TTTCAATGAT TTGGCCTGTC TATGTTAGGC
 TAAAAAATAA CCTTGTGTAT GCTACCAACT TAAAGTGCAT TATTTTGTGT
 CACTTTTTTT TTTCTTGTA AAATGACTTG GATTGAAAAT ATGTGGTAGC
 CTTTTATTT CTACATTAAG TTCTACCTAG GATATTTCCA AGGACTGCCA
 CAAAACCCAT ATGTGCAGTA CTTACTACT TTGGGAAAGC TGCATCTTTC
 TACCACATTT TAACATCTAA TATATTTAAT TTCTTTGAAG AGGGTTCTGT
 GTACGTTATT GTAGTTCCCA GTTTAATATA GTTCTTTGTA TCTCTTAACA
 GGTTGAAGTT ATTGCAAAAC ACTCTGGAAA GTAATAATTA CATCATAATC
 ATTTATTTTT TAAACTTAAA AGCCTAGAAA TTTCTAGAA AGAAAATAGG
 AGACATCTCA GAGCAATTG GTTTTGGTGT ATATGTTCTC AACAGAAAAC
 CAGTGTAAAT GAATATCATG CCTCAGCACT GTCACCTTTA AAACCTGTCA
 GGATCCCACT GTAAAATTGG AAATGGGCAG TTCTGAATTT TCACGTTTGA
 AATGTAAAT ATAACTTCA GTCAATATCC AGGTTTATTG TGTCTACTA
 TTTAATAATG AGAGAAGTAA TGGCAAGGCC TTTACTTTCA GGAAAGGATA
 GAAGTATAGA TTAATGACTG GAAAGTTTAT ATATATTTAG CCCAAAGGTT
 ACTTTGAATT GAAGTCTTTG CATTGACTGT TTGTGTTTGG TTTATTGTT
 TAGCTTTACA AGGTACACAT AAGTTAGGTT GAGGGGTTGT TAACCCTTCC
 GTGGTCTGCT TTCAATCCGT GTGCTTCTG TCACAGGTAA TGGAAAACAT
 AAGTAGAATA GGTGACCTCT TAGTTTTGAA CTTATTTAAG TGTGGGGATG
 AATTTTTCAT CAGAAGTGCT TACAGGGTTA CTACCTCAGT TTACAATCTA
 CCTGGTCATT ATTTTATTT TATCCAGTTC TAAGAACTGC CTCCACTGTT
 TATATATTCA TAATTAAACA CATTGAGAAT GCAACACTAT AAAAGCTGGT
 CAAATTTTTG CAGAGCCCTT ATTCTGTGTG TTTTTGTTT TTTTCTTTTT
 TTTTGTAGAC AGAGTCTCGT TCGGTCCCCC AGCTTGGAGT GCAGTGGCGC
 GATCTCGGCT CACTGCAACC TCCGCTCCT GGGTTCACGC GATTCTCCTG
 CCTCAGCCTC CCGAGTAGCT GGGATTACAG GCACACACCA CCACGCCCGG
 CTAATTTTTT GTGTCTTTTT AGTAGAGACG GGGTTTCGCT ATGTTGGCCA
 GACTGGTCTT GAACGTCTGA CCTCGTGATC CGCCCGCCTC GGCCTCTCAA
 AGTGCTGGGA TTCTGTGTGT TTTGTGCACC TCCACTTTAG GTAATCATAG
 GGAGCACATT TACAGGATGG TCTAATAACA TGAAAACAGG CTAGTTTCAA
 GCAACAGCAA TGTCGGTTGG AAAGCAGGCG TCATTTGCCT TGAAAAAAGC
 CTTTGTACAA CATAAGGCA TTCTTTTAAA ACCAGGCTGA AACATTTTAT
 TTCCGAGACT TAACGTTGTG TTCTCTGTTT CTAAACCTA GCACCTCTGT
 GTATTTGAAA ATAATGAGAC ATCTTTCATT GGATTTTGGG AAATTGTTCC
 CCATGGGATT CTAACCTCAC TACCAAATGA GTGAAAGCTT GATTAAGAGT

	TCTTCCATAT ACTAGCCTCC TTGGAAGAAG TGATCAGAAG GTGATAAGAA GGACAGAAAG GACTATTTTA AAGTTGGACT GAAGGAGAAA AAAGCAAAAT TCTTGTTC TCCAATTCT AGTTAGAACA AAGTTAAACC CCCGTAATCT TAAAGAGAAA ATCTTTGGAG GTTTTAATTA AACATTTTAT ACATTTAAAG TCTTGTTAAT GGTGCTTTAA GTGTCAATGT AGCATGTAAA AGGCTTTGTA CAGACAGGTA AAAGTTCCAT TTCTGAGTGA TGAAATGTAA CACTTCTTCA TCTTTAACTT GAAATCAAAA CTATCAGATT TTATTTTGT ATAATTTAAG GAAGGTAAAG TTAGGGGACT AGAAGACTCT AAATTGGCTT CTACAGATCA ATAATTTAAA TGTAAGTAGT TGGGATTTTA TAGTTAAAAT TATATTTGTG TATATAACAT AACTAATCTG TAAATTGTAA TAAATATATT TGCAATTATT AAATGTAA
2	UACGUGUAACGUGGAGAU
3	GAUGAAGCAGAGAAUCUU
4	UGUAUAUAAUUAUUAACU
5	GGCACACACCAUUAUGCC
6	AGCAGUCUGUUUUGUGAA
7	GAAGUUGCCAUUGGCUAC
8	UAAUGGGCUUUAUGGGUU
9	GGUGUCCCCUGCUGCAGA
10	UCUGAAUCAGACGUGGAA
11	UUAUAUUUUGGGAGGCGC
12	GUUUGGCUUGCACAUGGC
13	GACUGGGAAAGCGGGGUU
14	AGAAACGAAUUCAAGAAA
15	AAGAUAAUGGCUAUCUA
16	GCUAACAAAGGGCAAGAG
17	CGGUCGCCACCGCUUGCG
18	GGAAACGCCGCCGUCGUC
19	CGAUCGCACGCCUGCUCU
20	AUGGACCCACAACAUUGC
21	CUUCUGGAGGCAGGGGCU
22	UAACUAAUCUGUAAAUUG
23	UCCGCCUCUCGGGAGGCA
24	CGGGAGGAAUCUGCCGCU
25	AACUAGGGGGUAUUUGGG
26	UCUUUUUAAGAUUUUCC
27	GAGAAGCAAAGCAGAAAG
28	AACGCACAGGGCCCGGAA
29	CGCACGCCUGCUCUUCGG
30	GCGGCCAUUUUGAGCUUC
31	GAACUCCGCUCUGCCCGA
32	UGGACAUGUUUUUAAAGA
33	ACCAUAGUCCGGGGAGG

34	CGGAGCCCACUGAGAAAA
35	GCCGUUGCGGGCAGAGAU
36	GCCUCUUCUGAGGCUACA
37	CGCCUCUCUCUACAGAAG
38	GCAAACUGUCCAUUUGGA
39	GUGAGGCAAGUCCGCCUC
40	UCUCUGUAGCUUUAAGA
41	ACCAGAUGGCUAGAUUUU
42	CUUACUUUCUUGUAAGGC
43	UCACCUUUGGAACUCUUU
44	GAAACGAAUUAAGAAAC
45	UUUGCACUUUCAAACGU
46	UAUUAUAUAAGUGGUGAU
47	UAAGUGGUGAUGAGGAUC
48	CAACAAACUGAUAGAUUA
49	AUGGAUGCAGGUUCCAGA
50	GAGUAUUAUAUAAGUGGU
51	GCAGGUUCCAGAAACGAA
52	ACUACCUCAGUUUAUAAU
53	ACGAAUUAAGAAACAGA
54	GAUAGAUUAUAUUUUGGG
55	UAUAUAAGUGGUGAUGAG
56	AGGUUCCAGAAACGAAUU
57	CAGGUUCCAGAAACGAAU
58	UACCUCAGUUUAUAAUCU
59	UAGCAACAAACUGAUAGA
60	CCAUUUUGAGCUUCGCUU
61	AGGGAUGGAUGCAGGUUC
62	CACCCUGACCAAGAUAA
63	UUAAGGCUCCUUUUAAC
64	AUUCAGACGGCUGCCAGA
65	AACGAAUUAAGAAACAG
66	GAUGAGGAUCGCAAAGGA
67	UGAUAGAUUAUAUUUUGG
68	AAGGCCUUCACCUUUGGA
69	AUUAUAUUUUGGGAGGCG
70	GAUGGAUGCAGGUUCCAG
71	CAUACCUUACUUUCUUGU
72	GCAACAAACUGAUAGAUU
73	UAUCCAGGUUUGUUGUGU
74	GGCCAUUUUGAGCUUCGC

75	AGAUUAUAUUUUGGGAGG
76	CCAGAUGGCUAGAUUUUG
77	AAAAAAUGUUUAAUAGAC
78	UGAUGAGGAUCGCAAAGG
79	UUGAUUGGCUAGAGGAGG
80	UGAUUGGCUAGAGGAGGG
81	UUUACGUGUAACGUGGAGAU
82	CAGAUGAAGCAGAGAAUCUUA
83	UUUGUAUAUAAUUAUUAACUA
84	AAGGCACACACCAUUAUGCCA
85	GAAGCAGUCUGUUUUGUGAAA
86	CAGAAGUUGCCAUUGGCUACA
87	AUUAUUGGGCUUUAUGGGUUA
88	GCGGUGUCCCCUGCUGCAGAA
89	UGUCUGAAUCAGACGUGGAAA
90	GAUUAUAUUUUGGGAGGCGCA
91	UUGUUUGGCUUGCACAUGGCA
92	UUGACUGGGAAAGCGGGGUUA
93	CCAGAAACGAAUUCAAGAAAA
94	CCAAGAUAAUGGCUAUCAUAA
95	AGGCUAACAAGGGCAAGAGA
96	CGCGGUCGCCACCGCUUGCGA
97	CCGGAAACGCCGCCGUCGUCA
98	GGCGAUCGCACGCCUGCUCUA
99	GGAUGGACCCACAACAUUGCA
100	UUCUUCUGGAGGCAGGGGCUA
101	AUUAACUAAUCUGUAAAUUGA
102	AGUCCGCCUCUCGGGAGGCAA
103	GACGGGAGGAAUCUGCCGCUA
104	UUAACUAGGGGGUAAUUGGGA
105	GGUCUUUUUAAGAUUUUCCA
106	GAGAGAAGCAAAGCAGAAAGA
107	GGAACGCACAGGGCCCGGAAA
108	AUCGCACGCCUGCUCUUCGGA
109	CUGCGGCCAUUUUGAGCUUCA
110	GGGAACUCCGCUCUGCCCGAA
111	CUUGGACAUGUUUUUAAAGAA
112	CGACCAUAGUUCGCGGGAGGA
113	GCCGGAGCCCACUGAGAAAAA
114	CAGCCGUUGCGGGCAGAGAU
115	AGGCCUCUUCUGAGGCUACAA

116	UCCGCCUCUCUCUACAGAAGA
117	GUGCAAACUGUCCAUUUGGAA
118	GGGUGAGGCAAGUCCGCCUCA
119	GCUCUCUGUAGCUUUCAAGAA
120	CUACCAGAUGGCUAGAUUUUA
121	ACCUUACUUUCUUGUAAGGCA
122	CUUCACCUUUGGAACUCUUUA
123	CAGAAACGAAUUCAAGAAACA
124	AUUUUGCACUUUCAAACGUA
125	AGUAUUAUAUAAGUGGUGAUA
126	UAUAAGUGGUGAUGAGGAUCA
127	AGCAACAAACUGAUAGAUUAA
128	GGAUGGAUGCAGGUUCCAGAA
129	CUGAGUAUUAUAUAAGUGGUA
130	AUGCAGGUUCCAGAAACGAAA
131	AAACUACCUCAGUUUAUAAUA
132	AAACGAAUUCAAGAAACAGAA
133	CUGAUAGAUUAUAUUUUGGGA
134	AUUAUAUAAGUGGUGAUGAGA
135	GCAGGUUCCAGAAACGAAUUA
136	UGCAGGUUCCAGAAACGAAUA
137	ACUACCUCAGUUUAUAUAUCUA
138	UGUAGCAACAAACUGAUAGAA
139	GGCCAUUUUGAGCUUCGCUUA
140	CAAGGGAUGGAUGCAGGUUCA
141	CCCACCCCUGACCAAGAUAAA
142	UUUUAAGGCUCCUUUUCAACA
143	CGAUUCAGACGGCUGCCAGAA
144	GAAACGAAUUCAAGAAACAGA
145	GUGAUGAGGAUCGCAAAGGAA
146	ACUGAUAGAUUAUAUUUUGGA
147	GGAAGGCCUUCACCUUUGGAA
148	AGAUUAUAUUUUGGGAGGCCA
149	GGGAUGGAUGCAGGUUCCAGA
150	AUCAUACCUUACUUUCUUGUA
151	UAGCAACAAACUGAUAGAUUA
152	AAUAUCCAGGUUUGUUGUGUA
153	GCGGCCAUUUUGAGCUUCGCA
154	AUAGAUUAUAUUUUGGGAGGA
155	UACCAGAUGGCUAGAUUUUGA
156	AGAAAAAAUGUUUAAUAGACA

157	GGUGAUGAGGAUCGCAAAGGA
158	UCUUGAUUGGCUAGAGGAGGA
159	CUUGAUUGGCUAGAGGAGGGA
160	UAUCUCCACGUUACACGUAAAAU
161	UAAGAUUCUCUGCUUCAUCUGCA
162	UAGUAAUAAUUAUAUACAAAUA
163	UGGCAUAAUGGUGUGUGCCUUUG
164	UUUCACAAAACAGACUGCUUCCC
165	UGUAGCCAAUGGCAACUUCUGUU
166	UAACCCAUAAAGCCCAUUAUUU
167	UUCUGCAGCAGGGGACACCGCCU
168	UUUCCACGUCUGAUUCAGACAGG
169	UGCGCCUCCCCAAAUAUAUUCUA
170	UGCCAUGUGCAAGCCAAACAAGA
171	UAACCCCGCUUCCCCAGUCAAGA
172	UUUUCUUGAAUUCGUUUCUGGAA
173	UUAUGAUAGCCAUUAUCUUGGUC
174	UCUCUUGCCCUUUGUUAGCCUGG
175	UCGCAAGCGGUGGCGACCGCGGU
176	UGACGACGGCGGCGUUUCCGGUG
177	UAGAGCAGGCGUGCGAUCGCCGA
178	UGCAAUGUUGUGGGUCCAUCCGG
179	UAGCCCCUGCCUCCAGAAGAAAC
180	UCAAUUUACAGAUUAGUAAUAA
181	UUGCCUCCCGAGAGGCGGACUUG
182	UAGCGGCAGAUUCCUCCCGUCCU
183	UCCCAAAUACCCCCUAGUAAAAA
184	UGGAAAUAUUCUAAAAAAGACCUA
185	UCUUUCUGCUUUGCUUCUCUCUA
186	UUUCCGGGCCUGUGCGUUCUG
187	UCCGAAGAGCAGGCGUGCGAUCG
188	UGAAGCUCAAAAUGGCCGCAGCC
189	UUCGGGCAGAGCGGAGUCCCCGG
190	UUCUUUAAAAACAUGUCCAAGGA
191	UCCUCCCCGGAACUAUGGUCGGG
192	UUUUUCUCAGUGGGCUCCGGCCU
193	UAUCUCUGCCCGCAACGGCUGAG
194	UUGUAGCCUCAGAAGAGGCCUUU
195	UCUUCUGUAGAGAGAGGCGGACA
196	UUCAAAUGGACAGUUUGCACAG
197	UGAGGCGGACUUGCCUCACCCUC

198	UUCUUGAAAGCUACAGAGAGCCA
199	UAAAAUCUAGCCAUCUGGUAGGA
200	UGCCUUACAAGAAAGUAAGGUAU
201	UAAAGAGUUCCAAAGGUGAAGGC
202	UGUUUCUUGAAUUCGUUUCUGGA
203	UACGUUUUGAAAGUGCAAAAUUA
204	UAUCACCACUUAUAUAAUACUCA
205	UGAUCCUCAUACCACUUAUAUA
206	UUAUAUCUAUCAGUUUGUUGCUAC
207	UUCUGGAACCUGCAUCCAUCCCU
208	UACCACUUAUAUAAUACUCAGUA
209	UUUCGUUUCUGGAACCUGCAUCC
210	UAUUUAUAAACUGAGGUAGUUUAC
211	UUCUGUUUCUUGAAUUCGUUUCU
212	UCCCAAAAUAAAUUCUAUCAGUU
213	UCUCAUACCACUUAUAUAAUAC
214	UAAUUCGUUUCUGGAACCUGCAU
215	UAUUCGUUUCUGGAACCUGCAUC
216	UAGAUUAUAAACUGAGGUAGUUU
217	UUCUAUCAGUUUGUUGCUACAAA
218	UAAGCGAAGCUCAAAAUGGCCGC
219	UGAACCUGCAUCCAUCCCUUGCA
220	UUUAUCUUGGUCAGGGGUGGGUA
221	UGUUGAAAAGGAGCCUAAAAAUU
222	UUCUGGCAGCCGUCUGAAUCGUG
223	UCUGUUUCUUGAAUUCGUUUCUG
224	UUCUUUGCGAUCCUCAUCACCA
225	UCCAAAAUAUAAUCUAUCAGUUU
226	UUCCAAAGGUGAAGGCCUCCGA
227	UCGCCUCCCAAAAUAAAUUCUAU
228	UCUGGAACCUGCAUCCAUCCCUU
229	UACAAGAAAGUAAGGUAUGAUGG
230	UAAUCUAUCAGUUUGUUGCUACA
231	UACACAACAAACCUGGAUAUUGA
232	UGCGAAGCUCAAAAUGGCCGCAG
233	UCCUCCCAAAAUAAAUUCUAUCA
234	UCAAAAUUCUAGCCAUCUGGUAGG
235	UGUCUAUUAAACAUUUUUUCUCU
236	UCCUUUGCGAUCCUCAUCACCAC
237	UCCUCCUCUAGCCAAUCAAGAGA
238	UCCCUCCUCUAGCCAAUCAAGAG

239	mU*mU*mUmAmCmGmUmGfUfAfAmCmGmUmGmGmAmGmA*mU*mA
240	mC*mA*mGmAmUmGmAmAfGfCfAmGmAmGmAmAmUmCmU*mU*mA
241	mU*mU*mUmGmUmAmUmAfUfAfAmUmUmAmUmUmAmAmC*mU*mA
242	mA*mA*mGmGmCmAmCmAfCfAfCmCmAmUmUmAmUmGmC*mC*mA
243	mG*mA*mAmGmCmAmGmUfCfUfGmUmUmUmUmGmUmGmA*mA*mA
244	mC*mA*mGmAmAmGmUmUfGfCfCmAmUmUmGmGmCmUmA*mC*mA
245	mA*mU*mUmAmAmUmGmGfGfCfUmUmUmAmUmGmGmGmU*mU*mA
246	mG*mC*mGmGmUmGmUmCfCfCfCmUmGmCmUmGmCmAmG*mA*mA
247	mU*mG*mUmCmUmGmAmAfUfCfAmGmAmCmGmUmGmGmA*mA*mA
248	mG*mA*mUmUmAmUmAmUfUfUfUmGmGmGmAmGmGmCmG*mC*mA
249	mU*mU*mGmUmUmUmGmGfCfUfUmGmCmAmCmAmUmGmG*mC*mA
250	mU*mU*mGmAmCmUmGmGfGfAfAmAmGmCmGmGmGmU*mU*mA
251	mC*mC*mAmGmAmAmAmCfGfAfAmUmUmCmAmAmGmAmA*mA*mA
252	mC*mC*mAmAmGmAmUmAfAfUfGmGmCmUmAmUmCmAmU*mA*mA
253	mA*mG*mGmCmUmAmAmCfAfAfAmGmGmGmCmAmAmGmA*mG*mA
254	mC*mG*mCmGmGmUmCmGfCfCfAmCmCmGmCmUmUmGmC*mG*mA
255	mC*mC*mGmGmAmAmAmCfGfCfCmGmCmCmGmUmCmGmU*mC*mA
256	mG*mG*mCmGmAmUmCmGfCfAfCmGmCmCmUmGmCmUmC*mU*mA
257	mG*mG*mAmUmGmGmAmCfCfCfAmCmAmAmCmAmUmUmG*mC*mA
258	mU*mU*mCmUmUmCmUmGfGfAfGmGmCmAmGmGmGmC*mU*mA
259	mA*mU*mUmAmAmCmUmAfAfUfCmUmGmUmAmAmAmUmU*mG*mA
260	mA*mG*mUmCmCmGmCmCfUfCfUmCmGmGmAmGmGmC*mA*mA
261	mG*mA*mCmGmGmGmAmGfGfAfAmUmCmUmGmCmCmGmC*mU*mA
262	mU*mU*mAmAmCmUmAmGfGfGfGmGmUmAmUmUmUmGmG*mG*mA
263	mG*mG*mUmCmUmUmUmUfUfAfAmGmAmUmAmUmUmUmC*mC*mA
264	mG*mA*mGmAmGmAmAmGfCfAfAmAmGmCmAmGmAmAmA*mG*mA
265	mG*mG*mAmAmCmGmCmAfCfAfGmGmGmCmCmCmGmGmA*mA*mA
266	mA*mU*mCmGmCmAmCmGfCfCfUmGmCmUmCmUmUmCmG*mG*mA
267	mC*mU*mGmCmGmGmCmCfAfUfUmUmUmGmAmGmCmUmU*mC*mA
268	mG*mG*mGmAmAmCmUmCfCfGfCmUmCmUmGmCmCmCmG*mA*mA
269	mC*mU*mUmGmGmAmCmAfUfGfUmUmUmUmUmAmAmAmG*mA*mA
270	mC*mG*mAmCmCmAmUmAfGfUfUmCmCmGmGmGmAmG*mG*mA
271	mG*mC*mCmGmGmAmGmCfCfCfAmCmUmGmAmGmAmAmA*mA*mA
272	mC*mA*mGmCmCmGmUmUfGfCfGmGmGmCmAmGmAmGmA*mU*mA
273	mA*mG*mGmCmCmUmCmUfUfCfUmGmAmGmGmCmUmAmC*mA*mA
274	mU*mC*mCmGmCmCmUmCfUfCfUmCmUmAmCmAmGmAmA*mG*mA
275	mG*mU*mGmCmAmAmAmCfUfGfUmCmCmAmUmUmUmGmG*mA*mA
276	mG*mG*mGmUmGmAmGmGfCfAfAmGmUmCmCmGmCmUmU*mC*mA
277	mG*mC*mUmCmUmCmUmGfUfAfGmCmUmUmUmCmAmAmG*mA*mA
278	mC*mU*mAmCmCmAmGmAfUfGfGmCmUmAmGmAmUmUmU*mU*mA
279	mA*mC*mCmUmUmAmCmUfUfUfCmUmUmGmUmAmAmGmG*mC*mA

280	mC*mU*mUmCmAmCmCmUfUfUfGmGmAmAmCmUmCmUmU*mU*mA
281	mC*mA*mGmAmAmAmCmGfAfAfUmUmCmAmAmGmAmAmA*mC*mA
282	mA*mU*mUmUmUmGmCmAfCfUfUmUmCmAmAmAmAmCmG*mU*mA
283	mA*mG*mUmAmUmUmAmUfAfUfAmAmGmUmGmGmUmGmA*mU*mA
284	mU*mA*mUmAmAmGmUmGfGfUfGmAmUmGmAmGmGmAmU*mC*mA
285	mA*mG*mCmAmAmCmAmAfAfCfUmGmAmUmAmGmAmUmU*mA*mA
286	mG*mG*mAmUmGmGmAmUfGfCfAmGmGmUmUmCmCmAmG*mA*mA
287	mC*mU*mGmAmGmUmAmUfUfAfUmAmUmAmAmGmUmGmG*mU*mA
288	mA*mU*mGmCmAmGmGmUfUfCfCmAmGmAmAmAmCmGmA*mA*mA
289	mA*mA*mAmCmUmAmCmCfUfCfAmGmUmUmUmAmUmAmA*mU*mA
290	mA*mA*mAmCmGmAmAmUfUfCfAmAmGmAmAmAmCmAmG*mA*mA
291	mC*mU*mGmAmUmAmGmAfUfUfAmUmAmUmUmUmUmGmG*mG*mA
292	mA*mU*mUmAmUmAmUmAfAfGfUmGmGmUmGmAmUmGmA*mG*mA
293	mG*mC*mAmGmGmUmUmCfCfAfGmAmAmAmCmGmAmAmU*mU*mA
294	mU*mG*mCmAmGmGmUmUfCfCfAmGmAmAmAmCmGmAmA*mU*mA
295	mA*mC*mUmAmCmCmUmCfAfGfUmUmUmAmUmAmAmUmC*mU*mA
296	mU*mG*mUmAmGmCmAmAfCfAfAmAmCmUmGmAmUmAmG*mA*mA
297	mG*mG*mCmCmAmUmUmUfUfGfAmGmCmUmUmCmGmCmU*mU*mA
298	mC*mA*mAmGmGmGmAmUfGfGfAmUmGmCmAmGmGmUmU*mC*mA
299	mC*mC*mCmAmCmCmCmCfUfGfAmCmCmAmAmGmAmUmA*mA*mA
300	mU*mU*mUmUmAmAmGmGfCfUfCmCmUmUmUmUmCmAmA*mC*mA
301	mC*mG*mAmUmUmCmAmGfAfCfGmGmCmUmGmCmCmAmG*mA*mA
302	mG*mA*mAmAmCmGmAmAfUfUfCmAmAmGmAmAmAmCmA*mG*mA
303	mG*mU*mGmAmUmGmAmGfGfAfUmCmGmCmAmAmAmGmG*mA*mA
304	mA*mC*mUmGmAmUmAmGfAfUfUmAmUmAmUmUmUmUmG*mG*mA
305	mG*mG*mAmAmGmGmCmCfUfUfCmAmCmCmUmUmUmGmG*mA*mA
306	mA*mG*mAmUmUmAmUmAfUfUfUmUmGmGmGmAmGmGmC*mG*mA
307	mG*mG*mGmAmUmGmGmAfUfGfCmAmGmGmUmUmCmCmA*mG*mA
308	mA*mU*mCmAmUmAmCmCfUfUfAmCmUmUmUmCmUmUmG*mU*mA
309	mU*mA*mGmCmAmAmCmAfAfAfCmUmGmAmUmAmGmAmU*mU*mA
310	mA*mA*mUmAmUmCmCmAfGfGfUmUmUmGmUmUmGmUmG*mU*mA
311	mG*mC*mGmGmCmCmAmUfUfUfUmGmAmGmCmUmUmCmG*mC*mA
312	mA*mU*mAmGmAmUmUmAfUfAfUmUmUmUmGmGmGmAmG*mG*mA
313	mU*mA*mCmCmAmGmAmUfGfGfCmUmAmGmAmUmUmUmU*mG*mA
314	mA*mG*mAmAmAmAmAmAfUfGfUmUmUmAmAmUmAmGmA*mC*mA
315	mG*mG*mUmGmAmUmGmAfGfGfAmUmCmGmCmAmAmAmG*mG*mA
316	mU*mC*mUmUmGmAmUmUfGfGfCmUmAmGmAmGmGmAmG*mG*mA
317	mC*mU*mUmGmAmUmUmGfGfCfUmAmGmAmGmGmAmGmG*mG*mA
318	mU*mU*mUmAmCmGfUmGfUfAfAmCmGmUmGmGmAmGmA*mU*mA
319	mC*mA*mGmAmUmGfAmAfGfCfAmGmAmGmAmAmUmCmU*mU*mA
320	mU*mU*mUmGmUmAfUmAfUfAfAmUmUmAmUmUmAmAmC*mU*mA

[illegible]

362	PmU*fU*mGmUfAmGfCmCmUmCmAmGmAfAmGfAmGmGmCmCmU*mU*mU
363	PmU*fC*mUmUfCmUfGmUmAmGmAmGmAfGmAfGmGmCmGmGmA*mC*mA
364	PmU*fU*mCmCfAmAfAmUmGmGmAmCmAfGmUfUmUmGmCmAmC*mA*mG
365	PmU*fG*mAmGfGmCfGmGmAmCmUmUmGfCmCfUmCmAmCmC*mU*mC
366	PmU*fU*mCmUfUmGfAmAmAmGmCmUmAfCmAfGmAmGmAmGmC*mC*mA
367	PmU*fA*mAmAfAmUfCmUmAmGmCmCmAfUmCfUmGmGmUmAmG*mG*mA
368	PmU*fG*mCmCfUmUfAmCmAmAmGmAmAfAmGfUmAmAmGmGmU*mA*mU
369	PmU*fA*mAmAfGmAfGmUmUmCmCmAmAfAmGfGmUmGmAmAmG*mG*mC
370	PmU*fG*mUmUfUmCfUmUmGmAmAmUmUfCmGfUmUmUmCmUmG*mG*mA
371	PmU*fA*mCmGfUmUfUmUmGmAmAmAmGfUmGfCmAmAmAmU*mU*mA
372	PmU*fA*mUmCfAmCfCmAmCmUmUmAmUfAmUfAmAmUmAmCmU*mC*mA
373	PmU*fG*mAmUfCmCfUmCmAmUmCmAmCfCmAfCmUmUmAmUmA*mU*mA
374	PmU*fU*mAmAfUmCfUmAmUmCmAmGmUfUmUfGmUmUmGmCmU*mA*mC
375	PmU*fU*mCmUfGmGfAmAmCmCmUmGmCfAmUfCmCmAmUmCmC*mC*mU
376	PmU*fA*mCmCfAmCfUmUmAmUmAmUmAfAmUfAmCmUmCmAmG*mU*mA
377	PmU*fU*mUmCfGmUfUmUmCmUmGmGmAfAmCfCmUmGmCmAmU*mC*mC
378	PmU*fA*mUmUfAmUfAmAmAmCmUmGmAfGmGfUmAmGmUmUmU*mA*mC
379	PmU*fU*mCmUfGmUfUmUmCmUmUmGmAfAmUfUmCmGmUmUmU*mC*mU
380	PmU*fC*mCmCfAmAfAmAmUmAmUmAmAfUmCfUmAmUmCmAmG*mU*mU
381	PmU*fC*mUmCfAmUfCmAmCmCmAmCmUfUmAfUmAmUmAmAmU*mA*mC
382	PmU*fA*mAmUfUmCfGmUmUmUmCmUmGfGmAfAmCmCmUmGmC*mA*mU
383	PmU*fA*mUmUfCmGfUmUmUmCmUmGmGfAmAfCmCmUmGmCmA*mU*mC
384	PmU*fA*mGmAfUmUfAmUmAmAmAmCmUfGmAfGmGmUmAmGmU*mU*mU
385	PmU*fU*mCmUfAmUfCmAmGmUmUmUmGfUmUfGmCmUmAmCmA*mA*mA
386	PmU*fA*mAmGfCmGfAmAmGmCmUmCmAfAmAfAmUmGmGmCmC*mG*mC
387	PmU*fG*mAmAfCmCfUmGmCmAmUmCmCfAmUfCmCmCmUmUmG*mC*mA
388	PmU*fU*mUmAfUmCfUmUmGmGmUmCmAfGmGfGmGmUmGmGmG*mU*mA
389	PmU*fG*mUmUfGmAfAmAmAmGmGmAmGfCmCfUmUmAmAmAmA*mU*mU
390	PmU*fU*mCmUfGmGfCmAmGmCmCmGmUfCmUfGmAmAmUmCmG*mU*mG
391	PmU*fC*mUmGfUmUfUmCmUmUmGmAmAfUmUfCmGmUmUmUmC*mU*mG
392	PmU*fU*mCmCfUmUfUmGmCmGmAmUmCfCmUfCmAmUmCmAmC*mC*mA
393	PmU*fC*mCmAfAmAfAmUmAmUmAmAmUfCmUfAmUmCmAmGmU*mU*mU
394	PmU*fU*mCmCfAmAfAmGmGmUmGmAmAfGmGfCmCmUmUmCmC*mG*mA
395	PmU*fC*mGmCfCmUfCmCmCmAmAmAmAfUmAfUmAmAmUmCmU*mA*mU
396	PmU*fC*mUmGfGmAfAmCmCmUmGmCmAfUmCfCmAmUmCmCmC*mU*mU
397	PmU*fA*mCmAfAmGfAmAmAmGmUmAmAfGmGfUmAmUmGmAmU*mG*mG
398	PmU*fA*mAmUfCmUfAmUmCmAmGmUmUfUmGfUmUmGmCmUmA*mC*mA
399	PmU*fA*mCmAfCmAfAmCmAmAmAmCmCfUmGfGmAmUmAmUmU*mG*mA
400	PmU*fG*mCmGfAmAfGmCmUmCmAmAmAfAmUfGmGmCmCmGmC*mA*mG
401	PmU*fC*mCmUfCmCfCmAmAmAmAmUmAfUmAfAmUmCmUmAmU*mC*mA
402	PmU*fC*mAmAfAmAfUmCmUmAmGmCmCfAmUfCmUmGmGmUmA*mG*mG

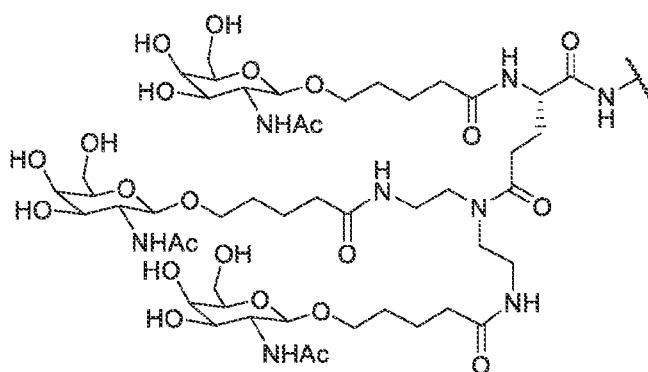
403	PmU*fG*mUmCfUmAfUmUmAmAmAmCmAfUmUfUmUmUmUmCmU*mC*mU
404	PmU*fC*mCmUfUmUfGmCmGmAmUmCmCfUmCfAmUmCmAmCmC*mA*mC
405	PmU*fC*mCmUfCmCfUmCmUmAmGmCmCfAmAfUmCmAmAmGmA*mG*mA
406	PmU*fC*mCmCfUmCfCmUmCmUmAmGmCfCmAfAmUmCmAmAmG*mA*mG
407	PmU*fG*mUmUfUmCfUfUmGmAmAmUmUfCmGmUmUmUmCmUmG*mG*mA
408	PmU*fG*mUmUfUmCfUmUfGmAmAmUmUfCmGmUmUmUmCmUmG*mG*mA
409	PmU*fG*mUmUfUmCfUmUmGfAmAmUmUfCmGmUmUmUmCmUmG*mG*mA
410	PmU*fG*mUmUfUmCfUmUmGmAfAmUmUfCmGmUmUmUmCmUmG*mG*mA
411	PmU*fG*mUmUfUmCfUmUmGmAmAfUmUfCmGmUmUmUmCmUmG*mG*mA
412	PmU*fG*mUmUfUmCfUmUmGmAmAmUfUfCmGmUmUmUmCmUmG*mG*mA
413	PmU*fA*mCmCfAmCfUfUmAmUmAmUmAfAmUmAmCmUmCmAmG*mU*mA
414	PmU*fA*mCmCfAmCfUmUfAmUmAmUmAfAmUmAmCmUmCmAmG*mU*mA
415	PmU*fA*mCmCfAmCfUmUmAfUmAmUmAfAmUmAmCmUmCmAmG*mU*mA
416	PmU*fA*mCmCfAmCfUmUmAmUfAmUmAfAmUmAmCmUmCmAmG*mU*mA
417	PmU*fA*mCmCfAmCfUmUmAmUmAfUmAfAmUmAmCmUmCmAmG*mU*mA
418	PmU*fA*mCmCfAmCfUmUmAmUmAmUfAfAmUmAmCmUmCmAmG*mU*mA
419	PmU*fU*mCmUfGmUfUfUmCmUmUmGmAfAmUmUmCmGmUmUmU*mC*mU
420	PmU*fU*mCmUfGmUfUmUfCmUmUmGmAfAmUmUmCmGmUmUmU*mC*mU
421	PmU*fU*mCmUfGmUfUmUmCfUmUmGmAfAmUmUmCmGmUmUmU*mC*mU
422	PmU*fU*mCmUfGmUfUmUmCmUfUmGmAfAmUmUmCmGmUmUmU*mC*mU
423	PmU*fU*mCmUfGmUfUmUmCmUmUfGmAfAmUmUmCmGmUmUmU*mC*mU
424	PmU*fU*mCmUfGmUfUmUmCmUmUmGfAfAmUmUmCmGmUmUmU*mC*mU
425	ACAGACGCGG CCAATCAGAG GCCACGCACG AGGGTGAGGC AAGTCCGCCT CTCGGGAGGC AAGGGTGGGG GTTCGGCGAA TGACGTGAGG CGCCGCTGGG CGGTAGGGAG TAGACGCCCT CGGTCTCCG TCTCGCCCTG CAGCTTCCGG GTGTGCGGCT GCGGCCATTT TGAGCTTCGC TTCTTTGCGC CCTCGCCTGC CACCCAGCCA CCCTTTCGCG CTTGGCGTTT CGCGCCTCCG TGCGGGCCAC CGGAAACGCC GCCGTCGTCT CCGTCGCCGC CGCGCGAGGG AGGGTCTTCT CTATGGTGGA GCGATCTCAC ACGGCCTAGG ACGTCTCCTT CCCTAGCCGG GATGGACCTA ACCGCGGTCTG CCACCGCTTG CGCGGGCCTC TGGGCCGTCC GGTGCAGCAC TCGTTGCGGA AGCCGCCGCT CTCTGGGCCT CCTCTGCCGG CGCGGGAATC GGA CTG CAGT ACCCACTCCG TGGCTGGGCA AGGCGGAGAC TGTGTAGACC TCGGATCCAG CCTGCGCTGA CGCCGCTGAG CTCTGTCTC CTCTGTCTG AGAAGCCGCC AAGGAAAGGA GATGGAGACA GGAACGCACA GGGCCCCGGA GCGGCCTGGC CCTCGGCTGG GCTCCTGGTT CCGGCTGCCC TTCCTTCGGC GATCGCACGC CTGCTCTTCG GAGTTCCCGC CGCCTTCCTC TCGACAAAAT CCCGGGAACT CCGCTCTGCC CGAGCGTCGG ACCAGGTACT GGACCAAATT GCTTCTCAG CTCCTTGCCC TGCTCCCTAG CCTATTCCAG AAGCTGCTGC TTTGGAGCCA GCTTTTCGGG GGCCTGATTC CTACCAGATG GCTAGATTTT GCCGCAAGTT ACAGCGCCCT GAGAGCTTTG AGAGGACGGG AGGAATCTGC CGCTCCACAG GTGCAGAAGT CTCTGAGTTC ACTGCGGCTG GACTCTTCGG AAGACTTGGT TGTCAGTTCT CTTGATTGGC TAGAGGAGGG ACTCCAGTGG CAGTGCTCGT CCTCAGACCT GGAGTTAAAA CTCAAGGCCC AGGAAAGAGC TTTAGACTCT GCAGCGCCCA CTTTCCTCCT GGAGCAGCAG CTGTGGGGAG TGGAGTTGCT GCCCAGTAGC CTTCAAGCTG GTCTAGTCTC CCACCGAGAA CTTGACTCTT CATCCTCTGG GCCTCTGAGC GTTCAGAGCT

TAGGTAATTT CAAGGTAGTT TCCTATCTCC TGAACCCCTTC CTACCTGGAC
 TACCTTCCCC AGTTAGGGCT GCGCTGTCAG AGCAGCGCTG GAGGTGGCCA
 GTTTGTGGGT TTCCGAACAC TAACCCCAAG GAGCTGCTAT CTTTCTGAAG
 ATGGTTGTCA CCCTCAGCCG TTGCGGGCAG AGATGTCGGC AACCGCCTGG
 AGAAGGTGTC CGCCTCTCTC TACAGAAGGC CTGCCGGAAG TCCACCACCT
 TCGTATGAAA CGGCTAGAAT TCCTCCAGGC TAACAAAGGG CAAGAGTTAC
 CCACCCCTGA CCAAGATAAT GGCTATCATA GCCTGGAGGA GGAACATAAC
 CTTCTCCGGA TGGACCCACA ACATTGCACA GATAACCCAG CACAGGCGGT
 GTCCCCTGCT GCAGACAGGC CGGAGCCAC TGAGAAAAAA CCAGAATTGG
 TGATTCAAGA AGTTTCACAG AGCCCCCAGG GAAGCAGTCT GTTTTGTGAA
 TTACCCGTGG AAAAAGAATG TGAAGAGGAC CACACTAATG CAACTGACCT
 CTCAGATAGA GGAGAGAGCC TTCTGTGTTT TACCAGACCA GTTTGTAGCA
 ACAAAGTAT AGATTATAAT TTGGGAGGCG CCCCCAGTGA CTTGGAAGCC
 AGCTCTGATT CTGAAAGTGA GGATTGGGGC GAGGAACCTG AGGACGATGG
 CTTTGATAGC GATGGCTCCC TGTCTGAATC AGACGTGGAA CAGGACTCGG
 AAGGCCTTCA CTTTGGGAAC TCTTCCACA GTGTAGATCC TTACAACCCC
 CAAAAGTTA CAGCCACGAT TCAGACGGCT GCCAGAATTG CCCCCAGAGA
 CCCATCAGAT TCAGGGACAT CCTGGTCTGG CAGCTGTGGT GTAGGGAGCT
 GTCAGGAGGG ACCCCTTCCG GAGACCCCCG ACCATAGTTC CGGGGAGGAA
 GATGACTGGG AACCGAGTGC AGATGAAGCA GAGAATCTTA AATTGTGGAA
 CTCTTTCTGT CATCTGAGG ACCCTACAA CTTTTAAAT TTTAAGGCTC
 CTTTCAACC GTCAGGGAAG AATTGGAAAG GCCGTCAGGA CTCAAAGGCC
 TCTCTGAGG CTACAGTGGC CTCTCTGGC CATCATACCT TACTTTCTTG
 TAAGGCCCAG CTGTTAGAGA GCCAAGAAGA TAATTGTCCA GGCTGTGGGC
 TGGGTGAGGC TCTTGCTGGA GAAAGATACA CCCATATCAA GAGAAAAAAG
 GTAACCTTCC TGGAAGAAGT TACTGAGTAT TATATAAGTG GTGATGAGGA
 TCGCAAAGGA CCATGGGAAG AATTGCAAG GGATGGATGC AGGTTCCAGA
 AACGAATTCA AGAAACAGAA GTTGCCATTG GCTACTGCTT GGCCTTTGAG
 CACAGAGAAA AAATGTTTAA TAGACTGAGG ATCGAGTCAA AGGACTTACT
 GTTGTACAGC AATGTTAAGA AGTGAACAGC CTGCAACCCG TGCCCACTCT
 GTCTCTTACT TGAGAGTTTC CCTTAAAAAC AAACACTGGC AGCTGTCCTT
 GGACATGTTT TTAAGAAAC AACTTGTATC TAGAGATGCA GTTTGATTAT
 TTTTGGGTAA TGTGTCTCAT TAGAAACACC AACTCCGATA ATGAAGAATC
 TCTTATCTGT AATCCTCTCT TTTCCTAATT AGTTGGATGT GGGTTTTGTC
 TTTTGGAGAG GGTCTCACTG CATAATTCCTG TTGGCCTAG GTCTATGTAT
 GTAGACCAGG TTGGCCTTGA AGTTGGTATT TCCTTGCCCTC GTTTTCTGT
 GCCACCATGC CCAGCTGGAA GTGTTTTTAA ATATCCTCTG CTTACCTGGG
 GTGAGAGTTT AATTTTGAC TTTCAAAACG TTTCTTCTGG AGGCAGGGGC
 TGGTCTGGTT TACATACAGG CTTAGGCCA GCTAGGGCTA TGTGGTGAGA
 CTAGTCTTA GAGGACAAAC AGAACAAAC AGTCAGGTTA CTGTGGAAC
 TGAGGCAGGA GGATAGGAAG GTCCAGGTAT GCCTGGAAC CAGTGAACCTC
 TGAACCTAAG GCCAGCATGG GGAGTTTAGC AAGACCTTTT TACACTCAGA
 ATGGAAAAGG AAGCTGGGA TATAGCTCGG TAGCAGAGGC CCCTGCCTAC
 ATGTGCAAGG TCCTGGGTTT AGTCCCCAGT ACTGCAAATA GAAAGAAAAA
 ACATTGTCTT GGATAACTAT AAGGTTTAA CCTCATAGTC AGTTCTAACT
 CAAATTATGC ATGCATTGAG TTCTTGTGTG CTTTTCTGT TCTAAAATTA
 ATGGGCTTTA TGGGTTTTGT TTTTGTATGT TTTTATGTCT GTTATATTT
 GAGGTAGGGG ATTGAGGCAG GGTCTCACTG TGGCCTTGAG CTCATGGCAG
 TTTTCTGCT TCAACTGAGT GTTTTGGTTT GTTTGTGTTT GTGTTTTTT
 ACTTTCATAG ATTTGACTTA ATGAAGGCAA AAACCTGTTA TCAACCTAAA
 AGACATTGAT GTGTCACCTC AGTGGTGGAT TTTCTCCCTC TTTTTTTTT

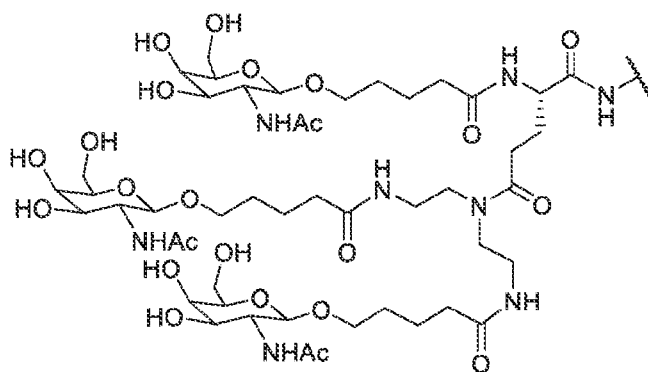
TCCCCAGAG CTGAGGACCA AACCCAGGGC TTTGCACTTG CTAGGCAAGC
GCTCTACCAC TGAGCTAAAT CCCCCAACCA CCCCCCCCCC TTTTCTTTT
TTAAAGACAT GGTCTTATAT AGTCTAGGCT GGCCTTAAAC TCATTACTTA
GCCAAGGATG GCTTTGAAAG ATCCTCCTGT CCTCTTGTTT GGCTTGCACA
TGGCATGTGC CATACTCCA GATTTTCTC TGTATCTAGG TCTTTTAAAG
ATATTTCCAA GGACTGCCA CAAATCCACA GTGCAGTACT TTCTTGACTG
GGAAAGCGGG GTTGGTGTGC TTTTCAAAGG CACACACCAT TATGCCCAGC
TGGTCTGCCA AACTTAACAT ATTTGGTTTC TGTGCAAAC GTCCATTGG
AAGGTTTCTG TGTGTTGTAG TTTCACTTGA ATGTGGCTCT CTGTAGCTTT
CAAGAATGGG TAGAAATCAT AAAGCACTCT TAAGTAATCA TTGCATTGTA
GACATTTTTT TTTTAACTA GGGGGTATTT GGGAGACATG TCAGATATTC
ACTTTTGTTT TATGTGCTT AAAACCAGTG TTAATTACAC CCTGCCCTCAG
CACTGGCACT TTTCAAACCT GTCCTGGAGA CACTGTAAAC TTGGATGGTG
CAGTTCTGGG TTTTCATGTG TAAAATGTCA ACTACAAAGG TCAATATCCA
GGTTTGTGT GTTCTACCTT ATGTAGAGAG AAGCAAAGCA GAAAGGGCAG
ATAGAGCAGC CAGAAAGTGC TAGTGTCCCC CCCCCAAGCG TGCTTCTAGA
TAGTGTGTGG ATCAGGTGTG CTGGTTTGT TCAGTTAGCG TCACCTGTTG
TGCATGGTTG AGGTAATGTG TTACCAGTTC TTTAGTGGTT ACATGCACAA
AAGAGAGGAC CTCTGAGTCG GGTGTGGGAT GAGCTTTCCA GACCTGGCAG
GGTAAACTAC CTCAGTTTAT AATCTCCCTG GTTATTTCG TTTGATGTGA
TCTAAGGTCT GCCTCAGTGG TGATGATGTT CATCCACACA CAAGGTTAGT
AAGAGTGCAC GACCAGAAAC GTTGGTCTTA TTTTGAGAA CCCCCATTTC
TGTTATTTT ATGCACCTGC CTTTAGTGAA CTCCAGAGTG CATTAAAGAG
TCTGGTTTAG TGCCGTGGGA ATGGGCTAGT TTAGAAGCTA TGTTTGGAAA
GCAGGCAAGT TGACTTTAGG AAGAAAAGCT GTGACAGTGT GTAGACATTT
CTTTTAAACC GGACTGCAGC TTAACAACAC TTGATTTTCTG ATGATTAGGT
TTTTGTTTCT GAGACCCAGC ACCTGTATAT TAAAAATTG TTCCAGATTA
CACCTTCACT ATCAAATGAG TAAATGACTC ATGCCTGCAG ACATGTCTTG
ATGGTGGCAA GAACAGAAGG ATCTTTGACT GAAGGAGAAA AACTGTCAAT
GTCATCCCAG CCCCCAGGAA AGAACACCTC CAAGGCAGGC AGGCAGGCAG
GCAGGCATGG TGGTTCTAGT TGAATACACA TTCAAGTCTT GCAGTGGTGC
TTTAGATCTG TGTAGCATGT GAGGCTCTGT ACAGGTGGGG GCCACACTTC
TGAGGGCTGA AATGTGGCAA CCCTTTATCT AACTTGAAAT CAAAACCGTC
AAATTTTATT TTTTATAATT TAAGAAAGAG TTGGGGAATG ACATTTTGTG
AGTTGGCCTT TTCAGCTCAG TCAATTTACG TGTAACGTGG AGATTTGATA
GCTCAGATTA TATTTGTATA TAATTATTAA CTAATCTGTA AATTGTAATA
AATATATTTG CAATTATTAA ATGCTATGTG ACTTTATG

CLAIMS

1. A PPP1R15B RNAi agent comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex, wherein the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.
2. The PPP1R15B RNAi agent of claim 1, wherein the sense strand is linked to a delivery moiety.
3. The PPP1R15B RNAi agent of claim 2, wherein the delivery moiety is linked to the 3' end of the sense strand, optionally via a linker (L).
4. The PPP1R15B RNAi agent of any one of claims 2-3, wherein the delivery moiety comprises a N-acetylgalactosamine (GalNAc) moiety.
5. The PPP1R15B RNAi agent of any one of claims 2-4, wherein the delivery moiety comprises the Formula of:



6. A PPP1R15B RNAi agent comprising the Formula of: R-L-D,
 wherein R is a double stranded RNA (dsRNA) comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to PPP1R15B mRNA,
 wherein L is a linker, or optionally absent, and
 wherein D is a delivery moiety comprising the Formula of:



7. The PPP1R15B RNAi agent of claim 6, wherein the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 2-80, wherein optionally one or more nucleotides of the sense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand are modified internucleotide linkages.
8. The PPP1R15B RNAi agent of claim 6, wherein the sense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 81-159, and the antisense strand comprises a nucleic acid sequence selected from any one of SEQ ID NOs: 160-238, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.
9. The PPP1R15B RNAi agent of any one of claims 1-8, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 1-79, wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified

nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

10. The PPP1R15B RNAi agent of any one of claims 1-9, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:
- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 93, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 172;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 123, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 202;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 125, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 204;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 129, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 208;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 132, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 211;
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 136, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 215; and
 - (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 157, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 236,

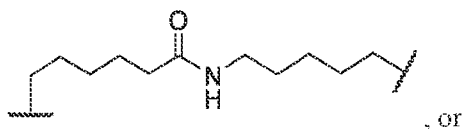
wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

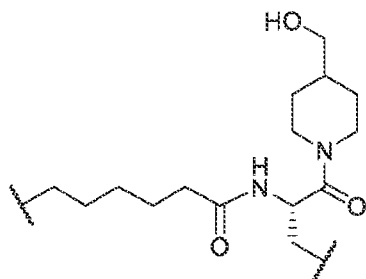
11. The PPP1R15B RNAi agent of any one of claims 1-10, wherein one or more nucleotides of the sense strand are modified nucleotides.
12. The PPP1R15B RNAi agent of claim 11, wherein each nucleotide of the sense strand is a modified nucleotide.

13. The PPP1R15B RNAi agent of any one of claims 1-12, wherein one or more nucleotides of the antisense strand are modified nucleotides.
14. The PPP1R15B RNAi agent of claim 13, wherein each nucleotide of the antisense strand is a modified nucleotide.
15. The PPP1R15B RNAi agent of any one of claims 11-14, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, 2' deoxy nucleotide (DNA), or 2'-O-alkyl modified nucleotide.
16. The PPP1R15B RNAi agent of any one of claims 11-15, wherein the sense strand has four 2'-fluoro modified nucleotides at positions 7, 9, 10, and 11 from the 5' end of the sense strand.
17. The PPP1R15B RNAi agent of claim 16, wherein nucleotides at positions other than positions 7, 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides.
18. The PPP1R15B RNAi agent of any one of claims 11-17, wherein the antisense strand has four 2'-fluoro modified nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand.
19. The PPP1R15B RNAi agent of claim 18, wherein nucleotides at positions other than positions 2, 6, 14 and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
20. The PPP1R15B RNAi agent of any one of claims 11-15, wherein the sense strand has three 2'-fluoro modified nucleotides at positions 9, 10, and 11 from the 5' end of the sense strand.
21. The PPP1R15B RNAi agent of claim 20, wherein nucleotides at positions other than positions 9, 10, and 11 of the sense strand are 2'-O-methyl modified nucleotides.
22. The PPP1R15B RNAi agent of any one of claims 11-17 and 20-21, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand.

23. The PPP1R15B RNAi agent of claim 22, wherein nucleotides at positions other than positions 2, 5, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
24. The PPP1R15B RNAi agent of any one of claims 11-17 and 20-21, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand.
25. The PPP1R15B RNAi agent of claim 24, wherein nucleotides at positions other than positions 2, 5, 8, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
26. The PPP1R15B RNAi agent of any one of claims 11-17 and 20-21, wherein the antisense strand has five 2'-fluoro modified nucleotides at positions 2, 3, 7, 14, and 16 from the 5' end of the antisense strand.
27. The PPP1R15B RNAi agent of claim 26, wherein nucleotides at positions other than positions 2, 3, 7, 14, and 16 of the antisense strand are 2'-O-methyl modified nucleotides.
28. The PPP1R15B RNAi agent of any one of claims 1-27, wherein the sense strand and the antisense strand have one or more modified internucleotide linkages.
29. The PPP1R15B RNAi agent of claim 28, wherein the modified internucleotide linkage is phosphorothioate linkage.
30. The PPP1R15B RNAi agent of claim 28 or 29, wherein the sense strand has four or five phosphorothioate linkages.
31. The PPP1R15B RNAi agent of any one of claims 28-30, wherein the antisense strand has four or five phosphorothioate linkages.
32. The PPP1R15B RNAi agent of any one of claims 1-31, wherein the antisense strand has 5' phosphate or 5' vinylphosphonate.

33. The PPP1R15B RNAi agent of any one of claims 1-32, wherein the sense strand comprises an abasic moiety or inverted abasic moiety.
34. The PPP1R15B RNAi agent of any one of claims 1-15 or 28-33, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences of the sense strand and the antisense strand of any one of dsRNA No. 80-186.
35. The PPP1R15B RNAi agent of any one of claims 1-15 or 28-34, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:
- (a) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 251, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 340;
 - (b) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 281, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 370;
 - (c) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 283, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 372;
 - (d) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 287, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 376;
 - (e) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 290, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 379;
 - (f) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 294, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 383; and
 - (g) the sense strand comprises a first nucleic acid sequence of SEQ ID NO: 315, and the antisense strand comprises a second nucleic acid sequence of SEQ ID NO: 404.
36. The PPP1R15B RNAi agent of any one of claims 3-35, wherein L (linker) is present and comprises any one of the following Formulas:





37. A pharmaceutical composition comprising the PPP1R15B RNAi agent of any one of claims 1-36 and a pharmaceutically acceptable carrier.
38. A method of treating a PPP1R15B associated metabolic disorder in a patient in need thereof, the method comprising administering to the patient an effective amount of the PPP1R15B RNAi agent of any one of claims 1-36, or the pharmaceutical composition of claim 37.
39. The method of claim 38, wherein the PPP1R15B associated metabolic disorder is obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome.
40. The method of claim 38 or 39, wherein the PPP1R15B RNAi agent or the pharmaceutical composition is administered to the patient intravenously or subcutaneously.
41. The method of any one of claims 38-40 further comprising administering a second therapeutic agent to the patient.
42. The method of claim 41, wherein the second therapeutic agent is an incretin.
43. A method of reducing PPP1R15B expression in a cell, the method comprising:
introducing the PPP1R15B RNAi agent of any one of claims 1-36 into the cell; and
incubating the cell for a time sufficient for degradation of PPP1R15B mRNA, thereby reducing PPP1R15B expression in the cell.

44. The PPP1R15B RNAi agent of any one of claims 1-36, or the pharmaceutical composition of claim 37, for use in a therapy.
45. The PPP1R15B RNAi agent of any one of claims 1-36, or the pharmaceutical composition of claim 37, for use in the treatment of a PPP1R15B associated metabolic disorder.
46. The PPP1R15B RNAi agent or pharmaceutical composition for use of claim 45, wherein the PPP1R15B associated metabolic disorder is obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome.
47. Use of the PPP1R15B RNAi agent of any one of claims 1-36 in the manufacture of a medicament for treating a PPP1R15B associated metabolic disorder.
48. The use of claim 47, wherein the PPP1R15B associated metabolic disorder is obesity, Type 2 diabetes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), dyslipidemia, or metabolic syndrome.
49. The PPP1R15B RNAi agent for use of any one of claim 45-46 or the use of any one of claims 47-48 further comprising administering a second therapeutic agent to the patient.
50. The PPP1R15B RNAi agent for use or the use of 49, wherein the second therapeutic agent is an incretin.

Figure 1

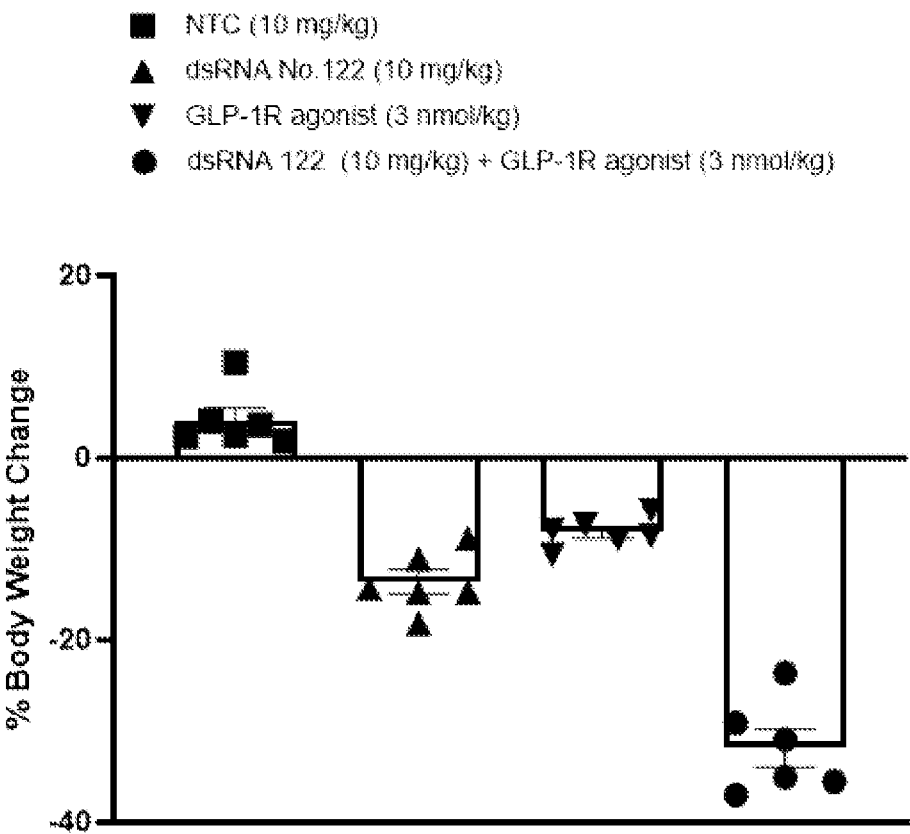
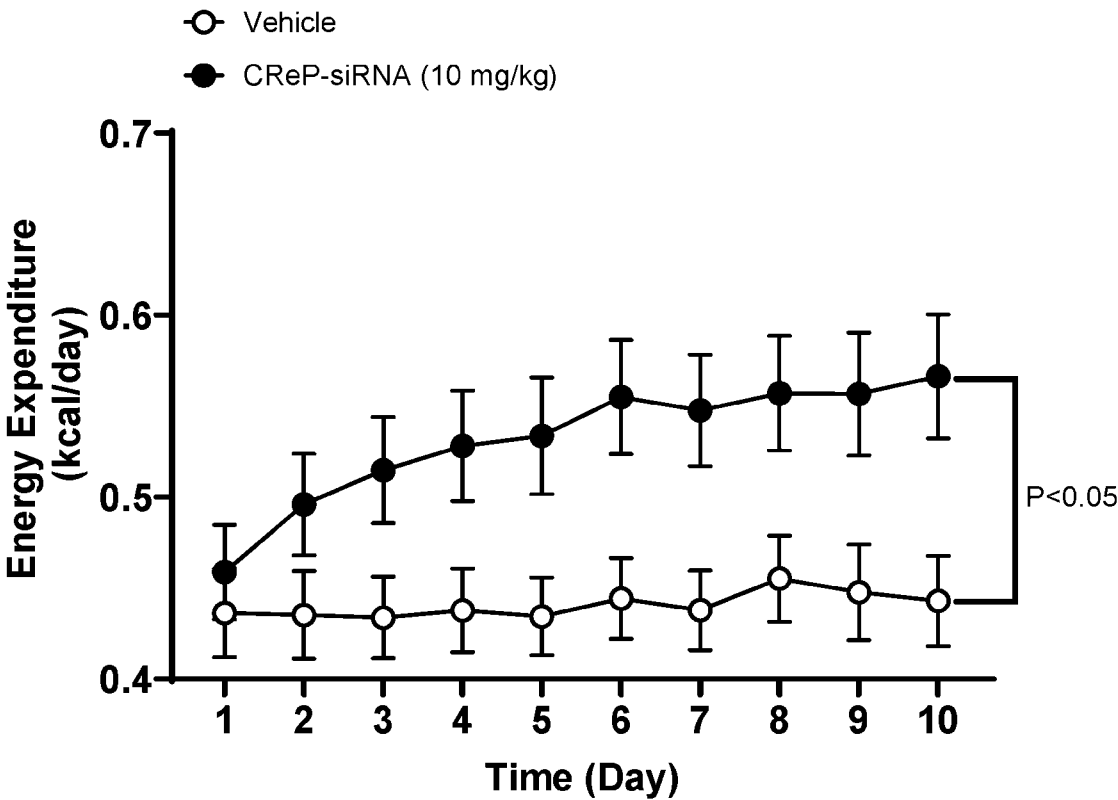


Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/048763**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C12N15/113

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ABDULKARIM BAROJ ET AL: "A Missense Mutation in PPP1R15B Causes a Syndrome Including Diabetes, Short Stature, and Microcephaly", DIABETES, vol. 64, no. 11, 1 November 2015 (2015-11-01), pages 3951-3962, XP093077206, ISSN: 0012-1797, DOI: 10.2337/db15-0477	1-4, 7-9, 34, 36-50
Y	figures 5,6 - / - -	5, 6, 11-33



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 December 2024

Date of mailing of the international search report

25/02/2025

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040,

Fax: (+31-70) 340-3016

Authorized officer

Romano, Alper

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/048763

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	- & Abdulkarim Baroj ET AL: "Supplementary Data: A Missense Mutation in PPP1R15B Causes a Syndrome Including Diabetes, Short Stature, and Microcephaly", Diabetes, 9 July 2015 (2015-07-09), pages 1-7, XP093232495, DOI: 10.2337/db15-0477 Retrieved from the Internet: URL: https://ada.silverchair-cdn.com/ada/content_public/journal/diabetes/64/11/10.2337_db15-0477/3/db150477supplementarydata.pdf table supp. table 2 -----	
A	MARIA SHAHMORADGOLI ET AL: "Protein phosphatase 1, regulatory subunit 15B is a survival factor for ER[alpha]-positive breast cancer", INTERNATIONAL JOURNAL OF CANCER, JOHN WILEY & SONS, INC, US, vol. 132, no. 11, 27 December 2012 (2012-12-27), pages 2714-2719, XP071287499, ISSN: 0020-7136, DOI: 10.1002/IJC.27945 figures 2-4 -----	1-9, 11-34, 36-50
A	KHAN RUKSHAR ET AL: "mir-98-5p regulates gluconeogenesis and lipogenesis by targeting PPP1R15B in hepatocytes", JOURNAL OF CELL COMMUNICATION AND SIGNALING, vol. 17, no. 3, 14 March 2023 (2023-03-14), pages 881-895, XP093232069, NL ISSN: 1873-9601, DOI: 10.1007/s12079-023-00735-0 figures 5,6 -----	1-9, 11-34, 36-50
Y	WO 2022/271806 A1 (LILLY CO ELI [US]) 29 December 2022 (2022-12-29) cited in the application page 2 -----	5,6, 11-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/048763

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/048763

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-9, 11-34, 36-50 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 11-34, 36-50 (all partially)

RNAi agent targeting PPP1R15B wherein the sense strand comprises SEQ ID NO:81 and antisense strand comprises SEQ ID NO:160.

2-79. claims: 1-50 (partially)

RNAi agents targeting PPP1R15B wherein the sense strand comprises SEQ ID NO:82-159 and antisense strand comprises SEQ ID NO:161-238

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/048763

Patent document cited in search report			Publication date		Patent family member(s)			Publication date	
WO 2022271806	A1	29-12-2022	AU	2022299173	A1	18-01-2024			
			CA	3224134	A1	29-12-2022			
			CL	2023003883	A1	15-11-2024			
			CN	117858948	A	09-04-2024			
			CO	2023018231	A2	25-01-2024			
			CR	20240003	A	25-01-2024			
			DO	P2023000285	A	15-02-2024			
			EC	SP23096498	A	31-01-2024			
			EP	4359529	A1	01-05-2024			
			IL	309503	A	01-02-2024			
			JP	2024522852	A	21-06-2024			
			KR	20240023631	A	22-02-2024			
			US	2024327839	A1	03-10-2024			
			WO	2022271806	A1	29-12-2022			
