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(71) Applicant: **DICERNA PHARMACEUTICALS, INC.** [US/US]; 75 Hayden Avenue, Lexington, Massachusetts 02421 (US).

(72) Inventors: **SAXENA, Utsav**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **DUDEK, Henryk T.**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **ABRAMS, Marc**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **TURANOV, Anton**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US). **BROWN, Bob Dale**; c/o Dicerna Pharmaceuticals, Inc., 75 Hayden Avenue, Lexington, Massachusetts 02421 (US).

(74) Agent: **REID, Andrea L.C.** et al.; c/o Dechert LLP, One International Place, 40th Floor, 100 Oliver Street, Boston, Massachusetts 02110-2605 (US).

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(54) Title: COMPOSITIONS AND METHODS FOR MODULATING PNPLA3 EXPRESSION

(57) Abstract: Oligonucleotides and compositions including the same are disclosed for inhibiting or reducing patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene expression. Methods of making and using the oligonucleotides also are disclosed, particularly uses relating to treating diseases, disorders and/or conditions associated with *PNPLA3* expression.

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COMPOSITIONS AND METHODS FOR MODULATING PNPLA3 EXPRESSION

SEQUENCE LISTING

[000] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 11, 2022, is named 400930-028WO_190156_SL.txt and is 374,357 bytes in size.

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] The present application claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Application No. 63/174,932, filed April 14, 2021, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[002] The disclosure relates generally to biology and medicine, and more particularly it relates to the use of oligonucleotide compositions for inhibiting or reducing patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene expression, as well as to uses thereof, particularly uses relating to treating diseases, disorders and/or conditions associated with PNPLA3.

BACKGROUND

[003] PNPLA3 is a protein encoded by *PNPLA3* and is a protein having triacylglycerol lipase and acylglycerol transacylase activities. Human *PNPLA3* is expressed highly in the liver and moderately in the adipose tissue, brain, kidney, and skin.

[004] Of particular interest herein is a mutation of an isoleucine (Ile/I) to a methionine (Met/M) at position 148 in human PNPLA3 (I148M or PNPLA3 148M; *i.e.*, PNPLA3 rs738409). *See*, Pingitore & Romeo (2019) BIOCHIM. BIOPHYS. ACTA MOL. CELL BIOL. LIPIDS 1864:900-906. Compared to wild-type PNPLA3, PNPLA3 148M lacks lipase activity but appears to have increased transacylase activity. *See*, Kumari *et al.* (2012) CELL METAB. 15:691-702.

[005] PNPLA3 148M is strongly associated with a wide spectrum of liver diseases resulting from triglyceride (TG) accumulation, liver injury and fibrosis, including alcoholic hepatitis

(AH), alcoholic liver disease (ALD), cirrhosis, hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). It appears that PNPLA3 148M degradation by proteasomes is delayed, which results in an accumulation of the protein on the surface of lipid droplets and which does not allow other proteins to metabolize TGs in hepatocytes. As such, reducing PNPLA3 148M expression may allow other lipases to function normally and reverse the adverse effects of PNPLA3 I148M across a variety of pathologies.

[006] Several RNA-based therapeutics are known for attempting to inhibit or reduce *PNPLA3* expression. For example, Intl. Patent Application Publication Nos. WO 2016/130806 and WO 2019/118638 describe double-stranded (ds) RNAi constructs for inhibiting or reducing *PNPLA3* expression, as well as methods of using the same for treating or preventing liver diseases such as NAFLD. Also, Intl. Patent Application Publication No. WO 2020/061200 describes antisense oligonucleotides for inhibiting or reducing *PNPLA3* expression.

[007] Despite the existence of some therapeutics directed toward *PNPLA3*, there is a need for additional therapeutics for inhibiting or reducing *PNPLA3* expression for treating liver disease.

BRIEF SUMMARY

[008] To address this need, the disclosure describes compositions and methods for treating a disease, disorder, and/or condition related to *PNPLA3* expression. The disclosure is based, in part, on discovering and developing ds oligonucleotides (*e.g.*, RNAi oligonucleotides) for selectively inhibiting and/or reducing *PNPLA3* expression in, for example, the liver. Accordingly, target sequences within *PNPLA3* have been identified, and RNAi oligonucleotides that bind to these target sequences and inhibit PNPLA3 mRNA expression have been generated. As shown herein, the RNAi oligonucleotides inhibit human and cynomolgus monkey *PNPLA3* expression in the liver. Without being bound by theory, the RNAi oligonucleotides herein are useful for treating a disease, disorder or condition associated with *PNPLA3* expression (*e.g.*, liver disease such as AH, ALD, cirrhosis, HCC, cholangiocarcinoma (CCA), primary sclerosing cholangitis (PSC), NAFLD, and NASH). In general, the RNAi oligonucleotides herein are useful for treating a disease, disorder, or condition associated with aberrant *PNPLA3* expression (*e.g.*, mutant *PNPLA3* allele

expression). In particular, the RNAi oligonucleotides herein are useful for treating a disease, disorder, or condition associated with mutant *PNPLA3* expression.

[009] Accordingly, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes a sense strand having a sequence as set forth in Table 1 (*e.g.*, SEQ ID NOs: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, and 775) or Table 3 (*e.g.*, SEQ ID NOs: 777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 809, 811, 813, 815, 817, 819, 821, 823, 825, 827, 829, 831, 833, 835, 837, 839, 841, 843, 845, 847, 849, 851, 853, 855, 857, 859, 861, 863, 865, 867, 869, 871, 873, 875, 877, 879, 881, 883, 885, 887, 889, 891, 893, 895, 897, 899, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, 945, 947, 949, 951, 953, 955, 957, 959, 961, 963, 965, 967, 969, 971, 973, 975, 977, 979, 981, 983, 985, 987, 989, 991, 993, 995, 997, 999, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, 1023, 1025, 1027, 1029, 1031, 1033, 1035, 1037, 1039, 1041, 1043, 1045, 1047, 1049, 1051, 1053,

1055, 1057, 1059, 1061, 1063, 1065, 1067, 1069, 1071, 1073, 1075, 1077, 1079, 1081, 1083, 1085, 1087, 1089, 1091, 1093, 1095, 1097, 1099, 1101, 1103, 1105, 1107, 1109, 1111, 1113, 1115, 1117, 1119, 1121, 1123, 1125, 1127, 1129, 1131, 1133, 1135, 1137, 1139, 1141, 1143, 1145, 1147, 1149, 1151, 1153, 1155, 1157, 1159, 1161, and 1163), especially any one of SEQ ID NOs: 787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163.

[0010] Alternatively, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes an antisense strand having a sequence as set forth in Table 1 (*e.g.*, SEQ ID NOs: 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, and 776) or Table 3 (*e.g.*, SEQ ID NOs: 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954,

956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 1000, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, 1024, 1026, 1028, 1030, 1032, 1034, 1036, 1038, 1040, 1042, 1044, 1046, 1048, 1050, 1052, 1054, 1056, 1058, 1060, 1062, 1064, 1066, 1068, 1070, 1072, 1074, 1076, 1078, 1080, 1082, 1084, 1086, 1088, 1090, 1092, 1094, 1096, 1098, 1100, 1102, 1104, 1106, 1108, 1110, 1112, 1114, 1116, 1118, 1120, 1122, 1124, 1126, 1128, 1130, 1132, 1134, 1136, 1138, 1140, 1142, 1144, 1146, 1148, 1150, 1152, 1154, 1156, 1158, 1160, 1162, and 1164), especially any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164.

[0011] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes a sense strand having a sequence as set forth in Table A, B , C or D (*e.g.*, SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300).

[0012] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes an antisense strand having a sequence as set forth in Table A, B , C or D (*e.g.*, SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301).

[0013] In some embodiments, RNAi oligonucleotides are described for reducing or inhibiting *PNPLA3* expression that include an antisense strand and a sense strand, where the antisense strand has a sequence as set forth in Table 1 or Table 3, and where the sense strand has a sequence as set forth in Table 1 or Table 3.

[0014] In some embodiments, RNAi oligonucleotides are described for reducing or inhibiting *PNPLA3* expression that include an antisense strand and a sense strand, where the antisense strand has a sequence as set forth in Table A, Table B, Table C, or Table D, and where the sense strand has a sequence as set forth in Table A, Table B, Table C, or Table D.

[0015] In some embodiments, RNAi oligonucleotides are described for reducing or inhibiting *PNPLA3* expression that include an antisense strand and a sense strand, where the

antisense and sense strands form a duplex region, and where the antisense strand has a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176.

[0016] In any of the embodiments above, the antisense strand is from about 15 nucleotides to about 30 nucleotides in length. In some embodiments, the antisense strand is from about 20 nucleotides to about 25 nucleotides. In some embodiments, the antisense strand is 22 nucleotides in length.

[0017] In any of the embodiments above, the sense strand is from about 15 nucleotides to about 50 nucleotides in length. In some instances, the sense strand is from about 20 nucleotides to about 40 nucleotides in length. In some embodiments, the sense strand is 36 nucleotides in length.

[0018] In any of the embodiments above, the duplex region is from about 19 nucleotides in length to about 21 nucleotides in length. In certain embodiment, the duplex region is 20 nucleotides in length.

[0019] In any of the embodiments above, the region of complementarity is at least 15 contiguous nucleotides in length. In some embodiments, the region of complementarity is from about 19 contiguous nucleotides in length to about 21 contiguous nucleotides in length. In other embodiments, the region of complementarity is 19 contiguous nucleotides in length or 21 contiguous nucleotides in length.

[0020] In any of the embodiments above, the RNAi oligonucleotides include on the sense strand a 3' end a stem-loop set forth as: S1-L-S2, where S1 is complementary to S2, and where L forms a loop between S1 and S2 of about 3 to about 5 nucleotides in length.

[0021] In any of the embodiments above, the antisense strand, the sense strand, or both have an overhang sequence. In some embodiments, the antisense strand includes a 3'-overhang of 1 or more nucleotides in length. In other embodiments, the 3'-overhang sequence is 2 nucleotides in length such as, for example, GG.

[0022] Oligonucleotides also are described that include an antisense strand and a sense strand, where the antisense strand can be from about 21 nucleotides to about 27 nucleotides in length and has a region of complementarity to *PNPLA3*, wherein the sense strand includes a stem-loop at its 3' end set forth as: S1-L-S2, wherein S1 is complementary to S2, wherein L forms a loop between S1 and S2 from about 3 nucleotides to about 5 nucleotides in length, and

wherein the antisense strand and the sense strand form a duplex structure of at least about 19 nucleotides in length but are not covalently linked.

[0023] In some embodiments, the loop L is a triloop or a tetraloop. In some instances, L is a tetraloop of 4 nucleotides in length. In other embodiments, L includes a sequence 5'-GAAA-3'.

[0024] In some embodiments, S1 and S2 are 1-10 nucleotides in length and have the same length. In other embodiments, S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length. In other embodiments, S1 and S2 are 6 nucleotides in length. In certain embodiments, the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:1177).

[0025] In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length. In other embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 36 nucleotides in length.

[0026] In the embodiments above, the duplex region includes a 3'-overhang sequence on the antisense strand. In some embodiments, the 3'-overhang sequence on the antisense strand is 2 nucleotides in length.

[0027] In any of the embodiments above, at least one nucleotide in an oligonucleotide is a modified nucleotide. In some instances, the modified nucleotide includes a 2'-modification such as, for example, 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl and 2'-deoxy-2'-fluoro-β-arabinonucleic acid. In certain instances, all nucleotides in an oligonucleotide include a 2'-modification such as, for example, 2'-fluoro or 2'-O-methyl.

[0028] In any of the embodiments above, at least one nucleotide in an oligonucleotide includes a modified internucleotide linkage. In some embodiments, the modified internucleotide linkage is a phosphorothioate linkage.

[0029] In any of the embodiments above, a 4'-carbon of a sugar of a 5'-nucleotide of the antisense strand includes a phosphate analog such as, for example, an oxymethylphosphonate, vinylphosphonate or malonylphosphonate. Alternatively, or optionally, the phosphate analog is a 4'-phosphate analog including 5'-methoxyphosphonate-4'-oxy.

[0030] In any of the embodiments above, at least one nucleotide of an oligonucleotide can be conjugated to one or more targeting ligands such as, for example, an amino sugar, carbohydrate, cholesterol, lipid, or polypeptide. In some embodiments, the targeting ligand is

a N-acetylgalactosamine (GalNAc) moiety. In other embodiments, the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

[0031] In some embodiments, the targeting ligands are conjugated to one or more nucleotides of L of the stem loop. In certain instances, up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

[0032] In any of the embodiments above, the oligonucleotide is an RNAi oligonucleotide. In some instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table 1 or Table 3, especially any one of SEQ ID NOs: 787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163. In certain embodiments, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table A, B, C, or D, especially any one of SEQ ID NOs: 1188, 1190, 1220, 1224, 1230, 1232, 1244, 1246, 1250, or 1254. In some instances, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set for the in Table 1 or Table 3, especially any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164. In some embodiments, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set for the in Table A, B, C or D, especially any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251, or 1255. In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163, or any one of SEQ ID NOs: 1188, 1190, 1220, 1224, 1230, 1232, 1244, 1246, 1250, or 1254 and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164, any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251, or 1255. In certain embodiments, the sense strand and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

(a) SEQ ID NOs: 787 and 788,

(b) SEQ ID NOs: 843 and 844,

(c) SEQ ID NOs: 867 and 868,

(d) SEQ ID NOs: 871 and 872,

(e) SEQ ID NOs: 937 and 938,

(f) SEQ ID NOs: 1003 and 1004,

(g) SEQ ID NOs: 1007 and 1008,

(h) SEQ ID NOs: 1017 and 1018,

(i) SEQ ID NOs: 1161 and 1162, and

(j) SEQ ID NOs: 1163 and 1164.

[0033] In some instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table A, Table B, Table C, or Table D, especially any one of SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300. In some instances, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set for the in Table A, Table B, Table C, or Table D, especially any one of SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1202, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301. In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301.

[0034] In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1188, 1190, 1200, 1216, 1218, 1220, 1224, 1230, 1232, 1234, 1244, 1246, 1250, 1254, 1262, 1288, 1290, 1292, 1294, 1296, 1298, or 1300, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1189, 1191, 1201, 1215, 1217, 1219, 1225, 1231, 1233, 1235, 1245, 1247, 1251, 1255, 1263, 1289, 1291, 1295, 1297, 1299, or 1301.

[0035] In particular instances, the sense strand and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

(a) SEQ ID NOs: 1220 and 1221,

(b) SEQ ID NOs: 1224 and 1225,

(c) SEQ ID NOs: 1230 and 1231,

(d) SEQ ID NOs: 1232 and 1233,

(e) SEQ ID NOs: 1188 and 1189,

(f) SEQ ID NOs: 1190 and 1191,

(g) SEQ ID NOs: 1244 and 1245,

(h) SEQ ID NOs: 1250 and 1251-,

(i) SEQ ID NOs: 1254 and 1255, and

(j) SEQ ID NOs: 1246 and 1247.

[0036] Oligonucleotides also are described for inhibiting or reducing *PNPLA3* expression that include a sense strand and an antisense strand, where the sense strand and the antisense strand form a duplex region, where all nucleotides of the sense strand and the antisense strand include a modification of a base, a sugar and/or an internucleotide linkage, where the antisense strand includes a region of complementarity to a PNPLA3 mRNA target sequence of one of SEQ ID NOs: 1167 to 1176, and where the region of complementarity is at least about 15 contiguous nucleotides in length.

[0037] In other aspects, pharmaceutical compositions are described that include at least one oligonucleotide herein and a pharmaceutically acceptable carrier, delivery agent or excipient. In some instances, the pharmaceutical compositions include an additional therapeutic agent such as, for example, an antidiabetic agent or anti-obesity agent.

[0038] In other aspects, methods are described for reducing *PNPLA3* expression in a cell, a population of cells, a tissue, an organ, or an individual that include at least a step of administering/contacting the cell, the population of cells, the tissue, the organ, or the individual with an oligonucleotide herein or a pharmaceutical composition herein. In some instances, reducing *PNPLA3* expression includes reducing an amount or level of PNPLA3 mRNA, an amount or level of PNPLA3 protein, or both in the cell, the population of cells, the tissue, the organ, or the individual. In some instances, the cell, the cell population, the tissue, the organ, or the individual has a disease, disorder, or condition associated with *PNPLA3* expression. In certain instances, the disease, disorder, or condition associated with *PNPLA3* expression is a

cardiometabolic disease, AH, ALD, cirrhosis, HCC, CCA, and other cholangiopathies (such as PSC), NAFLD, and NASH.

[0039] In other aspects, methods are described for treating an individual having or suspected of having a disease, disorder or condition associated with *PNPLA3* expression. The methods include at least a step of administering to an individual in need thereof an effective amount of an oligonucleotide herein or a pharmaceutical composition herein. In some instances, the disease, disorder, or condition associated with *PNPLA3* expression is a cardiometabolic disease, AH, ALD, CCA, cirrhosis, HCC, NAFLD, PSC, and NASH. In some instances, the oligonucleotide or pharmaceutical composition is administered daily, weekly, monthly, quarterly, yearly *via* SQ administration, especially monthly or quarterly.

[0040] In some instances, the individual has cirrhosis, diabetes, hepatic fibrosis, hepatic inflammation, hyperlipidemia, AH, ALD, CCA, cirrhosis, HCC, NAFLD, PSC, NASH, obesity, and/or steatosis.

[0041] In any of the embodiments above, the methods comprise additional steps such as measuring or obtaining genotype information, *PNPLA3* expression, PNPLA3 protein levels, the individual's weight and/or blood glucose and/or TGs and comparing such obtained values to one or more baseline values or previously obtained values to assess the effectiveness of contacting or administering. In some embodiments, the additional step comprises confirming that the individual has a PNPLA3 I148M variant. In some embodiments, the additional step comprises confirming that the individual does not have a PNPLA3 E434K variant. In some embodiments, the additional step comprises confirming that the individual does not have a protein truncating HSD17B13 variant (rs72613567).

[0042] In any of the embodiments above, the methods can include administering the RNAi oligonucleotide or pharmaceutical composition simultaneously, separately, or sequentially with a second composition or a second therapeutic agent. In some embodiments, the second composition or a second therapeutic agent is a PNPLA3 antibody or fragment thereof, an antidiabetic agent or anti-obesity agent. In some embodiments, the second composition or second therapeutic agent is administered with a frequency same as the RNAi oligonucleotide (*i.e.*, every other day, twice a week, or even weekly). In other embodiments, the second composition or second therapeutic agent is administered with a frequency distinct from the RNAi oligonucleotide. Likewise, in other embodiments, the second composition or second therapeutic agent is administered *via* the same route as the RNAi oligonucleotide (*e.g.*, SQ).

In still other embodiments, the second composition or second therapeutic agent is administered *via* a route that differs from the RNAi oligonucleotide).

[0043] In other aspects, uses are described for the RNAi oligonucleotides herein for treating a disease, disorder or condition associated with *PNPLA3* expression, which optionally are administered simultaneously, separately, or sequentially (*i.e.*, in combination) with a second composition or second therapeutic agent.

[0044] In other aspects, uses are described for the RNAi oligonucleotides herein in manufacturing a medicament for treating a disease, disorder, or condition associated with *PNPLA3* expression, where the medicament optionally further includes a second composition or second therapeutic agent.

[0045] In other aspects, kits are described that include at least one oligonucleotide herein, an optional pharmaceutically acceptable carrier, and a package insert having instructions for administering the same to an individual having a disease, disorder, or condition associated with *PNPLA3* expression.

[0046] An advantage of the oligonucleotides and compositions herein is that suppressed *PNPLA3* expression, especially PNPLA3 148M, exerts a beneficial effect on the entire spectrum of NAFLD including fibrosis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0047] The advantages, effects, features, and objects other than those set forth above will become more readily apparent when consideration is given to the detailed description below. Such detailed description refers to the following drawing(s), where:

[0048] FIG. 1 discloses a schematic depicting the structure and chemical modification pattern of a generic GalNAc-conjugated PNPLA3 oligonucleotide. FIG. 1 discloses SEQ ID NOS 1302-1303, respectively, in order of appearance.

[0049] FIG. 2 discloses a schematic depicting the structure and chemical modification pattern of an alternative generic GalNAc-conjugated PNPLA3 oligonucleotide.

DETAILED DESCRIPTION

Overview

[0050] ALD and NAFLD are serious public health burdens. ALD and NAFLD are chronic liver disorders that begin with hepatic TG accumulation (steatosis) and progress to hepatic

inflammation and fibrosis, cirrhosis, and even liver cancer. PNPLA3 148M is a genetic factor that has been shown to be associated with ALD and NAFLD, as well, as cirrhosis, HCC, and liver-related death.

[0051] RNA interference (RNAi) is a process of introducing exogeneous RNA into a cell leading to specific degradation of the mRNA encoding the targeted protein with a resultant decrease in target gene expression.

[0052] In humans, PNPLA3 is 481 amino acids in length with a predicted molecular weight of 52.865 kD. Exemplary nucleic acid sequences for *PNPLA3* can be found in NCBI Ref. Seq. No. NM_025225 (human), NM_054088 or XM_006520346 (mouse), NM_001282324 (rat), XM_015457081 (primate), XM_005567051 (primate) and XM_001109144 (primate). One of skill in the art, however, understands that additional examples of PNPLA3 mRNA sequences are readily available using publicly available databases such as, for example, GenBank and UniProt.

Definitions

[0053] As used herein, "about" means within a statistically meaningful range of a value or values such as, for example, a stated concentration, length, molecular weight, pH, sequence similarity, time frame, temperature, volume, *etc.* Such a value or range can be within an order of magnitude typically within 20%, more typically within 10%, and even more typically within 5% of a given value or range. The allowable variation encompassed by "about" will depend upon the system under study, and can be readily appreciated by one of skill in the art.

[0054] As used herein, "administer," "administering," "administration" and the like refers to providing a substance (*e.g.*, an oligonucleotide herein or a composition herein) to an individual in a manner that is pharmacologically useful (*e.g.*, to treat a disease, disorder, or condition in the individual).

[0055] As used herein, "antisense strand" means an oligonucleotide herein that is complimentary to a region of a target sequence. Likewise, and as used herein, "sense strand" means an oligonucleotide herein that is complimentary to a region of an antisense strand.

[0056] As used herein, "asialoglycoprotein receptor" or "ASGPR" means a bipartite C-type lectin formed by a major 48 kDa subunit (ASGPR-1) and minor 40 kDa subunit (ASGPR-2). ASGPR is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major

role in binding, internalizing and subsequent clearing of circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins).

[0057] As used herein, "attenuate," "attenuating," "attenuation" and the like refers to reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of AH, ALD, CCA, PSC, cirrhosis, HCC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual. This attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory, or immunological activity, *etc.*) of AH, ALD, cirrhosis, HCC, CCA, PSC, NAFLD, and NASH, as well as related diseases, disorders and conditions, no detectable progression (worsening) of one or more aspects of AH, ALD, cirrhosis, HCC, CCA, PSC, NAFLD, and NASH, as well as related diseases, disorders and conditions, or no detectable aspects of AH, ALD, cirrhosis, HCC, NAFLD, and NASH, as well as related diseases, disorders and conditions in an individual when they might otherwise be expected.

[0058] As used herein, "attenuate," "attenuating," "attenuation" and the like means reducing or effectively halting. As a non-limiting example, one or more of the treatments herein may reduce or effectively halt the onset or progression of dyslipidemia/hypertriglyceridemia/hyperlipidemia in a subject. This attenuation may be exemplified by, for example, a decrease in one or more aspects (*e.g.*, symptoms, tissue characteristics, and cellular, inflammatory, or immunological activity, *etc.*) of AH, ALD, cirrhosis, HCC, CCA, PSC, NAFLD, and NASH, as well as related diseases, disorders, and conditions in an individual when they might otherwise be expected.

[0059] 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) 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.

[0060] As used herein, "contact," "contacting" and the like means directly or indirectly introducing or delivering the RNAi into, for example, a cell by facilitating or effecting uptake or absorption into the cell.

[0061] As used herein, "deoxyribonucleotide" means a nucleotide having a hydrogen in place of a hydroxyl at the 2' position of its pentose sugar when compared with a ribonucleotide. A modified deoxyribonucleotide has one or more modifications substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

[0062] As used herein, "double-stranded oligonucleotide" or "ds oligonucleotide" means an oligonucleotide that is substantially in a duplex form. The complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed between antiparallel sequences of nucleotides of covalently separate nucleic acid strands. Likewise, complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed between antiparallel sequences of nucleotides of nucleic acid strands that are covalently linked. Moreover, complementary base-pairing of duplex region(s) of a ds oligonucleotide can be formed from single nucleic acid strand that is folded (*e.g.*, *via* a hairpin) to provide complementary antiparallel sequences of nucleotides that base pair together. A ds oligonucleotide can include two covalently separate nucleic acid strands that are fully duplexed with one another. However, a ds oligonucleotide can include two covalently separate nucleic acid strands that are partially duplexed (*e.g.*, having overhangs at one or both ends). A ds oligonucleotide can include an antiparallel sequence of nucleotides that are partially complementary, and thus, may have one or more mismatches, which may include internal mismatches or end mismatches.

[0063] As used herein, "duplex," in reference to nucleic acids (*e.g.*, oligonucleotides), means a structure formed through complementary base pairing of two antiparallel sequences of nucleotides.

[0064] As used herein, "excipient" means a non-therapeutic agent that may be included in a composition herein, for example, to provide or contribute to a desired consistency or stabilizing effect.

[0065] As used herein, "hepatocyte" or "hepatocytes" means cells of the parenchymal tissues of the liver. These cells make up about 70%-85% of the liver's mass and manufacture serum albumin, fibronectin (FBN) and the prothrombin group of clotting factors (except for Factors 3 and 4). Markers for hepatocyte lineage cells include, but are not limited to, transthyretin

(Ttr), glutamine synthetase (Glul), hepatocyte nuclear factor 1a (Hnf1a) and hepatocyte nuclear factor 4a (Hnf4a). Markers for mature hepatocytes may include, but are not limited to, cytochrome P450 (Cyp3a11), fumarylacetoacetate hydrolase (Fah), glucose 6-phosphate (G6p), albumin (Alb) and OC2-2F8. *See*, *e.g.*, Huch *et al.* (2013) NATURE 494:247-50.

[0066] As used herein, a "hepatotoxic agent" means a chemical compound, virus or other substance that is itself toxic to the liver or can be processed to form a metabolite that is toxic to the liver. Hepatotoxic agents may include, but are not limited to, carbon tetrachloride (CCl_4), acetaminophen (paracetamol), vinyl chloride, arsenic, chloroform, nonsteroidal anti-inflammatory drugs (such as aspirin and phenylbutazone).

[0067] As used herein, "labile linker" means a linker that can be cleaved (*e.g.*, by acidic pH). Likewise, "fairly stable linker" means a linker that cannot be cleaved.

[0068] As used herein, "liver inflammation" or "hepatitis" means a physical condition in which the liver becomes swollen, dysfunctional and/or painful, especially as a result of injury or infection, as may be caused by exposure to a hepatotoxic agent. Symptoms may include jaundice, fatigue, weakness, nausea, vomiting, appetite reduction and weight loss. Liver inflammation, if left untreated, may progress to fibrosis, cirrhosis, liver failure or liver cancer.

[0069] As used herein, "liver fibrosis," "hepatic fibrosis" or "fibrosis of the liver" refers to an excessive accumulation in the liver of extracellular matrix proteins, which could include collagens (I, III, and IV), FBN, undulin, elastin, laminin, hyaluronan, and proteoglycans resulting from inflammation and liver cell death. Liver fibrosis, if left untreated, may progress to cirrhosis, liver failure or liver cancer.

[0070] As used herein, "loop" means an unpaired region of a nucleic acid (*e.g.*, oligonucleotide) that is flanked by two antiparallel regions of the nucleic acid that are sufficiently complementary to one another, such that under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cells), the two antiparallel regions, which flank the unpaired region, hybridize to form a duplex (referred to as a "stem").

[0071] 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 nucleotide can be a non-naturally occurring linkage. Typically, a modified internucleotide linkage confers one or more desirable properties to a nucleic acid in which the modified internucleotide linkage is present. For example, a

modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0072] 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 be a non-naturally occurring nucleotide. 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. Typically, a modified nucleotide confers one or more desirable properties to a nucleic acid in which the modified nucleotide is present. For example, a modified nucleotide may improve thermal stability, resistance to degradation, nuclease resistance, solubility, bioavailability, bioactivity, reduced immunogenicity, *etc.*

[0073] As used herein, "nicked tetraloop structure" mean a structure of a RNAi oligonucleotide that is characterized by separate sense (passenger) and antisense (guide) strands, in which the sense strand has a region of complementarity with the antisense strand, and in which at least one of the strands, generally the sense strand, has a tetraloop configured to stabilize an adjacent stem region formed within the at least one strand.

[0074] As used herein, "nucleotide" means an organic molecule having a nucleoside (a nucleobase such as, for example, adenine, cytosine, guanine, thymine, or uracil; and a pentose sugar such as, for example, ribose or 2'-deoxyribose; and a phosphate group, which can serve as a monomeric unit of nucleic acid polymers such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

[0075] As used herein, "oligonucleotide" means a short nucleic acid molecule (*e.g.*, less than about 100 nucleotides in length). An oligonucleotide may be single-stranded (ss) or ds. An oligonucleotide may or may not have duplex regions. As a set of non-limiting examples, an oligonucleotide may be, but is not limited to, a small interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), dicer substrate interfering RNA (dsiRNA), antisense oligonucleotide (ASO), short siRNA, or ss siRNA. Typically, a ds oligonucleotide is a RNAi oligonucleotide.

[0076] As used herein, "overhang" means a terminal non-base pairing nucleotide(s) resulting from one strand or region extending beyond the terminus of a complementary strand with which the one strand or region forms a duplex. An overhang may include one or more unpaired nucleotides extending from a duplex region at the 5' terminus or 3' terminus of a ds oligonucleotide. The overhang can be a 3' or 5' overhang on the antisense strand or sense strand of a ds oligonucleotides.

[0077] 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, but are not limited to, 5' phosphonates, such as 5' methylene phosphonate (5'-MP) and 5'-(E)-vinylphosphonate (5'-VP). An oligonucleotide can have a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog") at a 5'-terminal nucleotide. An example of a 4'-phosphate analog is oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. *See*, *e.g.*, Intl. Patent Application Publication No. WO 2018/045317. Other modifications have been developed for the 5' end of oligonucleotides (*see*, *e.g.*, Intl. Patent Application No. WO 2011/133871; US Patent No. 8,927,513; and Prakash *et al.* (2015) NUCLEIC ACIDS RES. 43:2993-3011).

[0078] As used herein, "PNPLA3-associated disease," "PNPLA3-associated disorder" or "PNPLA3-associated condition" means conditions where increased PNPLA3 expression and/or the presence of, for example, the PNPLA3 I148M variant. Exemplary PNPLA3-associated conditions, diseases or disorders include, but are not limited to, accumulation of fat in the liver, cirrhosis of the liver, fatty liver (steatosis), hepatocellular necrosis, HCC, liver fibrosis, inflammation of the liver, NASH, NAFLD, or obesity.

[0079] As used herein, "reduced expression," and with respect to a gene (*e.g.*, *PNPLA3*) means a decrease in the amount or level of RNA transcript (*e.g.*, PNPLA3 mRNA) or protein encoded by the gene and/or a decrease in the amount or level of activity of the gene in a cell, a population of cells, a sample, or a subject, when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, sample, or subject). For example, the act of contacting a cell with an oligonucleotide herein (*e.g.*, an oligonucleotide having an antisense strand having a nucleotide sequence that is complementary to a nucleotide sequence including PNPLA3

mRNA) may result in a decrease in the amount or level of mRNA, protein, and/or activity (*e.g.*, *via* degradation of PNPLA3 mRNA by the RNAi pathway) when compared to a cell that is not treated with the ds oligonucleotide. Similarly, and as used herein, "reducing expression" means an act that results in reduced expression of a gene (*e.g.*, *PNPLA3*). Specifically, and as used herein, "reduction of PNPLA3 expression" means a decrease in the amount or level of PNPLA3 mRNA, PMPLA3 protein, and/or PNPLA3 activity in a cell, a population of cells, a sample, or a subject when compared to an appropriate reference (*e.g.*, a reference cell, population of cells, tissue, or subject).

[0080] As used herein, "region of complementarity" means a sequence of nucleotides of a nucleic acid (*e.g.*, a ds oligonucleotide) that is sufficiently complementary to an antiparallel sequence of nucleotides to permit hybridization between the two sequences of nucleotides under appropriate hybridization conditions (*e.g.*, in a phosphate buffer, in a cell, *etc.*). An oligonucleotide herein includes a targeting sequence having a region of complementary to a mRNA target sequence.

[0081] As used herein, "ribonucleotide" means a nucleotide having a ribose as its pentose sugar, which contains a hydroxyl group at its 2' position. A modified ribonucleotide is a ribonucleotide having one or more modifications or substitutions of atoms other than at the 2' position, including modifications or substitutions in or of the nucleobase, sugar, or phosphate group.

[0082] As used herein, "RNAi oligonucleotide" refers to either (a) a ds oligonucleotide having a sense strand (passenger) and antisense strand (guide), in which the antisense strand or part of the antisense strand is used by the *Argonaute* 2 (Ago2) endonuclease in the cleavage of a target mRNA or (b) a ss oligonucleotide having a single antisense strand, where that antisense strand (or part of that antisense strand) is used by the Ago2 endonuclease in the cleavage of a target mRNA.

[0083] 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).

[0084] As used herein, "subject" means any mammal, including cats, dogs, mice, rats, and primates, especially humans. Moreover, "individual" or "patient" may be used interchangeably with "subject."

[0085] As used herein, "synthetic" refers to a nucleic acid or other molecule that is artificially synthesized (*e.g.*, using a machine such as, for example, a solid-state nucleic acid synthesizer) or that is otherwise not derived from a natural source (*e.g.*, a cell or organism) that normally produces the nucleic acid or other molecule.

[0086] As used herein, "targeting ligand" means a molecule (*e.g.*, an amino sugar, carbohydrate, cholesterol, lipid, or polypeptide) that selectively binds to a cognate molecule (*e.g.*, a receptor) of a tissue or cell of interest and that is conjugatable to another substance for targeting another substance to the tissue or cell of interest. For example, a targeting ligand may be conjugated to an oligonucleotide herein for purposes of targeting the oligonucleotide to a specific tissue or cell of interest. A targeting ligand can selectively bind to a cell surface receptor. Accordingly, a targeting ligand, when conjugated to an oligonucleotide, facilitates delivery of the oligonucleotide into a particular cell through selective binding to a receptor expressed on the surface of the cell and endosomal internalization by the cell of the complex comprising the oligonucleotide, targeting ligand, and receptor. Moreover, a targeting ligand can be conjugated to an oligonucleotide *via* a linker that is cleaved following or during cellular internalization such that the oligonucleotide is released from the targeting ligand in the cell.

[0087] As used herein, "tetraloop" means a loop that increases stability of an adjacent duplex formed by hybridization of flanking sequences of nucleotides. The increase in stability is detectable as an increase in melting temperature (T_m) of an adjacent stem duplex that is higher than the T_m of the adjacent stem duplex expected, on average, from a set of loops of comparable length consisting of randomly selected sequences of nucleotides. For example, a tetraloop can confer a T_m of at least about 50°C, at least about 55°C, at least about 56°C, at least about 58°C, at least about 60°C, at least about 65°C, or at least about 75°C in 10 mM $NaHPO_4$ to a hairpin comprising a duplex of at least 2 base pairs (bp) in length. A tetraloop also may stabilize a bp in an adjacent stem duplex by stacking interactions. Additionally, interactions among the nucleotides in a tetraloop include, but are not limited to, non-Watson-Crick base pairing, stacking interactions, hydrogen bonding, and contact interactions (Cheong *et al.* (1990) NATURE 346:680-682; Heus & Pardi (1991) SCIENCE 253:191-194). Here, a tetraloop can include or can have about 3 to 6 nucleotides, and typically is about 4 to 5 nucleotides. A tetraloop therefore can have 3, 4, 5, or 6 nucleotides, which may or may not be modified (*e.g.*, which may or may not be conjugated to a targeting moiety), especially 4 nucleotides. Any nucleotide may be used in the tetraloop, and standard IUPAC-IUB symbols for such

nucleotides may be used as described in Cornish-Bowden (1985) NUCLEIC ACIDS RES. 13:3021-30. For example, the letter "N" may be used to mean that any base may be in that position, the letter "R" may be used to show that A (adenine) or G (guanine) may be in that position, and "B" may be used to show that C (cytosine), G (guanine), or T (thymine) may be in that position. Examples of tetraloops include the UNCG family of tetraloops (*e.g.*, UUCG), the GNRA family of tetraloops (*e.g.*, GAAA) and the CUUG tetraloop (Woese *et al.* (1990) PROC. NATL. ACAD. SCI. USA 87:8467-71; Antao *et al.* (1991) NUCLEIC ACIDS RES. 19:5901-05). Examples of DNA tetraloops include the d(GNNA) family of tetraloops (*e.g.*, d(GTTA)), the d(GNRA) family of tetraloops, the d(GNAB) family of tetraloops, the d(CNNG) family of tetraloops, and the d(TNCG) family of tetraloops (*e.g.*, d(TTCG)). *See*, *e.g.*, Nakano *et al.* (2002) BIOCHEM. 41:4281-92; and Shinji *et al.* (2000) NIPPON KAGAKKAI KOEN YOKOSHU 78:731. Here, the tetraloop can be within a nicked tetraloop structure.

[0088] As used herein, "treat" or "treating" means an act of providing care to an individual in need thereof, for example, by administering a therapeutic agent (*e.g.*, an oligonucleotide herein) to the individual for purposes of improving the health and/or well-being of the individual with respect to an existing condition (*e.g.*, a disease, disorder) or to prevent or decrease the likelihood of the occurrence of a condition. Treating also can involve reducing the frequency or severity of at least one sign, symptom or contributing factor of a condition (*e.g.*, disease, disorder) experienced by the individual.

[0089] As used herein, "iRNA," "iRNA agent," "RNAi," "RNAi agent" and "RNA interference agent" means an agent that contains RNA and that mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. iRNA directs sequence-specific degradation of mRNA *via* RNA interference. The iRNA modulates, inhibits, or reduces *PNPLA3* expression in a cell.

Compositions

[0090] According to some aspects, the disclosure provides oligonucleotides (*e.g.*, double-stranded RNAi oligonucleotides) that reduce, modulate, or inhibit expression of *PNPLA3* in the liver. In some embodiments, the oligonucleotides provided herein used to treat of diseases associated with *PNPLA3* expression. In some aspects, the disclosure provides methods of treatment a disease associated with *PNPLA3* expression by reducing, modulating, or inhibiting *PNPLA3* expression in the liver (*e.g.*, in cells comprising the liver).

Oligonucleotide Inhibitors of PNPLA3 Expression

[0091] I. PNPLA3 Target Sequences: The oligonucleotides herein (*e.g.*, RNAi oligonucleotides) are targeted to a target sequence comprising PNPLA3 mRNA (*i.e.*, a PNPLA3 target sequence). In some embodiments, the oligonucleotide or a portion, fragment, or strand thereof (*e.g.*, an antisense strand or a guide strand of a ds RNAi oligonucleotide) binds or anneals to a PNPLA3 target sequence, thereby inhibiting *PNPLA3* expression. In some embodiments, the oligonucleotide is targeted to a PNPLA3 target sequence for inhibiting *PNPLA3* expression *in vivo*. In some embodiments, the amount or extent of *PNPLA3* expression inhibition by an oligonucleotide targeted to a PNPLA3 target sequence correlates with the potency of the oligonucleotide. In some embodiments, the amount or extent of inhibition of *PNPLA3* expression by an oligonucleotide targeted to a PNPLA3 target sequence correlates with the amount or extent of therapeutic benefit in an individual having or suspected of having a disease, disorder, or condition associated with *PNPLA3* expression treated with the oligonucleotide.

[0092] Through examining and analyzing the nucleotide sequence of PNPLA3 mRNAs, including mRNAs of multiple different species (*e.g.*, human, cynomolgus monkey, and rhesus monkey; *see*, *e.g.*, Example 1) and as a result of *in vitro* and *in vivo* testing (*see*, *e.g.*, Examples 2-3), it is shown herein that certain nucleotide sequences of PNPLA3 mRNA are more amenable than others to oligonucleotide-based inhibition of *PNPLA3* expression and are thus useful as target sequences for the oligonucleotides herein. In some embodiments, a sense strand of an oligonucleotide (*e.g.*, a ds RNAi oligonucleotide) described herein (*e.g.*, in Tables 1 or 3, or tables A, B, C or D) comprises a PNPLA3 target sequence. In some embodiments, a portion or region of the sense strand of an oligonucleotide described herein (*e.g.*, in Tables 1 or 3, or tables A, B, C or D) comprises a PNPLA3 target sequence. In some embodiments, the PNPLA3 target sequence comprises, or consists of, a sequence of any one of SEQ ID NOs:1167 to 1176.

[0093] II. PNPLA3 mRNA Targeting Sequences: In some embodiments, the oligonucleotides herein have regions of complementarity to PNPLA3 mRNA (*e.g.*, within a target sequence of PNPLA3 mRNA) for targeting PNPLA3 mRNA in cells and inhibiting *PNPLA3* expression. In some embodiments, the oligonucleotides herein comprise a PNPLA3 targeting sequence (*e.g.*, an antisense strand or a guide strand of a ds oligonucleotide) having a region of complementarity that binds or anneals to a PNPLA3 mRNA target sequence by

complementary (Watson-Crick) base pairing. The targeting sequence or region of complementarity is of a suitable length and base content to enable binding or annealing of the oligonucleotide (or a strand thereof) to PNPLA3 mRNA for inhibiting its expression. In some embodiments, the targeting sequence or region of complementarity is at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 21, at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, or at least about 30 nucleotides in length. Alternatively, the targeting sequence or region of complementarity is about 12 to about 30 (*e.g.*, 12 to 30, 12 to 22, 15 to 25, 17 to 21, 18 to 27, 19 to 27, or 15 to 30) nucleotides in length. Alternatively, the targeting sequence or region of complementarity is about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 18 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 19 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 20 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 21 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 22 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 23 nucleotides in length. In certain embodiments, the targeting sequence or region of complementarity is 24 nucleotides in length.

[0094] In some embodiments, the oligonucleotides herein comprise a targeting sequence or a region of complementarity (*e.g.*, an antisense strand or a guide strand of a double-stranded oligonucleotide) that is fully complementary to PNPLA3 target sequence. In some embodiments, the targeting sequence or region of complementarity is partially complementary to a PNPLA3 target sequence. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is fully complementary to a sequence of any one of SEQ ID NOs: 1167 to 1176. In some embodiments, the oligonucleotide comprises a targeting sequence or region of complementarity that is partially complementary to a sequence of any one of SEQ ID NOs: 1167 to 1176.

[0095] Alternatively, in some embodiments, the oligonucleotides herein comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a PNPLA3 mRNA, wherein the contiguous sequence of nucleotides is

about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 28, 12 to 26, 12 to 24, 12 to 20, 12 to 18, 12 to 16, 14 to 22, 16 to 20, 18 to 20, or 18 to 19 nucleotides in length). In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a PNPLA3 mRNA, where the contiguous sequence of nucleotides is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a PNPLA3 mRNA, where the contiguous sequence of nucleotides is 19 nucleotides in length. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity that is complementary to a contiguous sequence of nucleotides comprising a PNPLA3 mRNA, where the contiguous sequence of nucleotides is 20 nucleotides in length. In other embodiments, the oligonucleotides comprise a targeting sequence or a region of complementarity that is complementary to a contiguous sequence of nucleotides of any one of SEQ ID NOs: 1167 to 1176, optionally where the contiguous sequence of nucleotides is 19 nucleotides in length.

[0096] With regard to the targeting sequence or region of complementarity of the oligonucleotides herein, it is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1167 to 1176 and spans the entire length of an antisense strand. In some embodiments, the region of complementarity of the oligonucleotides is complementary to contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 1167 to 1176 and spans a portion of the entire length of an antisense strand. In some additional embodiments, the oligonucleotides include a region of complementarity (*e.g.*, on an antisense strand of a ds oligonucleotide) that is at least partially (*e.g.*, fully) complementary to a contiguous stretch of nucleotides spanning nucleotides 1-20 of a sequence as set forth in any one of SEQ ID NOs: 1167 to 1176.

[0097] Alternatively, the oligonucleotides herein comprise a targeting sequence or region of complementarity having one or more base pair (bp) mismatches with the corresponding PNPLA3 target sequence. In some embodiments, the targeting sequence or region of complementarity is up to about 1, up to about 2, up to about 3, up to about 4, up to about 5, *etc.* mismatches with the corresponding PNPLA3 target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the PNPLA3 mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotide to reduce

or inhibit *PNPLA3* expression is maintained. Stated differently, the targeting sequence or region of complementarity is no more than 1, no more than 2, no more than 3, no more than 4, or no more than 5 mismatches with the corresponding PNPLA3 target sequence provided that the ability of the targeting sequence or region of complementarity to bind or anneal to the PNPLA3 mRNA under appropriate hybridization conditions and/or the ability of the oligonucleotides to reduce or inhibit *PNPLA3* expression is maintained. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 1 mismatch with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 2 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or a region of complementarity having 3 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 4 mismatches with the corresponding target sequence. In some embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity having 5 mismatches with the corresponding target sequence. In other embodiments, the oligonucleotides comprise a targeting sequence or a region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, where at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or where the mismatches are interspersed in any position throughout the targeting sequence or region of complementarity. In other embodiments, the oligonucleotides comprise a targeting sequence or region of complementarity more than one mismatch (*e.g.*, 2, 3, 4, 5 or more mismatches) with the corresponding target sequence, where at least 2 (*e.g.*, all) of the mismatches are positioned consecutively (*e.g.*, 2, 3, 4, 5 or more mismatches in a row), or where at least one or more non-mismatched base pair is located between the mismatches, or a combination thereof.

[0098] III. Types of Oligonucleotides: A variety of oligonucleotide types and/or structures are useful for targeting PNPLA3 mRNA including, but not limited to, RNAi oligonucleotides, antisense oligonucleotides, miRNAs, *etc.* Any of the oligonucleotide types described herein or elsewhere are contemplated for use as a framework to incorporate a targeting sequence herein for the purposes of inhibiting *PNPLA3* expression. In some embodiments, the oligonucleotides herein inhibit *PNPLA3* expression by engaging with RNAi pathways upstream or downstream of Dicer involvement. For example, RNAi oligonucleotides have

been developed with each strand having sizes of about 19-25 nucleotides with at least one 3' overhang of 1 to 5 nucleotides (*see*, *e.g.*, US Patent No. 8,372,968). Longer oligonucleotides also have been developed that are processed by Dicer to generate active RNAi products (*see*, *e.g.*, US Patent No. 8,883,996). Further work produced extended ds oligonucleotides where at least one end of at least one strand is extended beyond a duplex targeting region, including structures where one of the strands includes a thermodynamically stabilizing tetraloop structure (*see*, *e.g.*, US Patent Nos. 8,513,207 and 8,927,705, as well as Intl. Patent Application Publication No. WO 2010/033225). Such structures include ss extensions (on one or both sides of the molecule) as well as ds extensions.

[0099] The oligonucleotides herein engage with the RNAi pathway downstream of the involvement of Dicer (*e.g.*, Dicer cleavage). In some embodiments, the oligonucleotides have an overhang (*e.g.*, of 1, 2, or 3 nucleotides in length) in the 3' end of the sense strand. In some embodiments, the oligonucleotides (*e.g.*, siRNA) include a 21-nucleotide guide strand that is antisense to a target mRNA (*e.g.*, PNPLA3 mRNA) and a complementary passenger strand, in which both strands anneal to form a 19-bp duplex and 2 nucleotide overhangs at either or both 3' ends. Longer oligonucleotide designs also are contemplated, including oligonucleotides having a guide strand of 23 nucleotides and a passenger strand of 21 nucleotides, where there is a blunt end on the right side of the molecule (3' end of passenger strand/5' end of guide strand) and a two nucleotide 3'-guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 21 bp duplex region. *See*, *e.g.*, US Patent Nos. 9,012,138; 9,012,621 and 9,193,753.

[00100] The oligonucleotides herein comprise sense and antisense strands that are both in the range of about17 to about 26 (*e.g.*, 17 to 26, 20 to 25, or 21-23) nucleotides in length. In some embodiments, the oligonucleotides comprise a sense and antisense strand that are both in the range of about 19 to about 22 nucleotides in length. In some embodiments, the sense and antisense strands are of equal length. In some embodiments, the oligonucleotides comprise sense and antisense strands, such that there is a 3'-overhang on either the sense strand or the antisense strand, or both the sense and antisense strand. In some instances, for oligonucleotides having sense and antisense strands that are both in the range of about 21 to about 23 nucleotides in length, a 3'-overhang on the sense, antisense or both sense and antisense strands is 1 or 2 nucleotides in length. In some embodiments, the oligonucleotides comprise a guide strand of 22 nucleotides and a passenger strand of 20 nucleotides, where there is a blunt end on the right

side of the molecule (3' end of passenger strand/5' end of guide strand) and a 2 nucleotide 3' guide strand overhang on the left side of the molecule (5' end of the passenger strand/3' end of the guide strand). In such molecules, there is a 20-bp duplex region.

[00101] Other oligonucleotide designs for use herein include: 16-mer siRNAs (*see*, *e.g.*, "NUCLEIC ACIDS IN CHEMISTRY & BIOLOGY," Blackburn (ed.), Royal Society of Chemistry, 2006), shRNAs (*e.g.*, having 19 bp or shorter stems; *see*, *e.g.*, Moore *et al.* (2010) METHODS MOL. BIOL. 629:141-58), blunt siRNAs (*e.g.*, of 19 bps in length; *see*, *e.g.*, Kraynack & Baker (2006) *RNA* 12:163-76), asymmetrical siRNAs (aiRNA; *see*, *e.g.*, Sun *et al.* (2008) NAT. BIOTECHNOL. 26:1379-82), asymmetric shorter-duplex siRNA (*see*, *e.g.*, Chang *et al.* (2009) MOL. THER. 17:725-32), fork siRNAs (*see*, *e.g.*, Hohjoh (2004) FEBS LETT. 557:193-198), ss siRNAs (*see*, *e.g.*, Elsner (2012) NAT. BIOTECHNOL. 30:1063), dumbbell-shaped circular siRNAs (*see*, *e.g.*, Abe *et al.* (2007) J. AM. CHEM. SOC. 129:15108-09), and small internally segmented interfering RNA (sisiRNA; *see, e.g.*, Bramsen *et al.* (2007) NUCLEIC ACIDS RES. 35:5886-97). Further non-limiting examples of oligonucleotide structures that may be used herein to reduce or inhibit *PNPLA3* expression are miRNA, shRNA, and short siRNA (*see*, *e.g.*, Hamilton *et al.* (2002) EMBO J. 21:4671-79; *see also*, US Patent Application Publication No. 2009/0099115).

[00102] Alternatively, the oligonucleotides herein are single-stranded (ss). Such structures include, but are not limited to, ss RNAi molecules. Recent efforts have demonstrated the activity of ss RNAi molecules (*see*, *e.g.*, Matsui *et al.* (2016) MOL. THER. 24:946-55). In some embodiments, the oligonucleotides are ASOs. An ASO is a ss oligonucleotide that has a nucleobase sequence which, when written or depicted in the 5' to 3' direction, includes a reverse complement of a targeted segment of a particular nucleic acid and is suitably modified (*e.g.*, as a gapmer) to induce RNaseH-mediated cleavage of its target RNA in cells or (*e.g.*, as a mixmer) so as to inhibit translation of the target mRNA in cells. ASOs for use herein are modified in any suitable manner known in the art including, for example, as shown in US Patent No. 9,567,587 (including, for example, length, sugar moieties of the nucleobase (pyrimidine, purine), and alterations of the heterocyclic portion of the nucleobase). Further, ASOs have been used for decades to reduce expression of specific target genes (*see*, *e.g.*, Bennett *et al.* (2017) ANNU. REV. PHARMACOL. 57:81-105).

[00103] IV. Double-Stranded RNAi Oligonucleotides: ds oligonucleotides for targeting PNPLA3 mRNA and inhibiting *PNPLA3* expression (*e.g.*, *via* the RNAi pathway) comprising

a sense strand (*i.e.*, a passenger strand) and an antisense strand (*i.e.*, a guide strand). In some embodiments, the sense strand and antisense strand are separate strands and are not covalently linked. In some embodiments, the sense strand and antisense strand are covalently linked.

[00104] In some embodiments, the sense strand comprises a first region (R1) and a second region (R2), where R2 comprises a first subregion (S1), a tetraloop (L) or triloop (triL), and a second subregion (S2), where L or triL is located between S1 and S2, and where S1 and S2 form a second duplex (D2). D2 has various lengths. In some embodiments, D2 is about 1 to about 6 bp in length. In some embodiments, D2 is 2-6, 3-6, 4-6, 5-6, 1-5, 2-5, 3-5 or 4-5 bp in length. In other embodiments, D2 is 1, 2, 3, 4, 5 or 6 bp in length. In certain embodiments, D2 is 6 bp in length.

[00105] In some embodiments, R1 of the sense strand and the antisense strand forms a first duplex (D1). In some embodiments, D1 is at least about 15 (*e.g.*, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21) nucleotides in length. In some embodiments, D1 is about 12 to about 30 nucleotides in length (*e.g.*, 12 to 30, 12 to 27, 15 to 22, 18 to 22, 18 to 25, 18 to 27, 18 to 30 or 21 to 30 nucleotides in length). In other embodiments, D1 is at least 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 20, at least 25 or at least 30 nucleotides in length). In other embodiments, D1 is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 nucleotides in length. In certain embodiments, D1 is 20 nucleotides in length. In some instances, D1 does not span the entire length of the sense strand and/or antisense strand. In some instances, D1 spans the entire length of either the sense strand or antisense strand or both. In certain instances, D1 spans the entire length of both the sense strand and the antisense strand.

[00106] In certain instances, a ds oligonucleotide herein includes a sense strand having a sequence of any one of SEQ ID NOs: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355,

357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, and 775, and an antisense strand having a complementary sequence selected from SEQ ID NOs: 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, and 776, as is arranged in Table 1.

Alternatively, a ds oligonucleotide herein includes a sense strand having a sequence of any one of SEQ ID NOs: 777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 809, 811, 813, 815, 817, 819, 821, 823, 825, 827, 829, 831, 833, 835, 837, 839, 841, 843, 845, 847, 849, 851, 853, 855, 857, 859, 861, 863, 865, 867, 869, 871, 873, 875, 877, 879, 881, 883, 885, 887, 889, 891, 893, 895, 897, 899, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, 945, 947, 949, 951, 953, 955, 957, 959, 961, 963, 965, 967, 969, 971, 973, 975, 977, 979, 981, 983, 985, 987, 989, 991, 993, 995, 997, 999, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, 1023, 1025, 1027, 1029, 1031, 1033, 1035, 1037, 1039, 1041, 1043, 1045, 1047, 1049, 1051, 1053, 1055, 1057, 1059, 1061, 1063, 1065, 1067, 1069, 1071, 1073, 1075, 1077, 1079, 1081, 1083, 1085, 1087, 1089, 1091, 1093, 1095, 1097, 1099, 1101, 1103, 1105, 1107, 1109, 1111, 1113, 1115, 1117, 1119, 1121, 1123, 1125, 1127, 1129, 1131, 1133, 1135, 1137, 1139, 1141, 1143, 1145, 1147, 1149, 1151, 1153, 1155, 1157, 1159, 1161, and 1163, and an antisense strand having a complementary sequence selected from SEQ ID NOs: 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954, 956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 1000, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, 1024, 1026, 1028, 1030, 1032, 1034, 1036, 1038, 1040, 1042, 1044, 1046, 1048, 1050, 1052, 1054, 1056, 1058, 1060, 1062, 1064, 1066, 1068, 1070, 1072, 1074, 1076, 1078, 1080, 1082, 1084, 1086, 1088, 1090, 1092, 1094, 1096, 1098, 1100, 1102, 1104, 1106, 1108, 1110, 1112, 1114, 1116, 1118, 1120, 1122, 1124, 1126, 1128, 1130, 1132, 1134, 1136, 1138, 1140, 1142, 1144, 1146, 1148, 1150, 1152, 1154, 1156, 1158, 1160, 1162, and 1164, as is arranged in Table 3. In certain instances, the sense strand is any one of SEQ ID NOs: 787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163, and the antisense strand is any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164.

[00107] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes a sense strand having a sequence as set forth in Table A, B , C, or D (*e.g.*, SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222,

1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300).

[00108] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes an antisense strand having a sequence as set forth in Table A, B , C, or D (*e.g.*, SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301). In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes a sense strand having a sequence as set forth in Table A, B , C, or D (*e.g.*, SEQ ID Nos: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298 or 1300).

[00109] In certain embodiments, the disclosure describes RNAi oligonucleotides for reducing or inhibiting *PNPLA3* expression that includes an antisense strand having a sequence as set forth in Table A, B , C, or D (*e.g.*, SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301).

[00110] In some embodiments, RNAi oligonucleotides are described for reducing or inhibiting *PNPLA3* expression that include an antisense strand and a sense strand, where the antisense strand has a sequence as set forth in Table A, Table B, Table C, or Table D, and where the sense strand has a sequence as set forth in Table A, Table B, Table C, or Table D.

[00111] In some instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence as set forth in Table A, Table B, Table C, or Table D, especially any one of SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230,

1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300. In some instances, the RNAi oligonucleotide includes an antisense strand having a nucleotide sequence as set for the in Table A, Table B, Table C, or Table D, especially any one of SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1202, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301. In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298, or 1300, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299, or 1301.

[00112] In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1188, 1190, 1200, 1216, 1218, 1220, 1224, 1230, 1232, 1234, 1244, 1246, 1250, 1254, 1262, 1288, 1290, 1292, 1294, 1296, 1298, or 1300, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1189, 1191, 1201, 1215, 1217, 1221, 1225, 1231, 1233, 1235, 1245, 1247, 1251, 1255, 1263, 1289, 1291, 1295, 1297, 1299, or 1301.

[00113] In certain instances, the RNAi oligonucleotide includes a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1188, 1190, 1220, 1224, 1230, 1232, 1244, 1246, 1250, or 1254, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251, or 1255.

[00114] In certain instances, the sense strand and the antisense strand of the RNAi oligonucleotide, respectively, are selected from:

(a) SEQ ID NOs: 1220 and 1221,

(b) SEQ ID NOs: 1224 and 1225,

(c) SEQ ID NOs: 1230 and 1231,

(d) SEQ ID NOs: 1232 and 1233,

(e) SEQ ID NOs: 1188 and 1189,

(f) SEQ ID NOs: 1190 and 1191,

(g) SEQ ID NOs: 1244 and 1245,

(h) SEQ ID NOs: 1250 and 1251-,

(i) SEQ ID NOs: 1254 and 1255, and

(j) SEQ ID NOs: 1246 and 1247.

[00115] One of skill in the art appreciates that in some instances, the sequences presented in the Sequence Listing is referred to in describing the structure of an oligonucleotide (*e.g.*, a ds oligonucleotide) or other nucleic acid. In such instances, the actual oligonucleotide or other nucleic acid has one or more alternative nucleotides (*e.g.*, an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification when compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[00116] In some embodiments, a ds oligonucleotide herein includes a 25-nucleotide sense strand and a 27-nucleotide antisense strand that when acted upon by a Dicer enzyme results in an antisense strand that is incorporated into the mature RISC. In certain instances, the sense strand of the ds oligonucleotide is longer than 27 nucleotides (*e.g.*, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides). In certain instances, the sense strand of the ds oligonucleotide is longer than 25 nucleotides (*e.g.*, 26, 27, 28, 29, or 30 nucleotides).

[00117] In some instances, the ds oligonucleotides herein have one 5' end that is thermodynamically less stable when compared to the other 5' end. In some embodiments, the ds oligonucleotide is asymmetric and includes a blunt end at the 3' end of a sense strand and a 3'-overhang at the 3' end of an antisense strand. In some embodiments, the 3'-overhang on the antisense strand is about 1 to about 8 nucleotides in length (*e.g.*, 1, 2, 3, 4, 5, 6, 7 or 8 nucleotides in length). Typically, a ds oligonucleotide for RNAi has a two-nucleotide overhang on the 3' end of the antisense (guide) strand. However, other overhangs are possible. In some embodiments, an overhang is a 3'-overhang having a length of between about 1 to about 6

nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides. However, in other instances, the overhang is a 5'-overhang comprising a length of between about 1 to about 6 nucleotides, optionally 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 6, 2 to 5, 2 to 4, 2 to 3, 3 to 6, 3 to 5, 3 to 4, 4 to 6, 4 to 5, 5 to 6 nucleotides, or 1, 2, 3, 4, 5 or 6 nucleotides.

[00118] In some instances, two terminal nucleotides on the 3' end of an antisense strand are modified. In some instances, the two terminal nucleotides on the 3' end of the antisense strand are complementary with the target mRNA (*e.g.*, PNPLA3 mRNA). In other instances, the two terminal nucleotides on the 3' end of the antisense strand are not complementary with the target mRNA. In some instances, two terminal nucleotides on each 3' end of an oligonucleotide in the nicked tetraloop structure are GG. Typically, one or both of the two terminal GG nucleotides on each 3' end of a ds oligonucleotide is not complementary with the target mRNA.

[00119] In some instances, there is one or more (*e.g.*, 1, 2, 3, 4, or 5) mismatch(s) between the sense and antisense strand. If there is more than one mismatch between the sense and antisense strand, they may be positioned consecutively (*e.g.*, 2, 3, or more in a row), or interspersed throughout the region of complementarity. In some instances, the 3' end of the sense strand contains one or more mismatches. In certain instances, two mismatches are incorporated at the 3' end of the sense strand. In some instances, base mismatches, or destabilization of segments at the 3' end of the sense strand of the oligonucleotide improves or increases the potency of the ds oligonucleotide.

[00120] A. Antisense Strands: The oligonucleotides (*e.g.*, a ds oligonucleotide) herein for targeting PNPLA3 mRNA and inhibiting *PNPLA3* expression include an antisense strand including a sequence as set forth in the antisense strands of Table 1 or Table 3, or Table A, B, C or D. In some instances, the oligonucleotides include an antisense strand having at least about 12 (*e.g.*, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164, or an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251, or 1255

[00121] Further, the oligonucleotides (*e.g.*, a ds oligonucleotide) herein can include an antisense strand of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 35, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some instances,

the oligonucleotides can have an antisense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 22, at least 25, at least 27, at least 30, at least 35, or at least 38 nucleotides in length). Alternatively, the oligonucleotides can have an antisense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 22, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In certain instances, the oligonucleotide can have an antisense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length.

[00122] As noted above, the antisense strand of the oligonucleotides herein may be referred to as the "guide strand." For example, the antisense strand that engages with RISC and that binds to an *Argonaute* protein such as Ago2, or that engages with or that binds to one or more similar factors, and directs silencing of a target gene, the antisense strand is referred to as a guide strand (or "passenger strand").

[00123] B. Sense Strands: The oligonucleotides (*e.g.*, a ds oligonucleotide) herein for targeting PNPLA3 mRNA and inhibiting *PNPLA3* expression include a sense strand sequence including a sequence as set forth in the sense strands of Table 1 or Table 3, or Table A, B, C, or D. In some instances, the oligonucleotides include a sense strand that having at least about 12 (*e.g.*, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or at least 23) contiguous nucleotides of a sequence as set forth in in any one of SEQ ID NOs: 787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163.

[00124] Further, the oligonucleotides (*e.g.*, a ds oligonucleotide) herein include a sense strand (or passenger strand) of up to about 40 nucleotides in length (*e.g.*, up to 40, up to 36, up to 30, up to 27, up to 25, up to 21, up to 19, up to 17, or up to 12 nucleotides in length). In some instances, the oligonucleotides can have a sense strand of at least about 12 nucleotides in length (*e.g.*, at least 12, at least 15, at least 19, at least 21, at least 25, at least 27, at least 30, at least 36, or at least 38 nucleotides in length). Alternatively, the oligonucleotides can have a sense strand in a range of about 12 to about 40 (*e.g.*, 12 to 40, 12 to 36, 12 to 32, 12 to 28, 15 to 40, 15 to 36, 15 to 32, 15 to 28, 17 to 21, 17 to 25, 19 to 27, 19 to 30, 20 to 40, 22 to 40, 25 to 40, or 32 to 40) nucleotides in length. In certain instances, the oligonucleotides can have a sense strand of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides in length.

[00125] In some embodiments, the sense strand comprises a stem-loop structure at its 3' end. In other embodiments, the sense strand comprises a stem-loop structure at its 5' end. In additional embodiments, the stem is a duplex of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 bp in length. In some embodiments, the stem-loop provides the oligonucleotides protection against degradation (*e.g.*, enzymatic degradation) and facilitates or improves targeting and/or delivery to a target cell, tissue, or organ (*e.g.*, the liver), or both. For example, the loop of the stem-loop provides nucleotides having one or more modifications that facilitate, improve, or increase targeting to a target mRNA (*e.g.*, a PNPLA3 mRNA), inhibiting of target gene expression (*e.g.*, *PNPLA3* expression), and/or delivering to a target cell, tissue, or organ (*e.g.*, the liver), or both. In some embodiments, the stem-loop itself or modification(s) to the stem-loop do not substantially affect the inherent gene expression inhibition activity of the oligonucleotide, but facilitates, improves, or increases stability (*e.g.*, provides protection against degradation) and/or delivery of the oligonucleotide to a target cell, tissue, or organ (*e.g.*, the liver). In certain embodiments, the oligonucleotides comprise a sense strand including (*e.g.*, at its 3' end) a stem-loop set forth as: S1-L-S2, in which S1 is complementary to S2, and in which L forms a single-stranded loop between S1 and S2 of up to about 10 nucleotides in length (*e.g.*, 3, 4, 5, 6, 7, 8, 9 ,or 10 nucleotides in length). In certain embodiments, the loop (L) is 4 nucleotides in length. FIGS. 1 and 2 depict non-limiting examples of such an oligonucleotide. In some embodiments the loop (L) of the stem-loop having the structure S1-L-S2 as described above is a tetraloop (*e.g.*, within a nicked tetraloop structure). In some embodiments, the tetraloop comprises ribonucleotides, deoxyribonucleotides, modified nucleotides, delivery ligands and combinations thereof.

[00126] V. Oligonucleotide Modifications

[00127] A. Sugar Modifications: A modified sugar (also referred to herein as a sugar analog) includes a modified deoxyribose or ribose moiety in which, for example, one or more modifications occur at the 2', 3', 4' and/or 5' carbon position of the sugar. A modified sugar also includes non-natural, alternative, carbon structures such as those present in locked nucleic acids ("LNA"; *see*, *e.g.*, Koshkin *et al.* (1998) TETRAHEDRON 54:3607-3630), unlocked nucleic acids ("UNA"; *see*, *e.g.*, Snead *et al.* (2013) MOL. THER-NUC. ACIDS 2:e103) and bridged nucleic acids ("BNA"; *see*, *e.g.*, Imanishi & Obika (2002) CHEM. COMMUN. 16:1653-1659).

[00128] In some embodiments, the nucleotide modification in the sugar is a 2'-modification such as, for example, 2'-O-propargyl, 2'-O-propylamin, 2'-amino, 2'-ethyl, 2'-fluoro (2'-F), 2'-

aminoethyl (EA), 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), 2'-O-[2-(methylamino)-2-oxoethyl] (2'-O-NMA), or 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid (2'-FANA). In certain embodiments, the modification is 2'-F, 2'-OMe, or 2'-MOE. In other embodiments, the modification in the sugar is a modification of the sugar ring, which includes modification of one or more carbons of the sugar ring. For example, the modification in the sugar is a 2'-oxygen of the sugar linked to a 1'-carbon or 4'-carbon of the sugar, or a 2'-oxygen linked to the 1'-carbon or 4'-carbon *via* an ethylene or methylene bridge. In other embodiments, the modification is an acyclic sugar that lacks a 2'-carbon to 3'-carbon bond. In other embodiments, the modification is a thiol group such as, for example, in the 4' position of the sugar.

[00129] The oligonucleotides herein include at least 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, or more). In some embodiments, the sense strand comprises at least 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, or more). In some embodiments, the antisense strand comprises at least 1 modified nucleotide (*e.g.*, at least 1, at least 5, at least 10, at least 15, at least 20, or more).

[00130] In certain embodiments, all nucleotides of the sense strand are modified. Likewise, all nucleotides of the antisense strand are modified. In some embodiments, all the nucleotides of the oligonucleotides herein (*i.e.*, both the sense strand and the antisense strand) are modified. As above, and in some embodiments, the modified nucleotide is a 2'-modification (*e.g.*, a 2'-F, 2'-OMe, 2'-MOE, and/or 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid). In certain embodiments, the modified nucleotide is a 2'-modification such as, for example, a 2'-F or a 2'-OMe.

[00131] Moreover, the oligonucleotides herein have different modification patterns. In some embodiments, the modified oligonucleotides comprise an antisense strand having a modification pattern as set forth in any one of Tables A, B, C or D and comprise a sense strand sequence having a modification pattern as set forth in any one of Tables A, B, C or D (as well as FIG. 1). In some embodiments, one or more of positions 8, 9, 10, or 11 of the sense strand are modified with a 2'-F. In other embodiments, the sugar moiety at each nucleotide at positions 1 to 7 and 12 to 20 in the sense strand is modified with a 2'-OMe.

[00132] In some embodiments, the antisense strand includes 3 nucleotides that are modified at the 2'-position of the sugar moiety with a 2'-F. In some embodiments, the sugar moiety at

positions 2, 5, and 14 and optionally up to 3 of the nucleotides at positions 1, 3, 7, and 10 of the antisense strand are modified with a 2'-F. In other embodiments, the sugar moiety at positions 2, 5, and 14 of the antisense strand is modified with a 2'-F. In other embodiments, the sugar moiety at positions 1, 2, 5, and 14 of the antisense strand is modified with a 2'-F. In still other instances, the sugar moiety at positions 1, 2, 3, 5, 7, and 14 of the antisense strand is modified with a 2'-F. In yet other embodiments, the sugar moiety at positions 1, 2, 3, 5, 10, and 14 of the antisense strand is modified with a 2'-F. In yet other embodiments, the sugar moiety at positions 2, 3, 5, 7, 10, and 14 of the antisense strand is modified with a 2'-F.

[00133] B. 5'-Terminal Phosphates: 5'-terminal phosphate groups can be used to enhance the interaction of the oligonucleotides herein with Ago2. However, oligonucleotides having a 5'-phosphate group may be susceptible to degradation *via* phosphatases or other enzymes, which can limit their bioavailability *in vivo*. In some embodiments, the oligonucleotides (*e.g.*, a ds oligonucleotide) comprise analogs of 5' phosphates that are resistant to such degradation. Examples of such phosphate analogs include, but are not limited to, oxymethylphosphonate, vinylphosphonate, malonyl phosphonate, or a combination thereof. In certain embodiments the 3' end of a strand of the oligonucleotides is attached to a chemical moiety that mimics the electrostatic and steric properties of a natural 5'-phosphate group ("phosphate mimic").

[00134] Alternatively, or additionally, the oligonucleotides herein have a phosphate analog at a 4'-carbon position of the sugar (referred to as a "4'-phosphate analog"). *See*, *e.g.*, Intl. Patent Application Publication No. WO 2018/045317. In some embodiments, the oligonucleotides herein include a 4'-phosphate analog at a 5'-terminal nucleotide. In some embodiments, the phosphate analog is an oxymethylphosphonate, in which the oxygen atom of the oxymethyl group is bound to the sugar moiety (*e.g.*, at its 4'-carbon) or analog thereof. In other embodiments, the 4'-phosphate analog is a thiomethylphosphonate or an aminomethylphosphonate, in which the sulfur atom of the thiomethyl group or the nitrogen atom of the amino methyl group is bound to the 4'-carbon of the sugar moiety or analog thereof. In certain embodiments, the 4'-phosphate analog is an oxymethylphosphonate, which is represented by the formula $–O–CH_2–PO(OH)_2$ or $–O–CH_2–PO(OR)_2$, in which R is independently selected from H, CH_3, an alkyl group, CH_2CH_2CN, $CH_2OCOC(CH_3)_3$, $CH_2OCH_2CH_2Si(CH_3)_3$, or a protecting group. In certain embodiments, the alkyl group is CH_2CH_3. In certain other embodiments, R is independently selected from H, CH_3, or CH_2CH_3.

[00135] C. Modified Internucleoside Linkages: In addition to the above modifications, the oligonucleotides herein comprise a modified internucleoside linkage. In some instances, phosphate modifications or substitutions result in oligonucleotides that comprise at least about 1 (*e.g.*, at least 1, at least 2, at least 3, or at least 5) modified internucleotide linkages. In some embodiments, the oligonucleotides comprise about 1 to about 10 (*e.g.*, 1 to 10, 2 to 8, 4 to 6, 3 to 10, 5 to 10, 1 to 5, 1 to 3, or 1 to 2) modified internucleotide linkages. In certain additional embodiments, the oligonucleotides comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 modified internucleotide linkages.

[00136] Examples of modified internucleotide linkages include, but are not limited, to, a phosphorodithioate linkage, a phosphorothioate linkage, a phosphotriester linkage, a thionoalkylphosphonate linkage, a thionalkylphosphotriester linkage, a phosphoramidite linkage, a phosphonate linkage, or a boranophosphate linkage. In some embodiments, at least one modified internucleotide linkage of any one of the oligonucleotides as disclosed herein is a phosphorothioate linkage.

[00137] In some embodiments, the oligonucleotides herein comprise a phosphorothioate linkage between one or more of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 3 and 4 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand. In other embodiments, the oligonucleotides comprise a phosphorothioate linkage between each of positions 1 and 2 of the sense strand, positions 1 and 2 of the antisense strand, positions 2 and 3 of the antisense strand, positions 20 and 21 of the antisense strand, and positions 21 and 22 of the antisense strand.

[00138] D. Base Modifications: In addition to the above modifications, the oligonucleotides herein also comprise one or more modified nucleobases. In some embodiments, modified nucleobases (also referred to herein as base analogs) are linked at the 1' position of a nucleotide sugar moiety. In certain embodiments, the modified nucleobase is a nitrogenous base. In certain other embodiments, the modified nucleobase does not contain nitrogen atom. *See*, *e.g.*, US Patent Application Publication No. 2008/0274462. In some embodiments, the modified nucleotide is a universal base. However, in certain embodiments, the modified nucleotide does not contain a nucleobase (abasic).

[00139] With regard to universal bases, they comprise a heterocyclic moiety located at the 1' position of a nucleotide sugar moiety in a modified nucleotide, or the equivalent position in a

nucleotide sugar moiety substitution, that, when present in a duplex, is positioned opposite more than one type of base without substantially altering structure of the duplex. Moreover, and compared to a reference ss nucleic acid (*e.g.*, oligonucleotide) that is fully complementary to a target nucleic acid, a ss nucleic acid having a universal base forms a duplex with the target nucleic acid that has a lower T_m than a duplex formed with the complementary nucleic acid. However, when compared to a reference ss nucleic acid in which the universal base has been replaced with a base to generate a single mismatch, the ss nucleic acid having the universal base forms a duplex with the target nucleic acid that has a higher T_m than a duplex formed with the nucleic acid having the mismatched base.

[00140] Exemplary universal-binding nucleotides include, but are not limited to, inosine, 1-β-D-ribofuranosyl-5-nitroindole and/or 1-β-D-ribofuranosyl-3-nitropyrrole (*see*, *e.g.*, US Patent Application Publication No. 2007/0254362; Van Aerschot *et al.* (1995) NUCLEIC ACIDS RES. 23:4363-70; Loakes *et al.* (1995) NUCLEIC ACIDS RES. 23:2361-66; and Loakes & Brown (1994) NUCLEIC ACIDS RES. 22:4039-43).

[00141] E. Reversible Modifications: While certain modifications to protect the oligonucleotides herein from the *in vivo* environment before reaching target cells can be made, they also can reduce the potency or activity of the oligonucleotides once they reach the cytosol of the target cell. Reversible modifications therefore can be made such that the molecule retains desirable properties outside of the cell, which are then removed upon entering the cytosolic environment of the cell. Reversible modification can be removed, for example, by the action of an intracellular enzyme or by the chemical conditions inside of a cell (*e.g.*, through reduction by intracellular glutathione).

[00142] In some embodiments, a reversibly modified nucleotide comprises a glutathione-sensitive moiety. Typically, nucleic acid molecules are chemically modified with cyclic disulfide moieties to mask the negative charge created by the internucleotide diphosphate linkages and to improve cellular uptake and nuclease resistance. *See*, US Patent Application Publication No. 2011/0294869, Intl. Patent Application Publication Nos. WO 2014/088920 and WO 2015/188197, and Meade *et al.* (2014) NAT. BIOTECHNOL. 32:1256-63. This reversible modification of the internucleotide diphosphate linkages is designed to be cleaved intracellularly by the reducing environment of the cytosol (*e.g.*, glutathione). Earlier examples include neutralizing phosphotriester modifications that are reported to be cleavable inside cells (*see*, *e.g.*, Dellinger *et al.* (2003) J. AM. CHEM. SOC. 125:940-50).

[00143] Some reversible modifications protect the oligonucleotides during *in vivo* administration (*e.g.*, transit through the blood and/or lysosomal/endosomal compartments of a cell) where the oligonucleotides will be exposed to nucleases and other harsh environmental conditions (*e.g.*, pH). When released into the cytosol of a cell where the levels of glutathione are higher compared to extracellular space, the modification is reversed, and the result is cleaved oligonucleotides. Using reversible, glutathione-sensitive moieties, it is possible to introduce sterically larger chemical groups into the oligonucleotides when compared to the options available using irreversible chemical modifications. This is because these larger chemical groups will be removed in the cytosol and, therefore, should not interfere with the biological activity of the oligonucleotides inside the cytosol of a cell. As a result, these larger chemical groups can be engineered to confer various advantages to the oligonucleotides, such as nuclease resistance, lipophilicity, charge, thermal stability, specificity, and reduced immunogenicity. In some instances, the structure of the glutathione-sensitive moiety can be engineered to modify the kinetics of its release.

[00144] In some embodiments, the glutathione-sensitive moiety is attached to the sugar of the nucleotide. In certain embodiments, the glutathione-sensitive moiety is attached to the 2'-carbon of the sugar of a modified nucleotide. Additionally, or alternatively, the glutathione-sensitive moiety is attached to the 5'-carbon of a sugar, particularly when the modified nucleotide is the 5'-terminal nucleotide of the oligonucleotides. Additionally, or alternatively, the glutathione-sensitive moiety is attached to the 3'-carbon of sugar, particularly when the modified nucleotide is the 3'-terminal nucleotide of the oligonucleotides. In some embodiments, the glutathione-sensitive moiety includes a sulfonyl group (*see*, *e.g.,* Intl. Patent Application Publication No. WO 2018/039364).

[00145] VI. Targeting Ligands

[00146] It is desirable to target the oligonucleotides herein to one or more cells or one or more organs. Such a strategy can help to avoid undesirable effects in other organs or to avoid undue loss of the oligonucleotides to cells, tissue or organs that would not benefit therefrom. Accordingly, the oligonucleotides can be modified to facilitate targeting and/or delivering to a tissue, cell, or organ (*e.g.*, to facilitate delivering the oligonucleotides to the liver). In some embodiments, the oligonucleotides are modified to facilitate delivery of the oligonucleotide to the hepatocytes of the liver. In certain embodiments, the oligonucleotides comprise at least

one nucleotide (*e.g.*, 1, 2, 3, 4, 5, 6, or more nucleotides) conjugated to one or more targeting ligand(s).

[00147] Exemplary targeting ligands include, but are not limited to, a carbohydrate, amino sugar, cholesterol, peptide, polypeptide, protein, or part of a protein (*e.g.*, an antibody or antibody fragment), or lipid. In some embodiments, the targeting ligand is an aptamer. For example, the targeting ligand is an RGD peptide for targeting tumor vasculature or glioma cells, CREKA peptide for targeting tumor vasculature or stoma, transferrin, lactoferrin or an aptamer for targeting transferrin receptors expressed on CNS vasculature, or an anti-EGFR antibody for targeting EGFR on glioma cells. In certain embodiments, the targeting ligand is one or more GalNAc moieties.

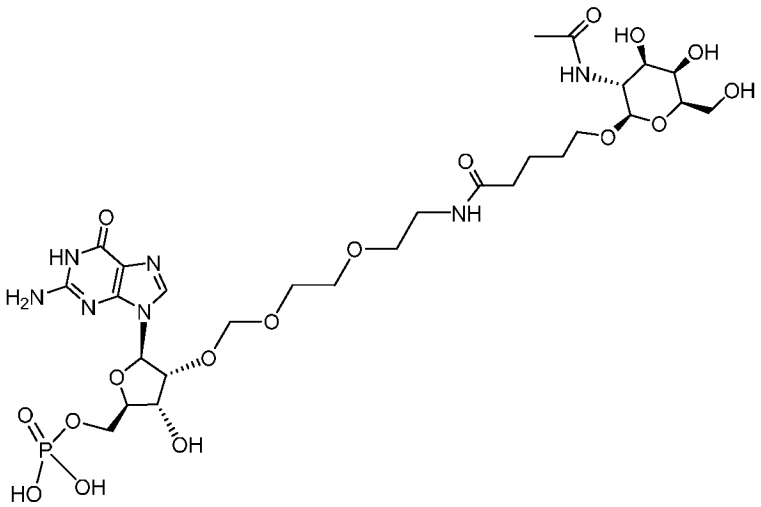
[00148] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of the oligonucleotides each can be conjugated to a separate targeting ligand. In some embodiments, 2 to 4 nucleotides of the oligonucleotides each are conjugated to a separate targeting ligand. In some embodiments, targeting ligands can be conjugated to 2 to 4 nucleotides at either ends of the sense strand or antisense strand (*e.g.*, targeting ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense strand or antisense strand) such that the targeting ligands resemble bristles of a toothbrush and the oligonucleotides resemble a toothbrush. For example, the oligonucleotides comprise a stem-loop at either the 5' or 3' end of the sense strand and 1, 2, 3, or 4 nucleotides of the loop of the stem may be individually conjugated to a targeting ligand. In some embodiments, the oligonucleotides (*e.g.*, a ds oligonucleotide) comprise a stem-loop at the 3' end of the sense strand, where the loop of the stem-loop includes a triloop or a tetraloop, and where the 3 or 4 nucleotides of the triloop or tetraloop, respectfully, are individually conjugated to a targeting ligand.

[00149] GalNAc is a high affinity ligand for the ASGPR, which is primarily expressed on the sinusoidal surface of hepatocyte cells and has a major role in binding, internalizing and subsequent clearing circulating glycoproteins that contain terminal galactose or GalNAc residues (asialoglycoproteins). Conjugation (either indirect or direct) of GalNAc moieties to the oligonucleotides herein are used to target them to the ASGPR expressed on cells. In some embodiments, the oligonucleotides are conjugated to at least one or more GalNAc moieties, where the GalNAc moieties target the oligonucleotides to an ASGPR expressed on human liver cells (*e.g.*, human hepatocytes).

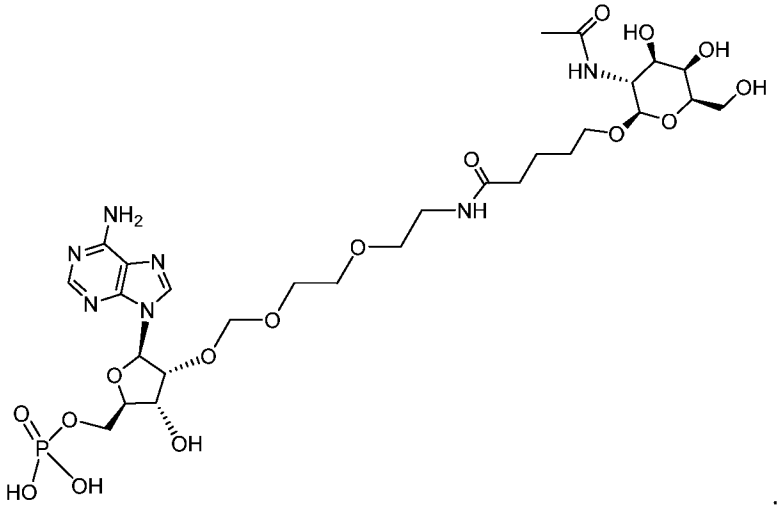
[00150] The oligonucleotides herein are conjugated directly or indirectly to a monovalent GalNAc. In some embodiments, the oligonucleotides are conjugated directly or indirectly to more than one monovalent GalNAc (*i.e.*, is conjugated to 2, 3, or 4 monovalent GalNAc moieties, and is typically conjugated to 3 or 4 monovalent GalNAc moieties). In some embodiments, the oligonucleotides are conjugated to one or more bivalent GalNAc, trivalent GalNAc or tetravalent GalNAc moieties.

[00151] In some embodiments, 1 or more (*e.g.*, 1, 2, 3, 4, 5, or 6) nucleotides of the oligonucleotides herein each can be conjugated to a GalNAc moiety. In some embodiments, 2 to 4 nucleotides of a tetraloop each are conjugated to a separate GalNAc. In other embodiments, 1 to 3 nucleotides of a triloop each are conjugated to a separate GalNAc. In some embodiments, the targeting ligands are conjugated to 2 to 4 nucleotides at either end of the sense or antisense strand (*e.g.*, ligands are conjugated to a 2 to 4 nucleotide overhang or extension on the 5' or 3' end of the sense or antisense strand) such that the GalNAc moieties resemble bristles of a toothbrush and the oligonucleotides resemble a toothbrush. In some embodiments, the GalNAc moieties are conjugated to a nucleotide of the sense strand. For example, 4 GalNAc moieties are conjugated to nucleotides in the tetraloop of the sense strand, where each GalNAc moiety is conjugated to 1 nucleotide. In certain embodiments, 3 GalNAc moieties are conjugated to nucleotides in the tetraloop of the sense strand, where each GalNAc moiety is conjugated to 1 nucleotide.

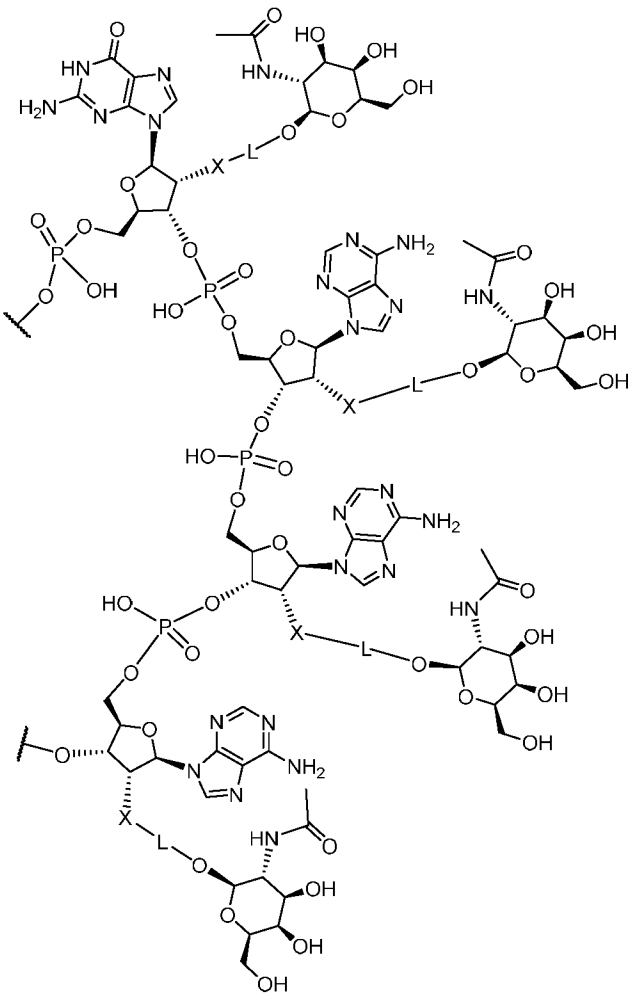
[00152] In certain embodiments, the oligonucleotides comprise a monovalent GalNAc attached to a guanine nucleotide referred to as [ademG-GalNAc] or 2'-aminodiethoxymethanol-Guanine-GalNAc, as depicted below:



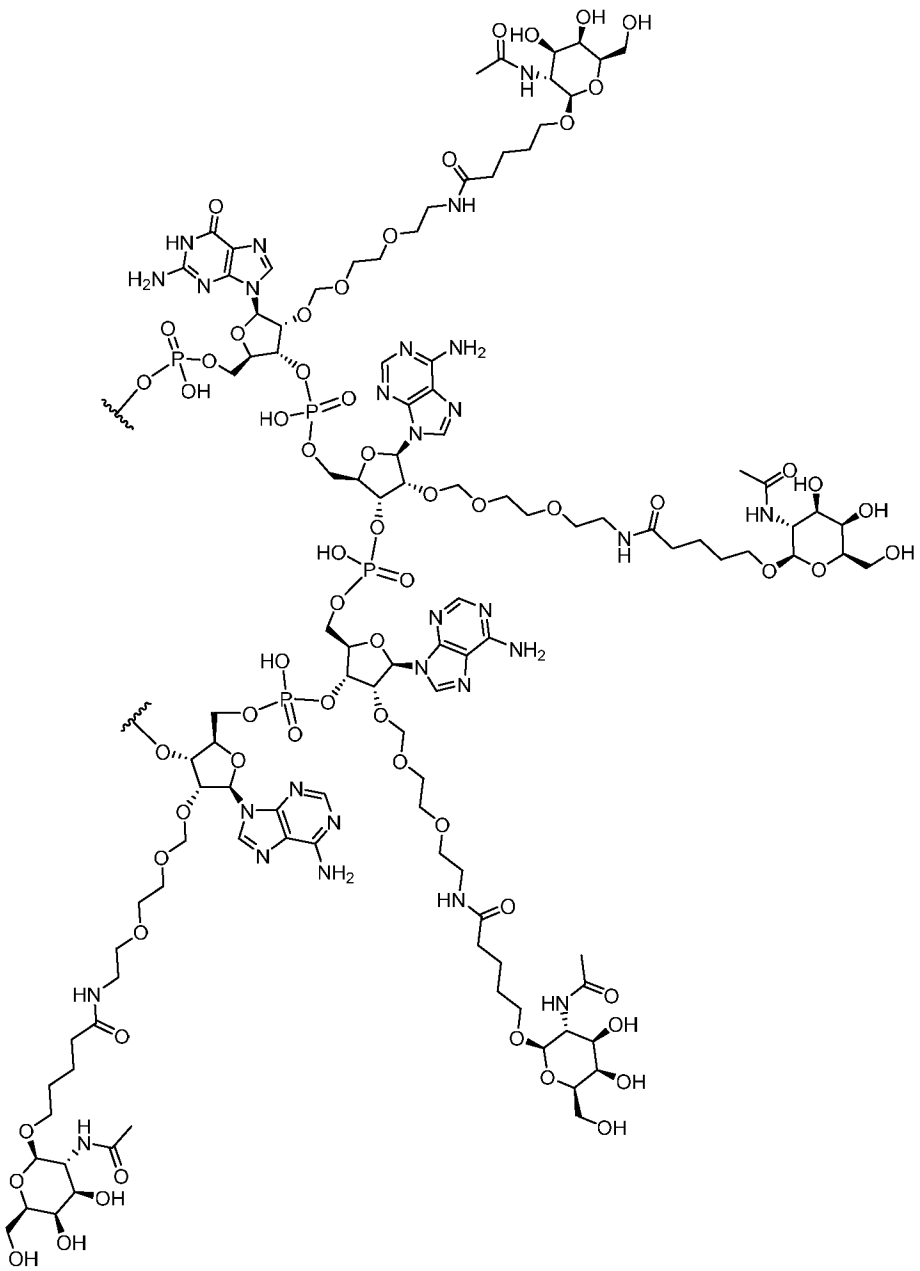
[00153] In certain embodiments, the oligonucleotides herein comprise a monovalent GalNAc attached to an adenine nucleotide, referred to as [ademA-GalNAc] or 2'-aminodiethoxymethanol-Adenine-GalNAc, as depicted below:



[00154] An example of such conjugation is shown below for a loop having from 5' to 3', the nucleotide sequence GAAA (L = linker, X = heteroatom), where stem attachment points are shown. Such a loop is present, for example, at positions 27-30 of the sense strand listed in Table 3, A, B, C or D and as shown in FIG. 1. In the chemical formula,  is used to describe an attachment point to the oligonucleotide strand:



[00155] Appropriate methods or chemistry (*e.g.*, click chemistry) are used to link a targeting ligand to a nucleotide. One way of conjugating the targeting ligand to a nucleotide is by using a click linker. In some embodiments, an acetal-based linker is used to conjugate the targeting ligand to a nucleotide of any one of the oligonucleotides herein. Acetal-based linkers are disclosed, for example, in Intl. Patent Application Publication No. WO 2016/100401. In some instances, the linker is a labile linker. However, in other instances, the linker is stable. An example is shown below for a loop having from 5' to 3', the nucleotides GAAA, in which GalNAc moieties are attached to nucleotides of the loop using an acetal linker. Such a loop is present, for example, at positions 27-30 of the any one of the sense strands listed in Table 3, A, B, C or D. In the chemical formula, $\sim$ is an attachment point to the oligonucleotide strand:



[00156] In some embodiments, a duplex extension (*e.g.*, of up to 3, 4, 5, or 6 bp in length) is provided between the targeting ligand (*e.g.*, a GalNAc moiety) and the oligonucleotides herein (*e.g.*, a ds oligonucleotide). In other embodiments, the oligonucleotides do not have a GalNAc conjugated thereto.

[00157] Formulations and Pharmaceutical Compositions

[00158] The oligonucleotides herein are incorporated into a formulation or pharmaceutical composition. Various formulations have been developed to facilitate oligonucleotide use. For

example, oligonucleotides can be delivered to a subject or a cellular environment using a formulation that minimizes degradation, facilitates delivery and/or uptake, or provides another beneficial property to the oligonucleotides in the formulation. In some embodiments, the oligonucleotides herein are formulated in buffer solutions such as phosphate buffered saline solutions, liposomes, micellar structures, and capsids.

[00159] Formulations of oligonucleotides with cationic lipids are used to facilitate transfection of the oligonucleotides into cells. For example, cationic lipids, such as lipofectin, cationic glycerol derivatives, and polycationic molecules (*e.g.*, polylysine) can be used. Suitable lipids include Oligofectamine, Lipofectamine (Life Technologies), NC388 (Ribozyme Pharmaceuticals, Inc.), or FuGene 6 (Roche), all of which are used according to the manufacturer's instructions.

[00160] Accordingly, in some embodiments, the formulations herein comprise a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere, or a nanoparticle (such as a lipid nanoparticle) or may be otherwise formulated for administration to the cells, tissues, organs, or body of an individual in need thereof (*see*, *e.g.*, Remington, "The Science and Practice of Pharmacy" (L.V. Allen Jr., ed., 22nd Edition, Pharmaceutical Press, 2013).

[00161] In some embodiments, the formulations herein further comprise an excipient, which can confer to a composition improved stability, improved absorption, improved solubility and/or therapeutic enhancement of the active ingredient. In some embodiments, the excipient is a buffering agent (*e.g.*, sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil). In some embodiments, the oligonucleotides herein are lyophilized for extending shelf-life and then made into a solution before use (*e.g.*, administration to an individual). Accordingly, the excipient in a pharmaceutical composition including one or more of the oligonucleotides is a lyoprotectant (*e.g.*, mannitol, lactose, polyethylene glycol, or polyvinylpyrrolidone) or a collapse temperature modifier (*e.g.*, dextran, Ficoll™, or gelatin).

[00162] Pharmaceutical compositions are formulated to be compatible with its intended route of administration. Routes of administration include, but are not limited to, parenteral (*e.g.*, intravenous, intramuscular, intraperitoneal, intradermal, and subcutaneous), oral (*e.g.*, inhalation), transdermal (*e.g.*, topical), transmucosal, and rectal administration.

[00163] Pharmaceutical compositions suitable for injectable use comprise sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous

preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include, but are not limited to, physiological saline, bacteriostatic water, Cremophor EL™ (BASF) or phosphate buffered saline (PBS). The carrier is a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, liquid polyethylene glycol, and the like), as well as suitable mixtures thereof. In many embodiments, it will be preferable to comprise in the compositions with isotonic agents such as, for example, sugars, polyalcohols such as mannitol, sorbitol and/or sodium chloride. Sterile injectable solutions are prepared by incorporating the oligonucleotides herein in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[00164] Moreover, the pharmaceutical compositions comprise at least about 0.1% of a therapeutic agent (*e.g.*, one or more of the oligonucleotides herein) or more, although the percentage of the therapeutic agent may be between about 1% to about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one of skill in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

[00165] Even though several examples are directed toward liver-targeted delivery of at least one of the oligonucleotides herein, targeting of other tissues also is contemplated.

[00166] Kits

[00167] The oligonucleotides herein can be incorporated into a kit comprising one or more of the oligonucleotides herein, and instructions for use. In some embodiments, the kit comprises one or more of the oligonucleotides, and a package insert containing instructions for use of the kit and/or any component thereof. In other embodiments, the kit comprises a suitable container, one or more of the oligonucleotides, one or more controls, and various buffers, reagents, enzymes, and other standard ingredients as are known in the art.

[00168] In some embodiments, the container can be at least one vial, well, test tube, flask, bottle, syringe, or other container means, into which the one or more oligonucleotides are placed, and in some instances, suitably aliquoted. In other embodiments, where an additional component is provided, the kit contains additional containers into which this component is placed. The kits also comprise a means for containing the one or more oligonucleotides and

any other reagent in close confinement for commercial sale. Such containers include injection or blow-molded plastic containers into which the desired vials are retained. Containers and/or kits comprise labeling with instructions for use and/or warnings.

[00169] In some embodiments, the kit comprises one or more oligonucleotides herein, and a pharmaceutically acceptable carrier, or a pharmaceutical composition comprising one or more of the oligonucleotides and instructions for treating or delaying progression of a disease, disorder, or condition associated with *PNPLA3* expression in an individual in need thereof.

[00170] *Methods*

[00171] Methods of Making

[00172] The oligonucleotides herein are made using methods and/or techniques known to one of skill in the art such as, for example, by using conventional nucleic acid solid phase synthesis. The polynucleotides of the oligonucleotides are assembled on a suitable nucleic acid synthesizer utilizing standard nucleotide or nucleoside precursors (*e.g.*, phosphoramidites). Automated nucleic acid synthesizers, including DNA/RNA synthesizers, are commercially available from, for example, Applied Biosystems (Foster City, CA), BioAutomation (Irving,TX), and GE Healthcare Life Sciences (Pittsburgh, PA).

[00173] As one of skill in the art understands, other methods and/or techniques of synthesizing the oligonucleotides herein are used. Additionally, the various synthetic steps are performed in an alternate sequence or order to give the desired compounds. Other synthetic chemistry transformations, protecting groups (*e.g.*, for hydroxyl, amino, *etc.* present on the bases), and protecting group methodologies (protection and deprotection) useful in synthesizing the oligonucleotides are known in the art and are described in, for example, Larock, "Comprehensive Organic Transformations," VCH Publishers (1989); Greene & Wuts, **PROTECTIVE GROUPS IN ORGANIC SYNTHESIS**, 2nd Ed., John Wiley & Sons (1991); Fieser & Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley & Sons (1994); and Paquette, ed., **ENCYCLOPEDIA OF REAGENTS FOR ORGANIC SYNTHESIS**, John Wiley & Sons (1995).

[00174] Methods of Using

[00175] I. Methods of Reducing *PNPLA3* Expression in Cells, Tissue, Organs, and Organisms

[00176] The oligonucleotides herein are used to reduce PNPLA3 mRNA in cells, tissues, organs, or individuals. The methods comprise the steps described herein, and these may be, but not necessarily, carried out in the sequence as described. Other sequences, however, also are conceivable. Moreover, individual, or multiple steps are carried out either in parallel and/or overlapping in time and/or individually or in multiply repeated steps. Furthermore, the methods comprise additional, unspecified steps.

[00177] The methods comprise contacting or delivering to a cell, population of cells, tissues, organs, or individuals an effective amount any of the oligonucleotides herein (*e.g.*, a ds oligonucleotide) for reducing *PNPLA3* expression. In some embodiments, reduced *PNPLA3* expression is determined by measuring a reduction in the amount or level of PNPLA3 mRNA, PNPLA3 protein, or PNPLA3 activity in a cell.

[00178] With regard to an appropriate cell type, the cell type is any cell that expresses mRNA (*e.g.*, hepatocytes, macrophages, monocyte-derived cells, prostate cancer cells, cells of the brain, endocrine tissue, bone marrow, lymph nodes, lung, gall bladder, liver, duodenum, small intestine, pancreas, kidney, gastrointestinal tract, bladder, adipose and soft tissue, and skin). In some embodiments, the cell is a primary cell obtained from an individual. In some embodiments, the primary cell has undergone a limited number of passages such that the cell substantially maintains is natural phenotypic properties. In some embodiments, the cell is an *ex vivo*, *in vivo*, or *in vitro* cell (*i.e.*, such that one or more of the oligonucleotides herein can be delivered to the cell in culture or to an organism in which the cell resides).

[00179] In some embodiments, the oligonucleotides herein are delivered to a cell or population of cells using a nucleic acid delivery method known in the art including, but not limited to, injecting a solution containing the oligonucleotides, bombarding by particles covered by the oligonucleotides, exposing the cell or population of cells to a solution containing the oligonucleotides, or electroporating cell membranes in the presence of the oligonucleotides. Other methods known in the art for delivering oligonucleotides to cells are used such as, for example, lipid-mediated carrier transport, chemical-mediated transport, and cationic liposome transfection such as calcium phosphate, and others.

[00180] Reduced *PNPLA3* expression is determined by an assay or technique that evaluates one or more molecules, properties or characteristics of a cell or population of cells associated with *PNPLA3* expression (*e.g.*, using a PNPLA3 expression biomarker) or by an assay or technique that evaluates molecules that are directly indicative of *PNPLA3* expression in a cell

or population of cells (*e.g.*, PNPLA3 mRNA or PNPLA3 protein). In some embodiments, the extent to which the oligonucleotides reduce *PNPLA3* expression are evaluated by comparing *PNPLA3* expression in a cell or population of cells contacted with the oligonucleotides to a control cell or population of cells (*e.g.*, a cell or population of cells not contacted with the oligonucleotides or contacted with a control oligonucleotide). In some embodiments, a control amount or level of *PNPLA3* expression in a control cell or population of cells is predetermined, such that the control amount or level need not be measured in every instance the assay or technique is performed. The predetermined level or value takes a variety of forms including, but not limited to, a single cut-off value, such as a median or mean.

[00181] Contacting or delivering the oligonucleotides herein (*e.g.*, a ds oligonucleotide) to a cell or a population of cells result in reduced *PNPLA3* expression. In some embodiments, reduced *PNPLA3* expression is relative to a control amount or level of *PNPLA3* expression in the cell or the population of cells not contacted with the oligonucleotides or contacted with a control oligonucleotide. In some embodiments, reduced *PNPLA3* expression is about 1% or lower, about 5% or lower, about 10% or lower, about 15% or lower, about 20% or lower, about 25% or lower, about 30% or lower, about 35% or lower, about 40% or lower, about 45% or lower, about 50% or lower, about 55% or lower, about 60% or lower, about 70% or lower, about 80% or lower, or about 90% or lower relative to a control amount or level of *PNPLA3* expression. In some embodiments, the control amount or level of *PNPLA3* expression is an amount or level of PNPLA3 mRNA and/or PNPLA3 protein in the cell or the population of cells that has not been contacted with oligonucleotides herein. In some embodiments, the effect of delivery of the oligonucleotides to the cell or the population of cells according to a method herein is assessed after any finite period or amount of time (*e.g.*, minutes, hours, days, weeks, and/or months). For example, *PNPLA3* expression is determined in the cell or the population of cells at least about 4 hours, about 8 hours, about 12 hours, about 18 hours, or about 24 hours. Alternatively, *PNPLA3* expression is determined in the cell or the population of cells at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, about 56 days, about 63 days, about 70 days, about 77 days, or about 84 days or more after contacting or delivering the oligonucleotides to the cell or population of cells. In other embodiments, *PNPLA3* expression is determined in the cell or the population of cells at least about 1 month,

about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months or more after contacting or delivering the oligonucleotides to the cell or the population of cells.

[00182] In some embodiments, the oligonucleotides herein are delivered in the form of a transgene that is engineered to express in a cell one or more of the oligonucleotides or strands (*e.g.*, sense and antisense strands). For example, the oligonucleotides are delivered using a transgene engineered to express any oligonucleotide herein. Transgenes may be delivered using viral vectors (*e.g.*, adenovirus, retrovirus, vaccinia virus, poxvirus, adeno-associated virus, or herpes simplex virus) or non-viral vectors (*e.g.*, plasmids or synthetic mRNAs). In some embodiments, the transgenes are injected directly to an individual.

[00183] II. Methods of Treatment:

[00184] Methods for treating an individual having, suspected of having or at risk of developing, a disease, disorder, or condition associated with *PNPLA3* expression comprise administering at least one or more of the oligonucleotides herein. Additionally, methods for treating or attenuating in an individual, an onset or progression of a disease, disorder, or condition associated with *PNPLA3* expression comprise using one or more of the oligonucleotides herein. Furthermore, methods for achieving one or more therapeutic benefits in an individual having a disease, disorder, or condition associated with *PNPLA3* expression comprise providing one or more of the oligonucleotides herein. In some embodiments, the individual can be treated by administering a therapeutically effective amount of any one or more of the oligonucleotides of any of the above disclosed embodiments. In some embodiments, the treatment comprises reducing *PNPLA3* expression. In some embodiments, the individual is treated therapeutically. In some embodiments, the individual is treated prophylactically. In all of these embodiments, the oligonucleotide is selected from Table A, B, C or D.

[00185] In some embodiments, the one or more oligonucleotides, or a pharmaceutical composition including the same, is administered to the individual having a disease, disorder, or condition associated with *PNPLA3* expression such that *PNPLA3* expression is reduced in the individual, thereby treating the individual. In some embodiments, an amount or level of PNPLA3 mRNA is reduced in the individual. In other embodiments, an amount or level of PNPLA3 protein is reduced in the individual. In still other embodiments, an amount or level of PNPLA3 activity is reduced in the individual. In yet other embodiments, an amount or level of liver TG (*e.g.*, one or more TG(s) or total TGs in liver) is reduced in the individual, especially

in the liver. In still other instances, an amount or level of liver inflammation can be reduced. In still other instances, an amount of level of liver fibrosis is reduced. In still other embodiments, an amount or level of plasma AST, plasma ALT, or even Pro-C3 is reduced. In any of the above disclosed embodiments, the oligonucleotides comprise a sense strand having a nucleotide sequence of any one of SEQ ID NOs: 1188, 1190, 1220, 1224, 1230, 1232, 1244, 1246, 1250 or 1254, and an antisense strand having a nucleotide sequence of any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251 or 1255.

[00186] In some embodiments, *PNPLA3* expression is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *PNPLA3* expression prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In other embodiments, *PNPLA3* expression is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to *PNPLA3* expression in an individual (*e.g.*, a reference or control subject) not receiving the one or more oligonucleotides or pharmaceutical composition or receiving a control oligonucleotide, pharmaceutical composition or treatment.

[00187] In certain embodiments, an amount or level of PNPLA3 mRNA is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 mRNA prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of PNPLA3 mRNA is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 mRNA in an individual (*e.g.*, a reference or control subject) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition, or treatment.

[00188] In certain embodiments, an amount or level of PNPLA3 protein is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%,

about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 protein prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In other embodiments, an amount or level of PNPLA3 protein is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 protein in an individual (*e.g.*, a reference or control subject) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00189] In certain embodiments, an amount or level of PNPLA3 activity is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 activity prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of PNPLA3 activity is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of PNPLA3 activity in an individual (*e.g.*, a reference or control subject) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00190] In certain embodiments, an amount or level of TG, especially liver TG, can be reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of TG prior to administering the one or more oligonucleotides or pharmaceutical composition thereof. In some embodiments, the amount or level of TG is reduced in the individual by at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99%, or greater than 99% when compared to an amount or level of TG in an individual (*e.g.*, a reference or control

subject) not administered the one or more oligonucleotides or pharmaceutical composition or administered a control oligonucleotide, pharmaceutical composition or treatment.

[00191] Here, *PNPLA3* expression, the amount or level of PNPLA3 mRNA, PNPLA3 protein, PNPLA3 activity, liver TG, or any combination thereof, is reduced in a cell (*e.g.*, a hepatocyte), a population or a group of cells (*e.g.*, an organoid), a tissue (*e.g.*, liver tissue), a sample (*e.g.*, a liver biopsy sample), an organ (*e.g.*, liver), blood or a fraction thereof (*e.g.*, plasma), or any other biological material obtained or isolated from the individual. In some embodiments, *PNPLA3* expression, the amount or level of PNPLA3 mRNA, PNPLA3 protein, PNPLA3 activity, TG, or any combination thereof, is reduced in more than one type of cell (*e.g.*, a hepatocyte and one or more other type(s) of cell), more than one groups of cells, more than one type of tissue (*e.g.*, liver tissue and one or more other type(s) of tissue), more than one type of sample (*e.g.*, a liver biopsy sample and one or more other type(s) of biopsy sample), more than one organ (*e.g.*, liver and one or more other organ(s)), more than one fraction of blood (*e.g.*, plasma and one or more other blood fraction(s)) obtained or isolated from the subject.

[00192] Examples of a disease, disorder, or condition associated with *PNPLA3* expression include, but are not limited to, AH, ALD, HCC, CCA, PSC, NAFLD, NASH, fatty liver (steatosis), inflammation of the liver, liver fibrosis, cirrhosis of the liver, or a combination thereof.

[00193] Because of their high specificity, the oligonucleotides herein specifically target mRNAs of target genes of cells, tissues, or organs (*e.g.*, liver). In preventing disease, the target gene is the one that is required for initiation or maintenance of the disease or that has been identified as being associated with a higher risk of contracting the disease. In treating disease, one or more of the oligonucleotides are brought into contact with the cells, tissue or organ exhibiting or responsible for mediating the disease. For example, an oligonucleotide substantially identical to all or part of a wild-type (*i.e.*, native) or mutated gene associated with a disorder or condition associated with *PNPLA3* expression is brought into contact with or introduced into a cell or tissue type of interest such as a hepatocyte or other liver cell.

[00194] In some embodiments, the target gene is from any mammal, such as a human. Any gene may be silenced according to the methods herein. Moreover, the methods herein typically involve administering to an individual a therapeutically effective amount of one or more oligonucleotides herein, that is, an amount capable of producing a desirable therapeutic result. The therapeutically acceptable amount is an amount that therapeutically treats a disease or

disorder or condition. The appropriate dosage for any one individual will depend on certain factors, including the individual′s size, body surface area, age, the composition to be administered, the active ingredient(s) in the composition, time and route of administration, general health, and other therapeutic agents being administered concurrently.

[00195] In the methods, the individual is administered any one of the oligonucleotides or compositions herein either enterally (*e.g.*, orally, by gastric feeding tube, by duodenal feeding tube, *via* gastrostomy, or rectally), parenterally (*e.g.*, subcutaneous injection, intravenous injection or infusion, intra-arterial injection or infusion, intraosseous infusion, intramuscular injection, intracerebral injection, intracerebroventricular injection, or intrathecal), topically (*e.g.*, epicutaneous, inhalational, *via* eye drops, or through a mucous membrane), or by direct injection into a target organ (*e.g.*, the liver of a subject). Typically, the oligonucleotides or compositions are administered intravenously or subcutaneously.

[00196] As a non-limiting set of examples, the oligonucleotides or compositions herein typically are administered quarterly (once every three months), bi-monthly (once every two months), monthly or weekly. For example, the oligonucleotides or compositions are administered every week or at intervals of two, or three weeks. In certain embodiments, the oligonucleotides, or compositions are administered daily. In some embodiments, an individual is administered one or more loading doses of the oligonucleotides or compositions followed by one or more maintenance doses of the oligonucleotides or compositions.

[00197] In some embodiments, the individual is a human, a non-human primate, or other mammalian subject. In other embodiments, the individual is a domesticated animal such as a dog or a cats; livestock such as a horse, cattle, pig, sheep, goat, or chicken; and animals such as a mouse, rat, guinea pig or hamster.

III. Medical Uses

[00198] The oligonucleotides herein can be used, or adapted for use, to treat an individual (*e.g.*, a human having a disease, disorder, or condition associated with *PNPLA3* expression) that would benefit from reducing *PNPLA3* expression. In some embodiments, the oligonucleotides are provided for use, or adapted for use, to treat an individual having a disease, disorder, or condition associated with *PNPLA3* expression. Also, the oligonucleotides are provided for use, or adaptable for use, in the manufacture of a medicament or pharmaceutical composition for treating a disease, disorder, or condition associated with *PNPLA3* expression.

In other embodiments, the oligonucleotides are provided for use, or adaptable for use, in targeting PNPLA3 mRNA and reducing *PNPLA3* expression (*e.g.*, *via* the RNAi pathway). In other embodiments, the oligonucleotides are provided for use, or adaptable for use, in targeting PNPLA3 mRNA and reducing an amount or level of PNPLA3 mRNA, PNPLA3 protein, and/or PNPLA3 activity.

[00199] In some embodiments, the methods comprise selecting an individual for treatment based upon the individual having a marker (*e.g.*, a biomarker) for a disease, disorder, or condition associated with *PNPLA3* expression, or someone predisposed to the same, such as, but not limited to, PNPLA3 mRNA, PNPLA3 protein or a combination thereof. Likewise, and as detailed below, the methods also comprise additional steps such as, for example, measuring or obtaining a baseline value for a marker of *PNPLA3* expression (*e.g.*, PNPLA3 protein) and then comparing such obtained value to one or more other baseline values or values obtained after the individual is administered one or more of the oligonucleotides to assess the effectiveness of treatment.

EXAMPLES

[00200] The following non-limiting examples are offered for purposes of illustration, not limitation.

[00201] SYNTHESIS OF OLIGONUCLEOTIDES

[00202] Example 1: Preparing ds RNAi Oligonucleotides

[00203] *Oligonucleotide synthesizing and purifying:* The ds RNAi oligonucleotides in the Examples are chemically synthesized using methods described herein. Generally, ds RNAi oligonucleotides are synthesized using solid phase oligonucleotide synthesis methods as described for 19-23mer siRNAs (*see*, *e.g.*, Scaringe *et al.* (1990) NUCLEIC ACIDS RES. 18:5433-41 and Usman *et al.* (1987) J. AM. CHEM. SOC. 109:7845-45; *see also*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,008,400; 6,111,086; 6,117,657; 6,353,098; 6,362,323; 6,437,117 and 6,469,158).

[00204] Individual RNA strands are synthesized and HPLC purified according to standard methods (Integrated DNA Technologies). For example, RNA oligonucleotides are synthesized using solid phase phosphoramidite chemistry, deprotected, and desalted on NAP-5 columns (Amersham Pharmacia Biotech; Piscataway, NJ) using standard techniques (Damha & Olgivie

(1993) METHODS MOL. BIOL. 20:81-114; Wincott *et al.* (1995) NUCLEIC ACIDS RES. 23:2677-84). The oligomers are purified using ion-exchange high performance liquid chromatography (IE-HPLC) on an Amersham Source 15Q column (1.0 cm×25 cm; Amersham Pharmacia Biotech) using a 15 min step-linear gradient. The gradient varies from 90:10 Buffers A:B to 52:48 Buffers A:B, where Buffer A is 100 mM Tris pH 8.5 and Buffer B is 100 mM Tris pH 8.5, 1 M NaCl. Samples are monitored at 260 nm and peaks corresponding to the full-length oligonucleotide species are collected, pooled, desalted on NAP-5 columns, and lyophilized.

[00205] The purity of each oligomer is determined by capillary electrophoresis (CE) on a Beckman PACE 5000 (Beckman Coulter, Inc.). The CE capillaries have a 100 μm inner diameter and contain ssDNA 100R Gel (Beckman-Coulter). Typically, about 0.6 nmole of oligonucleotide is injected into a capillary, is run in an electric field of 444 V/cm and is detected by UV absorbance at 260 nm. Denaturing Tris-Borate-7 M-urea running buffer is purchased from Beckman-Coulter. Oligoribonucleotides are obtained that are at least 90% pure as assessed by CE for use in experiments described below. Compound identity is verified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy on a Voyager DE™ Biospectometry Work Station (Applied Biosystems) following the manufacturer's recommended protocol. Relative molecular masses of all oligomers are obtained, often within 0.2% of expected molecular mass.

[00206] *Preparing duplexes:* ss RNA oligomers are resuspended (*e.g.*, at 100 μM concentration) in duplex buffer having 100 mM potassium acetate, 30 mM HEPES, pH 7.5. Complementary sense and antisense strands are mixed in equal molar amounts to yield a final solution of, for example, 50 μM duplex. Samples are heated to 100°C for 5 min in RNA buffer (IDT) and are allowed to cool to room temperature before use. The ds RNA oligonucleotides are stored at -20°C. ss RNA oligomers are stored lyophilized or in nuclease-free water at -80°C.

[00207] *IN VITRO* FUNCTION

[00208] Example 2: RNAi Oligonucleotide Inhibition of *PNPLA3* Expression *In Vitro*

[00209] *PNPLA3 target sequence identifying:* To identify RNAi oligonucleotide inhibitors of *PNPLA3* expression, a computer-based algorithm is used to computationally generate PNPLA3 target sequences suitable for assaying PNPLA3 expression inhibition by the RNAi pathway. The algorithm provides RNAi oligonucleotide guide (antisense) strand sequences that are

complementary to suitable *PNPLA3* target sequences of human PNPLA3 mRNA (*e.g.*, SEQ ID NO:1). Some of the guide strand sequences identified by the algorithm also are complementary to the corresponding *PNPLA3* target sequence of monkey PNPLA mRNA. Some of the antisense (guide) strand sequences identified by the algorithm also are complementary to the corresponding PNPLA3 target sequence of monkey PNPLA3 mRNA (*e.g.*, SEQ ID NO:5). From this, 384 ds RNAi oligonucleotides (formatted as DsiRNA oligonucleotides) are generated, each with a unique antisense strand having a region of complementarity to a PNPLA3 target sequence identified by the algorithm.

[00210] Table 1: DsiRNAs (unmodified) Targeting Human PNPLA3 mRNA and Controls Evaluated in Cells.

DsiRNA	Passenger (sense)	SEQ ID NO:	Guide (antisense)	SEQ ID NO:
1	UCUGCAGGUCCUCUCAGAUCUUGUG	9	CACAAGAUCUGAGAGGACCUGCAGAGU	10
2	AGGUCCUCUCAGAUCUUGUGCGGAA	11	UUCCGCACAAGAUCUGAGAGGACCUGC	12
3	AUUGGCAUCUUCCAUCCAUCCUUCA	13	UGAAGGAUGGAUGGAAGAUGCCAAUGU	14
4	AUCUUCCAUCCAUCCUUCAACUUAA	15	UUAAGUUGAAGGAUGGAUGGAAGAUGC	16
5	UCUUCCAUCCAUCCUUCAACUUAAG	17	CUUAAGUUGAAGGAUGGAUGGAAGAUG	18
6	CCAGAGUGUCUGAUGGGGAAAACGU	19	ACGUUUUCCCCAUCAGACACUCUGGUA	20
7	GAGUGUCUGAUGGGGAAAACGUUCU	21	AGAACGUUUUCCCCAUCAGACACUCUG	22
8	AUGGGGAAAACGUUCUGGUGUCUGA	23	UCAGACACCAGAACGUUUUCCCCAUCA	24
9	GGGGAAAACGUUCUGGUGUCUGACU	25	AGUCAGACACCAGAACGUUUUCCCCAU	26
10	GGGAAAACGUUCUGGUGUCUGACUU	27	AAGUCAGACACCAGAACGUUUUCCCCA	28
11	GGAAAACGUUCUGGUGUCUGACUUU	29	AAAGUCAGACACCAGAACGUUUUCCCC	30
12	GAAAACGUUCUGGUGUCUGACUUUC	31	GAAAGUCAGACACCAGAACGUUUUCCC	32
13	AAAACGUUCUGGUGUCUGACUUUCG	33	CGAAAGUCAGACACCAGAACGUUUUCC	34
14	AAACGUUCUGGUGUCUGACUUUCGG	35	CCGAAAGUCAGACACCAGAACGUUUUC	36
15	AACGUUCUGGUGUCUGACUUUCGGU	37	ACCGAAAGUCAGACACCAGAACGUUUU	38
16	ACGUUCUGGUGUCUGACUUUCGGUC	39	GACCGAAAGUCAGACACCAGAACGUUU	40
17	GUUCUGGUGUCUGACUUUCGGUCCA	41	UGGACCGAAAGUCAGACACCAGAACGU	42
18	GACGAAGUCGUGGAUGCCUUGGUAU	43	AUACCAAGGCAUCCACGACUUCGUCUU	44
19	ACGAAGUCGUGGAUGCCUUGGUAUG	45	CAUACCAAGGCAUCCACGACUUCGUCU	46
20	CGAAGUCGUGGAUGCCUUGGUAUGU	47	ACAUACCAAGGCAUCCACGACUUCGUC	48
21	CAGAGGCGUGCGAUAUGUGGAUGGA	49	UCCAUCCACAUAUCGCACGCCUCUGAA	50
22	GCGAUAUGUGGAUGGAGGAGUGAGU	51	ACUCACUCCUCCAUCCACAUAUCGCAC	52
23	GAUGGAGGAGUGAGUGACAACGUAC	53	GUACGUUGUCACUCACUCCUCCAUCCA	54
24	GAGGAGUGAGUGACAACGUACCCUU	55	AAGGGUACGUUGUCACUCACUCCUCCA	56

25	GAGUGAGUGACAACGUACCCUUCAU	57	AUGAAGGGUACGUUGUCACUCACUCCU	58
26	AGUGAGUGACAACGUACCCUUCAUU	59	AAUGAAGGGUACGUUGUCACUCACUCC	60
27	GUGAGUGACAACGUACCCUUCAUUG	61	CAAUGAAGGGUACGUUGUCACUCACUC	62
28	UGAGUGACAACGUACCCUUCAUUGA	63	UCAAUGAAGGGUACGUUGUCACUCACU	64
29	GAGUGACAACGUACCCUUCAUUGAU	65	AUCAAUGAAGGGUACGUUGUCACUCAC	66
30	AGUGACAACGUACCCUUCAUUGAUG	67	CAUCAAUGAAGGGUACGUUGUCACUCA	68
31	GUGACAACGUACCCUUCAUUGAUGC	69	GCAUCAAUGAAGGGUACGUUGUCACUC	70
32	UGACAACGUACCCUUCAUUGAUGCC	71	GGCAUCAAUGAAGGGUACGUUGUCACU	72
33	GACAACGUACCCUUCAUUGAUGCCA	73	UGGCAUCAAUGAAGGGUACGUUGUCAC	74
34	CAACGUACCCUUCAUUGAUGCCAAA	75	UUUGGCAUCAAUGAAGGGUACGUUGUC	76
35	AACGUACCCUUCAUUGAUGCCAAAA	77	UUUUGGCAUCAAUGAAGGGUACGUUGU	78
36	ACGUACCCUUCAUUGAUGCCAAAAC	79	GUUUUGGCAUCAAUGAAGGGUACGUUG	80
37	CGUACCCUUCAUUGAUGCCAAAACA	81	UGUUUUGGCAUCAAUGAAGGGUACGUU	82
38	UACCCUUCAUUGAUGCCAAAACAAC	83	GUUGUUUUGGCAUCAAUGAAGGGUACG	84
39	UUGAUGCCAAAACAACCAUCACCGU	85	ACGGUGAUGGUUGUUUUGGCAUCAAUG	86
40	GAUGCCAAAACAACCAUCACCGUGU	87	ACACGGUGAUGGUUGUUUUGGCAUCAA	88
41	AUGGGGAGUACGACAUCUGCCCUAA	89	UUAGGGCAGAUGUCGUACUCCCCAUAG	90
42	GUACGACAUCUGCCCUAAAGUCAAG	91	CUUGACUUUAGGGCAGAUGUCGUACUC	92
43	GACAUCUGCCCUAAAGUCAAGUCCA	93	UGGACUUGACUUUAGGGCAGAUGUCGU	94
44	ACAUCUGCCCUAAAGUCAAGUCCAC	95	GUGGACUUGACUUUAGGGCAGAUGUCG	96
45	GUCAAGUCCACGAACUUUCUUCAUG	97	CAUGAAGAAAGUUCGUGGACUUGACUU	98
46	UCAAGUCCACGAACUUUCUUCAUGU	99	ACAUGAAGAAAGUUCGUGGACUUGACU	100
47	CAAGUCCACGAACUUUCUUCAUGUG	101	CACAUGAAGAAAGUUCGUGGACUUGAC	102
48	GUCCACGAACUUUCUUCAUGUGGAC	103	GUCCACAUGAAGAAAGUUCGUGGACUU	104
49	CCACGAACUUUCUUCAUGUGGACAU	105	AUGUCCACAUGAAGAAAGUUCGUGGAC	106
50	CACGAACUUUCUUCAUGUGGACAUC	107	GAUGUCCACAUGAAGAAAGUUCGUGGA	108
51	ACGAACUUUCUUCAUGUGGACAUCA	109	UGAUGUCCACAUGAAGAAAGUUCGUGG	110
52	CGAACUUUCUUCAUGUGGACAUCAC	111	GUGAUGUCCACAUGAAGAAAGUUCGUG	112

53	GAACUUUCUUCAUGUGGACAUCACC	113	GGUGAUGUCCACAUGAAGAAAGUUCGU	114
54	AACUUUCUUCAUGUGGACAUCACCA	115	UGGUGAUGUCCACAUGAAGAAAGUUCG	116
55	ACUUUCUUCAUGUGGACAUCACCAA	117	UUGGUGAUGUCCACAUGAAGAAAGUUC	118
56	CUUUCUUCAUGUGGACAUCACCAAG	119	CUUGGUGAUGUCCACAUGAAGAAAGUU	120
57	UUUCUUCAUGUGGACAUCACCAAGC	121	GCUUGGUGAUGUCCACAUGAAGAAAGU	122
58	UUCUUCAUGUGGACAUCACCAAGCU	123	AGCUUGGUGAUGUCCACAUGAAGAAAG	124
59	CUUCAUGUGGACAUCACCAAGCUCA	125	UGAGCUUGGUGAUGUCCACAUGAAGAA	126
60	UUCAUGUGGACAUCACCAAGCUCAG	127	CUGAGCUUGGUGAUGUCCACAUGAAGA	128
61	UCAUGUGGACAUCACCAAGCUCAGU	129	ACUGAGCUUGGUGAUGUCCACAUGAAG	130
62	CAUGUGGACAUCACCAAGCUCAGUC	131	GACUGAGCUUGGUGAUGUCCACAUGAA	132
63	AUGUGGACAUCACCAAGCUCAGUCU	133	AGACUGAGCUUGGUGAUGUCCACAUGA	134
64	UGUGGACAUCACCAAGCUCAGUCUA	135	UAGACUGAGCUUGGUGAUGUCCACAUG	136
65	GUGGACAUCACCAAGCUCAGUCUAC	137	GUAGACUGAGCUUGGUGAUGUCCACAU	138
66	UGGACAUCACCAAGCUCAGUCUACG	139	CGUAGACUGAGCUUGGUGAUGUCCACA	140
67	AGCUUUUGUCCCCCCGGAUCUCAAG	141	CUUGAGAUCCGGGGGGACAAAAGCUCU	142
68	AAGGUGCUGGGAGAGAUAUGCCUUC	143	GAAGGCAUAUCUCUCCCAGCACCUUGA	144
69	GGGAGAGAUAUGCCUUCGAGGAUAU	145	AUAUCCUCGAAGGCAUAUCUCUCCCAG	146
70	GGAGAGAUAUGCCUUCGAGGAUAUU	147	AAUAUCCUCGAAGGCAUAUCUCUCCCA	148
71	AGAGAUAUGCCUUCGAGGAUAUUUG	149	CAAAUAUCCUCGAAGGCAUAUCUCUCC	150
72	GAGAUAUGCCUUCGAGGAUAUUUGG	151	CCAAAUAUCCUCGAAGGCAUAUCUCUC	152
73	AGAUAUGCCUUCGAGGAUAUUUGGA	153	UCCAAAUAUCCUCGAAGGCAUAUCUCU	154
74	GAUAUGCCUUCGAGGAUAUUUGGAU	155	AUCCAAAUAUCCUCGAAGGCAUAUCUC	156
72	AUAUGCCUUCGAGGAUAUUUGGAUG	157	CAUCCAAAUAUCCUCGAAGGCAUAUCU	158
76	AUGCCUUCGAGGAUAUUUGGAUGCA	159	UGCAUCCAAAUAUCCUCGAAGGCAUAU	160
77	UGCCUUCGAGGAUAUUUGGAUGCAU	161	AUGCAUCCAAAUAUCCUCGAAGGCAUA	162
78	GCCUUCGAGGAUAUUUGGAUGCAUU	163	AAUGCAUCCAAAUAUCCUCGAAGGCAU	164
79	UCAGGUUCUUGGAAGAGAAGGGCAU	165	AUGCCCUUCUCUUCCAAGAACCUGAAU	166
80	CAGGUUCUUGGAAGAGAAGGGCAUC	167	GAUGCCCUUCUCUUCCAAGAACCUGAA	168

81	AGGUUCUUGGAAGAGAAGGGCAUCU	169	AGAUGCCCUUCUCUUCCAAGAACCUGA	170
82	GGUUCUUGGAAGAGAAGGGCAUCUG	171	CAGAUGCCCUUCUCUUCCAAGAACCUG	172
83	UGGAAGAGAAGGGCAUCUGCAACAG	173	CUGUUGCAGAUGCCCUUCUCUUCCAAG	174
84	UGAAGUCAUCCUCAGAAGGGAUGGA	175	UCCAUCCCUUCUGAGGAUGACUUCAGG	176
85	GAAGUCAUCCUCAGAAGGGAUGGAU	177	AUCCAUCCCUUCUGAGGAUGACUUCAG	178
86	AAGUCAUCCUCAGAAGGGAUGGAUC	179	GAUCCAUCCCUUCUGAGGAUGACUUCA	180
87	GUCAUCCUCAGAAGGGAUGGAUCCU	181	AGGAUCCAUCCCUUCUGAGGAUGACUU	182
88	CAUCCUCAGAAGGGAUGGAUCCUGA	183	UCAGGAUCCAUCCCUUCUGAGGAUGAC	184
89	AUCCUCAGAAGGGAUGGAUCCUGAG	185	CUCAGGAUCCAUCCCUUCUGAGGAUGA	186
90	CUAGACCACCUGCGUCUCAGCAUCC	187	GGAUGCUGAGACGCAGGUGGUCUAGCA	188
91	AGUGAAGAAAUGAAAGACAAAGGUG	189	CACCUUUGUCUUUCAUUUCUUCACUCA	190
92	GUGAAGAAAUGAAAGACAAAGGUGG	191	CCACCUUUGUCUUUCAUUUCUUCACUC	192
93	UGAAGAAAUGAAAGACAAAGGUGGA	193	UCCACCUUUGUCUUUCAUUUCUUCACU	194
94	GAAGAAAUGAAAGACAAAGGUGGAU	195	AUCCACCUUUGUCUUUCAUUUCUUCAC	196
95	AAGAAAUGAAAGACAAAGGUGGAUA	197	UAUCCACCUUUGUCUUUCAUUUCUUCA	198
96	AGAAAUGAAAGACAAAGGUGGAUAC	199	GUAUCCACCUUUGUCUUUCAUUUCUUC	200
97	GAAAUGAAAGACAAAGGUGGAUACA	201	UGUAUCCACCUUUGUCUUUCAUUUCUU	202
98	AAAUGAAAGACAAAGGUGGAUACAU	203	AUGUAUCCACCUUUGUCUUUCAUUUCU	204
99	AAUGAAAGACAAAGGUGGAUACAUG	205	CAUGUAUCCACCUUUGUCUUUCAUUUC	206
100	AUGAAAGACAAAGGUGGAUACAUGA	207	UCAUGUAUCCACCUUUGUCUUUCAUUU	208
101	UGAAAGACAAAGGUGGAUACAUGAG	209	CUCAUGUAUCCACCUUUGUCUUUCAUU	210
102	GAAAGACAAAGGUGGAUACAUGAGC	211	GCUCAUGUAUCCACCUUUGUCUUUCAU	212
103	AAGACAAAGGUGGAUACAUGAGCAA	213	UUGCUCAUGUAUCCACCUUUGUCUUUC	214
104	AGACAAAGGUGGAUACAUGAGCAAG	215	CUUGCUCAUGUAUCCACCUUUGUCUUU	216
105	GACAAAGGUGGAUACAUGAGCAAGA	217	UCUUGCUCAUGUAUCCACCUUUGUCUU	218
106	ACAAAGGUGGAUACAUGAGCAAGAU	219	AUCUUGCUCAUGUAUCCACCUUUGUCU	220
107	AAGGUGGAUACAUGAGCAAGAUUUG	221	CAAAUCUUGCUCAUGUAUCCACCUUUG	222
108	AGGUGGAUACAUGAGCAAGAUUUGC	223	GCAAAUCUUGCUCAUGUAUCCACCUUU	224

109	UGGAUACAUGAGCAAGAUUUGCAAC	225	GUUGCAAAUCUUGCUCAUGUAUCCACC	226
110	GGAUACAUGAGCAAGAUUUGCAACU	227	AGUUGCAAAUCUUGCUCAUGUAUCCAC	228
111	GAUACAUGAGCAAGAUUUGCAACUU	229	AAGUUGCAAAUCUUGCUCAUGUAUCCA	230
112	AUACAUGAGCAAGAUUUGCAACUUG	231	CAAGUUGCAAAUCUUGCUCAUGUAUCC	232
113	UACAUGAGCAAGAUUUGCAACUUGC	233	GCAAGUUGCAAAUCUUGCUCAUGUAUC	234
114	ACAUGAGCAAGAUUUGCAACUUGCU	235	AGCAAGUUGCAAAUCUUGCUCAUGUAU	236
115	CAUGAGCAAGAUUUGCAACUUGCUA	237	UAGCAAGUUGCAAAUCUUGCUCAUGUA	238
116	AUGAGCAAGAUUUGCAACUUGCUAC	239	GUAGCAAGUUGCAAAUCUUGCUCAUGU	240
117	UGAGCAAGAUUUGCAACUUGCUACC	241	GGUAGCAAGUUGCAAAUCUUGCUCAUG	242
118	GAGCAAGAUUUGCAACUUGCUACCC	243	GGGUAGCAAGUUGCAAAUCUUGCUCAU	244
119	AGCAAGAUUUGCAACUUGCUACCCA	245	UGGGUAGCAAGUUGCAAAUCUUGCUCA	246
120	GCAAGAUUUGCAACUUGCUACCCAU	247	AUGGGUAGCAAGUUGCAAAUCUUGCUC	248
121	CAAGAUUUGCAACUUGCUACCCAUU	249	AAUGGGUAGCAAGUUGCAAAUCUUGCU	250
122	AAGAUUUGCAACUUGCUACCCAUUA	251	UAAUGGGUAGCAAGUUGCAAAUCUUGC	252
123	AGAUUUGCAACUUGCUACCCAUUAG	253	CUAAUGGGUAGCAAGUUGCAAAUCUUG	254
124	GAUUUGCAACUUGCUACCCAUUAGG	255	CCUAAUGGGUAGCAAGUUGCAAAUCUU	256
125	AUUUGCAACUUGCUACCCAUUAGGA	257	UCCUAAUGGGUAGCAAGUUGCAAAUCU	258
126	UUUGCAACUUGCUACCCAUUAGGAU	259	AUCCUAAUGGGUAGCAAGUUGCAAAUC	260
127	UUGCAACUUGCUACCCAUUAGGAUA	261	UAUCCUAAUGGGUAGCAAGUUGCAAAU	262
128	UGCAACUUGCUACCCAUUAGGAUAA	263	UUAUCCUAAUGGGUAGCAAGUUGCAAA	264
129	GCAACUUGCUACCCAUUAGGAUAAU	265	AUUAUCCUAAUGGGUAGCAAGUUGCAA	266
130	CAACUUGCUACCCAUUAGGAUAAUG	267	CAUUAUCCUAAUGGGUAGCAAGUUGCA	268
131	CUUGCUACCCAUUAGGAUAAUGUCU	269	AGACAUUAUCCUAAUGGGUAGCAAGUU	270
132	UUGCUACCCAUUAGGAUAAUGUCUU	271	AAGACAUUAUCCUAAUGGGUAGCAAGU	272
133	UGCUACCCAUUAGGAUAAUGUCUUA	273	UAAGACAUUAUCCUAAUGGGUAGCAAG	274
134	AUUAGGAUAAUGUCUUAUGUAAUGC	275	GCAUUACAUAAGACAUUAUCCUAAUGG	276
135	UUAGGAUAAUGUCUUAUGUAAUGCU	277	AGCAUUACAUAAGACAUUAUCCUAAUG	278
136	CUGUGGAAUCUGCCAUUGCGAUUGU	279	ACAAUCGCAAUGGCAGAUUCCACAGGC	280

137	GGAAUCUGCCAUUGCGAUUGUCCAG	281	CUGGACAAUCGCAAUGGCAGAUUCCAC	282
138	GAAUCUGCCAUUGCGAUUGUCCAGA	283	UCUGGACAAUCGCAAUGGCAGAUUCCA	284
139	AAUCUGCCAUUGCGAUUGUCCAGAG	285	CUCUGGACAAUCGCAAUGGCAGAUUCC	286
140	AUCUGCCAUUGCGAUUGUCCAGAGA	287	UCUCUGGACAAUCGCAAUGGCAGAUUC	288
141	CCAUUGCGAUUGUCCAGAGACUGGU	289	ACCAGUCUCUGGACAAUCGCAAUGGCA	290
142	CAUUGCGAUUGUCCAGAGACUGGUG	291	CACCAGUCUCUGGACAAUCGCAAUGGC	292
143	AUUGCGAUUGUCCAGAGACUGGUGA	293	UCACCAGUCUCUGGACAAUCGCAAUGG	294
144	UUGCGAUUGUCCAGAGACUGGUGAC	295	GUCACCAGUCUCUGGACAAUCGCAAUG	296
145	UGCGAUUGUCCAGAGACUGGUGACA	297	UGUCACCAGUCUCUGGACAAUCGCAAU	298
146	GCGAUUGUCCAGAGACUGGUGACAU	299	AUGUCACCAGUCUCUGGACAAUCGCAA	300
147	CGAUUGUCCAGAGACUGGUGACAUG	301	CAUGUCACCAGUCUCUGGACAAUCGCA	302
148	AUUGUCCAGAGACUGGUGACAUGGC	303	GCCAUGUCACCAGUCUCUGGACAAUCG	304
149	GUCCAGAGACUGGUGACAUGGCUUC	305	GAAGCCAUGUCACCAGUCUCUGGACAA	306
150	CCAGAGACUGGUGACAUGGCUUCCA	307	UGGAAGCCAUGUCACCAGUCUCUGGAC	308
151	CAGAGACUGGUGACAUGGCUUCCAG	309	CUGGAAGCCAUGUCACCAGUCUCUGGA	310
152	AGAGACUGGUGACAUGGCUUCCAGA	311	UCUGGAAGCCAUGUCACCAGUCUCUGG	312
153	GAGACUGGUGACAUGGCUUCCAGAU	313	AUCUGGAAGCCAUGUCACCAGUCUCUG	314
154	AGACUGGUGACAUGGCUUCCAGAUA	315	UAUCUGGAAGCCAUGUCACCAGUCUCU	316
155	GACUGGUGACAUGGCUUCCAGAUAU	317	AUAUCUGGAAGCCAUGUCACCAGUCUC	318
156	ACUGGUGACAUGGCUUCCAGAUAUG	319	CAUAUCUGGAAGCCAUGUCACCAGUCU	320
157	CUGGUGACAUGGCUUCCAGAUAUGC	321	GCAUAUCUGGAAGCCAUGUCACCAGUC	322
158	GACAUGGCUUCCAGAUAUGCCCGAC	323	GUCGGGCAUAUCUGGAAGCCAUGUCAC	324
159	CAUGGCUUCCAGAUAUGCCCGACGA	325	UCGUCGGGCAUAUCUGGAAGCCAUGUC	326
160	CAGAUAUGCCCGACGAUGUCCUGUG	327	CACAGGACAUCGUCGGGCAUAUCUGGA	328
161	CUCACAGGUGUUCACUCGAGUGCUG	329	CAGCACUCGAGUGAACACCUGUGAGGU	330
162	CACUCGAGUGCUGAUGUGUCUGCUC	331	GAGCAGACACAUCAGCACUCGAGUGAA	332
163	CUCGAGUGCUGAUGUGUCUGCUCCC	333	GGGAGCAGACACAUCAGCACUCGAGUG	334
164	CCCAAAUGCCAGUGAGCAGCCAACA	335	UGUUGGCUGCUCACUGGCAUUUGGGAC	336

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167	AGGUCCAGCCUGAACUUCUUCUUGG	341	CCAAGAAGAAGUUCAGGCUGGACCUGA	342
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177	CCUUUCCCAGUUUUUCACUAGAGAA	361	UUCUCUAGUGAAAAACUGGGAAAGGUG	362
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179	UCUAGCAGAUUCUUUCAGAGGUGCU	365	AGCACCUCUGAAAGAAUCUGCUAGACU	366
180	AGCAGAUUCUUUCAGAGGUGCUAAA	367	UUUAGCACCUCUGAAAGAAUCUGCUAG	368
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182	CAGAUUCUUUCAGAGGUGCUAAAGU	371	ACUUUAGCACCUCUGAAAGAAUCUGCU	372
183	AGAUUCUUUCAGAGGUGCUAAAGUU	373	AACUUUAGCACCUCUGAAAGAAUCUGC	374
184	GAUUCUUUCAGAGGUGCUAAAGUUU	375	AAACUUUAGCACCUCUGAAAGAAUCUG	376
185	AUUCUUUCAGAGGUGCUAAAGUUUC	377	GAAACUUUAGCACCUCUGAAAGAAUCU	378
186	AGGUGCUAAAGUUUCCCAUCUUUGU	379	ACAAAGAUGGGAAACUUUAGCACCUCU	380
187	GGUGCUAAAGUUUCCCAUCUUUGUG	381	CACAAAGAUGGGAAACUUUAGCACCUC	382
188	GUGCUAAAGUUUCCCAUCUUUGUGC	383	GCACAAAGAUGGGAAACUUUAGCACCU	384
189	GCUAAAGUUUCCCAUCUUUGUGCAG	385	CUGCACAAAGAUGGGAAACUUUAGCAC	386
190	CUAAAGUUUCCCAUCUUUGUGCAGC	387	GCUGCACAAAGAUGGGAAACUUUAGCA	388
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235	AGAGGGUCCCUUACUGACUGUUUCG	477	CGAAACAGUCAGUAAGGGACCCUCUGC	478
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383	ACUUUCAGCAUGAGAAAAUAACUCC	773	GGAGUUAUUUUCUCAUGCUGAAAGUGA	774
384	CUUUCAGCAUGAGAAAAUAACUCCT	775	AGGAGUUAUUUUCUCAUGCUGAAAGUG	776

[00211] *In vitro cell-based assays:* The ability of each of the 384 DsiRNAs listed in Table 1 to inhibit *PNPLA3* expression is determined using *in vitro* cell-based assays. Further, the nucleotide sequences for the passenger strand and guide strand of the DsiRNAs have a distinct pattern of modified nucleotides and phosphorothioate linkages (*see*, *e.g.*, FIG. 2). Briefly, HuH-7 human liver cells stably expressing *PNPLA3* are transfected with each of the DsiRNAs (0.5 nM) in separate wells of a multi-well cell culture plate. Cells are maintained for 24 hr. following transfection, and then levels of remaining PNPLA3 mRNA from the transfected cells are determined using TAQMAN®-based qPCR assays. Two qPCR assays, a 3' assay and a 5' assay, are used to determine mRNA levels as measured by HEX and FAM probes, respectively.

[00212] The results of the HuH-7 cell-based assay with the DsiRNAs are shown in Table 2. Table 2 shows the results of the HuH-7 cell-based assay with 384 DsiRNAs that have guide strands that are complementary to human and monkey PNPLA3 mRNA ("double-common"). Transfection of a double-common DsiRNA that results in less than or equal to 30% PNPLA3 mRNA remaining in the cells when compared to negative controls is considered a candidate PNPLA3 expression inhibitor (referred to herein as a "hit").

Table 2: Double-Common DsiRNA PNPLA3 Knockdown in HuH-7 Cells, 0.5 nM 24 hr-5'and -3' Assays % mRNA Remaining (normalized to HPRT1 and SFRS9 vs Mock Control).

	PNPLA3-F495		PNPLA3-F595		Averages	
DsiRNA	% Remaining	% SEM	% Remaining	% SEM	Average % Remaining	Average % SEM
1	--	--	41.276	5.253	41.2760	5.2530
2	24.048	5.091	33.293	8.521	28.6705	6.8060
3	23.686	3.496	36.027	2.441	29.8565	2.9685
4	20.851	2.728	31.34	4.013	26.0955	3.3705
5	19.609	4.442	30.014	4.678	24.8115	4.5600
6	17.737	2.25	38.518	5.495	28.1275	3.8725
7	42.296	6.654	--	--	42.2960	6.6540
8	30.019	2.843	35.275	5.401	32.6470	4.1220
9	107.259	15.824	77.986	22.381	92.6225	19.1025
10	69.476	36.895	83.554	28.116	76.5150	32.5055
11	39.447	10.162	31.949	3.604	35.6980	6.8830
12	--	--	31.418	19.31	31.4180	19.3100
13	82.71	31.376	81.104	20.936	81.9070	26.1560
14	35.657	4.964	54.326	6.388	44.9915	5.6760
15	32.849	4.61	28.693	2.08	30.7710	3.3450
16	--	--	--	--	--	--
17	--	--	38.503	11.845	38.5030	11.8450

18	35.771	6.677	53.554	4.637	44.6625	5.6570
19	13.754	5.708	23.172	6.037	18.4630	5.8725
20	30.11	15.649	40.907	11.249	35.5085	13.4490
21	29.368	4.354	51.409	11.578	40.3885	7.9660
22	55.824	19.324	56.734	15.375	56.2790	17.3495
23	27.853	4.585	30.09	5.153	28.9715	4.8690
24	38.262	20.656	42.106	12.679	40.1840	16.6675
25	27.359	2.988	33.97	4.654	30.6645	3.8210
26	34.444	22.868	75.891	39.63	55.1675	31.2490
27	52.207	13.773	37.602	4.715	44.9045	9.2440
28	27.654	4.589	26.822	3.115	27.2380	3.8520
29	40.199	5.272	35.055	4.257	37.6270	4.7645
30	27.071	6.617	27.672	4.172	27.3715	5.3945
31	26.453	4.251	31.149	2.751	28.8010	3.5010
32	44.932	8.656	32.93	3.5	38.9310	6.0780
33	97.873	67.085	132.571	104.973	115.2220	86.0290
34	27.054	5.653	44.814	11.339	35.9340	8.4960
35	178.389	145.305	220.361	218.004	199.3750	181.6545
36	22.973	7.112	39.55	6.188	31.2615	6.6500
37	32.844	4.1	40.917	5.782	36.8805	4.9410
38	36.642	13.921	34.387	13.321	35.5145	13.6210
39	43.801	18.504	54.98	32.264	49.3905	25.3840
40	38.178	18.519	103.356	40.968	70.7670	29.7435
41	33.309	13.99	36.814	10.58	35.0615	12.2850
42	25.27	4.156	26.624	4.591	25.9470	4.3735
43	22.02	2.478	39.928	6.08	30.9740	4.2790
44	19.086	1.83	28.238	2.134	23.6620	1.9820
45	60.907	30.543	77.064	28.815	68.9855	29.6790
46	32.715	4.298	45.502	4.177	39.1085	4.2375
47	32.36	7.13	50.54	6.722	41.4500	6.9260
48	28.239	8.334	52.43	10.568	40.3345	9.4510
49	49.22	7.374	44.676	7.588	46.9480	7.4810
50	64.843	20.454	53.307	13.88	59.0750	17.1670
51	31.516	10.842	28.143	3.648	29.8295	7.2450
52	38.404	7.542	29.373	4.595	33.8885	6.0685
53	55.094	5.175	65.67	8.678	60.3820	6.9265
54	56.104	4.672	48.547	3.664	52.3255	4.1680
55	78.803	6.549	50.57	4.167	64.6865	5.3580
56	56.816	6.257	42.303	4.046	49.5595	5.1515
57	22.321	1.477	24.024	1.797	23.1725	1.6370
58	42.104	8.901	86.02	10.205	64.0620	9.5530
59	37.617	4.933	41.69	3.548	39.6535	4.2405
60	49.219	7.084	45.388	4.609	47.3035	5.8465
61	28.515	4.427	34.695	4.696	31.6050	4.5615
62	24.048	2.942	27.275	2.209	25.6615	2.5755
63	33.399	2.377	34.226	3.995	33.8125	3.1860

64	17.981	2.846	34.171	6.769	26.0760	4.8075
65	27.426	1.916	31.928	4.955	29.6770	3.4355
66	26.094	3.248	23.97	3.488	25.0320	3.3680
67	21.158	2.466	24.938	2.599	23.0480	2.5325
68	35.62	4.572	34.261	2.97	34.9405	3.7710
69	21.882	3.332	33.373	3.622	27.6275	3.4770
70	40.405	4.812	42.552	4.601	41.4785	4.7065
71	22.1	2.422	34.351	2.553	28.2255	2.4875
72	33.555	4.796	36.455	3.012	35.0050	3.9040
73	25.822	3.189	34.328	2.337	30.0750	2.7630
74	35.156	8.593	42.12	6.588	38.6380	7.5905
75	30.278	2.948	39.251	2.5	34.7645	2.7240
76	54.252	11.633	55.948	7.739	55.1000	9.6860
77	32.7	2.948	32.575	2.223	32.6375	2.5855
78	47.513	9.443	41.285	5.205	44.3990	7.3240
79	27.208	6.712	30.186	2.302	28.6970	4.5070
80	41.53	8.596	40.294	7.195	40.9120	7.8955
81	24.351	5.957	30.338	1.908	27.3445	3.9325
82	32.801	2.291	36.67	2.213	34.7355	2.2520
83	24.892	2.701	31.062	3.006	27.9770	2.8535
84	37.631	5.376	33.714	3.496	35.6725	4.4360
85	36.987	1.676	39.783	1.568	38.3850	1.6220
86	54.723	3.207	55.297	3.214	55.0100	3.2105
87	77.564	4.28	69.537	3.448	73.5505	3.8640
88	52.849	5.817	56.297	6.566	54.5730	6.1915
89	26.699	2.653	41.509	3.837	34.1040	3.2450
90	30.182	4.019	42.498	2.662	36.3400	3.3405
91	25.266	4.57	27.045	2.857	26.1555	3.7135
92	26.577	3.612	30.034	2.501	28.3055	3.0565
93	26.538	2.286	34	2.564	30.2690	2.4250
94	48.767	5.695	30.921	2.911	39.8440	4.3030
95	30.369	4.104	32.567	4.019	31.4680	4.0615
96	33.205	8.907	38.475	5.665	35.8400	7.2860
97	14.726	1.561	11.303	0.555	13.0145	1.0580
98	22.478	4.813	16.728	2.957	19.6030	3.8850
99	18.627	2.295	16.015	1.822	17.3210	2.0585
100	13.055	2.262	11.896	1.013	12.4755	1.6375
101	15.753	2.573	11.243	0.971	13.4980	1.7720
102	24.287	1.728	15.82	0.749	20.0535	1.2385
103	17.645	3.371	10.338	1.306	13.9915	2.3385
104	22.114	6.098	12.625	2.184	17.3695	4.1410
105	33.791	5.469	18.178	2.526	25.9845	3.9975
106	34.826	4.934	16.945	1.304	25.8855	3.1190
107	25.682	1.01	13.707	0.505	19.6945	0.7575
108	23.086	1.758	12.884	1.012	17.9850	1.3850
109	20.041	3.132	10.126	1.13	15.0835	2.1310

110	28.606	2.003	13.448	0.804	21.0270	1.4035
111	43.662	4.981	20.448	1.281	32.0550	3.1310
112	20.181	1.863	12.302	1.629	16.2415	1.7460
113	20.934	6.186	15.977	2.091	18.4555	4.1385
114	38.491	7.949	23.525	4.479	31.0080	6.2140
115	21.566	1.511	14.963	0.928	18.2645	1.2195
116	18.051	1.808	11.863	1.114	14.9570	1.4610
117	15.962	2.707	11.739	0.976	13.8505	1.8415
118	37.771	4.761	25.737	2.365	31.7540	3.5630
119	47.032	11.179	22.511	4.506	34.7715	7.8425
120	66.607	3.571	32.035	2.004	49.3210	2.7875
121	35.025	9.645	15.594	4.295	25.3095	6.9700
122	33.49	9.414	14.094	2.996	23.7920	6.2050
123	27.725	6.288	15.172	2.581	21.4485	4.4345
124	29.415	3.434	10.892	1.452	20.1535	2.4430
125	21.307	2.786	12.129	1.254	16.7180	2.0200
126	26.243	4.681	8.668	1.375	17.4555	3.0280
127	27.085	4.693	10.576	1.527	18.8305	3.1100
128	20.768	4.12	12.92	2.463	16.8440	3.2915
129	18.319	1.349	13.094	1.028	15.7065	1.1885
130	28.795	2.276	15.029	1.164	21.9120	1.7200
131	17.799	2.265	12.145	0.808	14.9720	1.5365
132	27.693	7.219	12.343	1.574	20.0180	4.3965
133	24.005	2.76	13.061	0.765	18.5330	1.7625
134	21.903	3.009	11.031	1.763	16.4670	2.3860
135	14.058	1.645	10.457	1.234	12.2575	1.4395
136	15.21	4.068	12.22	0.846	13.7150	2.4570
137	21.482	3.191	15.113	1.482	18.2975	2.3365
138	24.386	4.677	13.694	1.354	19.0400	3.0155
139	26.608	4.511	17.112	1.574	21.8600	3.0425
140	32.503	3.692	20.895	3.738	26.6990	3.7150
141	23.794	1.508	16.334	1.555	20.0640	1.5315
142	31.213	7.279	15.566	3.053	23.3895	5.1660
143	27.265	4.596	18.117	2.525	22.6910	3.5605
144	36.408	5.816	22.612	3.627	29.5100	4.7215
145	57.79	8.838	24.119	3.876	40.9545	6.3570
146	49.794	6.232	59.38	7.58	54.5870	6.9060
147	47.063	10.454	33.805	4.167	40.4340	7.3105
148	37.932	3.753	30.31	3.198	34.1210	3.4755
149	61.573	12.448	30.541	3.873	46.0570	8.1605
150	58.524	6.231	39.629	3.33	49.0765	4.7805
151	43.03	4.916	21.046	2.885	32.0380	3.9005
152	44.872	8.77	21.007	2.636	32.9395	5.7030
153	40.396	5.688	22.825	2.132	31.6105	3.9100
154	65.539	13.255	45.417	6.461	55.4780	9.8580
155	48.703	9.937	31.374	2.867	40.0385	6.4020

156	37.181	4.937	29.617	2.937	33.3990	3.9370
157	35.186	4.535	17.878	1.581	26.5320	3.0580
158	51.661	2.695	33.002	1.991	42.3315	2.3430
159	30.77	4.109	19.233	1.542	25.0015	2.8255
160	36.094	3.542	17.974	1.657	27.0340	2.5995
161	35.409	2.366	33.483	2.737	34.4460	2.5515
162	33.433	2.074	26.398	3.543	29.9155	2.8085
163	42.491	4.39	22.276	1.604	32.3835	2.9970
164	33.078	3.228	32.84	3.386	32.9590	3.3070
165	45.275	3.204	39.092	3.755	42.1835	3.4795
166	29.602	1.738	24.219	1.898	26.9105	1.8180
167	27.784	3.443	22.843	1.792	25.3135	2.6175
168	74.683	10.617	49.732	3.286	62.2075	6.9515
169	48.336	4.662	44.463	3.058	46.3995	3.8600
170	50.128	9.574	41.486	4.115	45.8070	6.8445
171	47.25	9.041	37.456	4.455	42.3530	6.7480
172	53.153	7.175	30.582	6.503	41.8675	6.8390
173	39.084	6.244	25.727	2.191	32.4055	4.2175
174	45.005	1.875	33.581	2.379	39.2930	2.1270
175	47.646	6.625	26.629	4.836	37.1375	5.7305
176	55.395	7.326	34.511	6.658	44.9530	6.9920
177	33.771	3.981	34.434	3.484	34.1025	3.7325
178	67.077	10.657	56.357	7.847	61.7170	9.2520
179	35.008	4.54	28.283	2.932	31.6455	3.7360
180	42.068	3.42	28.527	1.676	35.2975	2.5480
181	40.143	2.884	23.643	3.134	31.8930	3.0090
182	55.98	12.403	27.675	2.591	41.8275	7.4970
183	45.856	4.074	26.554	3.411	36.2050	3.7425
184	47.638	13.905	23.569	4.462	35.6035	9.1835
185	29.627	2.072	28.727	2.788	29.1770	2.4300
186	25.87	1.617	24.308	1.641	25.0890	1.6290
187	28.469	3.789	28.409	2.228	28.4390	3.0085
188	43.256	3.532	29.637	1.678	36.4465	2.6050
189	35.294	2.99	26.036	1.809	30.6650	2.3995
190	41.63	3.818	31.807	1.941	36.7185	2.8795
191	33.432	2.727	26.418	1.23	29.9250	1.9785
192	38.533	3.055	26.167	2.676	32.3500	2.8655
193	52.145	7.633	66.647	7.649	59.3960	7.6410
194	78.674	19.973	77.211	18.407	77.9425	19.1900
195	61.3	14.568	47.323	8.818	54.3115	11.6930
196	82.319	28.729	49.804	10.153	66.0615	19.4410
197	47.078	7.783	46.383	6.365	46.7305	7.0740
198	43.554	13.721	39.919	8.064	41.7365	10.8925
199	40.89	12.488	44.564	5.499	42.7270	8.9935
200	46.423	6.179	34.111	2.888	40.2670	4.5335
201	44.093	8.793	52.982	7.827	48.5375	8.3100

202	51.569	12.11	47.774	10.111	49.6715	11.1105
203	39.021	4.874	51.153	5.821	45.0870	5.3475
204	52.055	9.223	31.552	3.951	41.8035	6.5870
205	41.044	5.775	34.923	3.705	37.9835	4.7400
206	31.351	3.687	32.129	2.472	31.7400	3.0795
207	43.82	4.633	28.098	1.853	35.9590	3.2430
208	36.337	6.743	29.077	3.006	32.7070	4.8745
209	36.945	7.059	29.934	3.642	33.4395	5.3505
210	37.592	3.376	37.793	2.909	37.6925	3.1425
211	36.686	3.72	35.615	3.93	36.1505	3.8250
212	36.654	4.758	32.036	2.656	34.3450	3.7070
213	42.177	6.122	31.067	4.128	36.6220	5.1250
214	37.527	8.471	32.699	4.645	35.1130	6.5580
215	37.302	6.865	29.908	3.386	33.6050	5.1255
216	39.019	8.467	28.36	2.817	33.6895	5.6420
217	53.521	13.053	25.512	3.686	39.5165	8.3695
218	41.043	11.011	27.355	5.791	34.1990	8.4010
219	51.988	10.693	31.329	3.319	41.6585	7.0060
220	54.023	6.301	41.112	4.76	47.5675	5.5305
221	58.76	6.462	39.758	2.97	49.2590	4.7160
222	236.787	43.566	243.617	53.774	240.2020	48.6700
223	61.825	6.104	39.095	4.733	50.4600	5.4185
224	60.335	8.345	42.762	5.15	51.5485	6.7475
225	42.422	4.628	33.442	3.115	37.9320	3.8715
226	48.764	5.455	26.922	2.335	37.8430	3.8950
227	57.581	7.579	42.222	4.06	49.9015	5.8195
228	46.242	5.713	32.37	2.362	39.3060	4.0375
229	59.85	6.227	37.452	3.019	48.6510	4.6230
230	42.275	3.602	32.725	2.969	37.5000	3.2855
231	54.799	3.621	33.443	2.238	44.1210	2.9295
232	52.778	5.345	35.823	3.952	44.3005	4.6485
233	54.107	6.101	33.629	3.781	43.8680	4.9410
234	57.658	5.363	42.349	3.414	50.0035	4.3885
235	39.81	6.669	29.299	2.818	34.5545	4.7435
236	49.078	4.885	31.99	2.007	40.5340	3.4460
237	57.23	6.733	36.45	3.148	46.8400	4.9405
238	51.689	4.587	33.588	2.816	42.6385	3.7015
239	44.895	5.883	33.621	3.034	39.2580	4.4585
240	59.327	4.174	43.637	4.972	51.4820	4.5730
241	63.766	13.264	50.677	5.209	57.2215	9.2365
242	66.835	12.5	52.004	7.592	59.4195	10.0460
243	54.29	6.239	38.992	4.219	46.6410	5.2290
244	72.508	13.528	36.851	5.599	54.6795	9.5635
245	65.646	9.098	55.163	6.389	60.4045	7.7435
246	51.051	6.557	46.828	6.46	48.9395	6.5085
247	60.801	6.585	41.571	5.728	51.1860	6.1565

248	50.195	6.174	39.365	4.661	44.7800	5.4175
249	37.378	5.543	42.906	6.632	40.1420	6.0875
250	43.321	5.067	30.966	3.133	37.1435	4.1000
251	45.472	4.875	32.346	3.885	38.9090	4.3800
252	43.062	3.621	28.848	2.106	35.9550	2.8635
253	37.701	3.518	25.509	2.268	31.6050	2.8930
254	58.2	18.808	36.005	9.635	47.1025	14.2215
255	31.77	3.926	27.901	4.411	29.8355	4.1685
256	38.708	3.847	36.377	3.262	37.5425	3.5545
257	30.508	3.645	31.26	2.622	30.8840	3.1335
258	44.359	5	34.497	2.636	39.4280	3.8180
259	67.139	7.485	40.465	2.943	53.8020	5.2140
260	66.589	6.837	39.106	3.29	52.8475	5.0635
261	48.322	10.679	26.008	2.39	37.1650	6.5345
262	50.546	4.737	32.219	2.427	41.3825	3.5820
263	59.307	7.82	29.231	2.967	44.2690	5.3935
264	97.302	11.857	53.08	6.094	75.1910	8.9755
265	76.539	14.949	85.905	13.021	81.2220	13.9850
266	57.905	6.615	64.596	7.651	61.2505	7.1330
267	69.77	6.607	53.074	4.276	61.4220	5.4415
268	48.668	10.684	40.916	5.466	44.7920	8.0750
269	47.46	7.531	42.844	4.1	45.1520	5.8155
270	70.579	11.73	61.976	6.502	66.2775	9.1160
271	115.007	12.121	67.306	4.174	91.1565	8.1475
272	82.348	12.571	104.237	16.188	93.2925	14.3795
273	72.215	14.678	53.943	7.425	63.0790	11.0515
274	49.167	8.023	49.69	6.118	49.4285	7.0705
275	41.439	3.584	29.44	2.996	35.4395	3.2900
276	53.402	8.54	50.701	3.872	52.0515	6.2060
277	56.148	3.835	32.342	3.153	44.2450	3.4940
278	67.762	15.057	45.771	7.974	56.7665	11.5155
279	53.393	3.781	31.896	2.753	42.6445	3.2670
280	62.738	14.71	39.414	4.46	51.0760	9.5850
281	40.384	8.034	38.263	3.196	39.3235	5.6150
282	40.763	5.446	40.712	4.898	40.7375	5.1720
283	46.465	10.212	46.647	6.183	46.5560	8.1975
284	38.536	4.547	41.452	2.836	39.9940	3.6915
285	42.301	4.416	43.768	4.259	43.0345	4.3375
286	46.313	8.357	38.798	5.187	42.5555	6.7720
287	50.769	6.505	43.597	4.509	47.1830	5.5070
288	38.562	8.297	37.896	4.33	38.2290	6.3135
289	97.407	9.944	84.032	7.979	90.7195	8.9615
290	96.276	16.596	80.344	14.757	88.3100	15.6765
291	97.306	19.495	65.589	6.382	81.4475	12.9385
292	55.475	9.264	45.599	8.096	50.5370	8.6800
293	62.494	8.981	44.842	6.356	53.6680	7.6685

294	64.097	10.104	45.876	4.721	54.9865	7.4125
295	54.142	14.352	44.557	6.065	49.3495	10.2085
296	45.915	5.238	42.595	4.868	44.2550	5.0530
297	52.489	10.839	40.88	3.707	46.6845	7.2730
298	63.515	15.058	48.368	7.137	55.9415	11.0975
299	68.855	5.952	39.142	4.218	53.9985	5.0850
300	41.279	2.923	42.539	2.744	41.9090	2.8335
301	61.222	5.21	35.294	2.489	48.2580	3.8495
302	61.31	7.946	54.541	6.669	57.9255	7.3075
303	72.478	6.439	34.292	3.108	53.3850	4.7735
304	67.572	16.336	42.125	6.87	54.8485	11.6030
305	50.921	8.983	33.358	4.008	42.1395	6.4955
306	57.53	5.6	69.86	6.547	63.6950	6.0735
307	64.026	11.056	39.867	4.008	51.9465	7.5320
308	49.409	3.059	42.979	2.509	46.1940	2.7840
309	54.897	4.814	31.307	1.962	43.1020	3.3880
310	41.554	2.628	37.128	1.841	39.3410	2.2345
311	51.666	8.47	40.257	4.367	45.9615	6.4185
312	49.509	6.575	28.02	4.538	38.7645	5.5565
313	--	--	194.826	68.134	194.8260	68.1340
314	121.989	16.822	138.651	21	130.3200	18.9110
315	80.309	31.932	61.6	21.185	70.9545	26.5585
316	92.927	25.688	67.475	19.158	80.2010	22.4230
317	90.794	26.314	68.783	17.49	79.7885	21.9020
318	78.946	5.722	89.051	5.366	83.9985	5.5440
319	78.528	22.516	68.248	14.662	73.3880	18.5890
320	88.504	27.66	74.364	17.313	81.4340	22.4865
321	80.819	11.586	72.082	9.362	76.4505	10.4740
322	66.905	11.106	59.407	7.519	63.1560	9.3125
323	56.665	7.201	65.996	7.423	61.3305	7.3120
324	58.472	14.789	52.989	6.283	55.7305	10.5360
325	73.835	10.27	45.629	3.865	59.7320	7.0675
326	83.653	12.949	55.705	5.376	69.6790	9.1625
327	48.135	5.765	47.686	2.973	47.9105	4.3690
328	58.846	13.768	64.173	8.7	61.5095	11.2340
329	46.418	3.234	43.86	4.767	45.1390	4.0005
330	48.925	5.8	47.32	5.483	48.1225	5.6415
331	60.81	13.53	36.129	3.04	48.4695	8.2850
332	56.142	10.276	41.861	5.196	49.0015	7.7360
333	57.072	5.485	46.44	1.828	51.7560	3.6565
334	57.031	14.153	47.644	5.986	52.3375	10.0695
335	63.616	8.355	62.766	7.336	63.1910	7.8455
336	61.994	10.795	49.157	4.36	55.5755	7.5775
337	109.966	11.513	73.307	11.438	91.6365	11.4755
338	110.715	15.908	92.237	13.006	101.4760	14.4570
339	75.364	14.03	67.654	10.63	71.5090	12.3300

340	109.658	7.631	67.114	6.374	88.3860	7.0025
341	81.366	8.105	61.479	4	71.4225	6.0525
342	64.415	15.53	79.511	24.66	71.9630	20.0950
343	74.24	10.057	46.431	5.731	60.3355	7.8940
344	86.963	13.807	54.298	8.525	70.6305	11.1660
345	71.074	6.207	57.396	6.551	64.2350	6.3790
346	91.626	10.114	74.902	8.206	83.2640	9.1600
347	77.149	8.202	53.758	5.371	65.4535	6.7865
348	80.631	9.944	56.546	8.401	68.5885	9.1725
349	60.505	5.38	37.207	4.379	48.8560	4.8795
350	64.783	11.132	46.827	8.602	55.8050	9.8670
351	70.732	7.768	42.967	3.442	56.8495	5.6050
352	85.716	13.405	56.756	5.896	71.2360	9.6505
353	49.942	6.657	49.317	3.253	49.6295	4.9550
354	38.757	3.56	37.798	2.633	38.2775	3.0965
355	45.029	2.934	38.812	2.665	41.9205	2.7995
356	38.688	3.896	34.3	2.617	36.4940	3.2565
357	52.918	9.736	35.223	3.54	44.0705	6.6380
358	52.294	3.336	44.793	5.552	48.5435	4.4440
359	53.158	3.096	41.327	3.233	47.2425	3.1645
360	103.51	27.753	62.923	11.824	83.2165	19.7885
361	122.759	25.999	106.083	13.134	114.4210	19.5665
362	106.559	19.744	101.161	14.303	103.8600	17.0235
363	109.834	19.943	79.727	14.271	94.7805	17.1070
364	102.297	10.688	78.932	9.566	90.6145	10.1270
365	82.014	8.363	73.591	5.609	77.8025	6.9860
366	67.391	23.514	69.264	11.51	68.3275	17.5120
367	95.165	15.862	42.233	5.102	68.6990	10.4820
368	95.977	20.567	51.602	9.654	73.7895	15.1105
369	65.153	14.652	46.363	7.328	55.7580	10.9900
370	58.571	7.578	50.496	6.145	54.5335	6.8615
371	84.037	13.739	52.431	5.879	68.2340	9.8090
372	67.564	8.585	48.839	4.307	58.2015	6.4460
373	57.82	10.735	38.625	4.956	48.2225	7.8455
374	84.402	27.865	37.659	6.895	61.0305	17.3800
375	72.533	12.7	45.661	5.549	59.0970	9.1245
376	68.34	7.43	44.068	4.428	56.2040	5.9290
377	70.417	6.309	53.79	6.279	62.1035	6.2940
378	61.427	3.64	47.649	2.676	54.5380	3.1580
379	95.519	18.074	57.492	7.143	76.5055	12.6085
380	65.481	5.625	42.825	2.2	54.1530	3.9125
381	59.761	9.824	33.808	2.686	46.7845	6.2550
382	58.179	4.499	36.306	3.105	47.2425	3.8020
383	73.232	3.793	41.961	2.581	57.5965	3.1870
384	69.482	14.129	34.575	5.662	52.0285	9.8955

[00213] These results show that DsiRNAs designed to target human PNPLA3 mRNA inhibit *PNPLA3* expression in cells (as determined by a reduced amount of PNPLA3 mRNA in DsiRNA-transfected cells) and that the nucleotide sequences including the DsiRNA hits are useful for generating RNAi oligonucleotides to inhibit *PNPLA3* expression. Further, these results demonstrate that multiple PNPLA3 target sequences are suitable for the RNAi-mediated inhibition of PNPLA3 expression.

IN VIVO FUNCTION

Example 3: RNAi Oligonucleotide Inhibition of PNPLA3 Expression *In Vivo*

[00214] Of the 384 DsiRNAs screened in the HuH-7 cell-based assays described in Example 2, the nucleotide sequences of 192 DsiRNAs hits (Table 3) are selected for further evaluation *in vivo*. Briefly, the nucleotide sequences the selected DsiRNAs are used to generate 194 corresponding ds RNAi oligonucleotides including a nicked tetraloop GalNAc-conjugated structure (referred to herein as "GalNAc-conjugated PNPLA3 oligonucleotides") having a 36-mer sense (passenger) strand and a 22-mer antisense (guide) strand. Further, the nucleotide sequences for the passenger strand and guide strand of the GalNAc-conjugated PNPLA3 oligonucleotides have a distinct pattern of modified nucleotides and phosphorothioate linkages (*see*, *e.g.*, FIG. 1 for a schematic of the generic structure and chemical modification pattern of the GalNAc-conjugated PNPLA3 oligonucleotides). The three adenosine nucleotides of the tetraloop each are conjugated to a GalNAc moiety (CAS#: 14131-60-3).

Table 3: **GalXC-PNPLA3: 192 GalXC Compound In Vitro Screen**.

			PNPLA3-F495		**PNPLA3-F595**	
PNPLA3 Oligonucleotide	**Passenger (sense) (SEQ ID NO:)**	**Guide (antisense) (SEQ ID NO:)**	**% Remaining**	**%SEM**	**% Remaining**	**%SEM**
1	777	778	47.485	10.196	42.315	9.325
2	779	780	88.393	13.374	74.853	8.613
3	781	782	71.522	13.389	62.163	8.489
4	783	784	48.2	12.808	59.051	15.527
5	785	786	87.111	20.654	74.136	14.422
6	787	788	52.772	4.946	32.37	3.842
7	789	790	60	4.856	56.847	3.105

8	791	792	89.452	17.034	90.454	16.078
9	793	794	76.773	16.13	58.479	11.665
10	795	796	85.463	9.685	66.419	7.575
11	797	798	108.216	4.243	70.258	3.457
12	799	800	57.964	8.916	47.12	9.746
13	801	802	91.802	15.466	80.834	14.834
14	803	804	108.246	8.747	102.424	9.238
15	805	806	102.556	8.612	91.909	8.507
16	807	808	123.63	8.863	110.429	6.112
17	809	810	70.82	7.935	48.198	3.957
18	811	812	105.252	5.434	76.73	5.427
19	813	814	73.737	7.411	63.414	3.163
20	815	816	53.275	5.084	40.621	3.768
21	817	818	73.13	8.636	54.227	4.991
22	819	820	69.662	5.077	65.603	4.833
23	821	822	115.648	7.396	93.812	6.834
24	823	824	113.539	8.877	95.22	8.13
25	825	826	72.315	22.04	65.007	19.295
26	827	828	52.756	8.42	52.681	4.521
27	829	830	50.002	5.36	45.103	6.461
28	831	832	65.906	5.919	61.42	3.683
29	833	834	85.13	15.786	81.4	13.245
30	835	836	94.2	7.683	92.984	6.53
31	837	838	79.41	9.652	78.856	9.311
32	839	840	110.611	10.798	121.904	11.977
33	841	842	61.132	15.106	54.942	10.832
34	843	844	22.997	2.613	26.894	3.012
35	845	846	69.893	7.912	71.053	6.942
36	847	848	42.209	6.514	37.063	6.765
37	849	850	32.369	6.443	30.326	5.18
38	851	852	98.013	5.195	99.493	5.551
39	853	854	108.745	12.02	109.98	14.348
40	855	856	108.242	5.703	106.183	7.088
41	857	858	62.227	18.716	47.683	7.008
42	859	860	77.369	5.452	72.082	4.805
43	861	862	97.72	6.492	104.918	2.468
44	863	864	95.316	16.953	81.092	8.169
45	865	866	65.563	3.105	63.593	5.933
46	867	868	45.891	2.704	41.178	2.034
47	869	870	70.44	8.4	69.907	11.675
48	871	872	42.793	4.981	41.802	4.578
49	873	874	69.377	12.858	75.563	14.64
50	875	876	94.54	12.65	113.746	13.701
51	877	878	96.644	9.928	88.742	7.236
52	879	880	57.675	7.9	54.023	9.11
53	881	882	45.257	4.671	41.066	8.781

54	883	884	64.216	13.821	57.326	9.308
55	885	886	80.64	10.056	83.19	12.71
56	887	888	53.489	6.288	60.359	10.933
57	889	890	43.058	8.468	67.338	7.905
58	891	892	92.209	4.675	88.981	4.725
59	893	894	125.612	12.186	131.574	15.729
60	895	896	56.646	7.227	58.75	7.18
61	897	898	63.963	4.129	64.01	3.511
62	899	900	35.42	4.93	43.575	3.839
63	901	902	80.942	5.673	99.785	7.605
64	903	904	28.438	9.671	41.409	10.949
65	905	906	78.01	12.28	70.329	13.215
66	907	908	63.519	7.735	56.465	6.226
67	909	910	102.482	9.653	86.816	7.212
68	911	912	73.153	6.21	76.354	7.251
69	913	914	115.319	14.233	109.375	11.395
70	915	916	50.507	16.055	61.744	17.75
71	917	918	64.122	18.86	67.106	19.792
72	919	920	45.025	11.057	36.962	8.699
73	921	922	64.691	7.735	70.342	7.008
74	923	924	91.612	17.728	73.763	9.075
75	925	926	30.626	5.128	34.089	2.646
76	927	928	85.724	5.965	98.425	5.178
77	929	930	77.837	24.988	65.493	20.924
78	931	932	66.549	13.96	70.219	13.374
79	933	934	88.812	9.773	93.579	14.174
80	935	936	126.281	13.138	125.405	9.847
81	937	938	33.474	12.471	36.472	7.102
82	939	940	36.521	6.105	36.344	12.791
83	941	942	79.756	28.563	79.725	24.95
84	943	944	91.352	9.565	103.633	12.963
85	945	946	79.374	11.693	88.146	11.711
86	947	948	104.203	12.127	111.907	13.828
87	949	950	78.157	5.154	100.371	7.36
88	951	952	117.96	7.199	130.066	9.106
89	953	954	84.233	7.043	78.918	4.772
90	955	956	70.825	5.146	76.977	8.968
91	957	958	59.621	7.853	65.538	7.22
92	959	960	91.443	6.954	99.109	6.096
93	961	962	46.844	11.633	51.957	9.244
94	963	964	81.508	6.389	87.195	8.633
95	965	966	91.805	8.83	108.782	9.098
96	967	968	96.733	4.922	125.597	5.479
97	969	970	92.658	10.451	110.074	12.159
98	971	972	100.916	7.648	107.715	9.441
99	973	974	108.731	9.204	130.037	11.933

100	975	976	80.886	6.51	82.486	5.492
101	977	978	114.601	6.354	125.063	7.668
102	979	980	64.486	7.636	81.933	8.887
103	981	982	48.127	7.673	70.594	9.464
104	983	984	98.266	10.023	125.396	13.292
105	985	986	78.835	8.422	85.896	6.258
106	987	988	65.38	6.01	75.699	5.561
107	989	990	82.332	16.715	110.985	21.204
108	991	992	50.805	3.714	49.059	3.238
109	993	994	82.297	10.387	74.612	6.957
110	995	996	56.254	4.26	51.783	3.569
111	997	998	37.191	3.673	43.781	4.781
112	999	1000	54.832	3.334	45.421	4.277
113	1001	1002	24.729	2.434	22.466	2.637
114	1003	1004	34.923	6.177	40.356	5.286
115	1005	1006	42.682	3.081	57.453	2.391
116	1007	1008	30.325	3.011	34.404	1.82
117	1009	1010	70.118	7.78	89.223	8.905
118	1011	1012	43.339	6.479	44.854	6.904
119	1013	1014	104.192	5.672	110.895	6.371
120	1015	1016	95.131	8.872	108.847	8.363
121	1017	1018	22.097	2.259	25.862	3.07
122	1019	1020	50.635	11.129	59.072	10.096
123	1021	1022	68.368	9.482	90.191	15.479
124	1023	1024	50.658	2.598	62.686	2.149
125	1025	1026	67.692	4.608	104.474	6.486
126	1027	1028	60.169	6.81	103.156	11.309
127	1029	1030	37.137	3.679	49.778	7.312
128	1031	1032	87.29	4.881	127.439	10.802
129	1033	1034	41.409	6.549	47.012	11.236
130	1035	1036	32.213	7.175	43.875	10.706
131	1037	1038	77.807	7.013	109.299	9.799
132	1039	1040	37.026	6.758	49.133	8.307
133	1041	1042	57.723	5.921	70.531	6.977
134	1043	1044	94.403	10.058	130.999	12.973
135	1045	1046	42.258	3.137	56.368	4.699
136	1047	1048	77.667	6.622	106.147	4.946
137	1049	1050	51.002	3.36	62.009	6.073
138	1051	1052	38.522	4.21	43.297	7.219
139	1053	1054	75.103	5.866	115.191	7.77
140	1055	1056	46.405	3.737	57.89	3.035
141	1057	1058	34.308	4.135	44.278	3.532
142	1059	1060	36.66	3.327	48.931	4.389
143	1061	1062	36.323	6.447	50.414	7.284
144	1063	1064	48.346	4.964	69.682	5.951
145	1065	1066	71.349	8.498	63.576	12.402

146	1067	1068	66.855	7.354	54.028	10.308
147	1069	1070	58.02	6.725	81.61	6.225
148	1071	1072	46.107	4.599	47.578	5.721
149	1073	1074	79.89	11.647	94.885	12.091
150	1075	1076	51.93	6.887	60.564	5.631
151	1077	1078	67.023	11.379	78.549	9.92
152	1079	1080	69.029	12.304	64.36	9.232
153	1081	1082	56.372	11.395	50.897	6.456
154	1083	1084	54.923	8.02	56.301	7.96
155	1085	1086	47.848	4.993	52.756	4.92
156	1087	1088	72.997	5.423	89.098	8.279
157	1089	1090	49.577	9.222	61.752	9.967
158	1091	1092	57.345	5.967	55.082	5.124
159	1093	1094	49.719	8.465	50.474	6.318
160	1095	1096	66.221	8.527	60.526	6.042
161	1097	1098	59.431	5.38	51.367	4.575
162	1099	1100	44.241	2.416	42.17	2.266
163	1101	1102	67.893	7.786	85.144	7.578
164	1103	1104	54.101	3.156	64.663	5.874
165	1105	1106	74.353	11.203	73.215	11.059
166	1107	1108	91.603	5.407	78.535	4.566
167	1109	1110	86.259	4.861	84.54	5.247
168	1111	1112	100.862	9.39	83.472	3.848
169	1113	1114	64.233	6.416	55.446	5.259
170	1115	1116	82.913	8.265	67.499	6.098
171	1117	1118	63.834	4.157	66.965	7.54
172	1119	1120	87.059	6.502	80.608	3.299
173	1121	1122	52.896	8.619	50.91	8.301
174	1123	1124	89.834	8.687	60.792	7.648
175	1125	1126	56.928	16.722	55.37	13.438
176	1127	1128	91.989	35.495	98.901	26.361
177	1129	1130	78.111	6.12	85.965	5.555
178	1131	1132	81.351	5.528	68.852	4.702
179	1133	1134	82.851	10.171	87.313	8.301
180	1135	1136	94.367	3.317	87.13	5.434
181	1137	1138	108.095	11.973	99.858	9.769
182	1139	1140	95.753	5.346	87.366	6.613
183	1141	1142	88.199	15.408	67.131	13.665
184	1143	1144	102.928	9.669	84.541	9.709
185	1145	1146	48.692	11.647	48.288	10.808
186	1147	1148	84.114	6.361	82.348	3.469
187	1149	1150	89.182	14.563	92.44	12.983
188	1151	1152	85.958	10.066	85.508	8.055
189	1153	1154	56.68	12.506	63.775	15.034
190	1155	1156	77.223	11.068	75.609	8.161
191	1157	1158	85.696	6.162	92.128	6.673

192	1159	1160	50.761	3.422	51.217	2.474

[00215] *Mouse studies:* Various GalNAc-conjugated PNPLA3 oligonucleotides, some of which are listed in Table 3, are evaluated in hydrodynamic injection (HDI) mouse model. Additional HDI studies are listed in tables 4, 5 and 6. For these HDI studies, the mice are engineered to transiently express human PNPLA3 mRNA in hepatocytes. A GalNAc-conjugated PNPLA3 oligonucleotide control (SEQ ID NOs: 1165 & 1166) is used as a benchmark control. Briefly, 6-8-week-old female CD-1 mice are treated SQ with a GalNAc-conjugated PNPLA3 oligonucleotide at a dose level of 1 mg/kg. Three days later (72 hr.), the mice are hydrodynamically injected with a DNA plasmid encoding the full human *PNPLA3* gene under control of a ubiquitous cytomegalovirus (CMV) promoter sequence. One day after introduction of the plasmid, liver samples are collected. Total RNA derived from these mice are subjected to qRT-PCR analysis for PNPLA3 mRNA, relative to mice treated only with an identical volume of PBS. The values are normalized for transfection efficiency using the NeoR gene included on the plasmid.

[00216] As shown in Tables 4, 5 and 6 a number of the GalNAc-conjugated PNPLA3 oligonucleotides tested inhibited *PNPLA3* expression, as determined by a reduced amount of PNPLA3 mRNA in liver samples from oligonucleotide-treated mice relative to mice treated with PBS. The mean % of remaining PNPLA3 mRNA in liver samples of mice treated with the benchmark GalNAc-conjugated PNPLA3 oligonucleotide control relative to mice treated with PBS. Table 4 shows that 18 of the 21 GalNAc-conjugated PNPLA3 oligonucleotides inhibit *PNPLA3* expression to a greater extent than the reference GalNAc-conjugated PNPLA3 oligonucleotide used as control. Sequences of these oligonucleotides along with the modification patterns and SEQ ID NOs. is disclosed in Table A

Table 4: discloses s*ingle 0.5 mg/kg GalXC-PNPLA3 S.c. Dose, Day 3 HDI, Day 4 Takedown, Liver qPCR*

	Group																					
Animal	PBS	-1170 (Ref.)	-643	-1110	-1162	-1170	-1699	-1703	-1708	-2104	-2143	-2155	-2156	-2157	-2163	-2165	-2170	-2195	-2200	-2204	-2205	-2210
1	105.7	96.7	78.2		69.2	76.5	65.0	41.6	68.1	56.7	82.5	60.7	63.1	104.4	41.1	93.9	66.8	91.3	144.7	76.6	57.0	64.5
2	104.5	66.6	101.7	88.0	72.0	89.3	82.9	81.8	98.1	69.3	61.6	81.5	76.4	81.6	31.0	50.7	48.1	57.0	109.8	77.0	33.9	

3	89.9	115.5	96.8	99.7	54.2	23.3	53.0	46.5	85.6	41.6	77.7	70.0	80.5	123.1	30.8	36.6	47.8	28.7	87.5	104.5	26.8	58.7
4	99.9	57.1	64.1	92.2	84.4	26.7	69.6	48.6	61.8	29.3	92.5	81.0	83.0	107.6	36.3	52.3	46.8	56.0	102.6	64.1	41.6	60.3
5		107.2	64.2	70.4	118.2	75.0	39.4	63.4	39.7	35.5	89.1	61.2	42.4	153.9	50.1	23.5	89.2	48.6	84.1	173.5	36.6	83.0
Average:	100.0	88.6	81.0	87.6	79.6	58.1	62.0	56.4	70.6	46.5	80.7	70.9	69.1	114.1	37.9	51.4	59.7	56.3	105.7	99.1	39.2	66.6
SEM:	3.6	11.4	7.9	6.2	10.8	13.8	7.4	7.3	10.0	7.3	5.4	4.5	7.5	11.9	3.6	11.8	8.3	10.1	10.8	19.7	5.1	5.6

[00217] Table 5 and 6 show 2 additional sets of HDI Studies with 18 GalNAc-conjugated PNPLA3 oligonucleotides in each set using the same reference oligonucleotide. Sequences of these oligonucleotides along with the modification patterns and SEQ ID NOs. are disclosed in Table B and Table C respectively.

[00218] Based on these results, 10 GalNAc-conjugated PNPLA3 oligonucleotides are selected for evaluation of their ability to inhibit PNPLA3 expression in non-human primates (NHPs). The GalNAc-conjugated PNPLA3 oligonucleotides have chemically modified nucleotides of the pattern as shown in FIG. 1.

Table 5: discloses a *Single 1 mg/kg s.c. dose, HDI 3 days post-dose, harvest 4 days post-dose*

	Group																		
Animal	PBS	-644	-745	-1126	-1129	-1130	-1143	-1147	-1152	-1229	-1698	-2137	-2138	-2140	-2142	-2144	-2146	-2149	-2205 (ref)
1		57.2	116.3	35.0	66.3	108.6	41.3	60.4		111.7	60.0	80.2	101.1	39.0	96.0	48.4	53.5		18.1
2	120.1	55.2	121.8	41.0	82.9	68.5		59.3	55.1	80.1	112.9	68.0	69.9	24.1	47.9		78.1		38.9
3	129.1	143.6	82.2	94.9	53.4	91.1	30.0			86.2	71.9	120.8	45.0	41.4	78.2	34.9		23.5	65.7
4	50.8		102.2	57.9	77.6	145.3	34.4	43.4	39.8	101.5	88.7		47.0	41.0	95.5	37.6	47.1	26.2	36.7
5		27.0	114.3	42.3	117.2	125.9	13.9	41.8	64.5	89.1	116.6	44.5	29.1	47.1	54.0	25.5		16.5	38.2
Average:	100.0	70.7	107.4	54.2	79.5	107.9	29.9	51.3	53.1	93.7	90.0	78.4	58.4	38.5	74.3	36.6	59.6	22.1	39.5
SEM:	24.8	25.2	7.1	10.9	10.7	13.3	5.8	5.0	7.2	5.7	11.1	16.0	12.5	3.9	10.1	4.7	9.5	2.9	7.6

Table 6: discloses a *Single 1 mg/kg s.c. dose, HDI 3 days post-dose, harvest 4 days post-dose*

	Group																		
Animal	PBS	-637	-641	-923	-1116	-1125	-1136	-1151	-1157	-1158	-1173	-1541	-1163	-1614	-1697	-2136	-2176	-2222	-2205 (ref)
1		80.3	114.9	88.9	48.9	203.5	156.1	49.0	113.6	113.6	42.2	91.1	62.5	56.4	24.4	145.3	64.1	97.3	26.9
2	76.6	140.7	116.7	122.7	78.6	115.6		101.3	72.8	95.2	99.6	50.1		79.5	57.3	85.7	28.2	137.8	58.6
3	78.7	115.4	57.8	142.4	122.0	119.8	130.1	91.9	186.4	134.1	20.5	135.3	110.5	60.2	104.6	65.7	71.4	107.5	34.6
4	133.6	90.3	84.3	85.6	150.0	80.0			98.2	113.6	25.0		203.1	44.8		132.5	44.8	50.1	52.7
5	111.1	119.9	198.0	75.0	41.6	166.4	84.6	121.0	114.0		44.2	45.9	96.0	44.9	52.0	179.6	35.4	90.3	55.6
Average:	100.0	109.4	114.3	102.9	88.2	137.1	123.6	90.8	117.0	114.1	46.3	80.6	118.0	57.2	59.6	121.8	48.8	96.6	45.7
SEM:	13.7	10.8	23.6	12.7	20.9	21.6	20.9	15.2	18.9	7.9	14.1	20.9	30.1	6.4	16.7	20.6	8.3	14.2	6.3

[00219] Table 7 discloses an additional HDI Study using the best GalNAc-conjugated PNPLA3 oligonucleotides (hits) based on the results obtained from the previous studies and previous 3 HDI screens, as disclosed in tables 4, 5 and 6. Sequences of the oligonucleotides along with the modification patterns and SEQ ID NOs. used in this HDI screen are disclosed in Table D.

Table 7: comparison of hits from earlier studies and 3 HDI screens with *Single 1 mg/kg s.c. dose, HDI 3 days post-dose, harvest 4 days post-dose.*

	Group																						
Animal	PBS	-639	-644	-729	-735	-743	-744	-838	-1126	-1143	-1147	-1152	-1173	-1697	-1699	-1703	-2140	-2144	-2149	-2156	-2195	-2205	PBS
1	98.7	58.8	22.9	114.6	119.1	106.5	94.7	45.3	64.6	24.8	70.5	55.2	26.0	88.2	18.7	44.9	29.4	13.4	32.7	76.2	62.3	36.2	85.1
2	99.9	62.3	30.7	108.6	85.0	105.4	55.4	48.1	30.4	16.8	24.7	71.6	10.7	53.5	27.3	34.6	22.1	20.4	20.1	56.4	48.8	29.2	127.9
3	143.0	87.9	10.1	106.3	97.4	76.2	61.1	91.8	39.1	18.4	33.4	50.5	18.2	72.2	43.1	34.3	51.1	31.8	21.1	55.1	31.2	40.9	97.7
4	115.1	89.6	19.2	99.5	84.0	99.8	56.5	68.5	61.2	26.7	59.3	58.2	10.8	27.8	33.0	22.2	34.2	73.1	17.1	40.8	43.5	30.7	74.6
5	89.2	91.4	41.1	94.5	105.8	115.0	113.8	48.6	54.6	30.3	47.2	59.8	35.5	25.0	26.1	23.9	19.1	59.8	16.7	62.5	88.6	30.5	68.9
Average:	109.2	78.0	24.8	104.7	98.3	100.6	76.3	60.5	50.0	23.4	47.0	59.1	20.2	53.3	29.6	32.0	31.2	39.7	21.5	58.2	54.9	33.5	90.8
SEM:	9.4	7.2	5.3	3.5	6.6	6.6	11.9	8.9	6.6	2.5	8.3	3.5	4.7	12.3	4.1	4.1	5.6	11.5	2.9	5.7	9.8	2.2	10.5

[00220] *NHP studies:* 10 GalNAc-conjugated PNPLA3 oligonucleotides selected from table 7 are evaluated in cynomolgus monkeys (*Macaca fascicularis*). Here, the NHPs are grouped so that their mean body weights (about 5.4 kg) are comparable between the control and experimental groups. Each cohort contains two male and three female subjects. The GalNAc-conjugated PNPLA3 oligonucleotides are administered SQ on Study Day 0. Blood samples are collected on Study Days -8, -5 and 0, and weekly after dosing. Ultrasound-guided core needle liver biopsies are collected on Study Days -7, 28 and 56. At each time point, total RNA derived from the liver biopsy samples is subjected to qRT-PCR analysis to measure PNPLA3 mRNA in oligonucleotide-treated monkeys relative to monkeys treated with a comparable volume of PBS. To normalize the data, the measurements are made relative to the geometric mean of two reference genes, PPIB and 18S rRNA. As shown in Table 8 (Day -7), Table 9 (Day 28), and Table 10 (Day 56), treating NHPs with the GalNAc-conjugated PNPLA3 oligonucleotides inhibits *PNPLA3* expression in the liver, as determined by a reduced amount of PNPLA3 mRNA in liver samples from oligonucleotide-treated NHPs relative to NHPs treated with PBS. For all time points evaluated, PNPLA3 oligonucleotides 34, 81 and 121 inhibit PNPLA3 expression to a greater extent than the benchmark PBS and time-matched controls. From the same NHP study, inhibition of *PNPLA3* expression is also determined by

measuring PNPLA3 protein in serum prepared from the pre-dose and weekly blood samples by ELISA. Taken together, these results demonstrate that treating NHPs with GalNAc-conjugated PNPLA3 oligonucleotides reduces the amount of PNPLA3 mRNA in the liver and concomitantly reduces the amount of PNPLA3 protein in the serum.

[00221] Table 8: PNPLA3 mRNA Knockdown of Select GalNAc-Conjugated PNPLA3 Oligonucleotides in NHP at Day -7.

Sequence	Passenger (sense) (SEQ ID NO:)	Guide (antisense) (SEQ ID NO:)	Mean %KD, Rel To Time-Matched PBS
PBS	--	--	0
644	1220	1221	29
1126	1224	1225	-4.9
1143	1230	1231	43
1147	1232	1233	-2.5
1699	1188	1189	44
1703	1190	1191	28
2140	1244	1245	27
2149	1250	1251	20
1697	1254	1255	5.9
2144	1246	1247	-15

[00222] Table 9: PNPLA3 mRNA Knockdown of Select GalNAc-Conjugated PNPLA3 Oligonucleotides in NHP at Day 28.

Sequence	Passenger (sense) (SEQ ID NO:)	Guide (antisense) (SEQ ID NO:)	Mean %KD, Rel To Time-Matched PBS	Mean %KD, Rel to mean of pre-dose	Mean % KD, Rel To Individual Animal Predose
PBS	--	--	0	-9.8	-30
644	1220	1221	34	-3	-17
1126	1224	1225	50	48	36
1143	1230	1231	54	11	-0.1
1147	1232	1233	-2.4	-9.8	11
1699	1188	1189	65	32	30
1703	1190	1191	60	39	19
2140	1244	1245	65	47	40
2149	1250	1251	64	51	48
1697	1254	1255	49	40	42
2144	1246	1247	50	53	51

Table 10: PNPLA3 mRNA Knockdown of Select GalNAc-Conjugated PNPLA3 Oligonucleotides in NHP at Day 56.

Sequence	Passenger (sense) (SEQ ID NO:)	Guide (antisense) (SEQ ID NO:)	Mean %KD, Rel to Time-Matched PBS	Mean %KD, Rel to Mean of Pre-Dose	Mean % KD, Rel to Individual Animal Predose
PBS	--	--	0	5	-12
644	1220	1221	46	28	28
1126	1224	1225	39	45	27
1143	1230	1231	35	-9.2	-32
1147	1232	1233	28	34	29
1699	1188	1189	51	18	14
1703	1190	1191	5.5	-24	-45
2140	1244	1245	-34	-73	-100
2149	1250	1251	48	39	36
1697	1254	1255	32	31	31
2144	1246	1247	-9.8	9.7	4.4

[00223] Taken together, these results show that GalNAc-conjugated PNPLA3 oligonucleotides designed to target human PNPLA3 mRNA inhibit *PNPLA3* expression *in vivo* (as determined by the reduction of the amount of PNPLA3 mRNA and PNPLA3 protein in treated animals).

SEQUENCES

[00224] The following nucleic acid sequences and/or amino acid sequences are referred to in the disclosure and are provided below for reference.

[00225] SEQ ID NO:1 – wild-type human PNPLA3 (2753 bp; NCBI Ref. Seq. No. NM_025225.3)

agagagcgcttgcgggcgccgggcggagctgctgcggatcaggacccgagccgattcccgatcccgacccagatcctaacccgc
gcccccgccccgccgccgccgccatgtacgacgcagagcgcggctggagcttgtccttcgcgggctgcggcttcctgggcttctac
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gaccagccccacatggtcagtgagtttctccccatgtgtggcgatgagagagtgtagaaataaagacacaagacaaagaga

[00226] SEQ ID NO:2 – wild-type human PNPLA3 (481 aa; NCBI Ref. Seq. No. NP_079501.2)

MYDAERGWSLSFAGCGFLGFYHVGATRCLSEHAPHLLRDARMLFGASAGALHCVG
VLSGIPLEQTLQVLSDLVRKARSRNIGIFHPSFNLSKFLRQGLCKCLPANVHQLISGKI
GISLTRVSDGENVLVSDFRSKDEVVDALVCSCFIPFYSGLIPPSFRGVRYVDGGVSDN
VPFIDAKTTITVSPFYGEYDICPKVKSTNFLHVDITKLSLRLCTGNLYLLSRAFVPPDL
KVLGEICLRGYLDAFRFLEEKGICNRPQPGLKSSSEGMDPEVAMPSWANMSLDSSPE
SAALAVRLEGDELLDHLRLSILPWDESILDTLSPRLATALSEEMKDKGGYMSKICNLL
PIRIMSYVMLPCTLPVESAIAIVQRLVTWLPDMPDDVLWLQWVTSQVFTRVLMCLLP
ASRSQMPVSSQQASPCTPEQDWPCWTPCSPKGCPAETKAEATPRSILRSSLNFFLGNK
VPAGAEGLSTFPSFSLEKSL

[00227] SEQ ID NO:3 – human PNPLA3 I148M (variant) mRNA

agagagcgcttgcgggcgccgggcggagctgctgcggatcaggacccgagccgattcccgatcccgacccagatcctaacccgc
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[00228] SEQ ID NO:4 – human PNPLA3 I148M (variant)
MYDAERGWSLSFAGCGFLGFYHVGATRCLSEHAPHLLRDARMLFGASAGALHCVG
VLSGIPLEQTLQVLSDLVRKARSRNIGIFHPSFNLSKFLRQGLCKCLPANVHQLISGKI
GISLTRVSDGENVLVSDFRSKDEVVDALVCSCFMPFYSGLIPPSFRGVRYVDGGVSD
NVPFIDAKTTITVSPFYGEYDICPKVKSTNFLHVDITKLSLRLCTGNLYLLSRAFVPPD
LKVLGEICLRGYLDAFRFLEEKGICNRPQPGLKSSSEGMDPEVAMPSWANMSLDSSP
ESAALAVRLEGDELLDHLRLSILPWDESILDTLSPRLATALSEEMKDKGGYMSKICNL
LPIRIMSYVMLPCTLPVESAIAIVQRLVTWLPDMPDDVLWLQWVTSQVFTRVLMCLL
PASRSQMPVSSQQASPCTPEQDWPCWTPCSPKGCPAETKAEATPRSILRSSLNFFLGN
KVPAGAEGLSTFPSFSLEKSL

[00229] SEQ ID NO:5 – primate PNPLA3 (2291 bp; NCBI Ref. Seq. No. XM_015457081.1)

cgagggaggcggggcggacgtcgcgcgtggaaagcccgggcggagacgcggcggctgggtcacgagcgcttgcgggcgccc
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[00230] SEQ ID NO:6 – primate PNPLA3 (480 aa; NCBI Ref. Seq. No. XP_015312567.1)
MYDAERGWSLSFAGCGFLGFYHVGATRCLSEHAPHLLRDARMLFGASAGALHCVG
VLSGIPLEQTLQVLSDLVRKARSRNIGIFHPSFNIGKFLRQDLYKYLPANVHQLISGKI
CVSLTRVSDGENVLVSDFQSKDEVVDALICSCFIPFYSGLIPPSFRGVRYVDGGASDN
VPFIDAKTTITVSPFYGEYDICPKVKSTNFLHVDITKLSLRLCTGNLYLLSRAFVPPDL

KVLGEICLRGYLDAFRFLEEKGICNKPQRGLKSSSEGMDSEVTAPGWENTSLDSSPEP
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RIISYVMLPCTLPVESAIAIVQRLVTWLPDMPDDVQWLQWVTSQVFTRALMCLLPAS
RSQMPVSSEQASPCKPEQDWHCWTPCSPEDCPAEAKAEATPRSILRSSLNFFWGNKV
PAGAEGLSTFPSFSLEKNL

[00231] SEQ ID NO:7 – mouse PNPLA3 (4675 bp; NCBI Ref. Seq. No. XM_006520346.5)

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cttgacttgtaagccccttagcaaggctggttcatttgtttattaaaagcaggtgtgggtgaatttatgcaaatgagtatgcaaactagtgg
aacagcagaaggattgaatggatacaccaaaaataaccacaactgtttaagggaaaagggtccataataaatgtggggaacaaaaaa
caaataaatgtgatttttttta

[00232] SEQ ID NO:8 – mouse PNPLA3 (367 aa; NCBI Ref. Seq. No. XP_006520409.1)
MEILMDLVRKARSRNIGTLHPFFNINKCIRDGLQESLPDNVHQVISGKVHISLTRVSD
GENVLVSEFHSKDEVVDALVCSCFIPLFSGLIPPSFRGERYVDGGVSDNVPVLDAKTT

ITVSPFYGEHDICPKVKSTNFFHVNITNLSLRLCTGNLQLLTRALFPSDVKVMGELCY
QGYLDAFRFLEENGICNGPQRSLSLSLVAPEACLENGKLVGDKVPVSLCFTDENIWET
LSPELSTALSEAIKDREGYLSKVCNLLPVRILSYIMLPCSLPVESAIAAVHRLVTWLPDI
QDDIQWLQWATSQVCARMTMCLLPSTSMRFLGQSQFLGLHCIKGLKTKGKAQLSLQ
HASSARTTARFGAQAVQTF

[00233] SEQ ID NO:9 – DsiRNA 1 passenger (sense) strand
UCUGCAGGUCCUCUCAGAUCUUGUG

[00234] SEQ ID NO:10 – DsiRNA 1 guide (antisense) strand
CACAAGAUCUGAGAGGACCUGCAGAGU

[00235] SEQ ID NO:11 – DsiRNA 2 passenger (sense) strand
AGGUCCUCUCAGAUCUUGUGCGGAA

[00236] SEQ ID NO:12 – DsiRNA 2 guide (antisense) strand
UUCCGCACAAGAUCUGAGAGGACCUGC

[00237] SEQ ID NO:13 – DsiRNA 3 passenger (sense) strand
AUUGGCAUCUUCCAUCCAUCCUUCA

[00238] SEQ ID NO:14 – DsiRNA 3 guide (antisense) strand
UGAAGGAUGGAUGGAAGAUGCCAAUGU

[00239] SEQ ID NO:15 – DsiRNA 4 passenger (sense) strand
AUCUUCCAUCCAUCCUUCAACUUAA

[00240] SEQ ID NO:16 – DsiRNA 4 guide (antisense) strand
UUAAGUUGAAGGAUGGAUGGAAGAUGC

[00241] SEQ ID NO:17 – DsiRNA 5 passenger (sense) strand
UCUUCCAUCCAUCCUUCAACUUAAG

[00242] SEQ ID NO:18 – DsiRNA 5 guide (antisense) strand
CUUAAGUUGAAGGAUGGAUGGAAGAUG

[00243] SEQ ID NO:19 – DsiRNA 6 passenger (sense) strand
CCAGAGUGUCUGAUGGGGAAAACGU

[00244] SEQ ID NO:20 – DsiRNA 6 guide (antisense) strand
ACGUUUUCCCCAUCAGACACUCUGGUA

[00245] SEQ ID NO:21 – DsiRNA 7 passenger (sense) strand
GAGUGUCUGAUGGGGAAAACGUUCU

[00246] SEQ ID NO:22 – DsiRNA 7 guide (antisense) strand
AGAACGUUUUCCCCAUCAGACACUCUG

[00247] SEQ ID NO:23 – DsiRNA 8 passenger (sense) strand
AUGGGGAAAACGUUCUGGUGUCUGA

[00248] SEQ ID NO:24 – DsiRNA 8 guide (antisense) strand
UCAGACACCAGAACGUUUUCCCCAUCA

[00249] SEQ ID NO:25 – DsiRNA 9 passenger (sense) strand
GGGGAAAACGUUCUGGUGUCUGACU

[00250] SEQ ID NO:26 – DsiRNA 9 guide (antisense) strand
AGUCAGACACCAGAACGUUUUCCCCAU

[00251] SEQ ID NO:27 – DsiRNA 10 passenger (sense) strand
GGGAAAACGUUCUGGUGUCUGACUU

[00252] SEQ ID NO:28 – DsiRNA 10 guide (antisense) strand

AAGUCAGACACCAGAACGUUUUCCCCA

[00253] SEQ ID NO:29 – DsiRNA 11 passenger (sense) strand
GGAAAACGUUCUGGUGUCUGACUUU

[00254] SEQ ID NO:30 – DsiRNA 11 guide (antisense) strand
AAAGUCAGACACCAGAACGUUUUCCCC

[00255] SEQ ID NO:31 – DsiRNA 12 passenger (sense) strand
GAAAACGUUCUGGUGUCUGACUUUC

[00256] SEQ ID NO:32 – DsiRNA 12 guide (antisense) strand
GAAAGUCAGACACCAGAACGUUUUCCC

[00257] SEQ ID NO:33 – DsiRNA 13 passenger (sense) strand
AAAACGUUCUGGUGUCUGACUUUCG

[00258] SEQ ID NO:34 – DsiRNA 13 guide (antisense) strand
CGAAAGUCAGACACCAGAACGUUUUCC

[00259] SEQ ID NO:35 – DsiRNA 14 passenger (sense) strand
AAACGUUCUGGUGUCUGACUUUCGG

[00260] SEQ ID NO:36 – DsiRNA 14 guide (antisense) strand
CCGAAAGUCAGACACCAGAACGUUUUC

[00261] SEQ ID NO:37 – DsiRNA 15 passenger (sense) strand
AACGUUCUGGUGUCUGACUUUCGGU

[00262] SEQ ID NO:38 – DsiRNA 15 guide (antisense) strand
ACCGAAAGUCAGACACCAGAACGUUUU

[00263] SEQ ID NO:39 – DsiRNA 16 passenger (sense) strand
ACGUUCUGGUGUCUGACUUUCGGUC

[00264] SEQ ID NO:40 – DsiRNA 16 guide (antisense) strand
GACCGAAAGUCAGACACCAGAACGUUU

[00265] SEQ ID NO:41 – DsiRNA 17 passenger (sense) strand
GUUCUGGUGUCUGACUUUCGGUCCA

[00266] SEQ ID NO:42 – DsiRNA 17 guide (antisense) strand
UGGACCGAAAGUCAGACACCAGAACGU

[00267] SEQ ID NO:43 – DsiRNA 18 passenger (sense) strand
GACGAAGUCGUGGAUGCCUUGGUAU

[00268] SEQ ID NO:44 – DsiRNA 18 guide (antisense) strand
AUACCAAGGCAUCCACGACUUCGUCUU

[00269] SEQ ID NO:45 – DsiRNA 19 passenger (sense) strand
ACGAAGUCGUGGAUGCCUUGGUAUG

[00270] SEQ ID NO:46 – DsiRNA 19 guide (antisense) strand
CAUACCAAGGCAUCCACGACUUCGUCU

[00271] SEQ ID NO:47 – DsiRNA 20 passenger (sense) strand
CGAAGUCGUGGAUGCCUUGGUAUGU

[00272] SEQ ID NO:48 – DsiRNA 20 guide (antisense) strand
ACAUACCAAGGCAUCCACGACUUCGUC

[00273] SEQ ID NO:49 – DsiRNA 21 passenger (sense) strand
CAGAGGCGUGCGAUAUGUGGAUGGA

[00274] SEQ ID NO:50 – DsiRNA 21 guide (antisense) strand
UCCAUCCACAUAUCGCACGCCUCUGAA

[00275] SEQ ID NO:51 – DsiRNA 22 passenger (sense) strand
GCGAUAUGUGGAUGGAGGAGUGAGU

[00276] SEQ ID NO: 52 – DsiRNA 22 guide (antisense) strand
ACUCACUCCUCCAUCCACAUAUCGCAC

[00277] SEQ ID NO:53 – DsiRNA 23 passenger (sense) strand
GAUGGAGGAGUGAGUGACAACGUAC

[00278] SEQ ID NO:54 – DsiRNA 23 guide (antisense) strand
GUACGUUGUCACUCACUCCUCCAUCCA

[00279] SEQ ID NO:55 – DsiRNA 24 passenger (sense) strand
GAGGAGUGAGUGACAACGUACCCUU

[00280] SEQ ID NO:56 – DsiRNA 24 guide (antisense) strand
AAGGGUACGUUGUCACUCACUCCUCCA

[00281] SEQ ID NO:57 – DsiRNA 25 passenger (sense) strand
GAGUGAGUGACAACGUACCCUUCAU

[00282] SEQ ID NO:58 – DsiRNA 25 guide (antisense) strand
AUGAAGGGUACGUUGUCACUCACUCCU

[00283] SEQ ID NO:59 – DsiRNA 26 passenger (sense) strand
AGUGAGUGACAACGUACCCUUCAUU

[00284] SEQ ID NO:60 – DsiRNA 26 guide (antisense) strand

AAUGAAGGGUACGUUGUCACUCACUCC

[00285] SEQ ID NO:61 – DsiRNA 27 passenger (sense) strand
GUGAGUGACAACGUACCCUUCAUUG

[00286] SEQ ID NO:62 – DsiRNA 27 guide (antisense) strand
CAAUGAAGGGUACGUUGUCACUCACUC

[00287] SEQ ID NO:63 – DsiRNA 28 passenger (sense) strand
UGAGUGACAACGUACCCUUCAUUGA

[00288] SEQ ID NO:64 – DsiRNA 28 guide (antisense) strand
UCAAUGAAGGGUACGUUGUCACUCACU

[00289] SEQ ID NO:65 – DsiRNA 29 passenger (sense) strand
GAGUGACAACGUACCCUUCAUUGAU

[00290] SEQ ID NO:66 – DsiRNA 29 guide (antisense) strand
AUCAAUGAAGGGUACGUUGUCACUCAC

[00291] SEQ ID NO:67 – DsiRNA 30 passenger (sense) strand
AGUGACAACGUACCCUUCAUUGAUG

[00292] SEQ ID NO:68 – DsiRNA 30 guide (antisense) strand
CAUCAAUGAAGGGUACGUUGUCACUCA

[00293] SEQ ID NO:69 – DsiRNA 31 passenger (sense) strand
GUGACAACGUACCCUUCAUUGAUGC

[00294] SEQ ID NO:70 – DsiRNA 31 guide (antisense) strand
GCAUCAAUGAAGGGUACGUUGUCACUC

[00295] SEQ ID NO:71 – DsiRNA 32 passenger (sense) strand
UGACAACGUACCCUUCAUUGAUGCC

[00296] SEQ ID NO:72 – DsiRNA 32 guide (antisense) strand
GGCAUCAAUGAAGGGUACGUUGUCACU

[00297] SEQ ID NO:73 – DsiRNA 33 passenger (sense) strand
GACAACGUACCCUUCAUUGAUGCCA

[00298] SEQ ID NO:74 – DsiRNA 33 guide (antisense) strand
UGGCAUCAAUGAAGGGUACGUUGUCAC

[00299] SEQ ID NO:75 – DsiRNA 34 passenger (sense) strand
CAACGUACCCUUCAUUGAUGCCAAA

[00300] SEQ ID NO:76 – DsiRNA 34 guide (antisense) strand
UUUGGCAUCAAUGAAGGGUACGUUGUC

[00301] SEQ ID NO:77 – DsiRNA 35 passenger (sense) strand
AACGUACCCUUCAUUGAUGCCAAAA

[00302] SEQ ID NO:78 – DsiRNA 35 guide (antisense) strand
UUUUGGCAUCAAUGAAGGGUACGUUGU

[00303] SEQ ID NO:79 – DsiRNA 36 passenger (sense) strand
ACGUACCCUUCAUUGAUGCCAAAAC

[00304] SEQ ID NO:80 – DsiRNA 36 guide (antisense) strand
GUUUUGGCAUCAAUGAAGGGUACGUUG

[00305] SEQ ID NO:81 – DsiRNA 37 passenger (sense) strand
CGUACCCUUCAUUGAUGCCAAAACA

[00306] SEQ ID NO:82 – DsiRNA 37 guide (antisense) strand
UGUUUUGGCAUCAAUGAAGGGUACGUU

[00307] SEQ ID NO:83 – DsiRNA 38 passenger (sense) strand
UACCCUUCAUUGAUGCCAAAACAAC

[00308] SEQ ID NO:84 – DsiRNA 38 guide (antisense) strand
GUUGUUUUGGCAUCAAUGAAGGGUACG

[00309] SEQ ID NO:85 – DsiRNA 39 passenger (sense) strand
UUGAUGCCAAAACAACCAUCACCGU

[00310] SEQ ID NO:86 – DsiRNA 39 guide (antisense) strand
ACGGUGAUGGUUGUUUUGGCAUCAAUG

[00311] SEQ ID NO:87 – DsiRNA 40 passenger (sense) strand
GAUGCCAAAACAACCAUCACCGUGU

[00312] SEQ ID NO:88 – DsiRNA 40 guide (antisense) strand
ACACGGUGAUGGUUGUUUUGGCAUCAA

[00313] SEQ ID NO:89 – DsiRNA 41 passenger (sense) strand
AUGGGGAGUACGACAUCUGCCCUAA

[00314] SEQ ID NO:90 – DsiRNA 41 guide (antisense) strand
UUAGGGCAGAUGUCGUACUCCCCAUAG

[00315] SEQ ID NO:91 – DsiRNA 42 passenger (sense) strand
GUACGACAUCUGCCCUAAAGUCAAG

[00316] SEQ ID NO:92 – DsiRNA 42 guide (antisense) strand

CUUGACUUUAGGGCAGAUGUCGUACUC

[00317] SEQ ID NO:93 – DsiRNA 43 passenger (sense) strand
GACAUCUGCCCUAAAGUCAAGUCCA

[00318] SEQ ID NO:94 – DsiRNA 43 guide (antisense) strand
UGGACUUGACUUUAGGGCAGAUGUCGU

[00319] SEQ ID NO:95 – DsiRNA 44 passenger (sense) strand
ACAUCUGCCCUAAAGUCAAGUCCAC

[00320] SEQ ID NO:96 – DsiRNA 44 guide (sense) strand
GUGGACUUGACUUUAGGGCAGAUGUCG

[00321] SEQ ID NO:97 – DsiRNA 45 passenger (sense) strand
GUCAAGUCCACGAACUUUCUUCAUG

[00322] SEQ ID NO:98 – DsiRNA 45 guide (antisense) strand
CAUGAAGAAAGUUCGUGGACUUGACUU

[00323] SEQ ID NO:99 – DsiRNA 46 passenger (sense) strand
UCAAGUCCACGAACUUUCUUCAUGU

[00324] SEQ ID NO:100 – DsiRNA 46 guide (antisense) strand
ACAUGAAGAAAGUUCGUGGACUUGACU

[00325] SEQ ID NO:101 – DsiRNA 47 passenger (sense) strand
CAAGUCCACGAACUUUCUUCAUGUG

[00326] SEQ ID NO:102 – DsiRNA 47 guide (antisense) strand
CACAUGAAGAAAGUUCGUGGACUUGAC

[00327] SEQ ID NO:103 – DsiRNA 48 passenger (sense) strand
GUCCACGAACUUUCUUCAUGUGGAC

[00328] SEQ ID NO:104 – DsiRNA 48 guide (antisense) strand
GUCCACAUGAAGAAAGUUCGUGGACUU

[00329] SEQ ID NO:105 – DsiRNA 49 passenger (sense) strand
CCACGAACUUUCUUCAUGUGGACAU

[00330] SEQ ID NO:106 – DsiRNA 49 guide (antisense) strand
AUGUCCACAUGAAGAAAGUUCGUGGAC

[00331] SEQ ID NO:107 – DsiRNA 50 passenger (sense) strand
CACGAACUUUCUUCAUGUGGACAUC

[00332] SEQ ID NO:108 – DsiRNA 50 guide (antisense) strand
GAUGUCCACAUGAAGAAAGUUCGUGGA

[00333] SEQ ID NO:109 – DsiRNA 51 passenger (sense) strand
ACGAACUUUCUUCAUGUGGACAUCA

[00334] SEQ ID NO:110 – DsiRNA 51 guide (antisense) strand
UGAUGUCCACAUGAAGAAAGUUCGUGG

[00335] SEQ ID NO:111 – DsiRNA 52 passenger (sense) strand
CGAACUUUCUUCAUGUGGACAUCAC

[00336] SEQ ID NO:112 – DsiRNA 52 guide (antisense) strand
GUGAUGUCCACAUGAAGAAAGUUCGUG

[00337] SEQ ID NO:113 – DsiRNA 53 passenger (sense) strand
GAACUUUCUUCAUGUGGACAUCACC

[00338] SEQ ID NO:114 – DsiRNA 53 guide (antisense) strand
GGUGAUGUCCACAUGAAGAAAGUUCGU

[00339] SEQ ID NO:115 – DsiRNA 54 passenger (sense) strand
AACUUUCUUCAUGUGGACAUCACCA

[00340] SEQ ID NO:116 – DsiRNA 54 guide (antisense) strand
UGGUGAUGUCCACAUGAAGAAAGUUCG

[00341] SEQ ID NO:117 – DsiRNA 55 passenger (sense) strand
ACUUUCUUCAUGUGGACAUCACCAA

[00342] SEQ ID NO:118 – DsiRNA 55 guide (antisense) strand
UUGGUGAUGUCCACAUGAAGAAAGUUC

[00343] SEQ ID NO:119 – DsiRNA 56 passenger (sense) strand
CUUUCUUCAUGUGGACAUCACCAAG

[00344] SEQ ID NO:120 – DsiRNA 56 guide (antisense) strand
CUUGGUGAUGUCCACAUGAAGAAAGUU

[00345] SEQ ID NO:121 – DsiRNA 57 passenger (sense) strand
UUUCUUCAUGUGGACAUCACCAAGC

[00346] SEQ ID NO:122 – DsiRNA 57 guide (antisense) strand
GCUUGGUGAUGUCCACAUGAAGAAAGU

[00347] SEQ ID NO:123 – DsiRNA 58 passenger (sense) strand
UUCUUCAUGUGGACAUCACCAAGCU

[00348] SEQ ID NO:124 – DsiRNA 58 guide (antisense) strand

AGCUUGGUGAUGUCCACAUGAAGAAAG

[00349] SEQ ID NO:125 – DsiRNA 59 passenger (sense) strand
CUUCAUGUGGACAUCACCAAGCUCA

[00350] SEQ ID NO:126 – DsiRNA 59 guide (antisense) strand
UGAGCUUGGUGAUGUCCACAUGAAGAA

[00351] SEQ ID NO:127 – DsiRNA 60 passenger (sense) strand
UUCAUGUGGACAUCACCAAGCUCAG

[00352] SEQ ID NO:128 – DsiRNA 60 guide (antisense) strand
CUGAGCUUGGUGAUGUCCACAUGAAGA

[00353] SEQ ID NO:129 – DsiRNA 61 passenger (sense) strand
UCAUGUGGACAUCACCAAGCUCAGU

[00354] SEQ ID NO:130 – DsiRNA 61 guide (antisense) strand
ACUGAGCUUGGUGAUGUCCACAUGAAG

[00355] SEQ ID NO:131 – DsiRNA 62 passenger (sense) strand
CAUGUGGACAUCACCAAGCUCAGUC

[00356] SEQ ID NO:132 – DsiRNA 62 guide (antisense) strand
GACUGAGCUUGGUGAUGUCCACAUGAA

[00357] SEQ ID NO:133 – DsiRNA 63 passenger (sense) strand
AUGUGGACAUCACCAAGCUCAGUCU

[00358] SEQ ID NO:134 – DsiRNA 63 guide (antisense) strand
AGACUGAGCUUGGUGAUGUCCACAUGA

[00359] SEQ ID NO:135 – DsiRNA 64 passenger (sense) strand
UGUGGACAUCACCAAGCUCAGUCUA

[00360] SEQ ID NO:136 – DsiRNA 64 guide (antisense) strand
UAGACUGAGCUUGGUGAUGUCCACAUG

[00361] SEQ ID NO:137 – DsiRNA 65 passenger (sense) strand
GUGGACAUCACCAAGCUCAGUCUAC

[00362] SEQ ID NO:138 – DsiRNA 65 guide (antisense) strand
GUAGACUGAGCUUGGUGAUGUCCACAU

[00363] SEQ ID NO:139 – DsiRNA 66 passenger (sense) strand
UGGACAUCACCAAGCUCAGUCUACG

[00364] SEQ ID NO:140 – DsiRNA 66 guide (antisense) strand
CGUAGACUGAGCUUGGUGAUGUCCACA

[00365] SEQ ID NO:141 – DsiRNA 67 passenger (sense) strand
AGCUUUUGUCCCCCCGGAUCUCAAG

[00366] SEQ ID NO:142 – DsiRNA 67 guide (antisense) strand
CUUGAGAUCCGGGGGGACAAAAGCUCU

[00367] SEQ ID NO:143 – DsiRNA 68 passenger (sense) strand
AAGGUGCUGGGAGAGAUAUGCCUUC

[00368] SEQ ID NO:144 – DsiRNA 68 guide (antisense) strand
GAAGGCAUAUCUCUCCCAGCACCUUGA

[00369] SEQ ID NO:145 – DsiRNA 69 passenger (sense) strand
GGGAGAGAUAUGCCUUCGAGGAUAU

[00370] SEQ ID NO:146 – DsiRNA 69 guide (antisense) strand
AUAUCCUCGAAGGCAUAUCUCUCCCAG

[00371] SEQ ID NO:147 – DsiRNA 70 passenger (sense) strand
GGAGAGAUAUGCCUUCGAGGAUAUU

[00372] SEQ ID NO:148 – DsiRNA 70 guide (antisense) strand
AAUAUCCUCGAAGGCAUAUCUCUCCCA

[00373] SEQ ID NO:149 – DsiRNA 71 passenger (sense) strand
AGAGAUAUGCCUUCGAGGAUAUUUG

[00374] SEQ ID NO:150 – DsiRNA 71 guide (antisense) strand
CAAAUAUCCUCGAAGGCAUAUCUCUCC

[00375] SEQ ID NO:151 – DsiRNA 72 passenger (sense) strand
GAGAUAUGCCUUCGAGGAUAUUUGG

[00376] SEQ ID NO:152 – DsiRNA 72 guide (antisense) strand
CCAAAUAUCCUCGAAGGCAUAUCUCUC

[00377] SEQ ID NO:153 – DsiRNA 73 passenger (sense) strand
AGAUAUGCCUUCGAGGAUAUUUGGA

[00378] SEQ ID NO:154 – DsiRNA 73 guide (antisense) strand
UCCAAAUAUCCUCGAAGGCAUAUCUCU

[00379] SEQ ID NO:155 – DsiRNA 74 passenger (sense) strand
GAUAUGCCUUCGAGGAUAUUUGGAU

[00380] SEQ ID NO:156 – DsiRNA 74 guide (antisense) strand
AUCCAAAUAUCCUCGAAGGCAUAUCUC

[00381] SEQ ID NO:157 – DsiRNA 75 passenger (sense) strand
AUAUGCCUUCGAGGAUAUUUGGAUG

[00382] SEQ ID NO:158 – DsiRNA 75 guide (antisense) strand
CAUCCAAAUAUCCUCGAAGGCAUAUCU

[00383] SEQ ID NO:159 – DsiRNA 76 passenger (sense) strand
AUGCCUUCGAGGAUAUUUGGAUGCA

[00384] SEQ ID NO:160 – DsiRNA 76 guide (antisense) strand
UGCAUCCAAAUAUCCUCGAAGGCAUAU

[00385] SEQ ID NO:161 – DsiRNA 77 passenger (sense) strand
UGCCUUCGAGGAUAUUUGGAUGCAU

[00386] SEQ ID NO:162 – DsiRNA 77 guide (antisense) strand
AUGCAUCCAAAUAUCCUCGAAGGCAUA

[00387] SEQ ID NO:163 – DsiRNA 78 passenger (sense) strand
GCCUUCGAGGAUAUUUGGAUGCAUU

[00388] SEQ ID NO:164 – DsiRNA 78 guide (antisense) strand
AAUGCAUCCAAAUAUCCUCGAAGGCAU

[00389] SEQ ID NO:165 – DsiRNA 79 passenger (sense) strand
UCAGGUUCUUGGAAGAGAAGGGCAU

[00390] SEQ ID NO:166 – DsiRNA 79 guide (antisense) strand
AUGCCCUUCUCUUCCAAGAACCUGAAU

[00391] SEQ ID NO:167 – DsiRNA 80 passenger (sense) strand
CAGGUUCUUGGAAGAGAAGGGCAUC

[00392] SEQ ID NO:168 – DsiRNA 80 guide (antisense) strand
GAUGCCCUUCUCUUCCAAGAACCUGAA

[00393] SEQ ID NO:169 – DsiRNA 81 passenger (sense) strand
AGGUUCUUGGAAGAGAAGGGCAUCU

[00394] SEQ ID NO:170 – DsiRNA 81 guide (antisense) strand
AGAUGCCCUUCUCUUCCAAGAACCUGA

[00395] SEQ ID NO:171 – DsiRNA 82 passenger (sense) strand
GGUUCUUGGAAGAGAAGGGCAUCUG

[00396] SEQ ID NO:172 – DsiRNA 82 guide (antisense) strand
CAGAUGCCCUUCUCUUCCAAGAACCUG

[00397] SEQ ID NO:173 – DsiRNA 83 passenger (sense) strand
UGGAAGAGAAGGGCAUCUGCAACAG

[00398] SEQ ID NO:174 – DsiRNA 83 guide (antisense) strand
CUGUUGCAGAUGCCCUUCUCUUCCAAG

[00399] SEQ ID NO:175 – DsiRNA 84 passenger (sense) strand
UGAAGUCAUCCUCAGAAGGGAUGGA

[00400] SEQ ID NO:176 – DsiRNA 84 guide (antisense) strand
UCCAUCCCUUCUGAGGAUGACUUCAGG

[00401] SEQ ID NO:177 – DsiRNA 85 passenger (sense) strand

GAAGUCAUCCUCAGAAGGGAUGGAU

[00402] SEQ ID NO:178 – DsiRNA 85 guide (antisense) strand
AUCCAUCCCUUCUGAGGAUGACUUCAG

[00403] SEQ ID NO:179 – DsiRNA 86 passenger (sense) strand
AAGUCAUCCUCAGAAGGGAUGGAUC

[00404] SEQ ID NO:180 – DsiRNA 86 guide (antisense) strand
GAUCCAUCCCUUCUGAGGAUGACUUCA

[00405] SEQ ID NO:181 – DsiRNA 87 passenger (sense) strand
GUCAUCCUCAGAAGGGAUGGAUCCU

[00406] SEQ ID NO:182 – DsiRNA 87 guide (antisense) strand
AGGAUCCAUCCCUUCUGAGGAUGACUU

[00407] SEQ ID NO:183 – DsiRNA 88 passenger (sense) strand
CAUCCUCAGAAGGGAUGGAUCCUGA

[00408] SEQ ID NO:184 – DsiRNA 88 guide (antisense) strand
UCAGGAUCCAUCCCUUCUGAGGAUGAC

[00409] SEQ ID NO:185 – DsiRNA 89 passenger (sense) strand
AUCCUCAGAAGGGAUGGAUCCUGAG

[00410] SEQ ID NO:186 – DsiRNA 89 guide (antisense) strand)
CUCAGGAUCCAUCCCUUCUGAGGAUGA

[00411] SEQ ID NO:187 – DsiRNA 90 passenger (sense) strand
CUAGACCACCUGCGUCUCAGCAUCC

[00412] SEQ ID NO:188 – DsiRNA 90 guide (antisense) strand
GGAUGCUGAGACGCAGGUGGUCUAGCA

[00413] SEQ ID NO:189 – DsiRNA 91 passenger (sense) strand
AGUGAAGAAAUGAAAGACAAAGGUG

[00414] SEQ ID NO:190 – DsiRNA 91 guide (antisense) strand
CACCUUUGUCUUUCAUUUCUUCACUCA

[00415] SEQ ID NO:191 – DsiRNA 92 passenger (sense) strand
GUGAAGAAAUGAAAGACAAAGGUGG

[00416] SEQ ID NO:192 – DsiRNA 92 guide (antisense) strand
CCACCUUUGUCUUUCAUUUCUUCACUC

[00417] SEQ ID NO:193 – DsiRNA 93 passenger (sense) strand
UGAAGAAAUGAAAGACAAAGGUGGA

[00418] SEQ ID NO:194 – DsiRNA 93 guide (antisense) strand
UCCACCUUUGUCUUUCAUUUCUUCACU

[00419] SEQ ID NO:195 – DsiRNA 94 passenger (sense) strand
GAAGAAAUGAAAGACAAAGGUGGAU

[00420] SEQ ID NO:196 – DsiRNA 94 guide (antisense) strand
AUCCACCUUUGUCUUUCAUUUCUUCAC

[00421] SEQ ID NO:197 – DsiRNA 95 passenger (sense) strand
AAGAAAUGAAAGACAAAGGUGGAUA

[00422] SEQ ID NO:198 – DsiRNA 95 guide (antisense) strand
UAUCCACCUUUGUCUUUCAUUUCUUCA

[00423] SEQ ID NO:199 – DsiRNA 96 passenger (sense) strand
AGAAAUGAAAGACAAAGGUGGAUAC

[00424] SEQ ID NO:200 – DsiRNA 96 guide (antisense) strand
GUAUCCACCUUUGUCUUUCAUUUCUUC

[00425] SEQ ID NO:201 – DsiRNA 97 passenger (sense) strand
GAAAUGAAAGACAAAGGUGGAUACA

[00426] SEQ ID NO:202 – DsiRNA 97 guide (antisense) strand
UGUAUCCACCUUUGUCUUUCAUUUCUU

[00427] SEQ ID NO:203 – DsiRNA 98 passenger (sense) strand
AAAUGAAAGACAAAGGUGGAUACAU

[00428] SEQ ID NO:204 – DsiRNA 98 guide (antisense) strand
AUGUAUCCACCUUUGUCUUUCAUUUCU

[00429] SEQ ID NO:205 – DsiRNA 99 passenger (sense) strand
AAUGAAAGACAAAGGUGGAUACAUG

[00430] SEQ ID NO:206 – DsiRNA 99 guide (antisense) strand
CAUGUAUCCACCUUUGUCUUUCAUUUC

[00431] SEQ ID NO:207 – DsiRNA 100 passenger (sense) strand
AUGAAAGACAAAGGUGGAUACAUGA

[00432] SEQ ID NO:208 – DsiRNA 100 guide (antisense) strand
UCAUGUAUCCACCUUUGUCUUUCAUUU

[00433] SEQ ID NO:209 – DsiRNA 101 passenger (sense) strand

UGAAAGACAAAGGUGGAUACAUGAG

[00434] SEQ ID NO:210 – DsiRNA 101 guide (antisense) strand
CUCAUGUAUCCACCUUUGUCUUUCAUU

[00435] SEQ ID NO:211 – DsiRNA 102 passenger (sense) strand
GAAAGACAAAGGUGGAUACAUGAGC

[00436] SEQ ID NO:212 – DsiRNA 102 guide (antisense) strand
GCUCAUGUAUCCACCUUUGUCUUUCAU

[00437] SEQ ID NO:213 – DsiRNA 103 passenger (sense) strand
AAGACAAAGGUGGAUACAUGAGCAA

[00438] SEQ ID NO:214 – DsiRNA 103 guide (antisense) strand
UUGCUCAUGUAUCCACCUUUGUCUUUC

[00439] SEQ ID NO:215 – DsiRNA 104 passenger (sense) strand
AGACAAAGGUGGAUACAUGAGCAAG

[00440] SEQ ID NO:216 – DsiRNA 104 guide (antisense) strand
CUUGCUCAUGUAUCCACCUUUGUCUUU

[00441] SEQ ID NO:217 – DsiRNA 105 passenger (sense) strand
GACAAAGGUGGAUACAUGAGCAAGA

[00442] SEQ ID NO:218 – DsiRNA 105 guide (antisense) strand
UCUUGCUCAUGUAUCCACCUUUGUCUU

[00443] SEQ ID NO:219 – DsiRNA 106 passenger (sense) strand
ACAAAGGUGGAUACAUGAGCAAGAU

[00444] SEQ ID NO:220 – DsiRNA 106 guide (antisense) strand
AUCUUGCUCAUGUAUCCACCUUUGUCU

[00445] SEQ ID NO:221 – DsiRNA 107 passenger (sense) strand
AAGGUGGAUACAUGAGCAAGAUUUG

[00446] SEQ ID NO:222 – DsiRNA 107 guide (antisense) strand
CAAAUCUUGCUCAUGUAUCCACCUUUG

[00447] SEQ ID NO:223 – DsiRNA 108 passenger (sense) strand
AGGUGGAUACAUGAGCAAGAUUUGC

[00448] SEQ ID NO:224 – DsiRNA 108 guide (antisense) strand
GCAAAUCUUGCUCAUGUAUCCACCUUU

[00449] SEQ ID NO:225 – DsiRNA 109 passenger (sense) strand
UGGAUACAUGAGCAAGAUUUGCAAC

[00450] SEQ ID NO:226 – DsiRNA 109 guide (antisense) strand
GUUGCAAAUCUUGCUCAUGUAUCCACC

[00451] SEQ ID NO:227 – DsiRNA 110 passenger (sense) strand
GGAUACAUGAGCAAGAUUUGCAACU

[00452] SEQ ID NO:228 – DsiRNA 110 guide (antisense) strand
AGUUGCAAAUCUUGCUCAUGUAUCCAC

[00453] SEQ ID NO:229 – DsiRNA 111 passenger (sense) strand
GAUACAUGAGCAAGAUUUGCAACUU

[00454] SEQ ID NO:230 – DsiRNA 111 guide (antisense) strand
AAGUUGCAAAUCUUGCUCAUGUAUCCA

[00455] SEQ ID NO:231 – DsiRNA 112 passenger (sense) strand
AUACAUGAGCAAGAUUUGCAACUUG

[00456] SEQ ID NO:232 –DsiRNA 112 guide (antisense) strand
CAAGUUGCAAAUCUUGCUCAUGUAUCC

[00457] SEQ ID NO:233 – DsiRNA 113 passenger (sense) strand
UACAUGAGCAAGAUUUGCAACUUGC

[00458] SEQ ID NO:234 – DsiRNA 113 guide (antisense) strand
GCAAGUUGCAAAUCUUGCUCAUGUAUC

[00459] SEQ ID NO:235 – DsiRNA 114 passenger (sense) strand
ACAUGAGCAAGAUUUGCAACUUGCU

[00460] SEQ ID NO:236 – DsiRNA 114 guide (antisense) strand
AGCAAGUUGCAAAUCUUGCUCAUGUAU

[00461] SEQ ID NO:237 – DsiRNA 115 passenger (sense) strand
CAUGAGCAAGAUUUGCAACUUGCUA

[00462] SEQ ID NO:238 – DsiRNA 115 guide (antisense) strand
UAGCAAGUUGCAAAUCUUGCUCAUGUA

[00463] SEQ ID NO:239: DsiRNA 116 passenger (sense) strand
AUGAGCAAGAUUUGCAACUUGCUAC

[00464] SEQ ID NO:240 – DsiRNA 116 guide (antisense) strand
GUAGCAAGUUGCAAAUCUUGCUCAUGU

[00465] SEQ ID NO:241 – DsiRNA 117 passenger (sense) strand

UGAGCAAGAUUUGCAACUUGCUACC

[00466] SEQ ID NO:242 – DsiRNA 117 guide (antisense) strand
GGUAGCAAGUUGCAAAUCUUGCUCAUG

[00467] SEQ ID NO:243 – DsiRNA 118 passenger (sense) strand
GAGCAAGAUUUGCAACUUGCUACCC

[00468] SEQ ID NO:244 – DsiRNA 118 guide (antisense) strand
GGGUAGCAAGUUGCAAAUCUUGCUCAU

[00469] SEQ ID NO:245 – DsiRNA 119 passenger (sense) strand
AGCAAGAUUUGCAACUUGCUACCCA

[00470] SEQ ID NO:246 – DsiRNA 119 guide (antisense) strand
UGGGUAGCAAGUUGCAAAUCUUGCUCA

[00471] SEQ ID NO:247 – DsiRNA 120 passenger (sense) strand
GCAAGAUUUGCAACUUGCUACCCAU

[00472] SEQ ID NO:248 – DsiRNA 120 guide (antisense) strand
AUGGGUAGCAAGUUGCAAAUCUUGCUC

[00473] SEQ ID NO:249 – DsiRNA 121 passenger (sense) strand
CAAGAUUUGCAACUUGCUACCCAUU

[00474] SEQ ID NO:250 – DsiRNA 121 guide (antisense) strand
AAUGGGUAGCAAGUUGCAAAUCUUGCU

[00475] SEQ ID NO:251 – DsiRNA 122 passenger (sense) strand
AAGAUUUGCAACUUGCUACCCAUUA

[00476] SEQ ID NO:252 – DsiRNA 122 guide (antisense) strand
UAAUGGGUAGCAAGUUGCAAAUCUUGC

[00477] SEQ ID NO:253 – DsiRNA 123 passenger (sense) strand
AGAUUUGCAACUUGCUACCCAUUAG

[00478] SEQ ID NO:254 – DsiRNA 123 guide (antisense) strand
CUAAUGGGUAGCAAGUUGCAAAUCUUG

[00479] SEQ ID NO:255 – DsiRNA 124 passenger (sense) strand
GAUUUGCAACUUGCUACCCAUUAGG

[00480] SEQ ID NO:256 – DsiRNA 124 guide (antisense) strand
CCUAAUGGGUAGCAAGUUGCAAAUCUU

[00481] SEQ ID NO:257 – DsiRNA 125 passenger (sense) strand
AUUUGCAACUUGCUACCCAUUAGGA

[00482] SEQ ID NO:258 – DsiRNA 125 guide (antisense) strand
UCCUAAUGGGUAGCAAGUUGCAAAUCU

[00483] SEQ ID NO:259 – DsiRNA 126 passenger (sense) strand
UUUGCAACUUGCUACCCAUUAGGAU

[00484] SEQ ID NO:260 – DsiRNA 126 guide (antisense) strand
AUCCUAAUGGGUAGCAAGUUGCAAAUC

[00485] SEQ ID NO:261 – DsiRNA 127 passenger (sense) strand
UUGCAACUUGCUACCCAUUAGGAUA

[00486] SEQ ID NO:262 – DsiRNA 127 guide (antisense) strand
UAUCCUAAUGGGUAGCAAGUUGCAAAU

[00487] SEQ ID NO:263 – DsiRNA 128 passenger (sense) strand
UGCAACUUGCUACCCAUUAGGAUAA

[00488] SEQ ID NO:264 – DsiRNA 128 guide (antisense) strand
UUAUCCUAAUGGGUAGCAAGUUGCAAA

[00489] SEQ ID NO:265 – DsiRNA 129 – passenger (sense) strand
GCAACUUGCUACCCAUUAGGAUAAU

[00490] SEQ ID NO:266 – DsiRNA 129 guide (antisense) strand
AUUAUCCUAAUGGGUAGCAAGUUGCAA

[00491] SEQ ID NO:267 – DsiRNA 130 passenger (sense) strand
CAACUUGCUACCCAUUAGGAUAAUG

[00492] SEQ ID NO:268 – DsiRNA 130 guide (antisense) strand
CAUUAUCCUAAUGGGUAGCAAGUUGCA

[00493] SEQ ID NO:269 – DsiRNA 131 passenger (sense) strand
CUUGCUACCCAUUAGGAUAAUGUCU

[00494] SEQ ID NO:270 – DsiRNA 131 guide (antisense) strand
AGACAUUAUCCUAAUGGGUAGCAAGUU

[00495] SEQ ID NO:271 – DsiRNA 132 passenger (sense) strand
UUGCUACCCAUUAGGAUAAUGUCUU

[00496] SEQ ID NO:272 – DsiRNA 132 guide (antisense) strand
AAGACAUUAUCCUAAUGGGUAGCAAGU

[00497] SEQ ID NO:273 – DsiRNA 133 passenger (sense) strand

UGCUACCCAUUAGGAUAAUGUCUUA

[00498] SEQ ID NO:274 – DsiRNA 133 guide (antisense) strand
UAAGACAUUAUCCUAAUGGGUAGCAAG

[00499] SEQ ID NO:275 – DsiRNA 134 passenger (sense) strand
AUUAGGAUAAUGUCUUAUGUAAUGC

[00500] SEQ ID NO:276 – DsiRNA 134 guide (antisense) strand
GCAUUACAUAAGACAUUAUCCUAAUGG

[00501] SEQ ID NO:277 – DsiRNA 135 passenger (sense) strand
UUAGGAUAAUGUCUUAUGUAAUGCU

[00502] SEQ ID NO:278 – DsiRNA 135 guide (antisense) strand
AGCAUUACAUAAGACAUUAUCCUAAUG

[00503] SEQ ID NO:279 – DsiRNA 136 passenger (sense) strand
CUGUGGAAUCUGCCAUUGCGAUUGU

[00504] SEQ ID NO:280 – DsiRNA 136 guide (antisense) strand
ACAAUCGCAAUGGCAGAUUCCACAGGC

[00505] SEQ ID NO:281 – DsiRNA 137 passenger (sense) strand
GGAAUCUGCCAUUGCGAUUGUCCAG

[00506] SEQ ID NO:282 – DsiRNA 137 guide (antisense) strand
CUGGACAAUCGCAAUGGCAGAUUCCAC

[00507] SEQ ID NO:283 – DsiRNA 138 passenger (sense) strand
GAAUCUGCCAUUGCGAUUGUCCAGA

[00508] SEQ ID NO:284 – DsiRNA 138 guide (antisense) strand
UCUGGACAAUCGCAAUGGCAGAUUCCA

[00509] SEQ ID NO:285 – DsiRNA 139 passenger (sense) strand
AAUCUGCCAUUGCGAUUGUCCAGAG

[00510] SEQ ID NO:286 – DsiRNA 139 guide (antisense) strand
CUCUGGACAAUCGCAAUGGCAGAUUCC

[00511] SEQ ID NO:287 – DsiRNA 140 passenger (sense) strand
AUCUGCCAUUGCGAUUGUCCAGAGA

[00512] SEQ ID NO:288 – DsiRNA 140 guide (antisense) strand
UCUCUGGACAAUCGCAAUGGCAGAUUC

[00513] SEQ ID NO:289 – DsiRNA 141 passenger (sense) strand
CCAUUGCGAUUGUCCAGAGACUGGU

[00514] SEQ ID NO:290 – DsiRNA 141 guide (antisense) strand
ACCAGUCUCUGGACAAUCGCAAUGGCA

[00515] SEQ ID NO:291 – DsiRNA 142 passenger (sense) strand
CAUUGCGAUUGUCCAGAGACUGGUG

[00516] SEQ ID NO:292 – DsiRNA 142 guide (antisense) strand
CACCAGUCUCUGGACAAUCGCAAUGGC

[00517] SEQ ID NO:293 – DsiRNA 143 passenger (sense) strand
AUUGCGAUUGUCCAGAGACUGGUGA

[00518] SEQ ID NO:294 – DsiRNA 143 guide (antisense) strand
UCACCAGUCUCUGGACAAUCGCAAUGG

[00519] SEQ ID NO:295 – DsiRNA 144 passenger (sense) strand
UUGCGAUUGUCCAGAGACUGGUGAC

[00520] SEQ ID NO:296 – DsiRNA 144 guide (antisense) strand
GUCACCAGUCUCUGGACAAUCGCAAUG

[00521] SEQ ID NO:297 – DsiRNA 145 passenger (sense) strand
UGCGAUUGUCCAGAGACUGGUGACA

[00522] SEQ ID NO:298 – DsiRNA 145 guide (antisense) strand
UGUCACCAGUCUCUGGACAAUCGCAAU

[00523] SEQ ID NO:299 – DsiRNA 146 passenger (sense) strand
GCGAUUGUCCAGAGACUGGUGACAU

[00524] SEQ ID NO:300 – DsiRNA 146 guide (antisense) strand
AUGUCACCAGUCUCUGGACAAUCGCAA

[00525] SEQ ID NO:301 – DsiRNA 147 passenger (sense) strand
CGAUUGUCCAGAGACUGGUGACAUG

[00526] SEQ ID NO:302 – DsiRNA 147 guide (antisense) strand
CAUGUCACCAGUCUCUGGACAAUCGCA

[00527] SEQ ID NO:303 – DsiRNA 148 passenger (sense)
AUUGUCCAGAGACUGGUGACAUGGC

[00528] SEQ ID NO:304 – DsiRNA 148 guide (antisense) strand
GCCAUGUCACCAGUCUCUGGACAAUCG

[00529] SEQ ID NO:305 – DsiRNA 149 passenger (sense) strand

GUCCAGAGACUGGUGACAUGGCUUC

[00530] SEQ ID NO:306 – DsiRNA 149 guide (antisense) strand
GAAGCCAUGUCACCAGUCUCUGGACAA

[00531] SEQ ID NO:307 – DsiRNA 150 passenger (sense) strand
CCAGAGACUGGUGACAUGGCUUCCA

[00532] SEQ ID NO:308 – DsiRNA 150 guide (antisense) strand
UGGAAGCCAUGUCACCAGUCUCUGGAC

[00533] SEQ ID NO:309 – DsiRNA 151 passenger (sense)
CAGAGACUGGUGACAUGGCUUCCAG

[00534] SEQ ID NO:310 – DsiRNA 151 guide (antisense) strand
CUGGAAGCCAUGUCACCAGUCUCUGGA

[00535] SEQ ID NO:311 – DsiRNA 152 passenger (sense) strand
AGAGACUGGUGACAUGGCUUCCAGA

[00536] SEQ ID NO:312 – DsiRNA 152 guide (antisense) strand
UCUGGAAGCCAUGUCACCAGUCUCUGG

[00537] SEQ ID NO:313 – DsiRNA 153 passenger (sense) strand
GAGACUGGUGACAUGGCUUCCAGAU

[00538] SEQ ID NO:314 – DsiRNA 153 guide (antisense) strand
AUCUGGAAGCCAUGUCACCAGUCUCUG

[00539] SEQ ID NO:315 – DsiRNA 154 passenger (sense) strand
AGACUGGUGACAUGGCUUCCAGAUA

[00540] SEQ ID NO:316 – DsiRNA 154 guide (antisense) strand
UAUCUGGAAGCCAUGUCACCAGUCUCU

[00541] SEQ ID NO:317 – DsiRNA 155 passenger (sense) strand
GACUGGUGACAUGGCUUCCAGAUAU

[00542] SEQ ID NO:318 – DsiRNA 155 guide (antisense) strand
AUAUCUGGAAGCCAUGUCACCAGUCUC

[00543] SEQ ID NO:319 – DsiRNA 156 passenger (sense) strand
ACUGGUGACAUGGCUUCCAGAUAUG

[00544] SEQ ID NO:320 – DsiRNA 156 guide (antisense) strand
CAUAUCUGGAAGCCAUGUCACCAGUCU

[00545] SEQ ID NO:321 – DsiRNA 157 passenger (sense) strand
CUGGUGACAUGGCUUCCAGAUAUGC

[00546] SEQ ID NO:322 – DsiRNA 157 guide (antisense) strand
GCAUAUCUGGAAGCCAUGUCACCAGUC

[00547] SEQ ID NO:323 – DsiRNA 158 passenger (sense) strand
GACAUGGCUUCCAGAUAUGCCCGAC

[00548] SEQ ID NO:324 – DsiRNA 158 guide (antisense) strand
GUCGGGCAUAUCUGGAAGCCAUGUCAC

[00549] SEQ ID NO:325 – DsiRNA 159 passenger (sense) strand
CAUGGCUUCCAGAUAUGCCCGACGA

[00550] SEQ ID NO:326 – DsiRNA 159 guide (antisense) strand
UCGUCGGGCAUAUCUGGAAGCCAUGUC

[00551] SEQ ID NO:327 – DsiRNA 160 passenger (sense) strand
CAGAUAUGCCCGACGAUGUCCUGUG

[00552] SEQ ID NO:328 – DsiRNA 160 guide (antisense) strand
CACAGGACAUCGUCGGGCAUAUCUGGA

[00553] SEQ ID NO:329 – DsiRNA 161 passenger (sense) strand
CUCACAGGUGUUCACUCGAGUGCUG

[00554] SEQ ID NO:330 – DsiRNA 161 guide (antisense) strand
CAGCACUCGAGUGAACACCUGUGAGGU

[00555] SEQ ID NO:331 – DsiRNA 162 passenger (sense) strand
CACUCGAGUGCUGAUGUGUCUGCUC

[00556] SEQ ID NO:332 – DsiRNA 162 guide (antisense) strand
GAGCAGACACAUCAGCACUCGAGUGAA

[00557] SEQ ID NO:333 – DsiRNA 163 passenger (sense) strand
CUCGAGUGCUGAUGUGUCUGCUCCC

[00558] SEQ ID NO:334 – DsiRNA 163 guide (antisense) strand
GGGAGCAGACACAUCAGCACUCGAGUG

[00559] SEQ ID NO:335 – DsiRNA 164 passenger (sense) strand
CCCAAAUGCCAGUGAGCAGCCAACA

[00560] SEQ ID NO:336 – DsiRNA 164 guide (antisense) strand
UGUUGGCUGCUCACUGGCAUUUGGGAC

[00561] SEQ ID NO:337 – DsiRNA 165 passenger (sense) strand
UCAGGUCCAGCCUGAACUUCUUCUU

[00562] SEQ ID NO:338 – DsiRNA 165 guide (antisense) strand
AAGAAGAAGUUCAGGCUGGACCUGAGG

[00563] SEQ ID NO:339 – DsiRNA 166 passenger (sense) strand
CAGGUCCAGCCUGAACUUCUUCUUG

[00564] SEQ ID NO:340 – DsiRNA 166 guide (antisense) strand
CAAGAAGAAGUUCAGGCUGGACCUGAG

[00565] SEQ ID NO:341 – DsiRNA 167 passenger (sense) strand
AGGUCCAGCCUGAACUUCUUCUUGG

[00566] SEQ ID NO:342 – DsiRNA 167 guide (antisense) strand

CCAAGAAGAAGUUCAGGCUGGACCUGA

[00567] SEQ ID NO:343 – DsiRNA 168 passenger (sense) strand
CAAUAAAGUACCUGCUGGUGCUGAG

[00568] SEQ ID NO:344 – DsiRNA 168 guide (antisense) strand
CUCAGCACCAGCAGGUACUUUAUUGCC

[00569] SEQ ID NO:345 – DsiRNA 169 passenger (sense) strand
AAUAAAGUACCUGCUGGUGCUGAGG

[00570] SEQ ID NO:346 – DsiRNA 169 guide (antisense) strand
CCUCAGCACCAGCAGGUACUUUAUUGC

[00571] SEQ ID NO:347 – DsiRNA 170 passenger (sense) strand
AUAAAGUACCUGCUGGUGCUGAGGG

[00572] SEQ ID NO:348 – DsiRNA 170 guide (antisense) strand
CCCUCAGCACCAGCAGGUACUUUAUUG

[00573] SEQ ID NO:349 – DsiRNA 171 passenger (sense) strand
CUCUCCACCUUUCCCAGUUUUUCAC

[00574] SEQ ID NO:350 – DsiRNA 171 guide (antisense) strand
GUGAAAAACUGGGAAAGGUGGAGAGCC

[00575] SEQ ID NO:351 – DsiRNA 172 passenger (sense) strand
CUCCACCUUUCCCAGUUUUUCACUA

[00576] SEQ ID NO:352 – DsiRNA 172 guide (antisense) strand
UAGUGAAAAACUGGGAAAGGUGGAGAG

[00577] SEQ ID NO:353 – DsiRNA 173 passenger (sense) strand
UCCACCUUUCCCAGUUUUUCACUAG

[00578] SEQ ID NO:354 – DsiRNA 173 guide (antisense) strand
CUAGUGAAAAACUGGGAAAGGUGGAGA

[00579] SEQ ID NO:355 – DsiRNA 174 passenger (sense) strand
CCACCUUUCCCAGUUUUUCACUAGA

[00580] SEQ ID NO:356 – DsiRNA 174 guide (antisense) strand
UCUAGUGAAAAACUGGGAAAGGUGGAG

[00581] SEQ ID NO:357 – DsiRNA 175 passenger (sense) strand
CACCUUUCCCAGUUUUUCACUAGAG

[00582] SEQ ID NO:358 – DsiRNA 175 guide (antisense) strand
CUCUAGUGAAAAACUGGGAAAGGUGGA

[00583] SEQ ID NO:359 – DsiRNA 176 passenger (sense) strand
ACCUUUCCCAGUUUUUCACUAGAGA

[00584] SEQ ID NO:360 – DsiRNA 176 guide (antisense) strand
UCUCUAGUGAAAAACUGGGAAAGGUGG

[00585] SEQ ID NO:361 – DsiRNA 177 passenger (sense) strand
CCUUUCCCAGUUUUUCACUAGAGAA

[00586] SEQ ID NO:362 – DsiRNA 177 guide (antisense) strand
UUCUCUAGUGAAAAACUGGGAAAGGUG

[00587] SEQ ID NO:363 – DsiRNA 178 passenger (sense) strand
AGUUUUUCACUAGAGAAGAGUCUGU

[00588] SEQ ID NO:364 – DsiRNA 178 guide (antisense) strand
ACAGACUCUUCUCUAGUGAAAAACUGG

[00589] SEQ ID NO:365 – DsiRNA 179 passenger (sense) strand
UCUAGCAGAUUCUUUCAGAGGUGCU

[00590] SEQ ID NO:366 – DsiRNA 179 guide (antisense) strand
AGCACCUCUGAAAGAAUCUGCUAGACU

[00591] SEQ ID NO:367 – DsiRNA 180 passenger (sense) strand
AGCAGAUUCUUUCAGAGGUGCUAAA

[00592] SEQ ID NO:368 – DsiRNA 180 guide (antisense) strand
UUUAGCACCUCUGAAAGAAUCUGCUAG

[00593] SEQ ID NO:369 – DsiRNA 181 passenger (sense) strand
GCAGAUUCUUUCAGAGGUGCUAAAG

[00594] SEQ ID NO:370 – DsiRNA 181 guide (antisense) strand
CUUUAGCACCUCUGAAAGAAUCUGCUA

[00595] SEQ ID NO:371 – DsiRNA 182 passenger (sense) strand
CAGAUUCUUUCAGAGGUGCUAAAGU

[00596] SEQ ID NO:372 – DsiRNA 182 guide (antisense) strand
ACUUUAGCACCUCUGAAAGAAUCUGCU

[00597] SEQ ID NO:373 – DsiRNA 183 passenger (sense) strand
AGAUUCUUUCAGAGGUGCUAAAGUU

[00598] SEQ ID NO:374 – DsiRNA 183 guide (antisense) strand

AACUUUAGCACCUCUGAAAGAAUCUGC

[00599] SEQ ID NO:375 – DsiRNA 184 passenger (sense) strand
GAUUCUUUCAGAGGUGCUAAAGUUU

[00600] SEQ ID NO:376 – DsiRNA 184 guide (antisense) strand
AAACUUUAGCACCUCUGAAAGAAUCUG

[00601] SEQ ID NO:377 – DsiRNA 185 passenger (sense) strand
AUUCUUUCAGAGGUGCUAAAGUUUC

[00602] SEQ ID NO:378 – DsiRNA 185 guide (antisense) strand
GAAACUUUAGCACCUCUGAAAGAAUCU

[00603] SEQ ID NO:379 – DsiRNA 186 passenger (sense) strand
AGGUGCUAAAGUUUCCCAUCUUUGU

[00604] SEQ ID NO:380 – DsiRNA 186 guide (antisense) strand
ACAAAGAUGGGAAACUUUAGCACCUCU

[00605] SEQ ID NO:381 – DsiRNA 187 passenger (sense) strand
GGUGCUAAAGUUUCCCAUCUUUGUG

[00606] SEQ ID NO:382 – DsiRNA 187 guide (antisense) strand
CACAAAGAUGGGAAACUUUAGCACCUC

[00607] SEQ ID NO:383 – DsiRNA 188 passenger (sense) strand
GUGCUAAAGUUUCCCAUCUUUGUGC

[00608] SEQ ID NO:384 – DsiRNA 188 guide (antisense) strand
GCACAAAGAUGGGAAACUUUAGCACCU

[00609] SEQ ID NO:385 – DsiRNA 189 passenger (sense) strand
GCUAAAGUUUCCCAUCUUUGUGCAG

[00610] SEQ ID NO:386 – DsiRNA 189 guide (antisense) strand
CUGCACAAAGAUGGGAAACUUUAGCAC

[00611] SEQ ID NO:387 – DsiRNA 190 passenger (sense) strand
CUAAAGUUUCCCAUCUUUGUGCAGC

[00612] SEQ ID NO:388 – DsiRNA 190 guide (antisense) strand
GCUGCACAAAGAUGGGAAACUUUAGCA

[00613] SEQ ID NO:389 – DsiRNA 191 passenger (sense) strand
UAAAGUUUCCCAUCUUUGUGCAGCU

[00614] SEQ ID NO:390 – DsiRNA 191 guide (antisense) strand
AGCUGCACAAAGAUGGGAAACUUUAGC

[00615] SEQ ID NO:391 – DsiRNA 192 passenger (sense) strand
AAAGUUUCCCAUCUUUGUGCAGCUA

[00616] SEQ ID NO:392 – DsiRNA 192 guide (antisense) strand
UAGCUGCACAAAGAUGGGAAACUUUAG

[00617] SEQ ID NO:393 – DsiRNA 193 passenger (sense) strand
AAGUUUCCCAUCUUUGUGCAGCUAC

[00618] SEQ ID NO:394 – DsiRNA 193 guide (antisense) strand
GUAGCUGCACAAAGAUGGGAAACUUUA

[00619] SEQ ID NO:395 – DsiRNA 194 passenger (sense) strand
AGUUUCCCAUCUUUGUGCAGCUACC

[00620] SEQ ID NO:396 – DsiRNA 194 guide (antisense) strand
GGUAGCUGCACAAAGAUGGGAAACUUU

[00621] SEQ ID NO:397 – DsiRNA 195 passenger (sense) strand
GUUUCCCAUCUUUGUGCAGCUACCU

[00622] SEQ ID NO:398 – DsiRNA 195 guide (antisense) strand
AGGUAGCUGCACAAAGAUGGGAAACUU

[00623] SEQ ID NO:399 – DsiRNA 196 passenger (sense) strand
AUCUUUGUGCAGCUACCUCCGCAUU

[00624] SEQ ID NO:400 – DsiRNA 196 guide (antisense) strand
AAUGCGGAGGUAGCUGCACAAAGAUGG

[00625] SEQ ID NO:401 – DsiRNA 197 passenger (sense) strand
GUGCAGCUACCUCCGCAUUGCUGUG

[00626] SEQ ID NO:402 – DsiRNA 197 guide (antisense) strand
CACAGCAAUGCGGAGGUAGCUGCACAA

[00627] SEQ ID NO:403 – DsiRNA 198 passenger (sense) strand
CCAGCCUCUGAGCUGAGUUGGUUUU

[00628] SEQ ID NO:404 – DsiRNA 198 guide (antisense) strand
AAAACCAACUCAGCUCAGAGGCUGGGA

[00629] SEQ ID NO:405 – DsiRNA 199 passenger (sense) strand
CAGCCUCUGAGCUGAGUUGGUUUUA

[00630] SEQ ID NO:406 – DsiRNA 199 guide (antisense) strand

UAAAACCAACUCAGCUCAGAGGCUGGG

[00631] SEQ ID NO:407 – DsiRNA 200 passenger (sense) strand
AGCCUCUGAGCUGAGUUGGUUUUAU

[00632] SEQ ID NO:408 – DsiRNA 200 guide (antisense) strand
AUAAAACCAACUCAGCUCAGAGGCUGG

[00633] SEQ ID NO:409 – DsiRNA 201 passenger (sense) strand
GCCUCUGAGCUGAGUUGGUUUUAUG

[00634] SEQ ID NO:410 – DsiRNA 201 guide (antisense) strand
CAUAAAACCAACUCAGCUCAGAGGCUG

[00635] SEQ ID NO:411 – DsiRNA 202 passenger (sense) strand
CCUCUGAGCUGAGUUGGUUUUAUGA

[00636] SEQ ID NO:412 – DsiRNA 202 guide (antisense) strand
UCAUAAAACCAACUCAGCUCAGAGGCU

[00637] SEQ ID NO:413 – DsiRNA 203 passenger (sense) strand
CUCUGAGCUGAGUUGGUUUUAUGAA

[00638] SEQ ID NO:414 – DsiRNA 203 guide (antisense) strand
UUCAUAAAACCAACUCAGCUCAGAGGC

[00639] SEQ ID NO:415 – DsiRNA 204 passenger (sense) strand
UCUGAGCUGAGUUGGUUUUAUGAAA

[00640] SEQ ID NO:416 – DsiRNA 204 guide (antisense) strand
UUUCAUAAAACCAACUCAGCUCAGAGG

[00641] SEQ ID NO:417 – DsiRNA 205 passenger (sense) strand
UGAGCUGAGUUGGUUUUAUGAAAAG

[00642] SEQ ID NO:418 – DsiRNA 205 guide (antisense) strand
CUUUUCAUAAAACCAACUCAGCUCAGA

[00643] SEQ ID NO:419 – DsiRNA 206 passenger (sense) strand
UGAGUUGGUUUUAUGAAAAGCUAGG

[00644] SEQ ID NO:420 – DsiRNA 206 guide (antisense) strand
CCUAGCUUUUCAUAAAACCAACUCAGC

[00645] SEQ ID NO:421 – DsiRNA 207 passenger (sense) strand
GAGUUGGUUUUAUGAAAAGCUAGGA

[00646] SEQ ID NO:422 – DsiRNA 207 guide (antisense) strand
UCCUAGCUUUUCAUAAAACCAACUCAG

[00647] SEQ ID NO:423 – DsiRNA 208 passenger (sense) strand
UUGGUUUUAUGAAAAGCUAGGAAGC

[00648] SEQ ID NO:424 – DsiRNA 208 guide (antisense) strand
GCUUCCUAGCUUUUCAUAAAACCAACU

[00649] SEQ ID NO:425 – DsiRNA 209 passenger (sense) strand
UGGUUUUAUGAAAAGCUAGGAAGCA

[00650] SEQ ID NO:426 – DsiRNA 209 guide (antisense) strand
UGCUUCCUAGCUUUUCAUAAAACCAAC

[00651] SEQ ID NO:427 – DsiRNA 210 passenger (sense) strand
GGUUUUAUGAAAAGCUAGGAAGCAA

[00652] SEQ ID NO:428 – DsiRNA 210 guide (antisense) strand
UUGCUUCCUAGCUUUUCAUAAAACCAA

[00653] SEQ ID NO:429 – DsiRNA 211 passenger (sense) strand
UUUUAUGAAAAGCUAGGAAGCAACC

[00654] SEQ ID NO:430 – DsiRNA 211 guide (antisense) strand
GGUUGCUUCCUAGCUUUUCAUAAAACC

[00655] SEQ ID NO:431 – DsiRNA 212 passenger (sense) strand
UUAUGAAAAGCUAGGAAGCAACCUU

[00656] SEQ ID NO:432 – DsiRNA 212 guide (antisense) strand
AAGGUUGCUUCCUAGCUUUUCAUAAAA

[00657] SEQ ID NO:433 – DsiRNA 213 passenger (sense) strand
UAUGAAAAGCUAGGAAGCAACCUUU

[00658] SEQ ID NO:434 – DsiRNA 213 guide (antisense) strand
AAAGGUUGCUUCCUAGCUUUUCAUAAA

[00659] SEQ ID NO:435 – DsiRNA 214 passenger (sense) strand
AUGAAAAGCUAGGAAGCAACCUUUC

[00660] SEQ ID NO:436 – DsiRNA 214 guide (antisense) strand
GAAAGGUUGCUUCCUAGCUUUUCAUAA

[00661] SEQ ID NO:437 – DsiRNA 215 passenger (sense) strand
CCAGCACUUAACUCUAAUACAUCAG

[00662] SEQ ID NO:438 – DsiRNA 215 guide (antisense) strand

CUGAUGUAUUAGAGUUAAGUGCUGGAC

[00663] SEQ ID NO:439 – DsiRNA 216 passenger (sense) strand
CAGCACUUAACUCUAAUACAUCAGC

[00664] SEQ ID NO:440 – DsiRNA 216 guide (antisense) strand
GCUGAUGUAUUAGAGUUAAGUGCUGGA

[00665] SEQ ID NO:441 – DsiRNA 217 passenger (sense) strand
UAAUACAUCAGCAUGCGUUAAUUCA

[00666] SEQ ID NO:442 – DsiRNA 217 guide (antisense) strand
UGAAUUAACGCAUGCUGAUGUAUUAGA

[00667] SEQ ID NO:443 – DsiRNA 218 passenger (sense) strand
AAUACAUCAGCAUGCGUUAAUUCAG

[00668] SEQ ID NO:444 – DsiRNA 218 guide (antisense) strand
CUGAAUUAACGCAUGCUGAUGUAUUAG

[00669] SEQ ID NO:445 – DsiRNA 219 passenger (sense) strand
AGCAUGCGUUAAUUCAGCUGGUUGG

[00670] SEQ ID NO:446 – DsiRNA 219 guide (antisense) strand
CCAACCAGCUGAAUUAACGCAUGCUGA

[00671] SEQ ID NO:447 – DsiRNA 220 passenger (sense) strand
GCAUGCGUUAAUUCAGCUGGUUGGG

[00672] SEQ ID NO:448 – DsiRNA 220 guide (antisense) strand
CCCAACCAGCUGAAUUAACGCAUGCUG

[00673] SEQ ID NO:449 – DsiRNA 221 passenger (sense) strand
UGCGUUAAUUCAGCUGGUUGGGAAA

[00674] SEQ ID NO:450 – DsiRNA 221 guide (antisense) strand
UUUCCCAACCAGCUGAAUUAACGCAUG

[00675] SEQ ID NO:451 – DsiRNA 222 passenger (sense) strand
GCGUUAAUUCAGCUGGUUGGGAAAU

[00676] SEQ ID NO:452 – DsiRNA 222 guide (antisense) strand
AUUUCCCAACCAGCUGAAUUAACGCAU

[00677] SEQ ID NO:453 – DsiRNA 223 passenger (sense) strand
CGUUAAUUCAGCUGGUUGGGAAAUG

[00678] SEQ ID NO:454 – DsiRNA 223 guide (antisense) strand
CAUUUCCCAACCAGCUGAAUUAACGCA

[00679] SEQ ID NO:455 – DsiRNA 224 passenger (sense) strand
GUUAAUUCAGCUGGUUGGGAAAUGA

[00680] SEQ ID NO:456 – DsiRNA 224 guide (antisense) strand
UCAUUUCCCAACCAGCUGAAUUAACGC

[00681] SEQ ID NO:457 – DsiRNA 225 passenger (sense) strand
UUAAUUCAGCUGGUUGGGAAAUGAC

[00682] SEQ ID NO:458 – DsiRNA 225 guide (antisense) strand
GUCAUUUCCCAACCAGCUGAAUUAACG

[00683] SEQ ID NO:459 – DsiRNA 226 passenger (sense) strand
UAAUUCAGCUGGUUGGGAAAUGACA

[00684] SEQ ID NO:460 – DsiRNA 226 guide (antisense) strand
UGUCAUUUCCCAACCAGCUGAAUUAAC

[00685] SEQ ID NO:461 – DsiRNA 227 passenger (sense) strand
AUUCAGCUGGUUGGGAAAUGACACC

[00686] SEQ ID NO:462 – DsiRNA 227 guide (antisense) strand
GGUGUCAUUUCCCAACCAGCUGAAUUA

[00687] SEQ ID NO:463 – DsiRNA 228 passenger (sense) strand
UUCAGCUGGUUGGGAAAUGACACCA

[00688] SEQ ID NO:464 – DsiRNA 228 guide (antisense) strand
UGGUGUCAUUUCCCAACCAGCUGAAUU

[00689] SEQ ID NO:465 – DsiRNA 229 passenger (sense) strand
UCAGCUGGUUGGGAAAUGACACCAG

[00690] SEQ ID NO:466 – DsiRNA 229 guide (antisense) strand
CUGGUGUCAUUUCCCAACCAGCUGAAU

[00691] SEQ ID NO:467 – DsiRNA 230 passenger (sense) strand
CAGCUGGUUGGGAAAUGACACCAGG

[00692] SEQ ID NO:468 – DsiRNA 230 guide (antisense) strand
CCUGGUGUCAUUUCCCAACCAGCUGAA

[00693] SEQ ID NO:469 – DsiRNA 231 passenger (sense) strand
AGCUGGUUGGGAAAUGACACCAGGA

[00694] SEQ ID NO:470 – DsiRNA 231 guide (antisense) strand

UCCUGGUGUCAUUUCCCAACCAGCUGA

[00695] SEQ ID NO:471 – DsiRNA 232 passenger (sense) strand
GCUGGUUGGGAAAUGACACCAGGAA

[00696] SEQ ID NO:472 – DsiRNA 232 guide (antisense) strand
UUCCUGGUGUCAUUUCCCAACCAGCUG

[00697] SEQ ID NO:473 – DsiRNA 233 passenger (sense) strand
GCAGAGGGUCCCUUACUGACUGUUU

[00698] SEQ ID NO:474 – DsiRNA 233 guide (antisense) strand
AAACAGUCAGUAAGGGACCCUCUGCAC

[00699] SEQ ID NO:475 – DsiRNA 234 passenger (sense) strand
CAGAGGGUCCCUUACUGACUGUUUC

[00700] SEQ ID NO:476 – DsiRNA 234 guide (antisense) strand
GAAACAGUCAGUAAGGGACCCUCUGCA

[00701] SEQ ID NO:477 – DsiRNA 235 passenger (sense) strand
AGAGGGUCCCUUACUGACUGUUUCG

[00702] SEQ ID NO:478 – DsiRNA 235 guide (antisense) strand
CGAAACAGUCAGUAAGGGACCCUCUGC

[00703] SEQ ID NO:479 – DsiRNA 236 passenger (sense) strand
CCUAUUAAUGGUCAGACUGUUCCAG

[00704] SEQ ID NO:480 – DsiRNA 236 guide (antisense) strand
CUGGAACAGUCUGACCAUUAAUAGGGC

[00705] SEQ ID NO:481 – DsiRNA 237 passenger (sense) strand
CUAUUAAUGGUCAGACUGUUCCAGC

[00706] SEQ ID NO:482 – DsiRNA 237 guide (antisense) strand
GCUGGAACAGUCUGACCAUUAAUAGGG

[00707] SEQ ID NO:483 – DsiRNA 238 passenger (sense) strand
UAUUAAUGGUCAGACUGUUCCAGCA

[00708] SEQ ID NO:484 – DsiRNA 238 guide (antisense) strand
UGCUGGAACAGUCUGACCAUUAAUAGG

[00709] SEQ ID NO:485 – DsiRNA 239 passenger (sense) strand
AUUAAUGGUCAGACUGUUCCAGCAU

[00710] SEQ ID NO:486 – DsiRNA 239 guide (antisense) strand
AUGCUGGAACAGUCUGACCAUUAAUAG

[00711] SEQ ID NO:487 – DsiRNA 240 passenger (sense) strand
UUAAUGGUCAGACUGUUCCAGCAUG

[00712] SEQ ID NO:488 – DsiRNA 240 guide (antisense) strand
CAUGCUGGAACAGUCUGACCAUUAAUA

[00713] SEQ ID NO:489 – DsiRNA 241 passenger (sense) strand
UAAUGGUCAGACUGUUCCAGCAUGA

[00714] SEQ ID NO:490 – DsiRNA 241 guide (antisense) strand
UCAUGCUGGAACAGUCUGACCAUUAAU

[00715] SEQ ID NO:491 – DsiRNA 242 passenger (sense) strand
AAUGGUCAGACUGUUCCAGCAUGAG

[00716] SEQ ID NO:492 – DsiRNA 242 guide (antisense) strand
CUCAUGCUGGAACAGUCUGACCAUUAA

[00717] SEQ ID NO:493 – DsiRNA 243 passenger (sense) strand
AGAACGACACUGCCUGUCAGGUGGU

[00718] SEQ ID NO:494 – DsiRNA 243 guide (antisense) strand
ACCACCUGACAGGCAGUGUCGUUCUUG

[00719] SEQ ID NO:495 – DsiRNA 244 passenger (sense) strand
CGACACUGCCUGUCAGGUGGUCUGC

[00720] SEQ ID NO:496 – DsiRNA 244 guide (antisense) strand
GCAGACCACCUGACAGGCAGUGUCGUU

[00721] SEQ ID NO:497 – DsiRNA 245 passenger (sense) strand
AACCUUGACUACUAAAAACGUCUCC

[00722] SEQ ID NO:498 – DsiRNA 245 guide (antisense) strand
GGAGACGUUUUUAGUAGUCAAGGUUAU

[00723] SEQ ID NO:499 – DsiRNA 246 passenger (sense) strand
UUUAGAACACCUUUUUCACCUAACU

[00724] SEQ ID NO:500 – DsiRNA 246 guide (antisense) strand
AGUUAGGUGAAAAAGGUGUUCUAAAAU

[00725] SEQ ID NO:501 – DsiRNA 247 passenger (sense) strand
UUAGAACACCUUUUUCACCUAACUA

[00726] SEQ ID NO:502 – DsiRNA 247 guide (antisense) strand
UAGUUAGGUGAAAAAGGUGUUCUAAAA

[00727] SEQ ID NO:503 – DsiRNA 248 passenger (sense) strand
UAGAACACCUUUUUCACCUAACUAA

[00728] SEQ ID NO:504 – DsiRNA 248 guide (antisense) strand
UUAGUUAGGUGAAAAAGGUGUUCUAAA

[00729] SEQ ID NO:505 – DsiRNA 249 passenger (sense) strand
AGAACACCUUUUUCACCUAACUAAA

[00730] SEQ ID NO:506 – DsiRNA 249 guide (antisense) strand
UUUAGUUAGGUGAAAAAGGUGUUCUAA

[00731] SEQ ID NO:507 – DsiRNA 250 passenger (sense) strand

GAACACCUUUUUCACCUAACUAAAA

[00732] SEQ ID NO:508 – DsiRNA 250 guide (antisense) strand
UUUUAGUUAGGUGAAAAAGGUGUUCUA

[00733] SEQ ID NO:509 – DsiRNA 251 passenger (sense) strand
AACACCUUUUUCACCUAACUAAAAU

[00734] SEQ ID NO:510 – DsiRNA 251 guide (antisense) strand
AUUUUAGUUAGGUGAAAAAGGUGUUCU

[00735] SEQ ID NO:511 – DsiRNA 252 passenger (sense) strand
ACACCUUUUUCACCUAACUAAAAUA

[00736] SEQ ID NO:512 – DsiRNA 252 guide (antisense) strand
UAUUUUAGUUAGGUGAAAAAGGUGUUC

[00737] SEQ ID NO:513 – DsiRNA 253 passenger (sense) strand
CACCUUUUUCACCUAACUAAAAUAA

[00738] SEQ ID NO:514 – DsiRNA 253 guide (antisense) strand
UUAUUUUAGUUAGGUGAAAAAGGUGUU

[00739] SEQ ID NO:515 – DsiRNA 254 passenger (sense) strand
ACCUUUUUCACCUAACUAAAAUAAU

[00740] SEQ ID NO:516 – DsiRNA 254 guide (antisense) strand
AUUAUUUUAGUUAGGUGAAAAAGGUGU

[00741] SEQ ID NO:517 – DsiRNA 255 passenger (sense) strand
CUUUUUCACCUAACUAAAAUAAUGU

[00742] SEQ ID NO:518 – DsiRNA 255 guide (antisense) strand
ACAUUAUUUUAGUUAGGUGAAAAAGGU

[00743] SEQ ID NO:519 – DsiRNA 256 passenger (sense) strand
UUUUCACCUAACUAAAAUAAUGUUU

[00744] SEQ ID NO:520 – DsiRNA 256 guide (antisense) strand
AAACAUUAUUUUAGUUAGGUGAAAAAG

[00745] SEQ ID NO:521 – DsiRNA 257 passenger (sense) strand
UUCACCUAACUAAAAUAAUGUUUAA

[00746] SEQ ID NO:522 – DsiRNA 257 guide (antisense) strand
UUAAACAUUAUUUUAGUUAGGUGAAAA

[00747] SEQ ID NO:523 – DsiRNA 258 passenger (sense) strand
UCACCUAACUAAAAUAAUGUUUAAA

[00748] SEQ ID NO:524 – DsiRNA 258 guide (antisense) strand
UUUAAACAUUAUUUUAGUUAGGUGAAA

[00749] SEQ ID NO:525 – DsiRNA 259 passenger (sense) strand
CACCUAACUAAAAUAAUGUUUAAAG

[00750] SEQ ID NO:526 – DsiRNA 259 guide (antisense) strand
CUUUAAACAUUAUUUUAGUUAGGUGAA

[00751] SEQ ID NO:527 – DsiRNA 260 passenger (sense) strand
ACCUAACUAAAAUAAUGUUUAAAGA

[00752] SEQ ID NO:528 – DsiRNA 260 guide (antisense) strand
UCUUUAAACAUUAUUUUAGUUAGGUGA

[00753] SEQ ID NO:529 – DsiRNA 261 passenger (sense) strand
CCUAACUAAAAUAAUGUUUAAAGAG

[00754] SEQ ID NO:530 – DsiRNA 261 guide (antisense) strand
CUCUUUAAACAUUAUUUUAGUUAGGUG

[00755] SEQ ID NO:531 – DsiRNA 262 passenger (sense) strand
CUAACUAAAAUAAUGUUUAAAGAGU

[00756] SEQ ID NO:532 – DsiRNA 262 guide (antisense) strand
ACUCUUUAAACAUUAUUUUAGUUAGGU

[00757] SEQ ID NO:533 – DsiRNA 263 passenger (sense) strand
UAACUAAAAUAAUGUUUAAAGAGUU

[00758] SEQ ID NO:534 – DsiRNA 263 guide (antisense) strand
AACUCUUUAAACAUUAUUUUAGUUAGG

[00759] SEQ ID NO:535 – DsiRNA 264 passenger (sense) strand
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[00760] SEQ ID NO:536 – DsiRNA 264 guide (antisense) strand
AAACUCUUUAAACAUUAUUUUAGUUAG

[00761] SEQ ID NO:537 – DsiRNA 265 passenger (sense) strand
ACUAAAAUAAUGUUUAAAGAGUUUU

[00762] SEQ ID NO:538 – DsiRNA 265 guide (antisense) strand
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[00763] SEQ ID NO:539 – DsiRNA 266 passenger (sense) strand

CUAAAAUAAUGUUUAAAGAGUUUUG

[00764] SEQ ID NO:540 – DsiRNA 266 guide (antisense) strand
CAAAACUCUUUAAACAUUAUUUUAGUU

[00765] SEQ ID NO:541 – DsiRNA 267 passenger (sense) strand
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[00766] SEQ ID NO:542 – DsiRNA 267 guide (antisense) strand
ACAAAACUCUUUAAACAUUAUUUUAGU

[00767] SEQ ID NO:543 – DsiRNA 268 passenger (sense) strand
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[00768] SEQ ID NO:544 – DsiRNA 268 guide (antisense) strand
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[00769] SEQ ID NO:545 – DsiRNA 269 passenger (sense) strand
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[00770] SEQ ID NO:546 – DsiRNA 269 guide (antisense) strand
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[00771] SEQ ID NO:547 – DsiRNA 270 passenger (sense) strand
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[00772] SEQ ID NO:548 – DsiRNA 270 guide (antisense) strand
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[00773] SEQ ID NO:549 – DsiRNA 271 passenger (sense) strand
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[00774] SEQ ID NO:550 – DsiRNA 271 guide (antisense) strand
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[00775] SEQ ID NO:551 – DsiRNA 272 passenger (sense) strand
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[00776] SEQ ID NO:552 – DsiRNA 272 guide (antisense) strand
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[00777] SEQ ID NO:553 – DsiRNA 273 passenger (sense) strand
UGUAUAAAAAUGUAAGGAAGCGUUG

[00778] SEQ ID NO:554 – DsiRNA 273 guide (antisense) strand
CAACGCUUCCUUACAUUUUUAUACAAA

[00779] SEQ ID NO:555 – DsiRNA 274 passenger (sense) strand
GUAUAAAAAUGUAAGGAAGCGUUGU

[00780] SEQ ID NO:556 – DsiRNA 274 guide (antisense) strand
ACAACGCUUCCUUACAUUUUUAUACAA

[00781] SEQ ID NO:557 – DsiRNA 275 passenger (sense) strand
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[00782] SEQ ID NO:558 – DsiRNA 275 guide (antisense) strand
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[00783] SEQ ID NO:559 – DsiRNA 276 passenger (sense) strand
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[00784] SEQ ID NO:560 – DsiRNA 276 guide (antisense) strand
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[00785] SEQ ID NO:561 – DsiRNA 277 passenger (sense) strand
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[00786] SEQ ID NO:562 – DsiRNA 277 guide (antisense) strand
AUCUCACUGAUUCACAUAAUACAAAAU

[00787] SEQ ID NO:563 – DsiRNA 278 passenger (sense) strand
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[00788] SEQ ID NO:564 – DsiRNA 278 guide (antisense) strand
CAUCUCACUGAUUCACAUAAUACAAAA

[00789] SEQ ID NO:565 – DsiRNA 279 passenger (sense) strand
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[00790] SEQ ID NO:566 – DsiRNA 279 guide (antisense) strand
ACAUCUCACUGAUUCACAUAAUACAAA

[00791] SEQ ID NO:567 – DsiRNA 280 passenger (sense) strand
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[00792] SEQ ID NO:568 – DsiRNA 280 guide (antisense) strand
AACAUCUCACUGAUUCACAUAAUACAA

[00793] SEQ ID NO:569 – DsiRNA 281 passenger (sense) strand
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[00794] SEQ ID NO:570 – DsiRNA 281 guide (antisense) strand
UAACAUCUCACUGAUUCACAUAAUACA

[00795] SEQ ID NO:571 – DsiRNA 282 passenger (sense) strand

AUUAUGUGAAUCAGUGAGAUGUUAG

[00796] SEQ ID NO:572 – DsiRNA 282 guide (antisense) strand
CUAACAUCUCACUGAUUCACAUAAUAC

[00797] SEQ ID NO:573 – DsiRNA 283 passenger (sense) strand
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[00798] SEQ ID NO:574 – DsiRNA 283 guide (antisense) strand
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[00799] SEQ ID NO:575 – DsiRNA 284 passenger (sense) strand
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[00800] SEQ ID NO:576 – DsiRNA 284 guide (antisense) strand
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[00802] SEQ ID NO:578 – DsiRNA 285 guide (antisense) strand
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[00803] SEQ ID NO:579 – DsiRNA 286 passenger (sense) strand
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[00804] SEQ ID NO:580 – DsiRNA 286 guide (antisense) strand
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[00805] SEQ ID NO:581 – DsiRNA 287 passenger (sense) strand
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[00806] SEQ ID NO:582 – DsiRNA 287 guide (antisense) strand
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[00807] SEQ ID NO:583 – DsiRNA 288 passenger (sense) strand
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[00808] SEQ ID NO:584 – DsiRNA 288 guide (antisense) strand
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[00809] SEQ ID NO:585 – DsiRNA 289 passenger (sense) strand
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[00810] SEQ ID NO:586 – DsiRNA 289 guide (antisense) strand
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[00811] SEQ ID NO:587 – DsiRNA 290 passenger (sense) strand
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[00812] SEQ ID NO:588 – DsiRNA 290 guide (antisense) strand
CUGUACUCAAAUGCAUAAAUAGAAAAA

[00813] SEQ ID NO:589 – DsiRNA 291 passenger (sense) strand
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[00814] SEQ ID NO:590 – DsiRNA 291 guide (antisense) strand
ACUGUACUCAAAUGCAUAAAUAGAAAA

[00815] SEQ ID NO:591 – DsiRNA 292 passenger (sense) strand
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[00816] SEQ ID NO:592 – DsiRNA 292 guide (antisense) strand
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[00817] SEQ ID NO:593 – DsiRNA 293 passenger (sense) strand
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[00818] SEQ ID NO:594 – DsiRNA 293 guide (antisense) strand
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[00819] SEQ ID NO: – DsiRNA 294 passenger (sense) strand
GCUCAAACUGUUAAAUGUUGGAAAA 595

[00820] SEQ ID NO:596 – DsiRNA 294 guide (antisense) strand
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[00821] SEQ ID NO:597 – DsiRNA 295 passenger (sense) strand
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[00822] SEQ ID NO:598 – DsiRNA 295 guide (antisense) strand
CUUUUCCAACAUUUAACAGUUUGAGCA

[00823] SEQ ID NO:599 – DsiRNA 296 passenger (sense) strand
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[00824] SEQ ID NO:600 – DsiRNA 296 guide (antisense) strand
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[00825] SEQ ID NO:601 – DsiRNA 297 passenger (sense) strand
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[00826] SEQ ID NO:602 – DsiRNA 297 guide (antisense) strand
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[00827] SEQ ID NO:603 – DsiRNA 298 passenger (sense) strand

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[00828] SEQ ID NO:604 – DsiRNA 298 guide (antisense) strand
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[00829] SEQ ID NO:605 – DsiRNA 299 passenger (sense) strand
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[00830] SEQ ID NO:606 – DsiRNA 299 guide (antisense) strand
CUUUCUUUUCCAACAUUUAACAGUUUG

[00831] SEQ ID NO:607 – DsiRNA 300 passenger (sense) strand
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[00832] SEQ ID NO:608 – DsiRNA 300 guide (antisense) strand
UCUUUCUUUUCCAACAUUUAACAGUUU

[00833] SEQ ID NO:609 – DsiRNA 301 passenger (sense) strand
CUGUUAAAUGUUGGAAAAGAAAGAT

[00834] SEQ ID NO:610 – DsiRNA 301 guide (antisense) strand
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[00835] SEQ ID NO:611 – DsiRNA 302 passenger (sense) strand
UGUUAAAUGUUGGAAAAGAAAGATA

[00836] SEQ ID NO:612 – DsiRNA 302 guide (antisense) strand
UAUCUUUCUUUUCCAACAUUUAACAGU

[00837] SEQ ID NO:613 – DsiRNA 303 passenger (sense) strand
GUUAAAUGUUGGAAAAGAAAGAUAC

[00838] SEQ ID NO:614 – DsiRNA 303 guide (antisense) strand
GUAUCUUUCUUUUCCAACAUUUAACAG

[00839] SEQ ID NO:615 – DsiRNA 304 passenger (sense) strand
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[00840] SEQ ID NO:616 – DsiRNA 304 guide (antisense) strand
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[00841] SEQ ID NO:617 – DsiRNA 305 passenger (sense) strand
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[00842] SEQ ID NO:618 – DsiRNA 305 guide (antisense) strand
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[00843] SEQ ID NO:619 – DsiRNA 306 passenger (sense) strand
GCACUUGACUGAGAAGACAGACCCT

[00844] SEQ ID NO:620 – DsiRNA 306 guide (antisense) strand
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[00845] SEQ ID NO:621 – DsiRNA 307 passenger (sense) strand
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[00846] SEQ ID NO:622 – DsiRNA 307 guide (antisense) strand
AUUUUCACAAGUAGCCUCUUUUCUCAA

[00847] SEQ ID NO:623 – DsiRNA 308 passenger (sense) strand
AGAAAAGAGGCUACUUGUGAAAATA

[00848] SEQ ID NO:624 – DsiRNA 308 guide (antisense) strand
UAUUUUCACAAGUAGCCUCUUUUCUCA

[00849] SEQ ID NO:625 – DsiRNA 309 passenger (sense) strand
GAAAAGAGGCUACUUGUGAAAAUAA

[00850] SEQ ID NO:626 – DsiRNA 309 guide (antisense) strand
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[00851] SEQ ID NO:627 – DsiRNA 310 passenger (sense) strand
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[00852] SEQ ID NO:628 – DsiRNA 310 guide (antisense) strand
AUUAUUUUCACAAGUAGCCUCUUUUCU

[00853] SEQ ID NO:629 – DsiRNA 311 passenger (sense) strand
AAAGAGGCUACUUGUGAAAAUAATG

[00854] SEQ ID NO:630 – DsiRNA 311 guide (antisense) strand
CAUUAUUUUCACAAGUAGCCUCUUUUC

[00855] SEQ ID NO:631 – DsiRNA 312 passenger (sense) strand
AAGAGGCUACUUGUGAAAAUAAUGA

[00856] SEQ ID NO:632 – DsiRNA 312 guide (antisense) strand
UCAUUAUUUUCACAAGUAGCCUCUUUU

[00857] SEQ ID NO:633 – DsiRNA 313 passenger (sense) strand
AGAGGCUACUUGUGAAAAUAAUGAG

[00858] SEQ ID NO:634 – DsiRNA 313 guide (antisense) strand
CUCAUUAUUUUCACAAGUAGCCUCUUU

[00859] SEQ ID NO:635 – DsiRNA 314 passenger (sense) strand

GAGGCUACUUGUGAAAAUAAUGAGC

[00860] SEQ ID NO:636 – DsiRNA 314 guide (antisense) strand
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[00861] SEQ ID NO:637 – DsiRNA 315 passenger (sense) strand
GGCUACUUGUGAAAAUAAUGAGCCC

[00862] SEQ ID NO:638 – DsiRNA 315 guide (antisense) strand
GGGCUCAUUAUUUUCACAAGUAGCCUC

[00863] SEQ ID NO:639 – DsiRNA 316 passenger (sense) strand
CUACUUGUGAAAAUAAUGAGCCCCC

[00864] SEQ ID NO:640 – DsiRNA 316 guide (antisense) strand
GGGGGCUCAUUAUUUUCACAAGUAGCC

[00865] SEQ ID NO:641 – DsiRNA 317 passenger (sense) strand
UGAACCUGCCUUCUUACAUCUUGAG

[00866] SEQ ID NO:642 – DsiRNA 317 guide (antisense) strand
CUCAAGAUGUAAGAAGGCAGGUUCAAA

[00867] SEQ ID NO:643 – DsiRNA 318 passenger (sense) strand
AAAGUUACAAGUUUCUUUUCCCAAG

[00868] SEQ ID NO:644 – DsiRNA 318 guide (antisense) strand
CUUGGGAAAAGAAACUUGUAACUUUCC

[00869] SEQ ID NO:645 – DsiRNA 319 passenger (sense) strand
AAGUUACAAGUUUCUUUUCCCAAGT

[00870] SEQ ID NO:646 – DsiRNA 319 guide (antisense) strand
ACUUGGGAAAAGAAACUUGUAACUUUC

[00871] SEQ ID NO:647 – DsiRNA 320 passenger (sense) strand
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[00872] SEQ ID NO:648 – DsiRNA 320 guide (antisense) strand
AACUUGGGAAAAGAAACUUGUAACUUU

[00873] SEQ ID NO:649 – DsiRNA 321 passenger (sense) strand
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[00874] SEQ ID NO:650 – DsiRNA 321 guide (antisense) strand
ACUGGGAAACUUGGGAAAAGAAACUUG

[00875] SEQ ID NO:651 – DsiRNA 322 passenger (sense) strand
CAACAGUAUUUUCUAAUAACCAGTA

[00876] SEQ ID NO:652 – DsiRNA 322 guide (antisense) strand
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[00877] SEQ ID NO:653 – DsiRNA 323 passenger (sense) strand
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[00878] SEQ ID NO:654 – DsiRNA 323 guide (antisense) strand
AUACUGGUUAUUAGAAAAUACUGUUGG

[00879] SEQ ID NO:655 – DsiRNA 324 passenger (sense) strand
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[00880] SEQ ID NO:656 – DsiRNA 324 guide (antisense) strand
UAUACUGGUUAUUAGAAAAUACUGUUG

[00881] SEQ ID NO:657 – DsiRNA 325 passenger (sense) strand
CAGUAUUUUCUAAUAACCAGUAUAT

[00882] SEQ ID NO:658 – DsiRNA 325 guide (antisense) strand
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[00883] SEQ ID NO:659 – DsiRNA 326 passenger (sense) strand
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[00884] SEQ ID NO:660 – DsiRNA 326 guide (antisense) strand
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[00885] SEQ ID NO:661 – DsiRNA 327 passenger (sense) strand
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[00886] SEQ ID NO:662 – DsiRNA 327 guide (antisense) strand
AUAUUUUUUCCUGAUAACAAUCACAAU

[00887] SEQ ID NO:663 – DsiRNA 328 passenger (sense) strand
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[00888] SEQ ID NO:664 – DsiRNA 328 guide (antisense) strand
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[00889] SEQ ID NO:665 – DsiRNA 329 passenger (sense) strand
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[00890] SEQ ID NO:666 – DsiRNA 329 guide (antisense) strand
AUAUAUUUUUUCCUGAUAACAAUCACA

[00891] SEQ ID NO:667 – DsiRNA 330 passenger (sense) strand
GAUUGUUAUCAGGAAAAAAUAUATT

[00892] SEQ ID NO:668 – DsiRNA 330 guide (antisense) strand
AAUAUAUUUUUUCCUGAUAACAAUCAC

[00893] SEQ ID NO:669 – DsiRNA 331 passenger (sense) strand
AUUGUUAUCAGGAAAAAAUAUAUTA

[00894] SEQ ID NO:670 – DsiRNA 331 guide (antisense) strand
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[00895] SEQ ID NO:671 – DsiRNA 332 passenger (sense) strand
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[00896] SEQ ID NO:672 – DsiRNA 332 guide (antisense) strand
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[00897] SEQ ID NO:673 – DsiRNA 333 passenger (sense) strand
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[00898] SEQ ID NO:674 – DsiRNA 333 guide (antisense) strand
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[00899] SEQ ID NO:675 – DsiRNA 334 passenger (sense) strand
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[00900] SEQ ID NO:676 – DsiRNA 334 guide (antisense) strand
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[00901] SEQ ID NO:677 – DsiRNA 335 passenger (sense) strand
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[00902] SEQ ID NO:678 – DsiRNA 335 guide (antisense) strand
CAUUUAAUAUAUUUUUUCCUGAUAACA

[00903] SEQ ID NO:679 – DsiRNA 336 passenger (sense) strand
UAUCAGGAAAAAAUAUAUUAAAUGG

[00904] SEQ ID NO:680 – DsiRNA 336 guide (antisense) strand
CCAUUUAAUAUAUUUUUUCCUGAUAAC

[00905] SEQ ID NO:681 – DsiRNA 337 passenger (sense) strand
AUCAGGAAAAAAUAUAUUAAAUGGC

[00906] SEQ ID NO:682 – DsiRNA 337 guide (antisense) strand
GCCAUUUAAUAUAUUUUUUCCUGAUAA

[00907] SEQ ID NO:683 – DsiRNA 338 passenger (sense) strand

AGGAAAAAAUAUAUUAAAUGGCUGA

[00908] SEQ ID NO:684 – DsiRNA 338 guide (antisense) strand
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[00909] SEQ ID NO:685 – DsiRNA 339 passenger (sense) strand
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[00910] SEQ ID NO:686 – DsiRNA 339 guide (antisense) strand
AUCAGCCAUUUAAUAUAUUUUUUCCUG

[00911] SEQ ID NO:687 – DsiRNA 340 passenger (sense) strand
GAAAAAAUAUAUUAAAUGGCUGATA

[00912] SEQ ID NO:688 – DsiRNA 340 guide (antisense) strand
UAUCAGCCAUUUAAUAUAUUUUUUCCU

[00913] SEQ ID NO:689 – DsiRNA 341 passenger (sense) strand
AAAAAAUAUAUUAAAUGGCUGAUAG

[00914] SEQ ID NO:690 – DsiRNA 341 guide (antisense) strand
CUAUCAGCCAUUUAAUAUAUUUUUUCC

[00915] SEQ ID NO:691 – DsiRNA 342 passenger (sense) strand
UAUUUUCUUUCUGCUUUUAAAAATT

[00916] SEQ ID NO:692 – DsiRNA 342 guide (antisense) strand
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[00917] SEQ ID NO:693 – DsiRNA 343 passenger (sense) strand
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[00918] SEQ ID NO:694 – DsiRNA 343 guide (antisense) strand
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[00919] SEQ ID NO:695 – DsiRNA 344 passenger (sense) strand
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[00920] SEQ ID NO:696 – DsiRNA 344 guide (antisense) strand
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[00921] SEQ ID NO:697 – DsiRNA 345 passenger (sense) strand
CUUUCUGCUUUUAAAAAUUAUUCAG

[00922] SEQ ID NO:698 – DsiRNA 345 guide (antisense) strand
CUGAAUAAUUUUUAAAAGCAGAAAGAA

[00923] SEQ ID NO:699 – DsiRNA 346 passenger (sense) strand
UUUCUGCUUUUAAAAAUUAUUCAGG

[00924] SEQ ID NO:700 – DsiRNA 346 guide (antisense) strand
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[00925] SEQ ID NO:701 – DsiRNA 347 passenger (sense) strand
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[00926] SEQ ID NO:702 – DsiRNA 347 guide (antisense) strand
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[00927] SEQ ID NO:703 – DsiRNA 348 passenger (sense) strand
CAAGAUAAGGAAAUCAGGAAGUGTA

[00928] SEQ ID NO:704 – DsiRNA 348 guide (antisense) strand
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[00929] SEQ ID NO:705 – DsiRNA 349 passenger (sense) strand
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[00930] SEQ ID NO:706 – DsiRNA 349 guide (antisense) strand
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[00931] SEQ ID NO:707 – DsiRNA 350 passenger (sense) strand
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[00932] SEQ ID NO:708 – DsiRNA 350 guide (antisense) strand
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[00933] SEQ ID NO:709 – DsiRNA 351 passenger (sense) strand
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[00934] SEQ ID NO:710 – DsiRNA 351 guide (antisense) strand
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[00935] SEQ ID NO:711 – DsiRNA 352 passenger (sense) strand
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[00936] SEQ ID NO:712 – DsiRNA 352 guide (antisense) strand
AUAUUACACUUCCUGAUUUCCUUAUCU

[00937] SEQ ID NO:713 – DsiRNA 353 passenger (sense) strand
UAAGGAAAUCAGGAAGUGUAAUATT

[00938] SEQ ID NO:714 – DsiRNA 353 guide (antisense) strand
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[00939] SEQ ID NO:715 – DsiRNA 354 passenger (sense) strand

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[00940] SEQ ID NO:716 – DsiRNA 354 guide (antisense) strand
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[00941] SEQ ID NO:717 – DsiRNA 355 passenger (sense) strand
AGGAAAUCAGGAAGUGUAAUAUUCT

[00942] SEQ ID NO:718 – DsiRNA 355 guide (antisense) strand
AGAAUAUUACACUUCCUGAUUUCCUUA

[00943] SEQ ID NO:719 – DsiRNA 356 passenger (sense) strand
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[00944] SEQ ID NO:720 – DsiRNA 356 guide (antisense) strand
AAGAAUAUUACACUUCCUGAUUUCCUU

[00945] SEQ ID NO:721 – DsiRNA 357 passenger (sense) strand
GAAAUCAGGAAGUGUAAUAUUCUTA

[00946] SEQ ID NO:722 – DsiRNA 357 guide (antisense) strand
UAAGAAUAUUACACUUCCUGAUUUCCU

[00947] SEQ ID NO:723 – DsiRNA 358 passenger (sense) strand
CUAUGAAUGCAUUCUUAUUUCUUCT

[00948] SEQ ID NO:724 – DsiRNA 358 guide (antisense) strand
AGAAGAAAUAAGAAUGCAUUCAUAGGC

[00949] SEQ ID NO:725 – DsiRNA 359 passenger (sense) strand
UAUGAAUGCAUUCUUAUUUCUUCTT

[00950] SEQ ID NO:726 – DsiRNA 359 guide (antisense) strand
AAGAAGAAAUAAGAAUGCAUUCAUAGG

[00951] SEQ ID NO:727 – DsiRNA 360 passenger (sense) strand
CUACCACACCCAGCUAGUUUUUUTT

[00952] SEQ ID NO:728 – DsiRNA 360 guide (antisense) strand
AAAAAAAACUAGCUGGGUGUGGUAGUG

[00953] SEQ ID NO:729 – DsiRNA 361 passenger (sense) strand
CCACACCCAGCUAGUUUUUUUUUGT

[00954] SEQ ID NO:730 – DsiRNA 361 guide (antisense) strand
ACAAAAAAAAACUAGCUGGGUGUGGUA

[00955] SEQ ID NO:731 – DsiRNA 362 passenger (sense) strand
CACACCCAGCUAGUUUUUUUUUGTA

[00956] SEQ ID NO:732 – DsiRNA 362 guide (antisense) strand
UACAAAAAAAAACUAGCUGGGUGUGGU

[00957] SEQ ID NO:733 – DsiRNA 363 passenger (sense) strand
GCUAGGAUUACAGGUGUGAGCUACC

[00958] SEQ ID NO:734 – DsiRNA 363 guide (antisense) strand
GGUAGCUCACACCUGUAAUCCUAGCAC

[00959] SEQ ID NO:735 – DsiRNA 364 passenger (sense) strand
CUAGGAUUACAGGUGUGAGCUACCA

[00960] SEQ ID NO:736 – DsiRNA 364 guide (antisense) strand
UGGUAGCUCACACCUGUAAUCCUAGCA

[00961] SEQ ID NO:737 – DsiRNA 365 passenger (sense) strand
CCAUGCCUGGUCCAACAUUCUUCAT

[00962] SEQ ID NO:738 – DsiRNA 365 guide (antisense) strand
AUGAAGAAUGUUGGACCAGGCAUGGUA

[00963] SEQ ID NO:739 – DsiRNA 366 passenger (sense) strand
UGCAGAGUAUGAGCCUGAUUUUGTT

[00964] SEQ ID NO:740 – DsiRNA 366 guide (antisense) strand
AACAAAAUCAGGCUCAUACUCUGCACU

[00965] SEQ ID NO:741 – DsiRNA 367 passenger (sense) strand
GCAGAGUAUGAGCCUGAUUUUGUTT

[00966] SEQ ID NO:742 – DsiRNA 367 guide (antisense) strand
AAACAAAAUCAGGCUCAUACUCUGCAC

[00967] SEQ ID NO:743 – DsiRNA 368 passenger (sense) strand
CAGAGUAUGAGCCUGAUUUUGUUTA

[00968] SEQ ID NO:744 – DsiRNA 368 guide (antisense) strand
UAAACAAAAUCAGGCUCAUACUCUGCA

[00969] SEQ ID NO:745 – DsiRNA 369 passenger (sense) strand
AGAGUAUGAGCCUGAUUUUGUUUAA

[00970] SEQ ID NO:746 – DsiRNA 369 guide (antisense) strand
UUAAACAAAAUCAGGCUCAUACUCUGC

[00971] SEQ ID NO:747 – DsiRNA 370 passenger (sense) strand

GAGUAUGAGCCUGAUUUUGUUUAAA

[00972] SEQ ID NO:748 – DsiRNA 370 guide (antisense) strand
UUUAAACAAAAUCAGGCUCAUACUCUG

[00973] SEQ ID NO:749 – DsiRNA 371 passenger (sense)
GGGUGAAACCCCAUCUCUACUAAAA

[00974] SEQ ID NO:750 – DsiRNA 371 guide (antisense) strand
UUUUAGUAGAGAUGGGGUUUCACCCAG

[00975] SEQ ID NO:751 – DsiRNA 372 passenger (sense) strand
GUGAAACCCCAUCUCUACUAAAAAA

[00976] SEQ ID NO:752 – DsiRNA 372 guide (antisense) strand
UUUUUUAGUAGAGAUGGGGUUUCACCC

[00977] SEQ ID NO:753 – DsiRNA 373 passenger (sense) strand
UGAAACCCCAUCUCUACUAAAAAAT

[00978] SEQ ID NO:754 – DsiRNA 373 guide (antisense) strand
AUUUUUUAGUAGAGAUGGGGUUUCACC

[00979] SEQ ID NO:755 – DsiRNA 374 passenger (sense) strand
GAAACCCCAUCUCUACUAAAAAATG

[00980] SEQ ID NO:756 – DsiRNA 374 guide (antisense) strand
CAUUUUUUAGUAGAGAUGGGGUUUCAC

[00981] SEQ ID NO:757 – DsiRNA 375 guide (antisense) strand
AAACCCCAUCUCUACUAAAAAAUGC

[00982] SEQ ID NO:758 – DsiRNA 375 guide (antisense) strand
GCAUUUUUUAGUAGAGAUGGGGUUUCA

[00983] SEQ ID NO:759 – DsiRNA 376 passenger (sense) strand
AACCCCAUCUCUACUAAAAAAUGCA

[00984] SEQ ID NO:760 – DsiRNA 376 guide (antisense) strand
UGCAUUUUUUAGUAGAGAUGGGGUUUC

[00985] SEQ ID NO:761 – DsiRNA 377 passenger (sense) strand
CCCAUCUCUACUAAAAAAUGCAAAA

[00986] SEQ ID NO:762 – DsiRNA 377 guide (antisense) strand
UUUUGCAUUUUUUAGUAGAGAUGGGGU

[00987] SEQ ID NO:763 – DsiRNA 378 passenger (sense) strand
AUCAAAACCCUUAUGGCAGACUGTT

[00988] SEQ ID NO:764 – DsiRNA 378 guide (antisense) strand
AACAGUCUGCCAUAAGGGUUUUGAUAU

[00989] SEQ ID NO:765 – DsiRNA 379 passenger (sense) strand
UAUUUUAUUUGUCGUGCUUAUAUGT

[00990] SEQ ID NO:766 – DsiRNA 379 guide (antisense) strand
ACAUAUAAGCACGACAAAUAAAAUACA

[00991] SEQ ID NO:767 – DsiRNA 380 passenger (sense) strand
GUGUUGCCCAAGUUUCUAUGGUGAA

[00992] SEQ ID NO:768 – DsiRNA 380 guide (antisense) strand
UUCACCAUAGAAACUUGGGCAACACAU

[00993] SEQ ID NO:769 – DsiRNA 381 passenger (sense) strand
GCCCAAGUUUCUAUGGUGAACGGTA

[00994] SEQ ID NO:770 – DsiRNA 381 guide (antisense) strand
UACCGUUCACCAUAGAAACUUGGGCAA

[00995] SEQ ID NO:771 – DsiRNA 382 passenger (sense) strand
CCCAAGUUUCUAUGGUGAACGGUAT

[00996] SEQ ID NO:772 – DsiRNA 382 guide (antisense) strand
AUACCGUUCACCAUAGAAACUUGGGCA

[00997] SEQ ID NO:773 – DsiRNA 383 passenger (sense) strand
ACUUUCAGCAUGAGAAAAUAACUCC

[00998] SEQ ID NO:774 – DsiRNA 383 guide (antisense) strand
GGAGUUAUUUUCUCAUGCUGAAAGUGA

[00999] SEQ ID NO:775 – DsiRNA 384 passenger (sense) strand
CUUUCAGCAUGAGAAAAUAACUCCT

[001000]SEQ ID NO:776 – DsiRNA 384 guide (antisense) strand
AGGAGUUAUUUUCUCAUGCUGAAAGUG

[001001]SEQ ID NO:777 –PNPLA3 oligonucleotide 1 passenger (sense) strand
UGAGUGACAACGUACCCUUAGCAGCCGAAAGGCUGC

[001002]SEQ ID NO:778 – PNPLA3 oligonucleotide 1 guide (antisense) strand
UAAGGGUACGUUGUCACUCAGG

[001003]SEQ ID NO:779 – PNPLA3 oligonucleotide 2 passenger (sense) strand

GAGUGACAACGUACCCUUCAGCAGCCGAAAGGCUGC

[001004]SEQ ID NO:780 – PNPLA3 oligonucleotide 2 guide (antisense) strand
UGAAGGGUACGUUGUCACUCGG

[001005]SEQ ID NO:781 – PNPLA3 oligonucleotide 3 passenger (sense) strand
AGUGACAACGUACCCUUCAAGCAGCCGAAAGGCUGC

[001006]SEQ ID NO:782 – PNPLA3 oligonucleotide 3 guide (antisense) strand
UUGAAGGGUACGUUGUCACUGG

[001007]SEQ ID NO:783 – PNPLA3 oligonucleotide 4 passenger (sense) strand
UGACAACGUACCCUUCAUUAGCAGCCGAAAGGCUGC

[001008]SEQ ID NO:784 – PNPLA3 oligonucleotide 4 guide (antisense) strand
UAAUGAAGGGUACGUUGUCAGG

[001009]SEQ ID NO:785 – PNPLA3 oligonucleotide 5 passenger (sense) strand
GACAACGUACCCUUCAUUGAGCAGCCGAAAGGCUGC

[001010]SEQ ID NO:786 – PNPLA3 oligonucleotide 5 guide (antisense) strand
UCAAUGAAGGGUACGUUGUCGG

[001011]SEQ ID NO:787 – PNPLA3 oligonucleotide 6 passenger (sense) strand
CAACGUACCCUUCAUUGAUAGCAGCCGAAAGGCUGC

[001012]SEQ ID NO:788 – PNPLA3 oligonucleotide 6 guide (antisense) strand
UAUCAAUGAAGGGUACGUUGGG

[001013]SEQ ID NO:789 – PNPLA3 oligonucleotide 7 passenger (sense) strand
AACGUACCCUUCAUUGAUGAGCAGCCGAAAGGCUGC

[001014]SEQ ID NO:790 – PNPLA3 oligonucleotide 7 guide (antisense) strand
UCAUCAAUGAAGGGUACGUUGG

[001015]SEQ ID NO:791 – PNPLA3 oligonucleotide 8 passenger (sense) strand
ACGUACCCUUCAUUGAUGCAGCAGCCGAAAGGCUGC

[001016]SEQ ID NO:792 – PNPLA3 oligonucleotide 8 guide (antisense) strand
UGCAUCAAUGAAGGGUACGUGG

[001017]SEQ ID NO:793 – PNPLA3 oligonucleotide 9 passenger (sense) strand
CGUACCCUUCAUUGAUGCCAGCAGCCGAAAGGCUGC

[001018]SEQ ID NO:794 – PNPLA3 oligonucleotide 9 guide (antisense) strand
UGGCAUCAAUGAAGGGUACGGG

[001019]SEQ ID NO:795 – PNPLA3 oligonucleotide 10 passenger (sense) strand
UACCCUUCAUUGAUGCCAAAGCAGCCGAAAGGCUGC

[001020]SEQ ID NO:796 – PNPLA3 oligonucleotide 10 guide (antisense) strand
UUUGGCAUCAAUGAAGGGUAGG

[001021]SEQ ID NO:797 – PNPLA3 oligonucleotide 11 passenger (sense) strand
CACGAACUUUCUUCAUGUGAGCAGCCGAAAGGCUGC

[001022]SEQ ID NO:798 – PNPLA3 oligonucleotide 11 guide (antisense) strand
UCACAUGAAGAAAGUUCGUGGG

[001023]SEQ ID NO:799 – PNPLA3 oligonucleotide 12 passenger (sense) strand
ACGAACUUUCUUCAUGUGGAGCAGCCGAAAGGCUGC

[001024]SEQ ID NO:800 – PNPLA3 oligonucleotide 12 guide (antisense) strand
UCCACAUGAAGAAAGUUCGUGG

[001025]SEQ ID NO:801 – PNPLA3 oligonucleotide 13 passenger (sense) strand
CGAACUUUCUUCAUGUGGAAGCAGCCGAAAGGCUGC

[001026]SEQ ID NO:802 – PNPLA3 oligonucleotide 13 guide (antisense) strand
UUCCACAUGAAGAAAGUUCGGG

[001027]SEQ ID NO:803 – PNPLA3 oligonucleotide 14 passenger (sense) strand
ACUUUCUUCAUGUGGACAUAGCAGCCGAAAGGCUGC

[001028]SEQ ID NO:804 – PNPLA3 oligonucleotide 14 guide (antisense) strand
UAUGUCCACAUGAAGAAAGUGG

[001029]SEQ ID NO:805 – PNPLA3 oligonucleotide 15 passenger (sense) strand
UUUCUUCAUGUGGACAUCAAGCAGCCGAAAGGCUGC

[001030]SEQ ID NO:806 – PNPLA3 oligonucleotide 15 guide (antisense) strand
UUGAUGUCCACAUGAAGAAAGG

[001031]SEQ ID NO:807 – PNPLA3 oligonucleotide 16 passenger (sense) strand
CUUCAUGUGGACAUCACCAAGCAGCCGAAAGGCUGC

[001032]SEQ ID NO:808 – PNPLA3 oligonucleotide 16 guide (antisense) strand
UUGGUGAUGUCCACAUGAAGGG

[001033]SEQ ID NO:809 – PNPLA3 oligonucleotide 17 passenger (sense) strand
AUGUGGACAUCACCAAGCUAGCAGCCGAAAGGCUGC

[001034]SEQ ID NO:810 – PNPLA3 oligonucleotide 17 guide (antisense) strand
UAGCUUGGUGAUGUCCACAUGG

[001035]SEQ ID NO:811 – PNPLA3 oligonucleotide 18 passenger (sense) strand
UGUGGACAUCACCAAGCUCAGCAGCCGAAAGGCUGC

[001036]SEQ ID NO:812 – PNPLA3 oligonucleotide 18 guide (antisense) strand
UGAGCUUGGUGAUGUCCACAGG

[001037]SEQ ID NO:813 – PNPLA3 oligonucleotide 19 passenger (sense) strand
GUGGACAUCACCAAGCUCAAGCAGCCGAAAGGCUGC

[001038]SEQ ID NO:814 – PNPLA3 oligonucleotide 19 guide (antisense) strand
UUGAGCUUGGUGAUGUCCACGG

[001039]SEQ ID NO:815 – PNPLA3 oligonucleotide 20 passenger (sense) strand
UGGACAUCACCAAGCUCAGAGCAGCCGAAAGGCUGC

[001040]SEQ ID NO:816 – PNPLA3 oligonucleotide 20 guide (antisense) strand
UCUGAGCUUGGUGAUGUCCAGG

[001041]SEQ ID NO:817 – PNPLA3 oligonucleotide 21 passenger (sense) strand
AGAUAUGCCUUCGAGGAUAAGCAGCCGAAAGGCUGC

[001042]SEQ ID NO:818 – PNPLA3 oligonucleotide 21 guide (antisense) strand
UUAUCCUCGAAGGCAUAUCUGG

[001043]SEQ ID NO:819 – PNPLA3 oligonucleotide 22 passenger (sense) strand
AUGCCUUCGAGGAUAUUUGAGCAGCCGAAAGGCUGC

[001044]SEQ ID NO:820 – PNPLA3 oligonucleotide 22 guide (antisense) strand
UCAAAUAUCCUCGAAGGCAUGG

[001045]SEQ ID NO:821 – PNPLA3 oligonucleotide 23 passenger (sense) strand
GCCUUCGAGGAUAUUUGGAAGCAGCCGAAAGGCUGC

[001046]SEQ ID NO:822 – PNPLA3 oligonucleotide 23 guide (antisense) strand
UUCCAAAUAUCCUCGAAGGCGG

[001047]SEQ ID NO:823 – PNPLA3 oligonucleotide 24 passenger (sense) strand
UGAAGUCAUCCUCAGAAGGAGCAGCCGAAAGGCUGC

[001048]SEQ ID NO:824 – PNPLA3 oligonucleotide 24 guide (antisense) strand
UCCUUCUGAGGAUGACUUCAGG

[001049]SEQ ID NO:825 – PNPLA3 oligonucleotide 25 passenger (sense) strand
GAAGUCAUCCUCAGAAGGGAGCAGCCGAAAGGCUGC

[001050]SEQ ID NO:826 – PNPLA3 oligonucleotide 25 guide (antisense) strand

UCCCUUCUGAGGAUGACUUCGG

[001051]SEQ ID NO:827 – PNPLA3 oligonucleotide 26 passenger (sense) strand
AUCCUCAGAAGGGAUGGAUAGCAGCCGAAAGGCUGC

[001052]SEQ ID NO:828 – PNPLA3 oligonucleotide 26 guide (antisense) strand
UAUCCAUCCCUUCUGAGGAUGG

[001053]SEQ ID NO:829 – PNPLA3 oligonucleotide 27 passenger (sense) strand
AGUGAAGAAAUGAAAGACAAGCAGCCGAAAGGCUGC

[001054]SEQ ID NO:830 – PNPLA3 oligonucleotide 27 guide (antisense) strand
UUGUCUUUCAUUUCUUCACUGG

[001055]SEQ ID NO:831 – PNPLA3 oligonucleotide 28 passenger (sense) strand
AAGAAAUGAAAGACAAAGGAGCAGCCGAAAGGCUGC

[001056]SEQ ID NO:832 – PNPLA3 oligonucleotide 28 guide (antisense) strand
UCCUUUGUCUUUCAUUUCUUGG

[001057]SEQ ID NO:833 – PNPLA3 oligonucleotide 29 passenger (sense) strand
AGAAAUGAAAGACAAAGGUAGCAGCCGAAAGGCUGC

[001058]SEQ ID NO:834 – PNPLA3 oligonucleotide 29 guide (antisense) strand
UACCUUUGUCUUUCAUUUCUGG

[001059]SEQ ID NO:835 – PNPLA3 oligonucleotide 30 passenger (sense) strand
GAAAUGAAAGACAAAGGUGAGCAGCCGAAAGGCUGC

[001060]SEQ ID NO:836 – PNPLA3 oligonucleotide 30 guide (antisense) strand
UCACCUUUGUCUUUCAUUUCGG

[001061]SEQ ID NO:837 – PNPLA3 oligonucleotide 31 passenger (sense) strand
AAAUGAAAGACAAAGGUGGAGCAGCCGAAAGGCUGC

[001062]SEQ ID NO:838 – PNPLA3 oligonucleotide 31 guide (antisense) strand
UCCACCUUUGUCUUUCAUUUGG

[001063]SEQ ID NO:839 – PNPLA3 oligonucleotide 32 passenger (sense) strand
AAUGAAAGACAAAGGUGGAAGCAGCCGAAAGGCUGC

[001064]SEQ ID NO:840 – PNPLA3 oligonucleotide 32 guide (antisense) strand
UUCCACCUUUGUCUUUCAUUGG

[001065]SEQ ID NO:841 – PNPLA3 oligonucleotide 33 passenger (sense) strand
AUGAAAGACAAAGGUGGAUAGCAGCCGAAAGGCUGC

[001066]SEQ ID NO:842 – PNPLA3 oligonucleotide 33 guide (antisense) strand
UAUCCACCUUUGUCUUUCAUGG

[001067]SEQ ID NO:843 – PNPLA3 oligonucleotide 34 passenger (sense) strand
UGAAAGACAAAGGUGGAUAAGCAGCCGAAAGGCUGC

[001068]SEQ ID NO:844 – PNPLA3 oligonucleotide 34 guide (antisense) strand
UUAUCCACCUUUGUCUUUCAGG

[001069]SEQ ID NO:845 – PNPLA3 oligonucleotide 35 passenger (sense) strand
GAAAGACAAAGGUGGAUACAGCAGCCGAAAGGCUGC

[001070]SEQ ID NO:846 – PNPLA3 oligonucleotide 35 guide (antisense) strand
UGUAUCCACCUUUGUCUUUCGG

[001071]SEQ ID NO:847 – PNPLA3 oligonucleotide 36 passenger (sense) strand
AAGACAAAGGUGGAUACAUAGCAGCCGAAAGGCUGC

[001072]SEQ ID NO:848 – PNPLA3 oligonucleotide 36 guide (antisense) strand
UAUGUAUCCACCUUUGUCUUGG

[001073]SEQ ID NO:849 – PNPLA3 oligonucleotide 37 passenger (sense) strand
AGACAAAGGUGGAUACAUGAGCAGCCGAAAGGCUGC

[001074]SEQ ID NO:850 – PNPLA3 oligonucleotide 37 guide (antisense) strand
UCAUGUAUCCACCUUUGUCUGG

[001075]SEQ ID NO:851 – PNPLA3 oligonucleotide 38 passenger (sense) strand
GACAAAGGUGGAUACAUGAAGCAGCCGAAAGGCUGC

[001076]SEQ ID NO:852 – PNPLA3 oligonucleotide 38 guide (antisense) strand
UUCAUGUAUCCACCUUUGUCGG

[001077]SEQ ID NO:853 – PNPLA3 oligonucleotide 39 passenger guide (sense) strand
ACAAAGGUGGAUACAUGAGAGCAGCCGAAAGGCUGC

[001078]SEQ ID NO:854 – PNPLA3 oligonucleotide 39 guide (antisense) strand
UCUCAUGUAUCCACCUUUGUGG

[001079]SEQ ID NO:855 – PNPLA3 oligonucleotide 40 passenger (sense) strand
AAGGUGGAUACAUGAGCAAAGCAGCCGAAAGGCUGC

[001080]SEQ ID NO:856 – PNPLA3 oligonucleotide 40 guide (antisense) strand
UUUGCUCAUGUAUCCACCUUGG

[001081]SEQ ID NO:857 – PNPLA3 oligonucleotide 41 passenger (sense) strand
AGGUGGAUACAUGAGCAAGAGCAGCCGAAAGGCUGC

[001082]SEQ ID NO:858 – PNPLA3 oligonucleotide 41 guide (antisense) strand

UCUUGCUCAUGUAUCCACCUGG

[001083]SEQ ID NO:859 – PNPLA3 oligonucleotide 42 passenger (sense) strand
UGGAUACAUGAGCAAGAUUAGCAGCCGAAAGGCUGC

[001084]SEQ ID NO:860 – PNPLA3 oligonucleotide 42 guide (antisense) strand
UAAUCUUGCUCAUGUAUCCAGG

[001085]SEQ ID NO:861 – PNPLA3 oligonucleotide 43 passenger (sense) strand
GGAUACAUGAGCAAGAUUUAGCAGCCGAAAGGCUGC

[001086]SEQ ID NO:862 – PNPLA3 oligonucleotide 43 guide (antisense) strand
[001087]UAAAUCUUGCUCAUGUAUCCGG

[001088]SEQ ID NO:863 – PNPLA3 oligonucleotide 44 passenger (sense) strand
GAUACAUGAGCAAGAUUUGAGCAGCCGAAAGGCUGC

[001089]SEQ ID NO:864 – PNPLA3 oligonucleotide 44 guide (antisense) strand
UCAAAUCUUGCUCAUGUAUCGG

[001090]SEQ ID NO:865 – PNPLA3 oligonucleotide 45 passenger (sense) strand
AUACAUGAGCAAGAUUUGCAGCAGCCGAAAGGCUGC

[001091]SEQ ID NO:866 – PNPLA3 oligonucleotide 45 guide (antisense) strand
UGCAAAUCUUGCUCAUGUAUGG

[001092]SEQ ID NO:867 – PNPLA3 oligonucleotide 46 passenger (sense) strand
UACAUGAGCAAGAUUUGCAAGCAGCCGAAAGGCUGC

[001093]SEQ ID NO:868 – PNPLA3 oligonucleotide 46 guide (antisense) strand
UUGCAAAUCUUGCUCAUGUAGG

[001094]SEQ ID NO:869 – PNPLA3 oligonucleotide 47 passenger (sense) strand
ACAUGAGCAAGAUUUGCAAAGCAGCCGAAAGGCUGC

[001095]SEQ ID NO:870 – PNPLA3 oligonucleotide 47 guide (antisense) strand
UUUGCAAAUCUUGCUCAUGUGG

[001096]SEQ ID NO:871 – PNPLA3 oligonucleotide 48 passenger (sense) strand
UGAGCAAGAUUUGCAACUUAGCAGCCGAAAGGCUGC

[001097]SEQ ID NO:872 – PNPLA3 oligonucleotide 48 guide (antisense) strand
UAAGUUGCAAAUCUUGCUCAGG

[001098]SEQ ID NO:873 – PNPLA3 oligonucleotide 49 passenger (sense) strand
GAGCAAGAUUUGCAACUUGAGCAGCCGAAAGGCUGC

[001099]SEQ ID NO:874 – PNPLA3 oligonucleotide 49 guide (antisense) strand
UCAAGUUGCAAAUCUUGCUCGG

[001100]SEQ ID NO:875 – PNPLA3 oligonucleotide 50 passenger (sense) strand
AGCAAGAUUUGCAACUUGCAGCAGCCGAAAGGCUGC

[001101]SEQ ID NO:876 – PNPLA3 oligonucleotide 50 guide (antisense) strand
UGCAAGUUGCAAAUCUUGCUGG

[001102]SEQ ID NO:877 – PNPLA3 oligonucleotide 51 passenger (sense) strand
GCAAGAUUUGCAACUUGCUAGCAGCCGAAAGGCUGC

[001103]SEQ ID NO:878 – PNPLA3 oligonucleotide 51 guide (antisense) strand
UAGCAAGUUGCAAAUCUUGCGG

[001104]SEQ ID NO:879 – PNPLA3 oligonucleotide 52 passenger (sense) strand
CAAGAUUUGCAACUUGCUAAGCAGCCGAAAGGCUGC

[001105]SEQ ID NO:880 – PNPLA3 oligonucleotide 52 guide (antisense) strand
UUAGCAAGUUGCAAAUCUUGGG

[001106]SEQ ID NO:881 – PNPLA3 oligonucleotide 53 passenger (sense) strand
AAGAUUUGCAACUUGCUACAGCAGCCGAAAGGCUGC

[001107]SEQ ID NO:882 – PNPLA3 oligonucleotide 53 guide (antisense) strand
UGUAGCAAGUUGCAAAUCUUGG

[001108]SEQ ID NO:883 – PNPLA3 oligonucleotide 54 passenger (sense) strand
AGAUUUGCAACUUGCUACCAGCAGCCGAAAGGCUGC

[001109]SEQ ID NO:884 – PNPLA3 oligonucleotide 54 guide (antisense) strand
UGGUAGCAAGUUGCAAAUCUGG

[001110]SEQ ID NO:885 – PNPLA3 oligonucleotide 55 passenger (sense) strand
AUUUGCAACUUGCUACCCAAGCAGCCGAAAGGCUGC

[001111]SEQ ID NO:886 – PNPLA3 oligonucleotide 55 guide (antisense) strand
UUGGGUAGCAAGUUGCAAAUGG

[001112]SEQ ID NO:887 – PNPLA3 oligonucleotide 56 passenger (sense) strand
UUGCAACUUGCUACCCAUUAGCAGCCGAAAGGCUGC

[001113]SEQ ID NO:888 – PNPLA3 oligonucleotide 56 guide (antisense) strand
UAAUGGGUAGCAAGUUGCAAGG

[001114]SEQ ID NO:889 – PNPLA3 oligonucleotide 57 passenger (sense) strand
UGCAACUUGCUACCCAUUAAGCAGCCGAAAGGCUGC

[001115]SEQ ID NO:890 – PNPLA3 oligonucleotide 57 guide (antisense) strand

UUAAUGGGUAGCAAGUUGCAGG

[001116]SEQ ID NO:891 – PNPLA3 oligonucleotide 58 passenger (sense) strand
GCAACUUGCUACCCAUUAGAGCAGCCGAAAGGCUGC

[001117]SEQ ID NO:892 – PNPLA3 oligonucleotide 58 guide (antisense) strand
UCUAAUGGGUAGCAAGUUGCGG

[001118]SEQ ID NO:893 – PNPLA3 oligonucleotide 59 passenger (sense) strand
CAACUUGCUACCCAUUAGGAGCAGCCGAAAGGCUGC

[001119]SEQ ID NO:894 – PNPLA3 oligonucleotide 59 guide (antisense) strand
UCCUAAUGGGUAGCAAGUUGGG

[001120]SEQ ID NO:895 – PNPLA3 oligonucleotide 60 passenger (sense) strand
CUUGCUACCCAUUAGGAUAAGCAGCCGAAAGGCUGC

[001121]SEQ ID NO:896 – PNPLA3 oligonucleotide 60 guide (antisense) strand
UUAUCCUAAUGGGUAGCAAGGG

[001122]SEQ ID NO:897 – PNPLA3 oligonucleotide 61 passenger (sense) strand
UGCUACCCAUUAGGAUAAUAGCAGCCGAAAGGCUGC

[001123]SEQ ID NO:898 – PNPLA3 oligonucleotide 61 guide (antisense) strand
UAUUAUCCUAAUGGGUAGCAGG

[001124]SEQ ID NO:899 – PNPLA3 oligonucleotide 62 passenger (sense) strand
AUUAGGAUAAUGUCUUAUGAGCAGCCGAAAGGCUGC

[001125]SEQ ID NO:900 – PNPLA3 oligonucleotide 62 guide (antisense) strand
UCAUAAGACAUUAUCCUAAUGG

[001126]SEQ ID NO:901 – PNPLA3 oligonucleotide 63 passenger (sense) strand
UUAGGAUAAUGUCUUAUGUAGCAGCCGAAAGGCUGC

[001127]SEQ ID NO:902 – PNPLA3 oligonucleotide 63 guide (antisense) strand
UACAUAAGACAUUAUCCUAAGG

[001128]SEQ ID NO:903 – PNPLA3 oligonucleotide 64 passenger (sense) strand
UGCGAUUGUCCAGAGACUGAGCAGCCGAAAGGCUGC

[001129]SEQ ID NO:904 – PNPLA3 oligonucleotide 64 guide (antisense) strand
UCAGUCUCUGGACAAUCGCAGG

[001130]SEQ ID NO:905 – PNPLA3 oligonucleotide 65 passenger (sense) strand
CGAUUGUCCAGAGACUGGUAGCAGCCGAAAGGCUGC

[001131]SEQ ID NO:906 – PNPLA3 oligonucleotide 65 guide (antisense) strand
UACCAGUCUCUGGACAAUCGGG

[001132]SEQ ID NO:907 – PNPLA3 oligonucleotide 66 passenger (sense) strand
GUCCAGAGACUGGUGACAUAGCAGCCGAAAGGCUGC

[001133]SEQ ID NO:908 – PNPLA3 oligonucleotide 66 guide (antisense) strand
UAUGUCACCAGUCUCUGGACGG

[001134]SEQ ID NO:909 – PNPLA3 oligonucleotide 67 passenger (sense) strand
AGAGACUGGUGACAUGGCUAGCAGCCGAAAGGCUGC

[001135]SEQ ID NO:910 – PNPLA3 oligonucleotide 67 guide (antisense) strand
UAGCCAUGUCACCAGUCUCUGG

[001136]SEQ ID NO:911 – PNPLA3 oligonucleotide 68 passenger (sense) strand
ACUGGUGACAUGGCUUCCAAGCAGCCGAAAGGCUGC

[001137]SEQ ID NO:912 – PNPLA3 oligonucleotide 68 guide (antisense) strand
UUGGAAGCCAUGUCACCAGUGG

[001138]SEQ ID NO:913 – PNPLA3 oligonucleotide 69 passenger (sense) strand
CUCCACCUUUCCCAGUUUUAGCAGCCGAAAGGCUGC

[001139]SEQ ID NO:914 – PNPLA3 oligonucleotide 69 guide (antisense) strand
UAAAACUGGGAAAGGUGGAGGG

[001140]SEQ ID NO:915 – PNPLA3 oligonucleotide 70 passenger (sense) strand
CACCUUUCCCAGUUUUUCAAGCAGCCGAAAGGCUGC

[001141]SEQ ID NO:916 – PNPLA3 oligonucleotide 70 guide (antisense) strand
UUGAAAAACUGGGAAAGGUGGG

[001142]SEQ ID NO:917 – PNPLA3 oligonucleotide 71 passenger (sense) strand
AGUUUUUCACUAGAGAAGAAGCAGCCGAAAGGCUGC

[001143]SEQ ID NO:918 – PNPLA3 oligonucleotide 71 guide (antisense) strand
UUCUUCUCUAGUGAAAAACUGG

[001144]SEQ ID NO:919 – PNPLA3 oligonucleotide 72 passenger (sense) strand
AGCAGAUUCUUUCAGAGGUAGCAGCCGAAAGGCUGC

[001145]SEQ ID NO:920 – PNPLA3 oligonucleotide 72 guide (antisense) strand
UACCUCUGAAAGAAUCUGCUGG

[001146]SEQ ID NO:921 – PNPLA3 oligonucleotide 73 passenger (sense) strand
GCAGAUUCUUUCAGAGGUGAGCAGCCGAAAGGCUGC

[001147]SEQ ID NO:922 – PNPLA3 oligonucleotide 73 guide (antisense) strand

UCACCUCUGAAAGAAUCUGCGG

[001148]SEQ ID NO:923 – PNPLA3 oligonucleotide 74 passenger (sense) strand
AGAUUCUUUCAGAGGUGCUAGCAGCCGAAAGGCUGC

[001149]SEQ ID NO:924 – PNPLA3 oligonucleotide 74 guide (antisense) strand
UAGCACCUCUGAAAGAAUCUGG

[001150]SEQ ID NO:925 – PNPLA3 oligonucleotide 75 passenger (sense) strand
AGGUGCUAAAGUUUCCCAUAGCAGCCGAAAGGCUGC

[001151]SEQ ID NO:926 – PNPLA3 oligonucleotide 75 guide (antisense) strand
UAUGGGAAACUUUAGCACCUGG

[001152]SEQ ID NO:927 – PNPLA3 oligonucleotide 76 passenger (sense) strand
AAAGUUUCCCAUCUUUGUGAGCAGCCGAAAGGCUGC

[001153]SEQ ID NO:928 – PNPLA3 oligonucleotide 76 guide (antisense) strand
UCACAAAGAUGGGAAACUUUGG

[001154]SEQ ID NO:929 – PNPLA3 oligonucleotide 77 passenger (sense) strand
AGUUUCCCAUCUUUGUGCAAGCAGCCGAAAGGCUGC

[001155]SEQ ID NO:930 – PNPLA3 oligonucleotide 77 guide (antisense) strand
UUGCACAAAGAUGGGAAACUGG

[001156]SEQ ID NO:931 – PNPLA3 oligonucleotide 78 passenger (sense) strand
AGCCUCUGAGCUGAGUUGGAGCAGCCGAAAGGCUGC

[001157]SEQ ID NO:932 – PNPLA3 oligonucleotide 78 guide (antisense) strand
UCCAACUCAGCUCAGAGGCUGG

[001158]SEQ ID NO:933 – PNPLA3 oligonucleotide 79 passenger (sense) strand
GCCUCUGAGCUGAGUUGGUAGCAGCCGAAAGGCUGC

[001159]SEQ ID NO:934 – PNPLA3 oligonucleotide 79 guide (antisense) strand
UACCAACUCAGCUCAGAGGCGG

[001160]SEQ ID NO:935 – PNPLA3 oligonucleotide 80 passenger (sense) strand
CCUCUGAGCUGAGUUGGUUAGCAGCCGAAAGGCUGC

[001161] SEQ ID NO:936 – PNPLA3 oligonucleotide 80 guide (antisense) strand
UAACCAACUCAGCUCAGAGGGG

[001162] SEQ ID NO:937 – PNPLA3 oligonucleotide 81 passenger (sense) strand
CUCUGAGCUGAGUUGGUUUAGCAGCCGAAAGGCUGC

[001163]SEQ ID NO:938 – PNPLA3 oligonucleotide 81 guide (antisense) strand
UAAACCAACUCAGCUCAGAGGG

[001164]SEQ ID NO:939 – PNPLA3 oligonucleotide 82 passenger (sense) strand
UCUGAGCUGAGUUGGUUUUAGCAGCCGAAAGGCUGC

[001165]SEQ ID NO:940 – PNPLA3 oligonucleotide 82 guide (antisense) strand
UAAAACCAACUCAGCUCAGAGG

[001166]SEQ ID NO:941 – PNPLA3 oligonucleotide 83 passenger (sense) strand
UGAGCUGAGUUGGUUUUAUAGCAGCCGAAAGGCUGC

[001167]SEQ ID NO:942 – PNPLA3 oligonucleotide 83 guide (antisense) strand
UAUAAAACCAACUCAGCUCAGG

[001168]SEQ ID NO:943 – PNPLA3 oligonucleotide 84 passenger (sense) strand
UGAGUUGGUUUUAUGAAAAAGCAGCCGAAAGGCUGC

[001169]SEQ ID NO:944 – PNPLA3 oligonucleotide 84 guide (antisense) strand
UUUUUCAUAAAACCAACUCAGG

[001170]SEQ ID NO:945 – PNPLA3 oligonucleotide 85 passenger (sense) strand
GAGUUGGUUUUAUGAAAAGAGCAGCCGAAAGGCUGC

[001171]SEQ ID NO:946 – PNPLA3 oligonucleotide 85 guide (antisense) strand
UCUUUUCAUAAAACCAACUCGG

[001172]SEQ ID NO:947 – PNPLA3 oligonucleotide 86 passenger (sense) strand
UUGGUUUUAUGAAAAGCUAAGCAGCCGAAAGGCUGC

[001173]SEQ ID NO:948 – PNPLA3 oligonucleotide 86 guide (antisense) strand
UUAGCUUUUCAUAAAACCAAGG

[001174]SEQ ID NO:949 – PNPLA3 oligonucleotide 87 passenger (sense) strand
UGGUUUUAUGAAAAGCUAGAGCAGCCGAAAGGCUGC

[001175]SEQ ID NO:950 – PNPLA3 oligonucleotide 87 guide (antisense) strand
UCUAGCUUUUCAUAAAACCAGG

[001176]SEQ ID NO:951 – PNPLA3 oligonucleotide 88 passenger (sense) strand
GGUUUUAUGAAAAGCUAGGAGCAGCCGAAAGGCUGC

[001177]SEQ ID NO:952 – PNPLA3 oligonucleotide 88 guide (antisense) strand
UCCUAGCUUUUCAUAAAACCGG

[001178]SEQ ID NO:953 – PNPLA3 oligonucleotide 89 passenger (sense) strand
UUUUAUGAAAAGCUAGGAAAGCAGCCGAAAGGCUGC

[001179]SEQ ID NO:954 – PNPLA3 oligonucleotide 89 guide (antisense) strand

UUUCCUAGCUUUUCAUAAAAGG

[001180]SEQ ID NO:955 – PNPLA3 oligonucleotide 90 passenger (sense) strand
UAUGAAAAGCUAGGAAGCAAGCAGCCGAAAGGCUGC

[001181]SEQ ID NO:956 – PNPLA3 oligonucleotide 90 guide (antisense) strand
UUGCUUCCUAGCUUUUCAUAGG

[001182]SEQ ID NO:957 – PNPLA3 oligonucleotide 91 passenger (sense) strand
AUGAAAAGCUAGGAAGCAAAGCAGCCGAAAGGCUGC

[001183]SEQ ID NO:958 – PNPLA3 oligonucleotide 91 guide (antisense) strand
UUUGCUUCCUAGCUUUUCAUGG

[001184]SEQ ID NO:959 – PNPLA3 oligonucleotide 92 passenger (sense) strand
CCAGCACUUAACUCUAAUAAGCAGCCGAAAGGCUGC

[001185]SEQ ID NO:960 – PNPLA3 oligonucleotide 92 guide (antisense) strand
UUAUUAGAGUUAAGUGCUGGGG

[001186]SEQ ID NO:961 – PNPLA3 oligonucleotide 93 passenger (sense) strand
CAGCACUUAACUCUAAUACAGCAGCCGAAAGGCUGC

[001187]SEQ ID NO:962 – PNPLA3 oligonucleotide 93 guide (antisense) strand
UGUAUUAGAGUUAAGUGCUGGG

[001188]SEQ ID NO:963 – PNPLA3 oligonucleotide 94 passenger (sense) strand
UAAUACAUCAGCAUGCGUUAGCAGCCGAAAGGCUGC

[001189]SEQ ID NO:964 – PNPLA3 oligonucleotide 94 guide (antisense) strand
UAACGCAUGCUGAUGUAUUAGG

[001190]SEQ ID NO:965 – PNPLA3 oligonucleotide 95 passenger (sense) strand
AAUACAUCAGCAUGCGUUAAGCAGCCGAAAGGCUGC

[001191]SEQ ID NO:966 – PNPLA3 oligonucleotide 95 guide (antisense) strand
UUAACGCAUGCUGAUGUAUUGG

[001192]SEQ ID NO:967 – PNPLA3 oligonucleotide 96 passenger (sense) strand
UGCGUUAAUUCAGCUGGUUAGCAGCCGAAAGGCUGC

[001193]SEQ ID NO:968 – PNPLA3 oligonucleotide 96 guide (antisense) strand
UAACCAGCUGAAUUAACGCAGG

[001194]SEQ ID NO:969 – PNPLA3 oligonucleotide 97 passenger (sense) strand
GCGUUAAUUCAGCUGGUUGAGCAGCCGAAAGGCUGC

[001195]SEQ ID NO:970 – PNPLA3 oligonucleotide 97 guide (antisense) strand
UCAACCAGCUGAAUUAACGCGG

[001196]SEQ ID NO:971 – PNPLA3 oligonucleotide 98 passenger (sense) strand
CGUUAAUUCAGCUGGUUGGAGCAGCCGAAAGGCUGC

[001197]SEQ ID NO:972 – PNPLA3 oligonucleotide 98 guide (antisense) strand
UCCAACCAGCUGAAUUAACGGG

[001198]SEQ ID NO:973 – PNPLA3 oligonucleotide 99 passenger (sense) strand
UUAAUUCAGCUGGUUGGGAAGCAGCCGAAAGGCUGC

[001199]SEQ ID NO:974 – PNPLA3 oligonucleotide 99 guide (antisense) strand
UUCCCAACCAGCUGAAUUAAGG

[001200]SEQ ID NO:975 – PNPLA3 oligonucleotide 100 passenger (sense) strand
UAAUUCAGCUGGUUGGGAAAGCAGCCGAAAGGCUGC

[001201]SEQ ID NO:976 – PNPLA3 oligonucleotide 100 guide (antisense) strand
UUUCCCAACCAGCUGAAUUAGG

[001202]SEQ ID NO:977 – PNPLA3 oligonucleotide 101 passenger (sense) strand
GCAGAGGGUCCCUUACUGAAGCAGCCGAAAGGCUGC

[001203]SEQ ID NO:978 – PNPLA3 oligonucleotide 101 guide (antisense) strand
UUCAGUAAGGGACCCUCUGCGG

[001204]SEQ ID NO:979 – PNPLA3 oligonucleotide 102 passenger (sense) strand
CUAUUAAUGGUCAGACUGUAGCAGCCGAAAGGCUGC

[001205]SEQ ID NO:980 – PNPLA3 oligonucleotide 102 guide (antisense) strand
UACAGUCUGACCAUUAAUAGGG

[001206]SEQ ID NO:981 – PNPLA3 oligonucleotide 103 passenger (sense) strand
UAUUAAUGGUCAGACUGUUAGCAGCCGAAAGGCUGC

[001207]SEQ ID NO:982 – PNPLA3 oligonucleotide 103 guide (antisense) strand
UAACAGUCUGACCAUUAAUAGG

[001208]SEQ ID NO:983 – PNPLA3 oligonucleotide 104 passenger (sense) strand
AUUAAUGGUCAGACUGUUCAGCAGCCGAAAGGCUGC

[001209]SEQ ID NO:984 – PNPLA3 oligonucleotide 104 guide (antisense) strand
UGAACAGUCUGACCAUUAAUGG

[001210]SEQ ID NO:985 – PNPLA3 oligonucleotide 105 passenger (sense) strand
UUAAUGGUCAGACUGUUCCAGCAGCCGAAAGGCUGC

[001211]SEQ ID NO:986 – PNPLA3 oligonucleotide 105 guide (antisense) strand
UGGAACAGUCUGACCAUUAAGG

[001212]SEQ ID NO:987 – PNPLA3 oligonucleotide 106 passenger (sense) strand
UAAUGGUCAGACUGUUCCAAGCAGCCGAAAGGCUGC

[001213]SEQ ID NO:988 – PNPLA3 oligonucleotide 106 guide (antisense) strand
UUGGAACAGUCUGACCAUUAGG

[001214]SEQ ID NO:989 – PNPLA3 oligonucleotide 107 passenger (sense) strand
AAUGGUCAGACUGUUCCAGAGCAGCCGAAAGGCUGC

[001215]SEQ ID NO:990 – PNPLA3 oligonucleotide 107 guide (antisense) strand
UCUGGAACAGUCUGACCAUUGG

[001216]SEQ ID NO:991 – PNPLA3 oligonucleotide 108 passenger (sense) strand
AGAACACCUUUUUCACCUAAGCAGCCGAAAGGCUGC

[001217]SEQ ID NO:992 – PNPLA3 oligonucleotide 108 guide (antisense) strand
UUAGGUGAAAAAGGUGUUCUGG

[001218]SEQ ID NO:993 – PNPLA3 oligonucleotide 109 passenger (sense) strand
GAACACCUUUUUCACCUAAAGCAGCCGAAAGGCUGC

[001219]SEQ ID NO:994 – PNPLA3 oligonucleotide 109 guide (antisense) strand
UUUAGGUGAAAAAGGUGUUCGG

[001220]SEQ ID NO:995 – PNPLA3 oligonucleotide 110 passenger (sense) strand
AACACCUUUUUCACCUAACAGCAGCCGAAAGGCUGC

[001221]SEQ ID NO:996 – PNPLA3 oligonucleotide 110 guide (antisense) strand
UGUUAGGUGAAAAAGGUGUUGG

[001222]SEQ ID NO:997 – PNPLA3 oligonucleotide 111 passenger (sense) strand
ACACCUUUUUCACCUAACUAGCAGCCGAAAGGCUGC

[001223]SEQ ID NO:998 – PNPLA3 oligonucleotide 111 guide (antisense) strand
UAGUUAGGUGAAAAAGGUGUGG

[001224]SEQ ID NO:999 – PNPLA3 oligonucleotide 112 passenger (sense) strand
CACCUUUUUCACCUAACUAAGCAGCCGAAAGGCUGC

[001225]SEQ ID NO:1000 – PNPLA3 oligonucleotide 112 guide (antisense) strand
UUAGUUAGGUGAAAAAGGUGGG

[001226]SEQ ID NO:1001 – PNPLA3 oligonucleotide 113 passenger (sense) strand

ACCUUUUUCACCUAACUAAAGCAGCCGAAAGGCUGC

[001227]SEQ ID NO:1002 – PNPLA3 oligonucleotide 113 guide (antisense) strand
UUUAGUUAGGUGAAAAAGGUGG

[001228]SEQ ID NO:1003 – PNPLA3 oligonucleotide 114 passenger (sense) strand
CUUUUUCACCUAACUAAAAAGCAGCCGAAAGGCUGC

[001229]SEQ ID NO:1004 – PNPLA3 oligonucleotide 114 guide (antisense) strand
UUUUUAGUUAGGUGAAAAAGGG

[001230]SEQ ID NO:1005 – PNPLA3 oligonucleotide 115 passenger (sense) strand
UUUUCACCUAACUAAAAUAAGCAGCCGAAAGGCUGC

[001231]SEQ ID NO:1006 – PNPLA3 oligonucleotide 115 guide (antisense) strand
UUAUUUUAGUUAGGUGAAAAGG

[001232]SEQ ID NO:1007 – PNPLA3 oligonucleotide 116 passenger (sense) strand
UUCACCUAACUAAAAUAAUAGCAGCCGAAAGGCUGC

[001233]SEQ ID NO:1008 – PNPLA3 oligonucleotide 116 guide (antisense) strand
UAUUAUUUUAGUUAGGUGAAGG

[001234]SEQ ID NO:1009 – PNPLA3 oligonucleotide 117 passenger (sense) strand
UCACCUAACUAAAAUAAUGAGCAGCCGAAAGGCUGC

[001235]SEQ ID NO:1010 – PNPLA3 oligonucleotide 117 guide (antisense) strand
UCAUUAUUUUAGUUAGGUGAGG

[001236]SEQ ID NO:1011 – PNPLA3 oligonucleotide 118 passenger (sense) strand
CACCUAACUAAAAUAAUGUAGCAGCCGAAAGGCUGC

[001237]SEQ ID NO:1012 – PNPLA3 oligonucleotide 118 guide (antisense) strand
UACAUUAUUUUAGUUAGGUGGG

[001238]SEQ ID NO:1013 – PNPLA3 oligonucleotide 119 passenger (sense) strand
ACCUAACUAAAAUAAUGUUAGCAGCCGAAAGGCUGC

[001239]SEQ ID NO:1014 – PNPLA3 oligonucleotide 119 guide (antisense) strand
UAACAUUAUUUUAGUUAGGUGG

[001240]SEQ ID NO:1015 – PNPLA3 oligonucleotide 120 passenger (sense) strand
CCUAACUAAAAUAAUGUUUAGCAGCCGAAAGGCUGC

[001241]SEQ ID NO:1016 – PNPLA3 oligonucleotide 120 guide (antisense) strand
UAAACAUUAUUUUAGUUAGGGG

[001242]SEQ ID NO:1017 – PNPLA3 oligonucleotide 121 passenger (sense) strand
CUAACUAAAAUAAUGUUUAAGCAGCCGAAAGGCUGC

[001243]SEQ ID NO:1018 – PNPLA3 oligonucleotide 121 guide (antisense) strand
UUAAACAUUAUUUUAGUUAGGG

[001244]SEQ ID NO:1019 – PNPLA3 oligonucleotide 122 passenger (sense) strand
UAACUAAAAUAAUGUUUAAAGCAGCCGAAAGGCUGC

[001245]SEQ ID NO:1020 – PNPLA3 oligonucleotide 122 guide (antisense) strand
UUUAAACAUUAUUUUAGUUAGG

[001246]SEQ ID NO:1021 – PNPLA3 oligonucleotide 123 passenger (sense) strand
AACUAAAAUAAUGUUUAAAAGCAGCCGAAAGGCUGC

[001247]SEQ ID NO:1022 – PNPLA3 oligonucleotide 123 guide (antisense) strand
UUUUAAACAUUAUUUUAGUUGG

[001248]SEQ ID NO:1023 – PNPLA3 oligonucleotide 124 passenger (sense) strand
ACUAAAAUAAUGUUUAAAGAGCAGCCGAAAGGCUGC

[001249]SEQ ID NO:1024 – PNPLA3 oligonucleotide 124 guide (antisense) strand
UCUUUAAACAUUAUUUUAGUGG

[001250]SEQ ID NO:1025 – PNPLA3 oligonucleotide 125 passenger (sense) strand
CUAAAAUAAUGUUUAAAGAAGCAGCCGAAAGGCUGC

[001251]SEQ ID NO:1026 – PNPLA3 oligonucleotide 125 guide (antisense) strand
UUCUUUAAACAUUAUUUUAGGG

[001252]SEQ ID NO:1027 – PNPLA3 oligonucleotide 126 passenger (sense) strand
UAAAAUAAUGUUUAAAGAGAGCAGCCGAAAGGCUGC

[001253]SEQ ID NO:1028 – PNPLA3 oligonucleotide 126 guide (antisense) strand
UCUCUUUAAACAUUAUUUUAGG

[001254]SEQ ID NO:1029 – PNPLA3 oligonucleotide 127 passenger (sense) strand
AAGAGUUUUGUAUAAAAAUAGCAGCCGAAAGGCUGC

[001255]SEQ ID NO:1030 – PNPLA3 oligonucleotide 127 guide (antisense) strand
UAUUUUUAUACAAAACUCUUGG

[001256]SEQ ID NO:1031 – PNPLA3 oligonucleotide 128 passenger (sense) strand
GUUUUGUAUAAAAAUGUAAAGCAGCCGAAAGGCUGC

[001257]SEQ ID NO:1032 – PNPLA3 oligonucleotide 128 guide (antisense) strand
UUUACAUUUUUAUACAAAACGG

[001258]SEQ ID NO:1033 – PNPLA3 oligonucleotide 129 passenger (sense) strand

UUGUAUAAAAAUGUAAGGAAGCAGCCGAAAGGCUGC

[001259]SEQ ID NO:1034 – PNPLA3 oligonucleotide 129 guide (antisense) strand
UUCCUUACAUUUUUAUACAAGG

[001260]SEQ ID NO:1035 – PNPLA3 oligonucleotide 130 passenger (sense) strand
UGUAUAAAAAUGUAAGGAAAGCAGCCGAAAGGCUGC

[001261]SEQ ID NO:1036 – PNPLA3 oligonucleotide 130 guide (antisense) strand
UUUCCUUACAUUUUUAUACAGG

[001262]SEQ ID NO:1037 – PNPLA3 oligonucleotide 131 passenger (sense) strand
GUAUAAAAAUGUAAGGAAGAGCAGCCGAAAGGCUGC

[001263]SEQ ID NO:1038 – PNPLA3 oligonucleotide 131 guide (antisense) strand
UCUUCCUUACAUUUUUAUACGG

[001264]SEQ ID NO:1039 – PNPLA3 oligonucleotide 132 passenger (sense) strand
AUGUAAGGAAGCGUUGUUAAGCAGCCGAAAGGCUGC

[001265]SEQ ID NO:1040 – PNPLA3 oligonucleotide 132 guide (antisense) strand
UUAACAACGCUUCCUUACAUGG

[001266]SEQ ID NO:1041 – PNPLA3 oligonucleotide 133 passenger (sense) strand
UUUUGUAUUAUGUGAAUCAAGCAGCCGAAAGGCUGC

[001267]SEQ ID NO:1042 – PNPLA3 oligonucleotide 133 guide (antisense) strand
UUGAUUCACAUAAUACAAAAGG

[001268]SEQ ID NO:1043 – PNPLA3 oligonucleotide 134 passenger (sense) strand
UUUGUAUUAUGUGAAUCAGAGCAGCCGAAAGGCUGC

[001269]SEQ ID NO:1044 – PNPLA3 oligonucleotide 134 guide (antisense) strand
UCUGAUUCACAUAAUACAAAGG

[001270]SEQ ID NO:1045 – PNPLA3 oligonucleotide 135 passenger (sense) strand
UUGUAUUAUGUGAAUCAGUAGCAGCCGAAAGGCUGC

[001271]SEQ ID NO:1046 – PNPLA3 oligonucleotide 135 guide (antisense) strand
UACUGAUUCACAUAAUACAAGG

[001272]SEQ ID NO:1047 – PNPLA3 oligonucleotide 136 passenger (sense) strand
GUAUUAUGUGAAUCAGUGAAGCAGCCGAAAGGCUGC

[001273]SEQ ID NO:1048 – PNPLA3 oligonucleotide 136 guide (antisense) strand
UUCACUGAUUCACAUAAUACGG

[001274]SEQ ID NO:1049 – PNPLA3 oligonucleotide 137 passenger (sense) strand
UAUUAUGUGAAUCAGUGAGAGCAGCCGAAAGGCUGC

[001275]SEQ ID NO:1050 – PNPLA3 oligonucleotide 137 guide (antisense) strand
UCUCACUGAUUCACAUAAUAGG

[001276]SEQ ID NO:1051 – PNPLA3 oligonucleotide 138 passenger (sense) strand
AUUAUGUGAAUCAGUGAGAAGCAGCCGAAAGGCUGC

[001277]SEQ ID NO:1052 – PNPLA3 oligonucleotide 138 guide (antisense) strand
UUCUCACUGAUUCACAUAAUGG

[001278]SEQ ID NO:1053 – PNPLA3 oligonucleotide 139 passenger (sense) strand
UUAUGUGAAUCAGUGAGAUAGCAGCCGAAAGGCUGC

[001279]SEQ ID NO:1054 – PNPLA3 oligonucleotide 139 guide (antisense) strand
UAUCUCACUGAUUCACAUAAGG

[001280]SEQ ID NO:1055 – PNPLA3 oligonucleotide 140 passenger (sense) strand
UAUGUGAAUCAGUGAGAUGAGCAGCCGAAAGGCUGC

[001281]SEQ ID NO:1056 – PNPLA3 oligonucleotide 140 guide (antisense) strand
UCAUCUCACUGAUUCACAUAGG

[001282]SEQ ID NO:1057 – PNPLA3 oligonucleotide 141 passenger (sense) strand
AUGUGAAUCAGUGAGAUGUAGCAGCCGAAAGGCUGC

[001283]SEQ ID NO:1058 – PNPLA3 oligonucleotide 141 guide (antisense) strand
UACAUCUCACUGAUUCACAUGG

[001284]SEQ ID NO:1059 – PNPLA3 oligonucleotide 142 passenger (sense) strand
UGUGAAUCAGUGAGAUGUUAGCAGCCGAAAGGCUGC

[001285]SEQ ID NO:1060 – PNPLA3 oligonucleotide 142 guide (antisense) strand
UAACAUCUCACUGAUUCACAGG

[001286]SEQ ID NO:1061 – PNPLA3 oligonucleotide 143 passenger (sense) strand
GUGAAUCAGUGAGAUGUUAAGCAGCCGAAAGGCUGC

[001287]SEQ ID NO:1062 – PNPLA3 oligonucleotide 143 guide (antisense) strand
UUAACAUCUCACUGAUUCACGG

[001288]SEQ ID NO:1063 – PNPLA3 oligonucleotide 144 passenger (sense) strand
GUGAGAUGUUAGUAGAAUAAGCAGCCGAAAGGCUGC

[001289]SEQ ID NO:1064 – PNPLA3 oligonucleotide 144 guide (antisense) strand
UUAUUCUACUAACAUCUCACGG

[001290]SEQ ID NO:1065 – PNPLA3 oligonucleotide 145 passenger (sense) strand

UUUCUAUUUAUGCAUUUGAAGCAGCCGAAAGGCUGC

[001291]SEQ ID NO:1066 – PNPLA3 oligonucleotide 145 guide (antisense) strand
UUCAAAUGCAUAAAUAGAAAGG

[001292]SEQ ID NO:1067 – PNPLA3 oligonucleotide 146 passenger (sense) strand
CUAUUUAUGCAUUUGAGUAAGCAGCCGAAAGGCUGC

[001293]SEQ ID NO:1068 – PNPLA3 oligonucleotide 146 guide (antisense) strand
UUACUCAAAUGCAUAAAUAGGG

[001294]SEQ ID NO:1069 – PNPLA3 oligonucleotide 147 passenger (sense) strand
UGCUCAAACUGUUAAAUGUAGCAGCCGAAAGGCUGC

[001295]SEQ ID NO:1070 – PNPLA3 oligonucleotide 147 guide (antisense) strand
UACAUUUAACAGUUUGAGCAGG

[001296]SEQ ID NO:1071 – PNPLA3 oligonucleotide 148 passenger (sense) strand
GCUCAAACUGUUAAAUGUUAGCAGCCGAAAGGCUGC

[001297]SEQ ID NO:1072 – PNPLA3 oligonucleotide 148 guide (antisense) strand
UAACAUUUAACAGUUUGAGCGG

[001298]SEQ ID NO:1073 – PNPLA3 oligonucleotide 149 passenger (sense) strand
CUCAAACUGUUAAAUGUUGAGCAGCCGAAAGGCUGC

[001299]SEQ ID NO:1074 – PNPLA3 oligonucleotide 149 guide (antisense) strand
UCAACAUUUAACAGUUUGAGGG

[001300]SEQ ID NO:1075 – PNPLA3 oligonucleotide 150 passenger (sense) strand
UCAAACUGUUAAAUGUUGGAGCAGCCGAAAGGCUGC

[001301]SEQ ID NO:1076 – PNPLA3 oligonucleotide 150 guide (antisense) strand
UCCAACAUUUAACAGUUUGAGG

[001302]SEQ ID NO:1077 – PNPLA3 oligonucleotide 151 passenger (sense) strand
CAAACUGUUAAAUGUUGGAAGCAGCCGAAAGGCUGC

[001303]SEQ ID NO:1078 – PNPLA3 oligonucleotide 151 guide (antisense) strand
UUCCAACAUUUAACAGUUUGGG

[001304]SEQ ID NO:1079 – PNPLA3 oligonucleotide 152 passenger (sense) strand
AAACUGUUAAAUGUUGGAAAGCAGCCGAAAGGCUGC

[001305]SEQ ID NO:1080 – PNPLA3 oligonucleotide 152 guide (antisense) strand
UUUCCAACAUUUAACAGUUUGG

[001306]SEQ ID NO:1081 – PNPLA3 oligonucleotide 153 passenger (sense) strand
AACUGUUAAAUGUUGGAAAAGCAGCCGAAAGGCUGC

[001307]SEQ ID NO:1082 – PNPLA3 oligonucleotide 153 guide (antisense) strand
UUUUCCAACAUUUAACAGUUGG

[001308]SEQ ID NO:1083 – PNPLA3 oligonucleotide 154 passenger (sense) strand
UGUUAAAUGUUGGAAAAGAAGCAGCCGAAAGGCUGC

[001309]SEQ ID NO:1084 – PNPLA3 oligonucleotide 154 guide (antisense) strand
UUCUUUUCCAACAUUUAACAGG

[001310]SEQ ID NO:1085 – PNPLA3 oligonucleotide 155 passenger (sense) strand
GUUAAAUGUUGGAAAAGAAAGCAGCCGAAAGGCUGC

[001311]SEQ ID NO:1086 – PNPLA3 oligonucleotide 155 guide (antisense) strand
UUUCUUUUCCAACAUUUAACGG

[001312]SEQ ID NO:1087 – PNPLA3 oligonucleotide 156 passenger (sense) strand
UUAAAUGUUGGAAAAGAAAAGCAGCCGAAAGGCUGC

[001313]SEQ ID NO:1088 – PNPLA3 oligonucleotide 156 guide (antisense) strand
UUUUCUUUUCCAACAUUUAAGG

[001314]SEQ ID NO:1089 – PNPLA3 oligonucleotide 157 passenger (sense) strand
UAAAUGUUGGAAAAGAAAGAGCAGCCGAAAGGCUGC

[001315]SEQ ID NO:1090 – PNPLA3 oligonucleotide 157 guide (antisense) strand
UCUUUCUUUUCCAACAUUUAGG

[001316]SEQ ID NO:1091 – PNPLA3 oligonucleotide 158 passenger (sense) strand
AGAAAAGAGGCUACUUGUGAGCAGCCGAAAGGCUGC

[001317]SEQ ID NO:1092 – PNPLA3 oligonucleotide 158 guide (antisense) strand
UCACAAGUAGCCUCUUUUCUGG

[001318]SEQ ID NO:1093 – PNPLA3 oligonucleotide 159 passenger (sense) strand
GAAAAGAGGCUACUUGUGAAGCAGCCGAAAGGCUGC

[001319]SEQ ID NO:1094 – PNPLA3 oligonucleotide 159 guide (antisense) strand
UUCACAAGUAGCCUCUUUUCGG

[001320]SEQ ID NO:1095 – PNPLA3 oligonucleotide 160 passenger (sense) strand
AAAAGAGGCUACUUGUGAAAGCAGCCGAAAGGCUGC

[001321]SEQ ID NO:1096 – PNPLA3 oligonucleotide 160 guide (antisense) strand
UUUCACAAGUAGCCUCUUUUGG

[001322]SEQ ID NO:1097 – PNPLA3 oligonucleotide 161 passenger (sense) strand

AGAGGCUACUUGUGAAAAUAGCAGCCGAAAGGCUGC

[001323]SEQ ID NO:1098 – PNPLA3 oligonucleotide 161 guide (antisense) strand
UAUUUUCACAAGUAGCCUCUGG

[001324]SEQ ID NO:1099 – PNPLA3 oligonucleotide 162 passenger (sense) strand
GAGGCUACUUGUGAAAAUAAGCAGCCGAAAGGCUGC

[001325]SEQ ID NO:1100 – PNPLA3 oligonucleotide 162 guide (antisense) strand
UUAUUUUCACAAGUAGCCUCGG

[001326]SEQ ID NO:1101 – PNPLA3 oligonucleotide 163 passenger (sense) strand
AAAGUUACAAGUUUCUUUUAGCAGCCGAAAGGCUGC

[001327]SEQ ID NO:1102 – PNPLA3 oligonucleotide 163 guide (antisense) strand
UAAAAGAAACUUGUAACUUUGG

[001328]SEQ ID NO:1103 – PNPLA3 oligonucleotide 164 passenger (sense) strand
CAACAGUAUUUUCUAAUAAAGCAGCCGAAAGGCUGC

[001329]SEQ ID NO:1104 – PNPLA3 oligonucleotide 164 guide (antisense) strand
UUUAUUAGAAAAUACUGUUGGG

[001330]SEQ ID NO:1105 – PNPLA3 oligonucleotide 165 passenger (sense) strand
AACAGUAUUUUCUAAUAACAGCAGCCGAAAGGCUGC

[001331]SEQ ID NO:1106 – PNPLA3 oligonucleotide 165 guide (antisense) strand
UGUUAUUAGAAAAUACUGUUGG

[001332]SEQ ID NO:1107 – PNPLA3 oligonucleotide 166 passenger (sense) strand
ACAGUAUUUUCUAAUAACCAGCAGCCGAAAGGCUGC

[001333]SEQ ID NO:1108 – PNPLA3 oligonucleotide 166 guide (antisense) strand
UGGUUAUUAGAAAAUACUGUGG

[001334]SEQ ID NO:1109 – PNPLA3 oligonucleotide 167 passenger (sense) strand
CAGUAUUUUCUAAUAACCAAGCAGCCGAAAGGCUGC

[001335]SEQ ID NO:1110 – PNPLA3 oligonucleotide 167 guide (antisense) strand
UUGGUUAUUAGAAAAUACUGGG

[001336]SEQ ID NO:1111 – PNPLA3 oligonucleotide 168 passenger (sense) strand
UUGUGAUUGUUAUCAGGAAAGCAGCCGAAAGGCUGC

[001337]SEQ ID NO:1112 – PNPLA3 oligonucleotide 168 guide (antisense) strand
UUUCCUGAUAACAAUCACAAGG

[001338]SEQ ID NO:1113 – PNPLA3 oligonucleotide 169 passenger (sense) strand
UGUGAUUGUUAUCAGGAAAAGCAGCCGAAAGGCUGC

[001339]SEQ ID NO:1114 – PNPLA3 oligonucleotide 169 guide (antisense) strand
UUUUCCUGAUAACAAUCACAGG

[001340]SEQ ID NO:1115 – PNPLA3 oligonucleotide 170 passenger (sense) strand
GUGAUUGUUAUCAGGAAAAAGCAGCCGAAAGGCUGC

[001341]SEQ ID NO:1116 – PNPLA3 oligonucleotide 170 guide (antisense) strand
UUUUUCCUGAUAACAAUCACGG

[001342]SEQ ID NO:1117 – PNPLA3 oligonucleotide 171 passenger (sense) strand
UGAUUGUUAUCAGGAAAAAAGCAGCCGAAAGGCUGC

[001343]SEQ ID NO:1118 – PNPLA3 oligonucleotide 171 guide (antisense) strand
UUUUUUCCUGAUAACAAUCAGG

[001344]SEQ ID NO:1119 – PNPLA3 oligonucleotide 172 passenger (sense) strand
GAUUGUUAUCAGGAAAAAAAGCAGCCGAAAGGCUGC

[001345]SEQ ID NO:1120 – PNPLA3 oligonucleotide 172 guide (antisense) strand
UUUUUUUCCUGAUAACAAUCGG

[001346]SEQ ID NO:1121 – PNPLA3 oligonucleotide 173 passenger (sense) strand
AUUGUUAUCAGGAAAAAAUAGCAGCCGAAAGGCUGC

[001347]SEQ ID NO:1122 – PNPLA3 oligonucleotide 173 guide (antisense) strand
UAUUUUUUCCUGAUAACAAUGG

[001348]SEQ ID NO:1123 – PNPLA3 oligonucleotide 174 passenger (sense) strand
UUGUUAUCAGGAAAAAAUAAGCAGCCGAAAGGCUGC

[001349]SEQ ID NO:1124 – PNPLA3 oligonucleotide 174 guide (antisense) strand
UUAUUUUUUCCUGAUAACAAGG

[001350]SEQ ID NO:1125 – PNPLA3 oligonucleotide 175 passenger (sense) strand
UGUUAUCAGGAAAAAAUAUAGCAGCCGAAAGGCUGC

[001351]SEQ ID NO:1126 – PNPLA3 oligonucleotide 175 guide (antisense) strand
UAUAUUUUUUCCUGAUAACAGG

[001352]SEQ ID NO:1127 – PNPLA3 oligonucleotide 176 passenger (sense) strand
GUUAUCAGGAAAAAAUAUAAGCAGCCGAAAGGCUGC

[001353]SEQ ID NO:1128 – PNPLA3 oligonucleotide 176 guide (antisense) strand
UUAUAUUUUUUCCUGAUAACGG

[001354]SEQ ID NO:1129 – PNPLA3 oligonucleotide 177 passenger (sense) strand

UUAUCAGGAAAAAAUAUAUAGCAGCCGAAAGGCUGC

[001355]SEQ ID NO:1130 – PNPLA3 oligonucleotide 177 guide (antisense) strand
UAUAUAUUUUUUCCUGAUAAGG

[001356]SEQ ID NO:1131 – PNPLA3 oligonucleotide 178 passenger (sense) strand
AGGAAAAAAUAUAUUAAAUAGCAGCCGAAAGGCUGC

[001357]SEQ ID NO:1132 – PNPLA3 oligonucleotide 178 guide (antisense) strand
UAUUUAAUAUAUUUUUUCCUGG

[001358]SEQ ID NO:1133 – PNPLA3 oligonucleotide 179 passenger (sense) strand
GGAAAAAAUAUAUUAAAUGAGCAGCCGAAAGGCUGC

[001359]SEQ ID NO:1134 – PNPLA3 oligonucleotide 179 guide (antisense) strand
UCAUUUAAUAUAUUUUUUCCGG

[001360]SEQ ID NO:1135 – PNPLA3 oligonucleotide 180 passenger (sense) strand
GAAAAAAUAUAUUAAAUGGAGCAGCCGAAAGGCUGC

[001361]SEQ ID NO:1136 – PNPLA3 oligonucleotide 180 guide (antisense) strand
UCCAUUUAAUAUAUUUUUUCGG

[001362]SEQ ID NO:1137 – PNPLA3 oligonucleotide 181 passenger (sense) strand
AUUUUCUUUCUGCUUUUAAAGCAGCCGAAAGGCUGC

[001363]SEQ ID NO:1138 – PNPLA3 oligonucleotide 181 guide (antisense) strand
UUUAAAAGCAGAAAGAAAAUGG

[001364]SEQ ID NO:1139 – PNPLA3 oligonucleotide 182 passenger (sense) strand
UCUUUCUGCUUUUAAAAAUAGCAGCCGAAAGGCUGC

[001365]SEQ ID NO:1140 – PNPLA3 oligonucleotide 182 guide (antisense) strand
UAUUUUUAAAAGCAGAAAGAGG

[001366]SEQ ID NO:1141 – PNPLA3 oligonucleotide 183 passenger (sense) strand
UAAGGAAAUCAGGAAGUGUAGCAGCCGAAAGGCUGC

[001367]SEQ ID NO:1142 – PNPLA3 oligonucleotide 183 guide (antisense) strand
UACACUUCCUGAUUUCCUUAGG

[001368]SEQ ID NO:1143 – PNPLA3 oligonucleotide 184 passenger (sense) strand
AAGGAAAUCAGGAAGUGUAAGCAGCCGAAAGGCUGC

[001369]SEQ ID NO:1144 – PNPLA3 oligonucleotide 184 guide (antisense) strand
UUACACUUCCUGAUUUCCUUGG

[001370]SEQ ID NO:1145 – PNPLA3 oligonucleotide 185 passenger (sense) strand
GGAAAUCAGGAAGUGUAAUAGCAGCCGAAAGGCUGC

[001371]SEQ ID NO:1146 – PNPLA3 oligonucleotide 185 guide (antisense) strand
UAUUACACUUCCUGAUUUCCGG

[001372]SEQ ID NO:1147 – PNPLA3 oligonucleotide 186 passenger (sense) strand
CCACACCCAGCUAGUUUUUAGCAGCCGAAAGGCUGC

[001373]SEQ ID NO:1148 – PNPLA3 oligonucleotide 186 guide (antisense) strand
UAAAAACUAGCUGGGUGUGGGG

[001374]SEQ ID NO:1149 – PNPLA3 oligonucleotide 187 passenger (sense) strand
CACACCCAGCUAGUUUUUUAGCAGCCGAAAGGCUGC

[001375]SEQ ID NO:1150 – PNPLA3 oligonucleotide 187 guide (antisense) strand
UAAAAAACUAGCUGGGUGUGGG

[001376]SEQ ID NO:1151 – PNPLA3 oligonucleotide 188 passenger (sense) strand
CUAGGAUUACAGGUGUGAGAGCAGCCGAAAGGCUGC

[001377]SEQ ID NO:1152 – PNPLA3 oligonucleotide 188 guide (antisense) strand
UCUCACACCUGUAAUCCUAGGG

[001378]SEQ ID NO:1153 – PNPLA3 oligonucleotide 189 passenger (sense) strand
AGAGUAUGAGCCUGAUUUUAGCAGCCGAAAGGCUGC

[001379]SEQ ID NO:1154 – PNPLA3 oligonucleotide 189 guide (antisense) strand
UAAAAUCAGGCUCAUACUCUGG

[001380]SEQ ID NO:1155 – PNPLA3 oligonucleotide 190 passenger (sense) strand
GAGUAUGAGCCUGAUUUUGAGCAGCCGAAAGGCUGC

[001381]SEQ ID NO:1156 – PNPLA3 oligonucleotide 190 guide (antisense) strand
UCAAAAUCAGGCUCAUACUCGG

[001382]SEQ ID NO:1157 – PNPLA3 oligonucleotide 191 passenger (sense) strand
CCCAUCUCUACUAAAAAAUAGCAGCCGAAAGGCUGC

[001383]SEQ ID NO:1158 – PNPLA3 oligonucleotide 191 guide (antisense) strand
UAUUUUUUAGUAGAGAUGGGGG

[001384]SEQ ID NO:1159 – PNPLA3 oligonucleotide 192 passenger (sense) strand
ACUUUCAGCAUGAGAAAAUAGCAGCCGAAAGGCUGC

[001385]SEQ ID NO:1160 – PNPLA3 oligonucleotide 192 guide (antisense) strand
UAUUUUCUCAUGCUGAAAGUGG

[001386]SEQ ID NO:1161 – PNPLA3 oligonucleotide 193 passenger (sense) strand
CUGAGCUGAGUUGGUUUUAGCAGCCGAAAGGCUGC

[001387]SEQ ID NO:1162 – PNPLA3 oligonucleotide 193 guide (antisense) strand
UUAAAACCAACUCAGCUCAGGG

[001388]SEQ ID NO:1163 – PNPLA3 oligonucleotide 194 passenger (sense) strand
GCUGAGUUGGUUUUAUGAAAGCAGCCGAAAGGCUGC

[001389]SEQ ID NO:1164 – PNPLA3 oligonucleotide 194 guide (sense) strand
UUUCAUAAAACCAACUCAGCGG

[001390]SEQ ID NO:1165 – PNPLA3 control passenger (sense) strand
CUGUUGAAUUUUGUAUUAUA

[001391]SEQ ID NO:1166 – PNPLA3 control guide (antisense) strand

UAUAAUACAAAAUUCAACAGGG

[001392]SEQ ID NO:1167 – Target Sequence 1
CAACGTACCCTTCATTGAT

[001393]SEQ ID NO:1168 – Target Sequence 2
TGAAAGACAAAGGTGGATA

[001394]SEQ ID NO:1169 – Target Sequence 3
TACATGAGCAAGATTTGCA

[001395]SEQ ID NO:1170 – Target Sequence 4
TGAGCAAGATTTGCAACTT

[001396]SEQ ID NO:1171 – Target Sequence 5
CTCTGAGCTGAGTTGGTTT

[001397]SEQ ID NO:1172 – Target Sequence 6
CTTTTTCACCTAACTAAAA

[001398]SEQ ID NO:1173 – Target Sequence 7
TTCACCTAACTAAAATAAT

[001399]SEQ ID NO:1174 – Target Sequence 8
CTAACTAAAATAATGTTTA

[001400]SEQ ID NO:1175 – Target Sequence 9
CTGAGCTGAGTTGGTTTTA

[001401]SEQ ID NO:1176 – Target Sequence 10
GCTGAGTTGGTTTTATGAA

SEQ ID NO:1177 – Artificial Sequence

GCAGCCGAAAGGCUGC

Table A:

No.	SEQ ID NO. and Mod. Pattern	DP Number	Modified Oligonucleotide
1	1170 SM1224 /ASM1508	DP17736 P:DP17735G	[mCs][mC][fC][mA][mU][mU][mA][fG][fG][fA][mU][fA][fA][mU][mG][mU][fC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1178) [MePhosphonate-4O-mUs][fAs][fAs][mG][fA][mC][fA][fU][mU][fA][mU][fC][mC][fU][mA][fA][mU][mG][fG][mGs][mGs][mG] (SEQ ID NO: 1179)
2	0643 SM1405 /ASM2028	DP17919 P:DP17918G	[mAs][mC][mA][mA][mC][mG][mU][fA][fC][fC][fC][mU][mU][mC][mA][mU][mU][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1180) [MePhosphonate-4O-mUs][fUs][fCs][fA][fA][mU][fG][mA][mA][fG][mG][mG][mU][fA][mC][mG][mU][mU][mG][mUs][mGs][mG] (SEQ ID NO: 1181)
3	1110 SM1405 /ASM2028	DP17921 P:DP17920G	[mGs][mC][mA][mC][mU][mG][mA][fG][fU][fG][fA][mA][mG][mA][mA][mA][mG][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1182) [MePhosphonate-4O-mUs][fUs][fCs][fA][fU][mU][fU][mC][mU][fU][mC][mA][mC][fU][mC][mA][mG][mU][mG][mCs][mGs][mG] (SEQ ID NO: 1183)
4	1162 SM1405 /ASM2028	DP17923 P:DP17922G	[mAs][mC][mU][mU][mG][mC][mU][fA][fC][fC][fC][mA][mU][mU][mA][mG][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1184) [MePhosphonate-4O-mUs][fAs][fUs][fC][fC][mU][fA][mA][mU][fG][mG][mG][mU][fA][mG][mC][mA][mA][mG][mUs][mGs][mG] (SEQ ID NO: 1185)
5	1170 SM1405 /ASM2028	DP17925 P:DP17924G	[mCs][mC][mC][mA][mU][mU][mA][fG][fG][fA][fU][mA][mA][mU][mG][mU][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1186) [MePhosphonate-4O-mUs][fAs][fAs][fG][fA][mC][fA][mU][mU][fA][mU][mC][mC][fU][mA][mA][mU][mG][mG][mGs][mGs][mG] (SEQ ID NO: 1187)

6	1699 SM1405/ASM2028	DP17927P:DP17926G	[mCs][mU][mG][mA][mG][mC][mU][fG][fA][fG][fU][mU][mG][mG][mU][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1188) [MePhosphonate-4O-mUs][fUs][fAs][fA][fA][mA][fC][mC][mA][fA][mC][mU][mC][fA][mG][mC][mU][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1189)
7	1703 SM1405/ASM2028	DP17929P:DP17928G	[mGs][mC][mU][mG][mA][mG][mU][fU][fG][fG][fU][mU][mU][mU][mA][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1190) [MePhosphonate-4O-mUs][fUs][fUs][fC][fA][mU][fA][mA][mA][fA][mC][mC][mA][fA][mC][mU][mC][mA][mG][mCs][mGs][mG] (SEQ ID NO: 1191)
8	1708 SM1405/ASM2028	DP17931P:DP17930G	[mGs][mU][mU][mG][mG][mU][mU][fU][fU][fA][fU][mG][mA][mA][mA][mA][mG][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1192) [MePhosphonate-4O-mUs][fAs][fGs][fC][fU][mU][fU][mU][mC][fA][mU][mA][mA][fA][mA][mC][mC][mA][mA][mCs][mGs][mG] (SEQ ID NO: 1193)
9	2104 SM1405/ASM2028	DP17933P:DP17932G	[mGs][mG][mU][mA][mA][mC][mA][fA][fG][fA][fU][mG][mA][mU][mA][mA][mU][mC][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1194) [MePhosphonate-4O-mUs][fAs][fGs][fA][fU][mU][fA][mU][mC][fA][mU][mC][mU][fU][mG][mU][mU][mA][mC][mCs][mGs][mG] (SEQ ID NO: 1195)
10	2143 SM1405/ASM2028	DP17935P:DP17934G	[mUs][mU][mU][mC][mA][mC][mC][fU][fA][fA][fC][mU][mA][mA][mA][mA][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1196) [MePhosphonate-4O-mUs][fUs][fUs][fA][fU][mU][fU][mU][mA][fG][mU][mU][mA][fG][mG][mU][mG][mA][mA][mAs][mGs][mG] (SEQ ID NO: 1197)
11	2155 SM1405/ASM2028	DP17937P:DP17936G	[mAs][mA][mA][mA][mU][mA][mA][fU][fG][fU][fU][mU][mA][mA][mA][mG][mA][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1198) [MePhosphonate-4O-mUs][fAs][fCs][fU][fC][mU][fU][mU][mA][fA][mA][mC][mA][fU][mU][mA][mU][mU][mU][mUs][mGs][mG] (SEQ ID NO: 1199)
12	2156	DP17939P:DP17938G	[mAs][mA][mA][mU][mA][mA][mU][fG][fU][fU][fU][mA][mA][mA][mG][mA][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1200)

	SM1405/ASM2028		[MePhosphonate-4O-mUs][fAs][fAs][fC][fU][mC][fU][mU][mU][fA][mA][mA][mC][fA][mU][mU][mA][mU][mU][mUs][mGs][mG] (SEQ ID NO: 1201)
13	2157 SM1405/ASM2028	DP17941P:DP17940G	[mAs][mA][mU][mA][mA][mU][mG][fU][fU][fU][fA][mA][mA][mG][mA][mG][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1202) [MePhosphonate-4O-mUs][fAs][fAs][fA][fC][mU][fC][mU][mU][fU][mA][mA][mA][fC][mA][mU][mU][mA][mU][mU][mUs][mGs][mG] (SEQ ID NO: 1203)
14	2163 SM1405/ASM2028	DP17943P:DP17942G	[mGs][mU][mU][mU][mA][mA][mA][fG][fA][fG][fU][mU][mU][mU][mG][mU][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1204) [MePhosphonate-4O-mUs][fUs][fAs][fU][fA][mC][fA][mA][mA][fA][mC][mU][mC][fU][mU][mU][mA][mA][mA][mCs][mGs][mG] (SEQ ID NO: 1205)
15	2165 SM1405/ASM2028	DP17945P:DP17944G	[mUs][mU][mA][mA][mA][mG][mA][fG][fU][fU][fU][mU][mG][mU][mA][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1206) [MePhosphonate-4O-mUs][fUs][fUs][fU][fA][mU][fA][mC][mA][fA][mA][mA][mC][fU][mC][mU][mU][mU][mA][mAs][mGs][mG] (SEQ ID NO: 1207)
16	2170 SM1405/ASM2028	DP17947P:DP17946G	[mGs][mA][mG][mU][mU][mU][mU][fG][fU][fA][fU][mA][mA][mA][mA][mA][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1208) [MePhosphonate-4O-mUs][fAs][fCs][fA][fU][mU][fU][mU][mU][fA][mU][mA][mC][fA][mA][mA][mA][mC][mU][mCs][mGs][mG] (SEQ ID NO: 1209)
17	2195 SM1405/ASM2028	DP17949P:DP17948G	[mGs][mC][mG][mU][mU][mG][mU][fU][fA][fC][fC][mU][mG][mU][mU][mG][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1210) [MePhosphonate-4O-mUs][fAs][fUs][fU][fC][mA][fA][mC][mA][fG][mG][mU][mA][fA][mC][mA][mA][mC][mG][mCs][mGs][mG] (SEQ ID NO: 1211)
18	2200 SM1405/ASM2028	DP17951P:DP17950G	[mGs][mU][mU][mA][mC][mC][mU][fG][fU][fU][fG][mA][mA][mU][mU][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1212) [MePhosphonate-4O-mUs][fAs][fCs][fA][fA][mA][fA][mU][mU][fC][mA][mA][mC][fA][mG][mG][mU][mA][mA][mCs][mGs][mG] (SEQ ID NO: 1213)

19	2204 SM1405/ASM2028	DP17953P:DP17952G	[mCs][mC][mU][mG][mU][mU][mG][fA][fA][fU][fU][mU][mU][mG][mU][mA][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1214) [MePhosphonate-4O-mUs][fUs][fAs][fA][fU][mA][fC][mA][mA][fA][mA][mU][mU][fC][mA][mA][mC][mA][mG][mGs][mGs][mG] (SEQ ID NO: 1215)
20	2205 SM1405/ASM2028	DP17955P:DP17954G	[mCs][mU][mG][mU][mU][mG][mA][fA][fU][fU][fU][mU][mG][mU][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1216) [MePhosphonate-4O-mUs][fAs][fUs][fA][fA][mU][fA][mC][mA][fA][mA][mA][mU][fU][mC][mA][mA][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1217)
21	2210 SM1405/ASM2028	DP17957P:DP17956G	[mGs][mA][mA][mU][mU][mU][mU][fG][fU][fA][fU][mU][mA][mU][mG][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1218) [MePhosphonate-4O-mUs][fUs][fUs][fC][fA][mC][fA][mU][mA][fA][mU][mA][mC][fA][mA][mA][mA][mU][mU][mCs][mGs][mG] (SEQ ID NO: 1219)

Table B

SEQ ID NO. and Mod. Pattern	DP Number	Modified Oligonucleotide
0644 SM1405/ ASM2028	DP18056P:DP18055G	[mCs][mA][mA][mC][mG][mU][mA][fC][fC][fC][fU][mU][mC][mA][mU][mU][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1220) [MePhosphonate-4O-mUs][fAs][fUs][fC][fA][mA][fU][mG][mA][fA][mG][mG][mG][fU][mA][mC][mG][mU][mU][mGs][mGs][mG] (SEQ ID NO: 1221)
0745 SM1405/ ASM2028	DP18084P:DP18083G	[mUs][mG][mG][mA][mC][mA][mU][fC][fA][fC][fC][mA][mA][mG][mC][mU][mC][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1222) [MePhosphonate-4O-mUs][fCs][fUs][fG][fA][mG][fC][mU][mU][fG][mG][mU][mG][fA][mU][mG][mU][mC][mC][mAs][mGs][mG] (SEQ ID NO: 1223)
1126 SM1405/ ASM2028	DP18112P:DP18111G	[mUs][mG][mA][mA][mA][mG][mA][fC][fA][fA][fA][mG][mG][mU][mG][mG][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1224) [MePhosphonate-4O-mUs][fUs][fAs][fU][fC][mC][fA][mC][mC][fU][mU][mU][mG][fU][mC][mU][mU][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1225)
1129 SM1405/ ASM2028	DP18116P:DP18115G	[mAs][mA][mG][mA][mC][mA][mA][fA][fG][fG][fU][mG][mG][mA][mU][mA][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1226) [MePhosphonate-4O-mUs][fAs][fUs][fG][fU][mA][fU][mC][mC][fA][mC][mC][mU][fU][mU][mG][mU][mC][mU][mUs][mGs][mG] (SEQ ID NO: 1227)
1130 SM1405/ ASM2028	DP18118P:DP18117G	[mAs][mG][mA][mC][mA][mA][mA][fG][fG][fU][fG][mG][mA][mU][mA][mC][mA][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1228) [MePhosphonate-4O-mUs][fCs][fAs][fU][fG][mU][fA][mU][mC][fC][mA][mC][mC][fU][mU][mU][mG][mU][mC][mUs][mGs][mG] (SEQ ID NO: 1229)
1143 SM1405/ ASM2028	DP18136P:DP18135G	[mUs][mA][mC][mA][mU][mG][mA][fG][fC][fA][fA][mG][mA][mU][mU][mU][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1230) [MePhosphonate-4O-mUs][fUs][fGs][fC][fA][mA][fA][mU][mC][fU][mU][mG][mC][fU][mC][mA][mU][mG][mU][mAs][mGs][mG] (SEQ ID NO: 1231)
1147	DP18140P:DP18139G	[mUs][mG][mA][mG][mC][mA][mA][fG][fA][fU][fU][mU][mG][mC][mA][mA][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1232)

SM1405/ ASM2028		[MePhosphonate-4O-mUs][fAs][fAs][fG][fU][mU][fG][mC][mA][fA][mA][mU][mC][fU][mU][mG][mC][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1233)
1152 SM1405/ ASM2028	DP18150P:DP18149G	[mAs][mA][mG][mA][mU][mU][mU][fG][fC][fA][fA][mC][mU][mU][mG][mC][mU][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1234) [MePhosphonate-4O-mUs][fGs][fUs][fA][fG][mC][fA][mA][mG][fU][mU][mG][mC][fA][mA][mA][mU][mC][mU][mUs][mGs][mG] (SEQ ID NO: 1235)
1229 SM1405/ ASM2028	DP18172P:DP18171G	[mUs][mG][mC][mG][mA][mU][mU][fG][fU][fC][fC][mA][mG][mA][mG][mA][mC][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1236) [MePhosphonate-4O-mUs][fCs][fAs][fG][fU][mC][fU][mC][mU][fG][mG][mA][mC][fA][mA][mU][mC][mG][mC][mAs][mGs][mG] (SEQ ID NO: 1237)
2142 SM1405/ ASM2028	DP18274P:DP18273G	[mUs][mU][mU][mU][mC][mA][mC][fC][fU][fA][fA][mC][mU][mA][mA][mA][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1238) [MePhosphonate-4O-mUs][fUs][fAs][fU][fU][mU][fU][mA][mG][fU][mU][mA][mG][fG][mU][mG][mA][mA][mA][mAs][mGs][mG] (SEQ ID NO: 1239)
1698 SM1405/ ASM2028	DP18208P:DP18207G	[mUs][mC][mU][mG][mA][mG][mC][fU][fG][fA][fG][mU][mU][mG][mG][mU][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1240) [MePhosphonate-4O-mUs][fAs][fAs][fA][fA][mC][fC][mA][mA][fC][mU][mC][mA][fG][mC][mU][mC][mA][mG][mAs][mGs][mG] (SEQ ID NO: 1241)
2138 SM1405/ ASM2028	DP18270P:DP18269G	[mAs][mC][mC][mU][mU][mU][mU][fU][fC][fA][fC][mC][mU][mA][mA][mC][mU][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1242) [MePhosphonate-4O-mUs][fUs][fUs][fA][fG][mU][fU][mA][mG][fG][mU][mG][mA][fA][mA][mA][mA][mG][mG][mUs][mGs][mG] (SEQ ID NO: 1243)
2140 SM1405/ ASM2028	DP18272P:DP18271G	[mCs][mU][mU][mU][mU][mU][mC][fA][fC][fC][fU][mA][mA][mC][mU][mA][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1244) [MePhosphonate-4O-mUs][fUs][fUs][fU][fU][mA][fG][mU][mU][fA][mG][mG][mU][fG][mA][mA][mA][mA][mA][mGs][mGs][mG] (SEQ ID NO: 1245)
2144 SM1405/ ASM2028	DP18276P:DP18275G	[mUs][mU][mC][mA][mC][mC][mU][fA][fA][fC][fU][mA][mA][mA][mA][mU][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1246) [MePhosphonate-4O-mUs][fAs][fUs][fU][fA][mU][fU][mU][mU][fA][mG][mU][mU][fA][mG][mG][mU][mG][mA][mAs][mGs][mG] (SEQ ID NO: 1247)

2146 SM1405/ASM2028	DP18280P:DP18279G	[mCs][mA][mC][mC][mU][mA][mA][fC][fU][fA][fA][mA][mA][mU][mA][mA][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1248) [MePhosphonate-4O-mUs][fAs][fCs][fA][fU][mU][fA][mU][mU][fU][mU][mA][mG][fU][mU][mA][mG][mG][mU][mGs][mGs][mG] (SEQ ID NO: 1249)
2149 SM1405/ASM2028	DP18286P:DP18285G	[mCs][mU][mA][mA][mC][mU][mA][fA][fA][fA][fU][mA][mA][mU][mG][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1250) [MePhosphonate-4O-mUs][fUs][fAs][fA][fA][mC][fA][mU][mU][fA][mU][mU][mU][fU][mA][mG][mU][mU][mA][mGs][mGs][mG] (SEQ ID NO: 1251)
2137 SM1405/ASM2028	DP18268P:DP18267G	[mCs][mA][mC][mC][mU][mU][mU][fU][fU][fC][fA][mC][mC][mU][mA][mA][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1252) [MePhosphonate-4O-mUs][fUs][fAs][fG][fU][mU][fA][mG][mG][fU][mG][mA][mA][fA][mA][mA][mG][mG][mU][mGs][mGs][mG] (SEQ ID NO: 1253)
2205 SM1405/ASM2028	DP17955P:DP17954G	[mCs][mU][mG][mU][mU][mG][mA][fA][fU][fU][fU][mU][mG][mU][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1216) [MePhosphonate-4O-mUs][fAs][fUs][fA][fA][mU][fA][mC][mA][fA][mA][mA][mU][fU][mC][mA][mA][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1217)

Table C

SEQ ID NO. and Mod. Pattern	DP Number	Modified Oligonucleotide
1697 SM1405/ASM2028	DP18206P:DP18205G	[mCs][mU][mC][mU][mG][mA][mG][fC][fU][fG][fA][mG][mU][mU][mG][mG][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1254) [MePhosphonate-4O-mUs][fAs][fAs][fA][fC][mC][fA][mA][mC][fU][mC][mA][mG][fC][mU][mC][mA][mG][mA][mGs][mGs][mG] (SEQ ID NO: 1255)
1614 SM1405/ASM2028	DP18194P:DP18193G	[mAs][mG][mG][mU][mG][mC][mU][fA][fA][fA][fG][mU][mU][mU][mC][mC][mC][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1256) [MePhosphonate-4O-mUs][fAs][fUs][fG][fG][mG][fA][mA][mA][fC][mU][mU][mU][fA][mG][mC][mA][mC][mC][mUs][mGs][mG] (SEQ ID NO: 1257)
2176 SM1405/ASM2028	DP18304P:DP18303G	[mUs][mG][mU][mA][mU][mA][mA][fA][fA][fA][fU][mG][mU][mA][mA][mG][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1258) [MePhosphonate-4O-mUs][fUs][fUs][fC][fC][mU][fU][mA][mC][fA][mU][mU][mU][fU][mU][mA][mU][mA][mC][mAs][mGs][mG] (SEQ ID NO: 1259)
2222 SM1405/ASM2028	DP18326P:DP18325G	[mAs][mU][mG][mU][mG][mA][mA][fU][fC][fA][fG][mU][mG][mA][mG][mA][mU][mG][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1260) [MePhosphonate-4O-mUs][fAs][fCs][fA][fU][mC][fU][mC][mA][fC][mU][mG][mA][fU][mU][mC][mA][mC][mA][mUs][mGs][mG] (SEQ ID NO: 1261)
1173 SM1405/ASM2028	DP18168P:DP18167G	[mAs][mU][mU][mA][mG][mG][mA][fU][fA][fA][fU][mG][mU][mC][mU][mU][mA][mU][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1262) [MePhosphonate-4O-mUs][fCs][fAs][fU][fA][mA][fG][mA][mC][fA][mU][mU][mA][fU][mC][mC][mU][mA][mA][mUs][mGs][mG] (SEQ ID NO: 1263)
2136	DP18266P:DP18265G	[mAs][mC][mA][mC][mC][mU][mU][fU][fU][fU][fC][mA][mC][mC][mU][mA][mA][mC][mU][mA][mG][mC][mA][mG][m

SM1405/ASM2028		C][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1264) [MePhosphonate-4O-mUs][fAs][fGs][fU][fU][mA][fG][mG][mU][fG][mA][mA][mA][fA][mA][mG][mG][mU][mG][mUs][mGs][mG] (SEQ ID NO: 1265)
0637 SM1405/ASM2028	DP18046P:DP18045G	[mUs][mG][mA][mG][mU][mG][mA][fC][fA][fA][fC][mG][mU][mA][mC][mC][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1266) [MePhosphonate-4O-mUs][fAs][fAs][fG][fG][mG][fU][mA][mC][fG][mU][mU][mG][fU][mC][mA][mC][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1267)
1116 SM1405/ASM2028	DP18098P:DP18097G	[mAs][mG][mU][mG][mA][mA][mG][fA][fA][fA][fU][mG][mA][mA][mA][mG][mA][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1268) [MePhosphonate-4O-mUs][fUs][fGs][fU][fC][mU][fU][mU][mC][fA][mU][mU][mU][fC][mU][mU][mC][mA][mC][mUs][mGs][mG] (SEQ ID NO: 1269)
0923 SM1405/ASM2028	DP18096P:DP18095G	[mAs][mU][mC][mC][mU][mC][mA][fG][fA][fA][fG][mG][mG][mA][mU][mG][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1270) [MePhosphonate-4O-mUs][fAs][fUs][fC][fC][mA][fU][mC][mC][fC][mU][mU][mC][fU][mG][mA][mG][mG][mA][mUs][mGs][mG] (SEQ ID NO: 1271)
0641 SM1405/ASM2028	DP18052P:DP18051G	[mUs][mG][mA][mC][mA][mA][mC][fG][fU][fA][fC][mC][mC][mU][mU][mC][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1272) [MePhosphonate-4O-mUs][fAs][fAs][fU][fG][mA][fA][mG][mG][fG][mU][mA][mC][fG][mU][mU][mG][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1273)
1136 SM1405/ASM2028	DP18126P:DP18125G	[mAs][mG][mG][mU][mG][mG][mA][fU][fA][fC][fA][mU][mG][mA][mG][mC][mA][mA][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1274) [MePhosphonate-4O-mUs][fCs][fUs][fU][fG][mC][fU][mC][mA][fU][mG][mU][mA][fU][mC][mC][mA][mC][mC][mUs][mGs][mG] (SEQ ID NO: 1275)

1158 SM1405/ASM2028	DP18158P:DP18157G	[mUs][mG][mC][mA][mA][mC][mU][fU][fG][fC][fU][mA][mC][mC][mC][mA][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1276) [MePhosphonate-4O-mUs][fUs][fAs][fA][fU][mG][fG][mG][mU][fA][mG][mC][mA][fA][mG][mU][mU][mG][mC][mAs][mGs][mG] (SEQ ID NO: 1277)
1151 SM1405/ASM2028	DP18148P:DP18147G	[mCs][mA][mA][mG][mA][mU][mU][fU][fG][fC][fA][mA][mC][mU][mU][mG][mC][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1278) [MePhosphonate-4O-mUs][fUs][fAs][fG][fC][mA][fA][mG][mU][fU][mG][mC][mA][fA][mA][mU][mC][mU][mU][mGs][mGs][mG] (SEQ ID NO: 1279)
1541 SM1405/ASM2028	DP18184P:DP18183G	[mCs][mA][mC][mC][mU][mU][mU][fC][fC][fC][fA][mG][mU][mU][mU][mU][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1280) [MePhosphonate-4O-mUs][fUs][fGs][fA][fA][mA][fA][mA][mC][fU][mG][mG][mG][fA][mA][mA][mG][mG][mU][mGs][mGs][mG] (SEQ ID NO: 1281)
1157 SM1405/ASM2028	DP18156P:DP18155G	[mUs][mU][mG][mC][mA][mA][mC][fU][fU][fG][fC][mU][mA][mC][mC][mC][mA][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1282) [MePhosphonate-4O-mUs][fAs][fAs][fU][fG][mG][fG][mU][mA][fG][mC][mA][mA][fG][mU][mU][mG][mC][mA][mAs][mGs][mG] (SEQ ID NO: 1283)
1163 SM1405/ASM2028	DP18164P:DP18163G	[mCs][mU][mU][mG][mC][mU][mA][fC][fC][fC][fA][mU][mU][mA][mG][mG][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1284) [MePhosphonate-4O-mUs][fUs][fAs][fU][fC][mC][fU][mA][mA][fU][mG][mG][mG][fU][mA][mG][mC][mA][mA][mGs][mGs][mG] (SEQ ID NO: 1285)
1125 SM1405/ASM2028	DP18110P:DP18109G	[mAs][mU][mG][mA][mA][mA][mG][fA][fC][fA][fA][mA][mG][mG][mU][mG][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1286) [MePhosphonate-4O-mUs][fAs][fUs][fC][fC][mA][fC][mC][mU][fU][mU][mG][mU][fC][mU][mU][mU][mC][mA][mUs][mGs][mG] (SEQ ID NO: 1287)

2205 SM1405/ASM2028	DP17955P:DP17954G	[mCs][mU][mG][mU][mU][mG][mA][fA][fU][fU][fU][mU][mG][mU][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1216) [MePhosphonate-4O-mUs][fAs][fUs][fA][fA][mU][fA][mC][mA][fA][mA][mA][mU][fU][mC][mA][mA][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1217)

Table D

SEQ ID NO. and Mod. Pattern	DP Number	Modified Oligonucleotide
0639 SM1405/A SM2028	DP18050P: DP18049G	[mAs][mG][mU][mG][mA][mC][mA][fA][fC][fG][fU][mA][mC][mC][mC][mU][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1288) [MePhosphonate-4O-mUs][fUs][fGs][fA][fA][mG][fG][mG][mU][fA][mC][mG][mU][fU][mG][mU][mC][mA][mC][mUs][mGs][mG] (SEQ ID NO: 1289)
0644 SM1405/A SM2028	DP18056P: DP18055G	[mCs][mA][mA][mC][mG][mU][mA][fC][fC][fC][fU][mU][mC][mA][mU][mU][mG][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1220) [MePhosphonate-4O-mUs][fAs][fUs][fC][fA][mA][fU][mG][mA][fA][mG][mG][mG][fU][mA][mC][mG][mU][mU][mGs][mGs][mG] (SEQ ID NO: 1221)
0729 SM1405/A SM2028	DP18068P: DP18067G	[mAs][mC][mG][mA][mA][mC][mU][fU][fU][fC][fU][mU][mC][mA][mU][mG][mU][mG][mG][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1290) [MePhosphonate-4O-mUs][fCs][fCs][fA][fC][mA][fU][mG][mA][fA][mG][mA][mA][fA][mG][mU][mU][mC][mG][mUs][mGs][mG] (SEQ ID NO: 1291)
0735 SM1405/A SM2028	DP18074P: DP18073G	[mUs][mU][mU][mC][mU][mU][mC][fA][fU][fG][fU][mG][mG][mA][mC][mA][mU][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1292) [MePhosphonate-4O-mUs][fUs][fGs][fA][fU][mG][fU][mC][mC][fA][mC][mA][mU][fG][mA][mA][mG][mA][mA][mAs][mGs][mG] (SEQ ID NO: 1293)
0743 SM1405/A SM2028	DP18080P: DP18079G	[mUs][mG][mU][mG][mG][mA][mC][fA][fU][fC][fA][mC][mC][mA][mA][mG][mC][mU][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1294) [MePhosphonate-4O-mUs][fGs][fAs][fG][fC][mU][fU][mG][mG][fU][mG][mA][mU][fG][mU][mC][mC][mA][mC][mAs][mGs][mG] (SEQ ID NO: 1295)
0744	DP18082P: DP18081G	[mGs][mU][mG][mG][mA][mC][mA][fU][fC][fA][fC][mC][mA][mA][mG][mC][mU][mC][mA][mA][mG][mC][mA][mG][mC][

SM1405/A SM2028		mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1296) [MePhosphonate-4O-mUs][fUs][fGs][fA][fG][mC][fU][mU][mG][fG][mU][mG][mA][fU][mG][mU][mC][mC][mA][mCs][mGs][mG] (SEQ ID NO: 1297)
0838 SM1405/A SM2028	DP18086P: DP18085G	[mAs][mG][mA][mU][mA][mU][mG][fC][fC][fU][fU][mC][mG][mA][mG][mG][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1298) [MePhosphonate-4O-mUs][fUs][fAs][fU][fC][mC][fU][mC][mG][fA][mA][mG][mG][fC][mA][mU][mA][mU][mC][mUs][mGs][mG] (SEQ ID NO: 1299)
1126 SM1405/A SM2028	DP18112P: DP18111G	[mUs][mG][mA][mA][mA][mG][mA][fC][fA][fA][fA][mG][mG][mU][mG][mG][mA][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1224) [MePhosphonate-4O-mUs][fUs][fAs][fU][fC][mC][fA][mC][mC][fU][mU][mU][mG][fU][mC][mU][mU][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1225)
1143 SM1405/A SM2028	DP18136P: DP18135G	[mUs][mA][mC][mA][mU][mG][mA][fG][fC][fA][fA][mG][mA][mU][mU][mU][mG][mC][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1230) [MePhosphonate-4O-mUs][fUs][fGs][fC][fA][mA][fA][mU][mC][fU][mU][mG][mC][fU][mC][mA][mU][mG][mU][mAs][mGs][mG] (SEQ ID NO: 1231)
1147 SM1405/A SM2028	DP18140P: DP18139G	[mUs][mG][mA][mG][mC][mA][mA][fG][fA][fU][fU][mU][mG][mC][mA][mA][mC][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1232) [MePhosphonate-4O-mUs][fAs][fAs][fG][fU][mU][fG][mC][mA][fA][mA][mU][mC][fU][mU][mG][mC][mU][mC][mAs][mGs][mG] (SEQ ID NO: 1233)
1152 SM1405/A SM2028	DP18150P: DP18149G	[mAs][mA][mG][mA][mU][mU][mU][fG][fC][fA][fA][mC][mU][mU][mG][mC][mU][mA][mC][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1234) [MePhosphonate-4O-mUs][fGs][fUs][fA][fG][mC][fA][mA][mG][fU][mU][mG][mC][fA][mA][mA][mU][mC][mU][mUs][mGs][mG] (SEQ ID NO: 1235)
1173	DP18168P: DP18167G	[mAs][mU][mU][mA][mG][mG][mA][fU][fA][fA][fU][mG][mU][mC][mU][mU][mA][mU][mG][mA][mG][mC][mA][mG][mC][

SM1405/A SM2028		mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1262) [MePhosphonate-4O-mUs][fCs][fAs][fU][fA][mA][fG][mA][mC][fA][mU][mU][mA][fU][mC][mC][mU][mA][mA][mUs][mGs][mG] (SEQ ID NO: 1263)
1697 SM1405/A SM2028	DP18206P: DP18205G	[mCs][mU][mC][mU][mG][mA][mG][fC][fU][fG][fA][mG][mU][mU][mG][mG][mU][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1254) [MePhosphonate-4O-mUs][fAs][fAs][fA][fC][mC][fA][mA][mC][fU][mC][mA][mG][fC][mU][mC][mA][mG][mA][mGs][mGs][mG] (SEQ ID NO: 1255)
1699 SM1405/A SM2028	DP17927P: DP17926G	[mCs][mU][mG][mA][mG][mC][mU][fG][fA][fG][fU][mU][mG][mG][mU][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1188) [MePhosphonate-4O-mUs][fUs][fAs][fA][fA][mA][fC][mC][mA][fA][mC][mU][mC][fA][mG][mC][mU][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1189)
1703 SM1405/A SM2028	DP17929P: DP17928G	[mGs][mC][mU][mG][mA][mG][mU][fU][fG][fG][fU][mU][mU][mU][mA][mU][mG][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1190) [MePhosphonate-4O-mUs][fUs][fUs][fC][fA][mU][fA][mA][mA][fA][mC][mC][mA][fA][mC][mU][mC][mA][mG][mCs][mGs][mG] (SEQ ID NO: 1191)
2140 SM1405/A SM2028	DP18272P: DP18271G	[mCs][mU][mU][mU][mU][mU][mC][fA][fC][fC][fU][mA][mA][mC][mU][mA][mA][mA][mA][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1244) [MePhosphonate-4O-mUs][fUs][fUs][fU][fU][mA][fG][mU][mU][fA][mG][mG][mU][fG][mA][mA][mA][mA][mA][mGs][mGs][mG] (SEQ ID NO: 1245)
2144 SM1405/A SM2028	DP18276P: DP18275G	[mUs][mU][mC][mA][mC][mC][mU][fA][fA][fC][fU][mA][mA][mA][mA][mU][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1246) [MePhosphonate-4O-mUs][fAs][fUs][fU][fA][mU][fU][mU][mU][fA][mG][mU][mU][fA][mG][mG][mU][mG][mA][mAs][mGs][mG] (SEQ ID NO: 1247)
2149	DP18286P: DP18285G	[mCs][mU][mA][mA][mC][mU][mA][fA][fA][fA][fU][mA][mA][mU][mG][mU][mU][mU][mA][mA][mG][mC][mA][mG][mC][

SM1405/A SM2028		mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1250) [MePhosphonate-4O-mUs][fUs][fAs][fA][fA][mC][fA][mU][mU][fA][mU][mU][mU][fU][mA][mG][mU][mU][mA][mGs][mGs][mG] (SEQ ID NO: 1251)
2156 SM1405/A SM2028	DP17939P: DP17938G	[mAs][mA][mA][mU][mA][mA][mU][fG][fU][fU][fU][mA][mA][mA][mG][mA][mG][mU][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1200) [MePhosphonate-4O-mUs][fAs][fAs][fC][fU][mC][fU][mU][mU][fA][mA][mA][mC][fA][mU][mU][mA][mU][mU][mUs][mGs][mG] (SEQ ID NO: 1201)
2195 SM1405/A SM2028	DP17949P: DP17948G	[mGs][mC][mG][mU][mU][mG][mU][fU][fA][fC][fC][mU][mG][mU][mU][mG][mA][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1300) [MePhosphonate-4O-mUs][fAs][fUs][fU][fC][mA][fA][mC][mA][fG][mG][mU][mA][fA][mC][mA][mA][mC][mG][mCs][mGs][mG] (SEQ ID NO: 1301)
2205 SM1405/A SM2028	DP17955P: DP17954G	[mCs][mU][mG][mU][mU][mG][mA][fA][fU][fU][fU][mU][mG][mU][mA][mU][mU][mA][mU][mA][mG][mC][mA][mG][mC][mC][mG][ademA-GalNAc][ademA-GalNAc][ademA-GalNAc][mG][mG][mC][mU][mG][mC] (SEQ ID NO: 1216) [MePhosphonate-4O-mUs][fAs][fUs][fA][fA][mU][fA][mC][mA][fA][mA][mA][mU][fU][mC][mA][mA][mC][mA][mGs][mGs][mG] (SEQ ID NO: 1217)

CLAIMS

The invention claimed is:

1. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

2. The RNAi oligonucleotide of claim 1, wherein the sense strand is 15 to 50 nucleotides in length.

3. The RNAi oligonucleotide of claims 1 or 2, wherein the sense strand is 18 to 36 nucleotides in length.

4. The RNAi oligonucleotide of any one of claims 1 to 3, wherein the antisense strand is 15 to 30 nucleotides in length.

5. The RNAi oligonucleotide of any one of claims 1 to 4, wherein the antisense strand is 22 nucleotides in length and where in the antisense strand and the sense strand form a duplex region of at least 19 nucleotides in length, optionally at least 20 nucleotides in length.

6. The RNAi oligonucleotide of any one of claims 1 to 5, wherein the region of complementarity is at least 19 contiguous nucleotide in length, optionally at least 20 nucleotides in length.

7. The RNAi oligonucleotide of any one of claims 1 to 6, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementarity to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length.

8. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein

the sense strand and the antisense strand form a duplex region, wherein the wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

9. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

10. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

11. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

12. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

13. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 18 to 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

14. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

15. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand of 36 nucleotides in length and an antisense strand of 22 nucleotides in length, wherein the sense strand and the antisense strand form a duplex region of at least 19 nucleotides in length, optionally 20 nucleotides in length, wherein the 3' end of the sense strand comprises a stem-loop set forth as S1-L-S2, wherein S1 is complementary to S2, and wherein L forms a loop between S1 and S2 of 3 to 5 nucleotides in length, wherein the antisense strand comprises a region of complementarity to a *PNPLA3* mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is 19 contiguous nucleotides in length, optionally 20 nucleotides in length.

16. The RNAi oligonucleotide of any one of Claims 7 and 13 to 15, wherein L is a triloop or a tetraloop.

17. The RNAi oligonucleotide of Claim 16, wherein L is a tetraloop.

18. The RNAi oligonucleotide of Claim 17, wherein the tetraloop comprises the sequence 5'-GAAA-3'.

19. The RNAi oligonucleotide of any one of Claims 16 to 18, wherein S1 and S2 are 1-10 nucleotides in length and have the same length.

20. The RNAi oligonucleotide of Claim 19, wherein S1 and S2 are 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides in length.

21. The RNAi oligonucleotide of Claim 20, wherein S1 and S2 are 6 nucleotides in length.

22. The RNAi oligonucleotide of any one of Claims 16 to 21, wherein the stem-loop comprises the sequence 5'-GCAGCCGAAAGGCUGC-3' (SEQ ID NO:1177).

23. The RNAi oligonucleotide of any one of Claims 1 to 22, wherein the antisense strand comprises a 3' overhang sequence of one or more nucleotides in length.

24. The RNAi oligonucleotide of Claim 23, wherein the 3' overhang sequence is 2 nucleotides in length, optionally wherein the 3' overhang sequence is GG.

25. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.

26. The RNAi oligonucleotide of Claim 25, wherein the modified nucleotide comprises a 2'-modification.

27. The RNAi oligonucleotide of Claim 26, wherein the 2'-modification is a modification selected from the group consisting of 2'-aminoethyl, 2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl, and 2'-deoxy-2'-fluoro-β-d-arabinonucleic acid.

28. The RNAi oligonucleotide of any one of Claims 25 to 27, wherein all nucleotides comprising the oligonucleotide are modified, optionally wherein the modification is a 2'-modification selected from the group consisting of 2'-fluoro and 2'-O-methyl.

29. The RNAi oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

30. The RNAi oligonucleotide of Claim 29, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

31. The RNAi oligonucleotide of any one of the preceding claims, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog.

32. The RNAi oligonucleotide of Claim 31, wherein the phosphate analog is oxymethylphosphonate, vinylphosphonate or malonylphosphonate, optionally wherein the phosphate analog is a 4'-phosphate analog comprising 5'-methoxyphosphonate-4'-oxy.

33. The RNAi oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

34. The RNAi oligonucleotide of Claim 33, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide, or lipid.

35. The RNAi oligonucleotide of Claim 33, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

36. The RNAi oligonucleotide of Claim 35, wherein the GalNAc moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

37. The RNAi oligonucleotide of any one of Claims 16 to 32, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

38. The RNAi oligonucleotide of any one of Claims 1 to 37, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 563, 565, 567, 569, 571, 573, 575, 577, 579, 581, 583, 585, 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, and 775, or

wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs:777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 809, 811, 813, 815, 817, 819, 821, 823, 825, 827, 829, 831, 833, 835, 837, 839, 841, 843, 845, 847, 849, 851, 853, 855, 857, 859, 861, 863, 865, 867, 869, 871, 873, 875, 877, 879, 881, 883, 885, 887, 889, 891, 893, 895, 897, 899, 901, 903, 905, 907, 909, 911, 913, 915, 917, 919, 921, 923, 925, 927, 929, 931, 933, 935, 937, 939, 941, 943, 945, 947, 949, 951, 953, 955, 957, 959, 961, 963, 965, 967, 969, 971, 973, 975, 977, 979, 981, 983, 985, 987, 989, 991, 993, 995, 997, 999, 1001, 1003, 1005,

1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, 1023, 1025, 1027, 1029, 1031, 1033, 1035, 1037, 1039, 1041, 1043, 1045, 1047, 1049, 1051, 1053, 1055, 1057, 1059, 1061, 1063, 1065, 1067, 1069, 1071, 1073, 1075, 1077, 1079, 1081, 1083, 1085, 1087, 1089, 1091, 1093, 1095, 1097, 1099, 1101, 1103, 1105, 1107, 1109, 1111, 1113, 1115, 1117, 1119, 1121, 1123, 1125, 1127, 1129, 1131, 1133, 1135, 1137, 1139, 1141, 1143, 1145, 1147, 1149, 1151, 1153, 1155, 1157, 1159, 1161, and 1163 or wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 1178, 1180, 1182, 1184, 1186, 1188, 1190, 1192, 1194, 1196, 1198, 1200, 1202, 1204, 1206, 1208, 1210, 1212, 1214, 1216, 1218, 1220, 1222, 1224, 1226, 1228, 1230, 1232, 1234, 1236, 1238, 1240, 1242, 1244, 1246, 1248, 1250, 1252, 1254, 1256, 1258, 1260, 1262, 1264, 1266, 1268, 1270, 1272, 1274, 1276, 1278, 1280, 1282, 1284, 1286, 1288, 1290, 1292, 1294, 1296, 1298 or 1300.

39. The RNAi oligonucleotide of any one of Claims 1 to 38, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs:10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728,

730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, and 776, or

wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs:778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 810, 812, 814, 816, 818, 820, 822, 824, 826, 828, 830, 832, 834, 836, 838, 840, 842, 844, 846, 848, 850, 852, 854, 856, 858, 860, 862, 864, 866, 868, 870, 872, 874, 876, 878, 880, 882, 884, 886, 888, 890, 892, 894, 896, 898, 900, 902, 904, 906, 908, 910, 912, 914, 916, 918, 920, 922, 924, 926, 928, 930, 932, 934, 936, 938, 940, 942, 944, 946, 948, 950, 952, 954, 956, 958, 960, 962, 964, 966, 968, 970, 972, 974, 976, 978, 980, 982, 984, 986, 988, 990, 992, 994, 996, 998, 1000, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, 1024, 1026, 1028, 1030, 1032, 1034, 1036, 1038, 1040, 1042, 1044, 1046, 1048, 1050, 1052, 1054, 1056, 1058, 1060, 1062, 1064, 1066, 1068, 1070, 1072, 1074, 1076, 1078, 1080, 1082, 1084, 1086, 1088, 1090, 1092, 1094, 1096, 1098, 1100, 1102, 1104, 1106, 1108, 1110, 1112, 1114, 1116, 1118, 1120, 1122, 1124, 1126, 1128, 1130, 1132, 1134, 1136, 1138, 1140, 1142, 1144, 1146, 1148, 1150, 1152, 1154, 1156, 1158, 1160, 1162, and 1164;

or wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID Nos: 1179, 1181, 1183, 1185, 1187, 1189, 1191, 1193, 1195, 1197, 1199, 1201, 1203, 1205, 1207, 1209, 1211, 1213, 1215, 1217, 1219, 1221, 1223, 1225, 1227, 1229, 1231, 1233, 1235, 1237, 1239, 1241, 1243, 1245, 1247, 1249, 1251, 1253, 1255, 1257, 1259, 1261, 1263, 1265, 1267, 1269, 1271, 1273, 1275, 1277, 1279, 1281, 1283, 1285, 1287, 1289, 1291, 1293, 1295, 1297, 1299 or 1301.

40. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOS:787 and 788,

(b) SEQ ID NOS:843 and 844,

(c) SEQ ID NOS:867 and 868,

(d) SEQ ID NOS:871 and 872,

(e) SEQ ID NOS:937 and 938,

(f) SEQ ID NOS:1003 and 1004,

(g) SEQ ID NOS:1007 and 1008,

(h) SEQ ID NOS:1017 and 1018,

(i) SEQ ID NOS:1161 and 1162,
(j) SEQ ID NOS: 1163 and 1164,
(k) SEQ ID NOs: 1220 and 1221,
(l) SEQ ID NOs: 1224 and 1225,
(m) SEQ ID NOs: 1230 and 1231,
(n) SEQ ID NOs: 1232 and 1233,
(o) SEQ ID NOs: 1188 and 1189,
(p) SEQ ID NOs: 1190 and 1191,
(q) SEQ ID NOs: 1244 and 1245,
(r) SEQ ID NOs: 1250 and 1251-,
(s) SEQ ID NOs: 1254 and 1255, and
(t) SEQ ID NOs: 1246 and 1247.

41. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1220 and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1221.

42. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1224 and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1225.

43. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1230, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1231.

44. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1232, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1233.

45. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1188, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1189.

46. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1190, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1191.

47. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1244, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1245.

48. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1250, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1251.

49. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1254, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1255.

50. The RNAi oligonucleotide of any one of Claims 1 to 39, wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1246, and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1247.

51. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

52. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense

strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

53. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and antisense strand are modified, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a *PNPLA3* mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

54. An RNAi oligonucleotide for reducing *PNPLA3* expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein all nucleotides comprising the sense strand and the antisense strand are modified, wherein the antisense strand and the sense strand comprise one or more 2'-fluoro and 2'-O-methyl modified nucleotides and at least one phosphorothioate linkage, wherein the 4'-carbon of the sugar of the 5'-nucleotide of the antisense strand comprises a phosphate analog, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOs:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

55. The RNAi oligonucleotide of any one of Claims 51 to 54, wherein the sense strand comprises of any one of SEQ ID NOs:787, 843, 867, 871, 937, 1003, 1007, 1017, 1161, or 1163, or wherein the sense strand comprises of any one of SEQ ID Nos: 1188, 1190, 1220, 1224, 1230, 1232, 1244, 1246, 1250 or 1254.

56. The RNAi oligonucleotide of any one of claims 51 to 55, wherein the antisense strand comprises of any one of SEQ ID NOs: 788, 844, 868, 872, 938, 1004, 1008, 1018, 1162, or 1164, or wherein the antisense strand comprises of any one of SEQ ID NOs: 1189, 1191, 1221, 1225, 1231, 1233, 1245, 1247, 1251 or 1255.

57. The RNAi oligonucleotide of any one of claims 51 to 56, wherein the sense strand and antisense strands are selected from the group consisting of:

(a) SEQ ID NOS:787 and 788,

(b) SEQ ID NOS:843 and 844,

(c) SEQ ID NOS:867 and 868,

(d) SEQ ID NOS:871 and 872,

(e) SEQ ID NOS:937 and 938,

(f) SEQ ID NOS:1003 and 1004,

(g) SEQ ID NOS:1007 and 1008,

(h) SEQ ID NOS:1017 and 1018,

(i) SEQ ID NOS:1161 and 1162, and

(j) SEQ ID NOS: 1163 and 1164,

(k) SEQ ID NOs: 1220 and 1221,

(l) SEQ ID NOs: 1224 and 1225,

(m) SEQ ID NOs: 1230 and 1231,

(n) SEQ ID NOs: 1232 and 1233,

(o) SEQ ID NOs: 1188 and 1189,

(p) SEQ ID NOs: 1190 and 1191,

(q) SEQ ID NOs: 1244 and 1245,

(r) SEQ ID NOs: 1250 and 1251-,

(s) SEQ ID NOs: 1254 and 1255, and

(t) SEQ ID NOs: 1246 and 1247.

58. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO: 1220 and wherein the antisense strand comprises SEQ ID NO:1221.

59. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1224, and wherein the antisense strand comprises SEQ ID NO:1225.

60. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1230, and wherein the antisense strand comprises SEQ ID NO:1231.

61. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1232, and wherein the antisense strand comprises SEQ ID NO:1233.

62. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1188, and wherein the antisense strand comprises SEQ ID NO:1189.

63. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1190, and wherein the antisense strand comprises SEQ ID NO:1191.

64. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1244, and wherein the antisense strand comprises SEQ ID NO:1245.

65. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1250, and wherein the antisense strand comprises SEQ ID NO:1251.

66. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1254, and wherein the antisense strand comprises SEQ ID NO:1255.

67. The RNAi oligonucleotide of any one of Claims 51 to 56, wherein the sense strand comprises SEQ ID NO:1246, and wherein the antisense strand comprises SEQ ID NO:1247.

68. A method for treating a subject having a disease, disorder or condition associated with *PNPLA3* expression, the method comprising administering to the subject a therapeutically effective amount of the RNAi oligonucleotide of any one of the preceding claims, or pharmaceutical composition thereof, thereby treating the subject.

69. A pharmaceutical composition comprising the RNAi oligonucleotide of any one of Claims 1 to 67, and a pharmaceutically acceptable carrier, delivery agent or excipient.

70. A method of delivering an oligonucleotide to a subject, the method comprising administering pharmaceutical composition of Claim 69 to the subject.

71. A method for reducing *PNPLA3* expression in a cell, a population of cells or a subject, the method comprising the step of:

i. contacting the cell or the population of cells with the RNAi oligonucleotide of any one of Claims 1 to 67, or the pharmaceutical composition of Claim 69; or

ii. administering to the subject the RNAi oligonucleotide of any one of Claims 1 to 67, or the pharmaceutical composition of Claim 69.

72. The method of Claim 71, wherein reducing *PNPLA3* expression comprises reducing an amount or level of PNPLA3 mRNA, an amount or level of PNPLA3 protein, or both.

73. The method of Claim 71 or 72, wherein the subject has a disease, disorder or condition associated with *PNPLA3* expression.

74. The method of claim 73, wherein the disease, disorder or condition associated with *PNPLA3* expression is cardiometabolic disease, alcoholic hepatitis (AH), alcoholic liver disease (ALD), cirrhosis, hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

75. The method of any one of claims 68 and 70 to 74, wherein the RNAi oligonucleotide, or pharmaceutical composition, is administered in combination with a second composition or therapeutic agent.

76. A method for treating a subject having a disease, disorder or condition associated with *PNPLA3* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1167 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

77. A method for treating a subject having a disease, disorder or condition associated with *PNPLA3* expression, the method comprising administering to the subject a therapeutically

effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand selected from a row set forth in Table 1, Table 3, Table A, Table B, Table C or Table D or a pharmaceutical composition thereof, thereby treating the subject.

78. A method for treating a subject having a disease, disorder or condition associated with *PNPLA3* expression, the method comprising administering to the subject a therapeutically effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and antisense strands comprise nucleotide sequences selected from the group consisting of:

(a) SEQ ID NOS:787 and 788,
(b) SEQ ID NOS:843 and 844,
(c) SEQ ID NOS:867 and 868,
(d) SEQ ID NOS:871 and 872,
(e) SEQ ID NOS:937 and 938,
(f) SEQ ID NOS:1003 and 1004,
(g) SEQ ID NOS:1007 and 1008,
(h) SEQ ID NOS:1017 and 1018,
(i) SEQ ID NOS:1161 and 1162, and
(j) SEQ ID NOS: 1163 and 1164,
(k) SEQ ID NOs: 1220 and 1221,
(l) SEQ ID NOs: 1224 and 1225,
(m) SEQ ID NOs: 1230 and 1231,
(n) SEQ ID NOs: 1232 and 1233,
(o) SEQ ID NOs: 1188 and 1189,
(p) SEQ ID NOs: 1190 and 1191,
(q) SEQ ID NOs: 1244 and 1245,
(r) SEQ ID NOs: 1250 and 1251-,
(s) SEQ ID NOs: 1254 and 1255, and
(t) SEQ ID NOs: 1246 and 1247.

79. A method for treating a subject having a disease, disorder or condition associated with *PNPLA3* expression, the method comprising administering to the subject a therapeutically

effective amount of an RNAi oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and antisense strands are selected from the group consisting of:

(a) SEQ ID NOS:787 and 788,
(b) SEQ ID NOS:843 and 844,
(c) SEQ ID NOS:867 and 868,
(d) SEQ ID NOS:871 and 872,
(e) SEQ ID NOS:937 and 938,
(f) SEQ ID NOS:1003 and 1004,
(g) SEQ ID NOS:1007 and 1008,
(h) SEQ ID NOS:1017 and 1018,
(i) SEQ ID NOS:1161 and 1162, and
(j) SEQ ID NOS: 1163 and 1164,
(k) SEQ ID NOs: 1220 and 1221,
(l) SEQ ID NOs: 1224 and 1225,
(m) SEQ ID NOs: 1230 and 1231,
(n) SEQ ID NOs: 1232 and 1233,
(o) SEQ ID NOs: 1188 and 1189,
(p) SEQ ID NOs: 1190 and 1191,
(q) SEQ ID NOs: 1244 and 1245,
(r) SEQ ID NOs: 1250 and 1251-,
(s) SEQ ID NOs: 1254 and 1255, and
(t) SEQ ID NOs: 1246 and 1247.

80. The method of claim 79, wherein the sense strand comprises SEQ ID NO:1224, and wherein the antisense strand comprises SEQ ID NO:1225; or wherein the sense strand comprises a nucleotide sequence as set forth in SEQ ID NO: 1220 and wherein the antisense strand comprises a nucleotide sequence as set forth in SEQ ID NO:1221.

81. The method of claim 79, wherein the sense strand comprises SEQ ID NO: 1230, and wherein the antisense strand comprises SEQ ID NO: 1231.

82. The method of claim 79, wherein the sense strand comprises SEQ ID NO: 1232, and wherein the antisense strand comprises SEQ ID NO: 1233.

83. The method of claim 79, wherein the sense strand comprises SEQ ID NO: 1188, and wherein the antisense strand comprises SEQ ID NO: 1189.

84. The method of claim 79, wherein the sense strand comprises SEQ ID NO: 1190, and wherein the antisense strand comprises SEQ ID NO: 1191.

85. The method of claim 79, wherein the sense strand comprises SEQ ID NO: 1244, and wherein the antisense strand comprises SEQ ID NO: 1245.

86. The method of claim 79, wherein the sense strand comprises SEQ ID NO:1250, and wherein the antisense strand comprises SEQ ID NO:1251.

87. The method of claim 79, wherein the sense strand comprises SEQ ID NO:1254, and wherein the antisense strand comprises SEQ ID NO:1255.

88. The method of claim 79, wherein the sense strand comprises SEQ ID NO:1246, and wherein the antisense strand comprises SEQ ID NO:1247.

89. The method of any one of Claims 76 to 88, wherein the disease, disorder or condition associated with *PNPLA3* expression is selected from the group consisting of cardiometabolic disease, alcoholic hepatitis (AH), alcoholic liver disease (ALD), cirrhosis, hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

90. Use of the RNAi oligonucleotide of any one of Claims 1 to 67, or the pharmaceutical composition of Claim 69, in the manufacture of a medicament for the treatment of a disease, disorder or condition associated with *PNPLA3* expression, optionally for the treatment of cardiometabolic disease, alcoholic hepatitis (AH), alcoholic liver disease (ALD), cirrhosis,

hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

91. The RNAi oligonucleotide of any one of Claims 1 to 67, or the pharmaceutical composition of Claim 69, for use, or adaptable for use, in the treatment of a disease, disorder or condition associated with *PNPLA3* expression, optionally for the treatment of cardiometabolic disease, alcoholic hepatitis (AH), CCA, PSC, alcoholic liver disease (ALD), cirrhosis, hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

92. A kit comprising the RNAi oligonucleotide of any one of Claims 1 to 67, an optional pharmaceutically acceptable carrier, and a package insert comprising instructions for administration to a subject having a disease, disorder or condition associated with *PNPLA3* expression.

93. The use of Claim 90, the RNAi oligonucleotide or pharmaceutical composition for use, or adaptable for use, of Claim 91, or the kit of Claim 92, wherein the disease, disorder or condition associated with *PNPLA3* expression is cardiometabolic disease, alcoholic hepatitis (AH), alcoholic liver disease (ALD), cirrhosis, hepatocellular carcinoma (HCC), non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

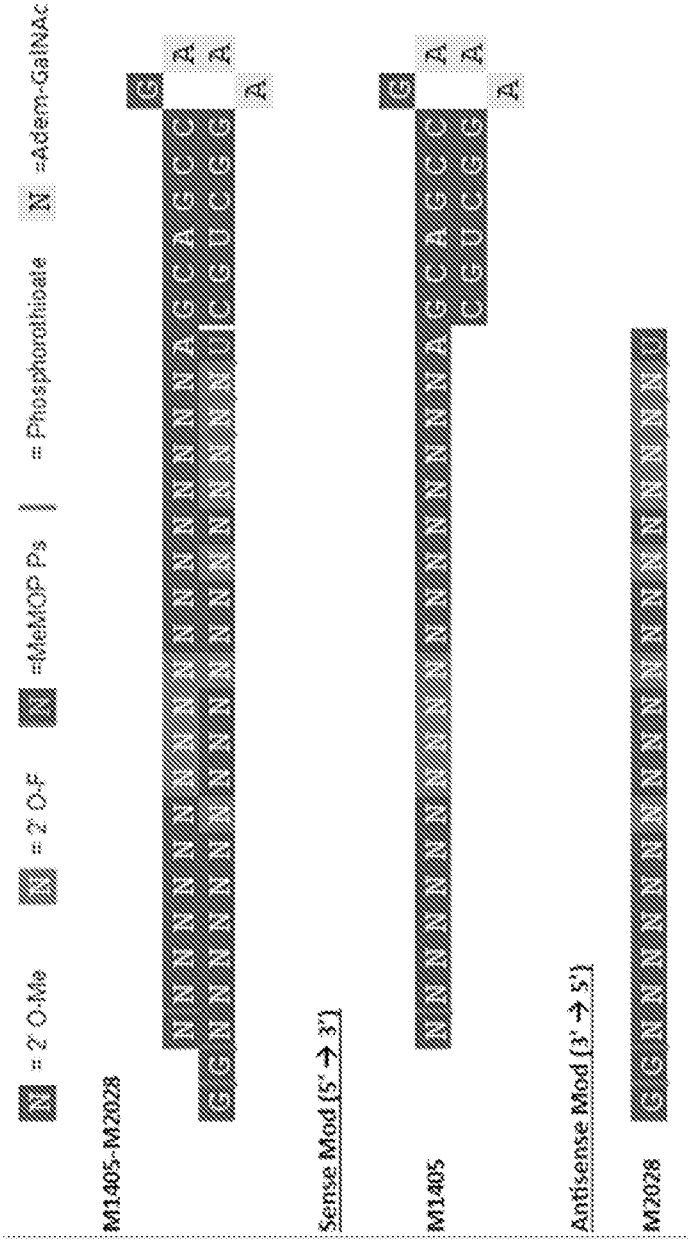
= 2' O-Me
= 2' O-F
=MeMOP Ps
= Phosphorothioate
N =Adem-GalNAc
M1405-M2028
Sense Mod (5' → 3')
M1405
Antisense Mod (3' → 5')
M2028

FIG. 1

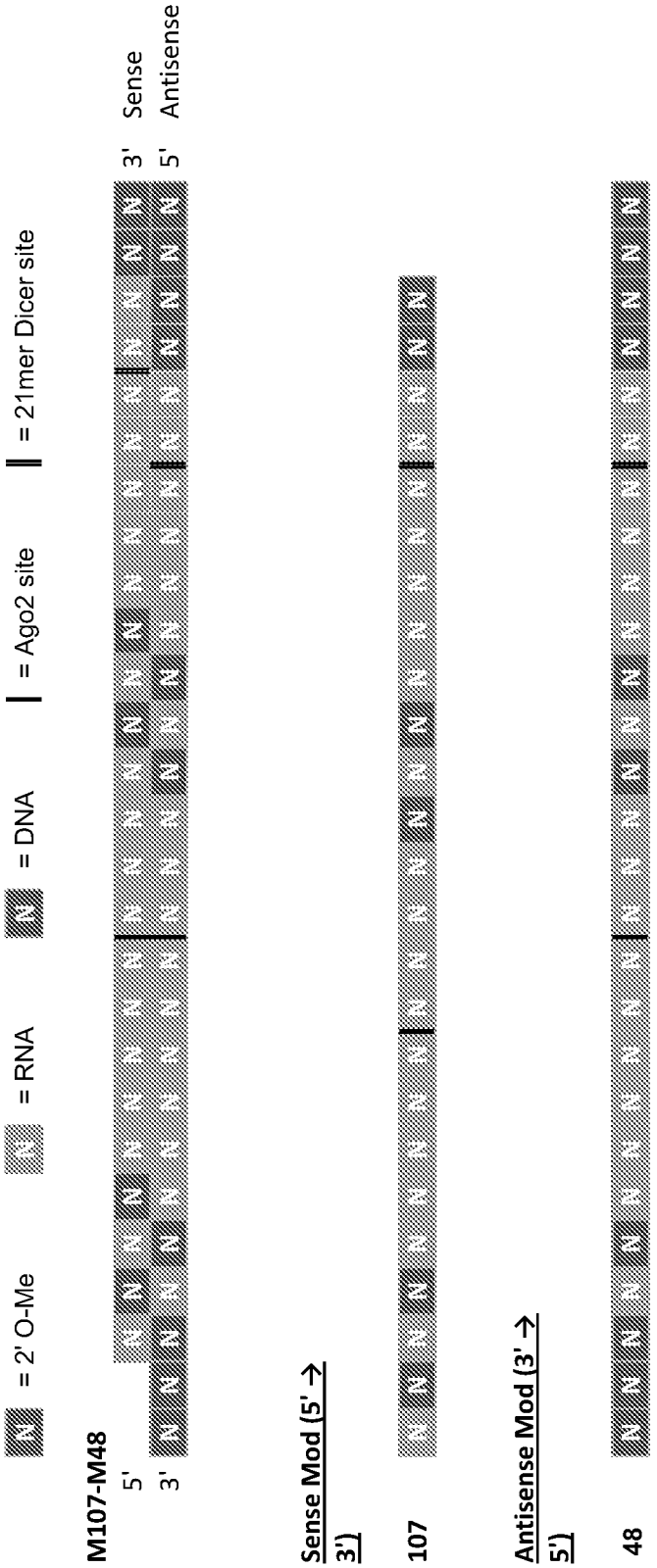
= 2' O-Me
= RNA
= DNA
= Ago2 site
= 21mer Dicer site
M107-M48
5'
3'
3'
5'
Sense
Antisense
Sense Mod (5' → 3')
107
Antisense Mod (3' → 5')
48

FIG. 2

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/713 A61P1/16
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 A61K A61P

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, WPI Data, Sequence Search, EMBL, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/118638 A2 (AMGEN INC [US]) 20 June 2019 (2019-06-20)	1-6, 8-12, 23-36, 51, 68-77, 89-93
Y	paragraphs [0037], [0047], [0053], [0131] - [0144], [0153]; claims 1-15,23-28,39-41; examples 1-6; tables 1,2; sequences 613,614,1585,1586	7,13-22, 37-41, 52-58, 78-80

-/--

[x] Further documents are listed in the continuation of Box C.

[x] 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	Date of mailing of the international search report
18 July 2022	26/09/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bucka, Alexander

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/123508 A2 (AMGEN INC [US]) 18 June 2020 (2020-06-18) paragraphs [0038], [0054], [0132] - [0137]; claims 1-30,41-43; examples 1-8; tables 1,2; sequences 1585,1586,2035,2036	1-6, 8-12, 23-36, 51, 68-77, 89-93
A	WO 2016/130806 A2 (ALNYLAM PHARMACEUTICALS INC [US]) 18 August 2016 (2016-08-18) claims 1-17,45-52,78-99; examples 1-4; sequences 54,146,1239,1329,1419,1509	1-41, 51-58, 68-80, 89-93
Y	WO 2021/067744 A1 (DICERNA PHARMACEUTICALS INC [US]) 8 April 2021 (2021-04-08) page 30, paragraph 102 - paragraph 108; claims 1-23,28-30	7,13-22, 37-41, 52-58, 78-80
A	WO 2018/223081 A1 (WAVE LIFE SCIENCES LTD [SG]; PFIZER [US]) 6 December 2018 (2018-12-06) claims 1,35-39,48-50,73-85; table 1A	1-41, 51-58, 68-80, 89-93
A	WO 2015/085158 A1 (DICERNA PHARMACEUTICALS INC [US]) 11 June 2015 (2015-06-11) figures 8A, 8B; sequence 3479	1-41, 51-58, 68-80, 89-93
A	BJÖRN CARLSSON ET AL: "Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis", ALIMENTARY PHARMACOLOGY & THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, GB, vol. 51, no. 12, 7 May 2020 (2020-05-07), pages 1305-1320, XP071546361, ISSN: 0269-2813, DOI: 10.1111/APT.15738 the whole document	1-41, 51-58, 68-80, 89-93

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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. [X] forming part of the international application as filed:

      [ ] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

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

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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PCT/US2022/024657

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.:

41, 58(completely); 1-40, 51-57, 68-80, 89-93(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: 41, 58(completely); 1-40, 51-57, 68-80, 89-93(partially)

An RNAi oligonucleotide for reducing PNPLA3 expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein the antisense strand comprises a region of complementarity to the PNPLA3 mRNA target sequence of SEQ ID NO:1167, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

2-10. claims: 1-40, 42-57, 59-93(all partially)

An RNAi oligonucleotide for reducing PNPLA3 expression, the oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a duplex region, wherein in each separate invention the antisense strand comprises a region of complementarity to a PNPLA3 mRNA target sequence of any one of SEQ ID NOS:1168 to 1176, and wherein the region of complementarity is at least 15 contiguous nucleotides in length.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/024657

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