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(71) Applicant: ROCHE INNOVATION CENTER COPENHAGEN A/S [DK/DK]; Fremtidsvej 3, 2970 Hørsholm (DK).

(72) Inventors: PEDERSEN, Lykke; c/o Roche Innovation Center Copenhagen A/S Fremtidsvej 3, 2970 Hørsholm (DK). RASMUSSEN, Søren; c/o Roche Innovation Center Copenhagen A/S Fremtidsvej 3, 2970 Hørsholm (DK). LICHINCHI, Gianluigi; c/o Roche Innovation Center Copenhagen A/S Fremtidsvej 3, 2970 Hørsholm (DK). SONDERGAARD, Christoffer; c/o Roche Innovation Center Copenhagen A/S Fremtidsvej 3, 2970 Hørsholm (DK).

(74) Agent: RUDOLPH HANSEN, Marianne; Fremtidsvej 3, 2970 Hørsholm (DK).

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(54) Title: OLIGONUCLEOTIDES FOR MODULATING SCN9A EXPRESSION

(57) Abstract: The present invention relates to oligonucleotides (oligomers) that are complementary to voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A, which encodes the voltage-gated sodium channel Na_v1.7. The oligonucleotides of the invention are capable of inhibiting the expression of voltage-gated sodium ion channels, such as Na_v1.7, and are useful in the prevention or the treatment of pain.



WO 2019/243430 A1

OLIGONUCLEOTIDES FOR MODULATING SCN9A EXPRESSION

FIELD OF INVENTION

The present invention relates to oligonucleotides (oligomers) that are complementary to voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A, which encodes the voltage-gated sodium channel Nav1.7. The oligonucleotides of the invention are capable of inhibiting the expression of voltage-gated sodium ion channels, such as Nav1.7, and are useful in the prevention or the treatment of pain.

BACKGROUND

Voltage-gated sodium channels (Navs) play essential roles in excitable tissues, with their activation and opening resulting in the initial phase of the action potential. The cycling of Navs through open, closed and inactivated states, and their closely choreographed relationships with the activities of other ion channels lead to exquisite control of intracellular ion concentrations

Nav1.7 is a voltage activated ion channel involved expressed almost exclusively in the small cell peripheral sensory nerves. Mice with a conditional knock-out of Nav1.7 in sensory neurons

displayed an antinociceptive phenotype (Nassar et al., 2004, Proc Natl Acad Sci U S A. 2004 Aug 24;101(34):12706-11). The role of Nav1.7 in pain sensation in humans was demonstrated by association between the spontaneous pain syndrome inherited erythromelalgia (IEM) (Yang et al., J Med Genet. 2004;41(3):171-4) and paroxysmal extreme pain disorder (PEPD) (Fertleman et al., J Neurol Neurosurg Psychiatry. 2006 Nov;77(11):1294-5) and gain of function mutation in Nav1.7 of these patients (Cummins et al., J Neurosci. 2004;24(38):8232-8236) .

Further support for Nav1.7 was generated by identification of loss of function mutations that resulted in congenital insensitivity to pain (Cox et al., Nature AAA. 2006;7121:894-8). These findings have kicked of a number of small molecule drug discovery programs for identification of Nav1.7 modulators, however it appears that finding good compounds with high selectivity and good PK/PD properties have been challenging.

US2016024208 discloses human antibodies to Nav1.7.

WO02083945 refers to synthetic oligonucleotides with antisense sequence to specific regions of SCN5A and optionally also SCN9A for use in the treatment of breast cancer.

US2007/212685 refers to methods of identifying analgesic agents and mentions that specific compounds which will modulate the gene expression or gene transcript levels in a cell of SCN9A include antisense nucleic acids.

US2010273857A refers to methods, sequences and nucleic acid molecules used to treat pain via locally administering siRNA molecules that suppress the expression of amino acid sequences that encode for Nav1.7 channels or that otherwise inhibit the function of Nav1.7

channels, and reports that local suppression of Nav1.7 channel levels and/or function will occur in the peripheral sensory neurons of the dorsal root ganglia.

WO12162732 relates to novel screening assays for modulating sodium channels, particularly voltage-gated sodium channels.

5 KR20110087436 discloses an SCN9A antisense oligonucleotide.

Mohan *et al.*, Pain (2018) Volume 159·Number 1, p139 – 149 discloses antisense oligonucleotides targeting Nav1.7, and characterize the pharmacodynamic activity of ASOs in spinal cord and dorsal root ganglia (DRG) in rodents.

10 WO18051175 discloses SCN9A antisense peptide nucleic acid oligonucleotides targeting a part of the human SCN9A pre-mRNA. The peptide nucleic acid derivatives potentially induce splice variants of the SCN9A mRNA in cells, and are useful to safely treat pains or conditions involving Nav1.7 activity.

There is therefore a need for antisense oligonucleotides therapeutics which are effective in inhibiting expression of voltage-gated sodium ion channel encoding nucleic acids, such as

15 SCN9A in humans, such as for the prevention or treatment of pain.

OBJECTIVE OF THE INVENTION

The present invention provides oligonucleotides, including LNA antisense oligonucleotides targeting SCN9A which are capable of inhibiting the expression of Nav1.7 in a cell which is expressing Nav1.7. The present invention further provides oligonucleotides targeting SCN10A
20 which inhibit the expression of Nav1.8 in a cell which is expressing Nav1.8. In some aspects, the invention provides oligonucleotides which target both SCN9A and SCN10A nucleic acid targets. The oligonucleotide of the invention may be used in the prevention or treatment of pain. The invention further provides advantageous target site sequences on the human Nav1.7 pre-mRNA which may be targeted by oligonucleotide inhibitors of human Nav1.7 such as
25 antisense oligonucleotides or RNAi agents, such as siRNAs or shRNAs.

SUMMARY OF INVENTION

The present invention relates to oligonucleotides targeting a nucleic acid encoding a voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A or SCN10A, or in some embodiments both SCN9A (a Nav1.7 nucleic acid target) and SCN10A (a Nav1.8 nucleic acid
30 target).

The oligonucleotide of the invention may be an antisense oligonucleotide.

The oligonucleotides of the invention are capable of inhibiting the expression of the target nucleic acid, such as SCN9A or SCN10A, or in some embodiments are capable of inhibiting the expression of both SCN9A and SCN10A, in a cell which is expressing said target nucleic
35 acid(s). Suitably the target nucleic acid expressed in the cell may be a mammalian cell, such as

cynomolgus monkey cell or a pig cell, or preferably a human SCN9A or a human SCN10A mRNA or pre-mRNA sequence.

Alternatively stated, the oligonucleotides of the invention are capable of inhibiting the expression of Nav1.7 or Nav1.8 in a cell, such as a mammalian or human cell, or in some

5 embodiments are capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell such as in a mammalian, such as a cynomolgus monkey cell or a pig cell, or preferably in a human cell. The cell is expressing the target voltage-gated sodium ion channel protein.

The invention further provides target sequences of the human SCN9A pre-mRNA which are useful in targeting complementary oligonucleotides for inhibition of SCN9A expression.

10 Advantageously the oligonucleotide of the invention is an antisense oligonucleotide such as an LNA antisense oligonucleotide.

The invention provides an antisense oligonucleotide (e.g. an LNA antisense oligonucleotide) of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to

15 SEQ ID NO: 1.

The invention provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 and Nav1.8 in a

20 cell, wherein the contiguous nucleotide sequence is complementary to human Nav1.7 and human Nav1.8 target nucleic acids, for example the target nucleic acids shown as SEQ ID NO 1 and SEQ ID NO 651 respectively.

The invention provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90%

25 complementarity, such as 100% complementarity, to a human Nav1.7 target nucleic acid and a human Nav1.8 target nucleic acid, and is which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell. In some embodiments, the contiguous nucleotide sequence of the oligonucleotide of the invention is 100% complementary to SEQ ID NO 1, and is at least 90% complementary such as advantageously

30 100% complementary to SEQ ID NO 651.

The invention provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a

cell, wherein the contiguous nucleotide sequence is 100% complementary to SEQ ID NO 1 and is at least 90% complementary such as 100% complementary to SEQ ID NO 651.

In some embodiments, the oligonucleotide of the invention comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID
5 NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

The invention provides an antisense oligonucleotide selected from the group consisting of CMP
ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ;
63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1
10 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ;
90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ;
103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ;
114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ;
125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ;
15 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ;
147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ;
158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ;
169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ;
180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ;
20 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ;
202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ;
213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ;
224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ;
235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ;
25 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ;
257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ;
268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ;
279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ;
290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ;
30 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ;
312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ;
323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ;
334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ; 343_1 ; 344_1 ;
345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ;
35 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ;
367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ;

378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ;
389_1 ; 390_1 ; 391_1 ; 392_1 ; 393_1 ; 394_1 ; 395_1 ; 396_1 ; 397_1 ; 398_1 ; 399_1 ;
400_1 ; 401_1 ; 402_1 ; 403_1 ; 404_1 ; 405_1 ; 406_1 ; 407_1 ; 408_1 ; 409_1 ; 410_1 ;
411_1 ; 412_1 ; 413_1 ; 414_1 ; 415_1 ; 416_1 ; 417_1 ; 418_1 ; 419_1 ; 420_1 ; 421_1 ;
5 422_1 ; 423_1 ; 424_1 ; 425_1 ; 426_1 ; 427_1 ; 428_1 ; 429_1 ; 430_1 ; 431_1 ; 432_1 ;
433_1 ; 434_1 ; 435_1 ; 436_1 ; 437_1 ; 438_1 ; 439_1 ; 440_1 ; 441_1 ; 442_1 ; 443_1 ;
444_1 ; 445_1 ; 446_1 ; 447_1 ; 448_1 ; 449_1 ; 450_1 ; 451_1 ; 452_1 ; 453_1 ; 454_1 ;
455_1 ; 456_1 ; 457_1 ; 458_1 ; 459_1 ; 460_1 ; 461_1 ; 462_1 ; 463_1 ; 464_1 ; 465_1 ;
466_1 ; 467_1 ; 468_1 ; 469_1 ; 470_1 ; 471_1 ; 472_1 ; 473_1 ; 474_1 ; 475_1 ; 476_1 ;
10 477_1 ; 478_1 ; 479_1 ; 480_1 ; 481_1 ; 482_1 ; 483_1 ; 484_1 ; 485_1 ; 486_1 ; 487_1 ;
488_1 ; 489_1 ; 490_1 ; 491_1 ; 492_1 ; 493_1 ; 494_1 ; 495_1 ; 496_1 ; 497_1 ; 498_1 ;
499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ; 506_1 ; 507_1 ; 508_1 ; 509_1 ;
510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ; 513_3 ; 513_4 ; 514_1 ; 514_2 ;
514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ; 515_6 ; 516_1 ; 516_2 ; 516_3 ;
15 516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ; 517_4 ; 517_5 ; 517_6 ; 517_7 ;
517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ; 519_1 ; 519_2 ; 519_3 ; 519_4 ;
519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ; 521_1 ; 521_2 ; 521_3 ; 521_4 ;
521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ; 523_3 ; 523_4 ; 523_5 ; 524_1 ;
525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ; 532_1 ; 533_1 ; 534_1 ; 535_1 ;
20 536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ; 543_1 ; 544_1 ; 545_1 ; 546_1 ;
547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ; 554_1 ; 555_1 ; 556_1 ; 557_1 ;
558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ; 565_1 ; 566_1 ; 567_1 ; 568_1 ;
569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ; 576_1 ; 577_1 ; 578_1 ; 579_1 ;
580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ; 587_1 ; 588_1 ; 589_1 ; 590_1 ;
25 591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ; 598_1 ; 599_1 ; 600_1 ; 601_1 ;
602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ; 609_1 ; 610_1 ; 611_1 ; 612_1 ;
613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ; 620_1 ; 621_1 ; 622_1 ; 623_1 ;
624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ; 631_1 ; 632_1 ; 633_1 ; 634_1 ;
635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1 ; and 641_1 ; or selected from the group
30 selected of 642_1 , 643_1 , 644_1 , 645_1 , 646_1 , 647_1 , 648_1 , 649_1 and 650_1 .

The invention provides an oligonucleotide capable of inhibiting the expression of human SNC9A
in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising
at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group
consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158,
35 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339,
256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472,
471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415,

199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 5 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321, 305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155, 450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218, 182, 448, 300, 481, 427, 207, 367, 240, 231, 364, 355, 431, 497, 397, 465, 271, 502, 151, 178, 499, 421, 131, 309, 491, 261, 121, 128, 84, 304, 264, 493, 185, 237, 139, 441, 169, 160, 102, 296, 164, 362, 500, and 10 100.

The invention provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 642, 643, 644, 645, 646, 647, 648, 649 and 650.

15 The invention provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The invention provides an oligonucleotide capable of inhibiting the expression of human SNC9A 20 in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The invention provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide 25 sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The invention provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide 30 sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The invention provides an antisense gapmer oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The invention provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

- 5 The invention provides an antisense gapmer oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 14 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

- 10 The invention provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The invention provides a conjugate comprising the antisense oligonucleotide according to the invention and at least one conjugate moiety covalently attached to said oligonucleotide.

- 15 The invention provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell.

- 20 The invention provides for an antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell.

25

In some embodiments of the invention the oligonucleotide comprises a contiguous nucleotide sequence which comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

- 30 In some embodiments of the invention the oligonucleotide comprises a contiguous nucleotide sequence which comprises at least 14 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

The invention provides a pharmaceutically acceptable salt of the antisense oligonucleotide according to the invention, or the conjugate according to the invention.

The invention provides a pharmaceutical composition comprising the antisense oligonucleotide of the invention or the conjugate of the invention and a pharmaceutically acceptable diluent,
5 solvent, carrier, salt and/or adjuvant.

The invention provides an in vivo or in vitro method for inhibiting SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention in an effective amount to said cell.

10 The invention provides an in vivo or in vitro method for inhibiting SCN9A and SCN10A expression in a target cell which is expressing SCN9A and SCN10A, said method comprising administering an oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention in an effective amount to said cell.

The invention provides a method for treating or preventing pain in a subject such as a human,
15 who is suffering from or is likely to suffer pain, comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention, such as to prevent or alleviate the pain.

The invention provides for the antisense oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention for use in medicine.
20

The invention provides for the antisense oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention for use in the treatment or prevention or alleviation of pain

The invention provides for the use of the antisense oligonucleotide of the invention or the conjugate of the invention or the pharmaceutical salt or composition of the invention, for the
25 preparation of a medicament for the treatment, prevention or alleviation of pain.

In some embodiments the pain is chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain.

In some embodiments the pain is caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or
30

In some embodiments the pain is caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or

In some embodiments the pain is neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

DEFINITIONS

5 ***Oligonucleotide***

The term "oligonucleotide" as used herein is defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such covalently bound nucleosides may also be referred to as nucleic acid molecules or oligomers.

Oligonucleotides are commonly made in the laboratory by solid-phase chemical synthesis
10 followed by purification and isolation. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide of the invention is man-made, and is chemically synthesized, and is typically purified or isolated. The oligonucleotide of the invention may comprise one or more modified nucleosides or nucleotides, such as 2' sugar
15 modified nucleosides.

The oligonucleotide of the invention may be an antisense oligonucleotide, or may form part of a siRNA, such as the antisense strand of a siRNA targeting the target nucleic acid.

Advantageously, the oligonucleotide is an antisense oligonucleotide. Advantageous designs of antisense oligonucleotides for use in the antisense oligonucleotide of the invention, or
20 contiguous nucleotide sequence thereof, include gapmers.

RNAi Agents

The terms "iRNA," "RNAi agent," "iRNA agent," and "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA nucleosides herein and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex
25 (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process as RNA interference (RNAi). The iRNA modulates. e.g., inhibits, the expression of the target nucleic acid in a cell. e.g. a cell within a subject. such as a mammalian subject. RNAi agents includes single stranded RNAi agents and double stranded siRNAs, as well as short hairpin RNAs (shRNAs). The oligonucleotide of the invention or contiguous nucleotide sequence
30 thereof may be in the form of a RNAi agent, or form part of a RNAi agent, such as an siRNA or shRNA. In some embodiments of the invention, the oligonucleotide of the invention or contiguous nucleotide sequence thereof is a RNAi agent, such as a siRNA.

siRNAs

The term siRNA refers to a small interfering ribonucleic acid RNAi agents, is a class of double-stranded RNA molecules, also known in the art as short interfering RNA or silencing RNA.

siRNAs typically comprise a sense strand (also referred to as a passenger strand) and an antisense strand (also referred to as the guide strand), wherein each strand are of 17 – 30

5 nucleotides in length, typically 19 – 25 nucleosides in length, wherein the antisense strand is complementary, such as fully complementary, to the target nucleic acid (suitably a mature mRNA sequence), and the sense strand is complementary to the antisense strand so that the sense strand and antisense strand form a duplex or duplex region. siRNA strands may form a blunt ended duplex, or advantageously the sense and antisense strand 3' ends may form a 3' overhang of e.g. 1, 2 or 3 nucleosides. In some embodiments, both the sense strand and antisense strand have a 2nt 3' overhang. The duplex region may therefore be, for example 17 – 25 nucleotides in length, such as 21-23 nucleotide in length.

Once inside a cell the antisense strand is incorporated into the RISC complex which mediate target degradation or target inhibition of the target nucleic acid. siRNAs typically comprise modified nucleosides in addition to RNA nucleosides, or in some embodiments all of the nucleotides of an siRNA strand may be modified (the sense . 2' sugar modified nucleosides such as LNA (see WO2004083430, WO2007085485 for example), 2'-fluoro, 2'-O-methyl or 2'-O-methoxyethyl may be incorporated into siRNAs. In some embodiments the passenger strand of the siRNA may be discontinuous (see WO2007107162 for example). The incorporation of thermally destabilizing nucleotides occurring at a seed region of the antisense strand of siRNAs have been reported as useful in reducing off-target activity of siRNAs (see WO18098328 for example).

In some embodiments, the dsRNA agent, such as the siRNA of the invention, comprises at least one modified nucleotide. In some embodiments, substantially all of the nucleotides of the sense strand comprise a modification; substantially all of the nucleotides of the antisense strand comprise a modification or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification. In yet other embodiments, all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In some embodiments, the modified nucleotides may be independently selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O -allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl

modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, an unlinked nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide, and a 2'-O-(N-methylacetamide) modified nucleotide, and combinations thereof. Suitable the siRNA comprises a 5' phosphate group or a 5'-phosphate mimic at the 5' end of the antisense strand. In some embodiments the 5' end of the antisense strand is a RNA nucleoside.

In one embodiment, the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

The phosphorothioate or methylphosphonate internucleotide linkage may be at the 3'-terminus one or both strand (e.g., the antisense strand; or the sense strand); or the phosphorothioate or methylphosphonate internucleoside linkage may be at the 5'-terminus of one or both strands (e.g., the antisense strand; or the sense strand); or the phosphorothioate or methylphosphonate internucleoside linkage may be at the both the 5'- and 3'-terminus of one or both strands (e.g., the antisense strand; or the sense strand). In some embodiments the remaining internucleoside linkages are phosphodiester linkages.

The dsRNA agent may further comprise a ligand. In some embodiments, the ligand is conjugated to the 3' end of the sense strand.

For biological distribution, siRNAs may be conjugated to a targeting ligand, and/or be formulated into lipid nanoparticles, for example.

Other aspects of the invention relate to pharmaceutical compositions comprising these dsRNA, such as siRNA molecules suitable for therapeutic use, and methods of inhibiting the expression of the target gene by administering the dsRNA molecules such as siRNAs of the invention, e.g., for the treatment of various disease conditions as disclosed herein.

Antisense oligonucleotides

The term "Antisense oligonucleotide" as used herein is defined as oligonucleotides capable of modulating expression of a target gene by hybridizing to a target nucleic acid, in particular to a contiguous sequence on a target nucleic acid. The antisense oligonucleotides are not essentially double stranded and are therefore not siRNAs or shRNAs. Preferably, the antisense oligonucleotides of the present invention are single stranded. It is understood that single stranded oligonucleotides of the present invention can form hairpins or intermolecular duplex structures (duplex between two molecules of the same oligonucleotide), as long as the degree

of intra or inter self-complementarity is less than 50% across of the full length of the oligonucleotide.

Advantageously, the single stranded antisense oligonucleotide of the invention does not contain RNA nucleosides (2'-OH unmodified ribose).

- 5 Advantageously, the antisense oligonucleotide of the invention comprises one or more modified nucleosides or nucleotides, such as 2' sugar modified nucleosides. Furthermore, it is advantageous that the nucleosides which are not modified are DNA nucleosides. LNA antisense oligonucleotides are highly advantageous in the context of the antisense oligonucleotide of the invention.

10 ***Contiguous Nucleotide Sequence***

The term "contiguous nucleotide sequence" refers to the region of the oligonucleotide which is complementary to the target nucleic acid. The term is used interchangeably herein with the term "contiguous nucleobase sequence" and the term "oligonucleotide motif sequence". In some embodiments all the nucleotides of the oligonucleotide constitute the contiguous nucleotide
15 sequence. In some embodiments the oligonucleotide comprises the contiguous nucleotide sequence, such as a gapmer region (as illustrated herein by the formula F-G-F'), and may optionally comprise further nucleotide(s), for example a nucleotide linker region which may be used to attach a functional group to the contiguous nucleotide sequence. The nucleotide linker region may or may not be complementary to the target nucleic acid.

20 ***Nucleotides***

Nucleotides are the building blocks of oligonucleotides and polynucleotides, and for the purposes of the present invention include both naturally occurring and non-naturally occurring nucleotides. In nature, nucleotides, such as DNA and RNA nucleotides comprise a ribose sugar moiety, a nucleobase moiety and one or more phosphate groups (which is absent in
25 nucleosides). Nucleosides and nucleotides may also interchangeably be referred to as "units" or "monomers".

Modified nucleoside

The term "modified nucleoside" or "nucleoside modification" as used herein refers to nucleosides modified as compared to the equivalent DNA or RNA nucleoside by the introduction
30 of one or more modifications of the sugar moiety or the (nucleo)base moiety. In a preferred embodiment the modified nucleoside comprise a modified sugar moiety. The term modified nucleoside may also be used herein interchangeably with the term "nucleoside analogue" or modified "units" or modified "monomers". Nucleosides with an unmodified DNA or RNA sugar moiety are termed DNA or RNA nucleosides herein. Nucleosides with modifications in the base

region of the DNA or RNA nucleoside are still generally termed DNA or RNA if they allow Watson Crick base pairing.

Modified internucleoside linkage

The term “modified internucleoside linkage” is defined as generally understood by the skilled person as linkages other than phosphodiester (PO) linkages, that covalently couples two nucleosides together. The oligonucleotides of the invention may therefore comprise modified internucleoside linkages. In some embodiments, the modified internucleoside linkage increases the nuclease resistance of the oligonucleotide compared to a phosphodiester linkage. For naturally occurring oligonucleotides, the internucleoside linkage includes phosphate groups creating a phosphodiester bond between adjacent nucleosides. Modified internucleoside linkages are particularly useful in stabilizing oligonucleotides for *in vivo* use, and may serve to protect against nuclease cleavage at regions of DNA or RNA nucleosides in the oligonucleotide of the invention, for example within the gap region G of a gapmer oligonucleotide, as well as in regions of modified nucleosides, , such as region F and F’.

In an embodiment, the oligonucleotide comprises one or more internucleoside linkages modified from the natural phosphodiester. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified, such as at least 60%, such as at least 70%, such as at least 75%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are modified. It will be recognized that, in some embodiments the nucleosides which link the oligonucleotide of the invention to a non-nucleotide functional group, such as a conjugate, may be phosphodiester. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages.

With the oligonucleotides of the invention it is advantageous to use phosphorothioate internucleoside linkages.

Phosphorothioate internucleoside linkages are particularly useful due to nuclease resistance, beneficial pharmacokinetics and ease of manufacture. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate, such as at least 60%, such as at least 70%, such as at least 75%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate.

Advantageously, all the internucleoside linkages of the contiguous nucleotide sequence of the oligonucleotide are phosphorothioate, or all the internucleoside linkages of the oligonucleotide are phosphorothioate linkages.

It is recognized that, as disclosed in EP 2 742 135, antisense oligonucleotides may comprise other internucleoside linkages (other than phosphodiester and phosphorothioate), for example alkyl phosphonate/methyl phosphonate internucleoside, which according to EP 2 742 135 may for example be tolerated in an otherwise DNA phosphorothioate the gap region.

Nucleobase

The term nucleobase includes the purine (e.g. adenine and guanine) and pyrimidine (e.g. uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present invention the term nucleobase also encompasses modified nucleobases which may differ from naturally occurring nucleobases, but are functional during nucleic acid hybridization. In this context "nucleobase" refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymidine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1.

In some embodiments the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobase selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiazolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil 5-thiazolo-uracil, 2-thio-uracil, 2-thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine and 2-chloro-6-aminopurine.

The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, e.g. A, T, G, C or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the nucleobase moieties are selected from A, T, G, C, and 5-methyl cytosine. Optionally, for LNA gapmers, 5-methyl cytosine LNA nucleosides may be used.

Modified oligonucleotide

The term modified oligonucleotide describes an oligonucleotide comprising one or more sugar-modified nucleosides and/or modified internucleoside linkages. The term chimeric oligonucleotide is a term that has been used in the literature to describe oligonucleotides with modified nucleosides.

Complementarity

The term “complementarity” describes the capacity for Watson-Crick base-pairing of nucleosides/nucleotides. Watson-Crick base pairs are guanine (G)-cytosine (C) and adenine (A) - thymine (T)/uracil (U). It will be understood that oligonucleotides may comprise

5 nucleosides with modified nucleobases, for example 5-methyl cytosine is often used in place of cytosine, and as such the term complementarity encompasses Watson Crick base-pairing between non-modified and modified nucleobases (see for example Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1).

10 The term “% complementary” as used herein, refers to the proportion of nucleotides (in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are complementary to a reference sequence (e.g. a target sequence or sequence motif). The percentage of complementarity is thus calculated by counting the number of aligned nucleobases that are complementary (from Watson Crick base
15 pair) between the two sequences (when aligned with the target sequence 5'-3' and the oligonucleotide sequence from 3'-5'), dividing that number by the total number of nucleotides in the oligonucleotide and multiplying by 100. In such a comparison a nucleobase/nucleotide which does not align (form a base pair) is termed a mismatch. Insertions and deletions are not allowed in the calculation of % complementarity of a contiguous nucleotide sequence. It will be
20 understood that in determining complementarity, chemical modifications of the nucleobases are disregarded as long as the functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5'-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

The term “fully complementary”, refers to 100% complementarity.

Identity

25 The term “Identity” as used herein, refers to the proportion of nucleotides (expressed in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are identical to a reference sequence (e.g. a sequence motif). The percentage of identity is thus calculated by counting the number of
30 aligned nucleobases that are identical (a Match) between two sequences (in the contiguous nucleotide sequence of the compound of the invention and in the reference sequence), dividing that number by the total number of nucleotides in the oligonucleotide and multiplying by 100. Therefore, Percentage of Identity = (Matches x 100)/Length of aligned region (e.g. the contiguous nucleotide sequence). Insertions and deletions are not allowed in the calculation the
35 percentage of identity of a contiguous nucleotide sequence. It will be understood that in determining identity, chemical modifications of the nucleobases are disregarded as long as the

functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

Hybridization

The term “hybridizing” or “hybridizes” as used herein is to be understood as two nucleic acid strands (e.g. an oligonucleotide and a target nucleic acid) forming hydrogen bonds between base pairs on opposite strands thereby forming a duplex. The affinity of the binding between two nucleic acid strands is the strength of the hybridization. It is often described in terms of the melting temperature (T_m) defined as the temperature at which half of the oligonucleotides are duplexed with the target nucleic acid. At physiological conditions T_m is not strictly proportional to the affinity (Mergny and Lacroix, 2003, *Oligonucleotides* 13:515–537). The standard state Gibbs free energy ΔG° is a more accurate representation of binding affinity and is related to the dissociation constant (K_d) of the reaction by $\Delta G^\circ = -RT \ln(K_d)$, where R is the gas constant and T is the absolute temperature. Therefore, a very low ΔG° of the reaction between an oligonucleotide and the target nucleic acid reflects a strong hybridization between the oligonucleotide and target nucleic acid. ΔG° is the energy associated with a reaction where aqueous concentrations are 1M, the pH is 7, and the temperature is 37°C. The hybridization of oligonucleotides to a target nucleic acid is a spontaneous reaction and for spontaneous reactions ΔG° is less than zero. ΔG° can be measured experimentally, for example, by use of the isothermal titration calorimetry (ITC) method as described in Hansen et al., 1965, *Chem. Comm.* 36–38 and Holdgate et al., 2005, *Drug Discov Today*. The skilled person will know that commercial equipment is available for ΔG° measurements. ΔG° can also be estimated numerically by using the nearest neighbor model as described by SantaLucia, 1998, *Proc Natl Acad Sci USA*. 95: 1460–1465 using appropriately derived thermodynamic parameters described by Sugimoto et al., 1995, *Biochemistry* 34:11211–11216 and McTigue et al., 2004, *Biochemistry* 43:5388–5405. In order to have the possibility of modulating its intended nucleic acid target by hybridization, oligonucleotides of the present invention hybridize to a target nucleic acid with estimated ΔG° values below -10 kcal for oligonucleotides that are 10-30 nucleotides in length. In some embodiments the degree or strength of hybridization is measured by the standard state Gibbs free energy ΔG° . The oligonucleotides may hybridize to a target nucleic acid with estimated ΔG° values below the range of -10 kcal, such as below -15 kcal, such as below -20 kcal and such as below -25 kcal for oligonucleotides that are 8-30 nucleotides in length. In some embodiments the oligonucleotides hybridize to a target nucleic acid with an estimated ΔG° value of -10 to -60 kcal, such as -12 to -40, such as from -15 to -30 kcal or -16 to -27 kcal such as -18 to -25 kcal.

Target nucleic acid

According to the present invention, the target nucleic acid is a nucleic acid which encodes mammalian or human voltage-gated sodium ion channel and may for example be a gene, a RNA, a mRNA, and pre-mRNA, a mature mRNA or a cDNA sequence.

- 5 The target may therefore be referred to as a target nucleic acid. The oligonucleotide of the invention may for example target exon regions of a mammalian such as a human SCN9A target nucleic acid, or may for example target intron region of a mammalian such as a human SCN9A pre-mRNA (see Table 1).

Table 1. Human SCN9A Exons and Introns – Based upon SCN9A transcript SCN9A-201:

Exon Number	Position on SEQ ID NO 1		Intron Number	Position on SEQ ID NO 1	
	Exon start	Exon end		Intron Start	Intron End
E1	101	298	I1	298	64196
E2	64196	64503	I2	64503	68928
E3	68928	69046	I3	69046	69403
E4	69403	69492	I4	69492	70082
E5	70082	70210	I5	70210	71673
E6	71673	71764	I6	71764	72700
E7	72700	72912	I7	72912	81340
E8	81340	81403	I8	81403	82630
E9	82630	82771	I9	82771	87359
E10	87359	87565	I10	87565	89379
E11	89379	89666	I11	89666	91178
E12	91178	91549	I12	91549	94194
E13	94194	94323	I13	94323	95407
E14	95407	95645	I14	95645	97689
E15	97689	97862	I15	97862	98663
E16	98663	99019	I16	99019	103127
E17	103127	103603	I17	103603	124117
E18	124117	124237	I18	124237	133346
E19	133346	133500	I19	133500	137735
E20	137735	137908	I20	137908	142540
E21	142540	142662	I21	142662	147030
E22	147030	147311	I22	147311	148279
E23	148279	148332	I23	148332	149298
E24	149298	149435	I24	149435	171538
E25	171538	171642	I25	171642	171777
E26	171777	172047	I26	172047	176138
E27	176138	180813			

According to ENSEMBL, there are at least 13 human SCN9A transcript variants – the target nucleic acid may therefore be a SCN9A transcript (mRNA) selected from the group consisting of SEQ ID NOs 4-16:

Tname	Strand	Tstart (chr2)	Tend (chr2)	rel_start (SEQ ID NO1)	rel_end (SEQ ID NO1)	SEQ ID NO
SCN9A-203	-1	166195185	166375993	9	180817	4
SCN9A-201	-1	166195189	166375901	101	180813	5
SCN9A-212	-1	166197462	166375901	101	178540	6
SCN9A-213	-1	166198299	166205239	170763	177703	7
SCN9A-209	-1	166198411	166311756	64246	177591	8
SCN9A-207	-1	166198611	166375914	88	177391	9
SCN9A-202	-1	166198672	166311756	64246	177330	10
SCN9A-208	-1	166242624	166272749	103253	133378	11
SCN9A-210	-1	166276417	166278313	97689	99585	12
SCN9A-205	-1	166277716	166375969	33	98286	13
SCN9A-204	-1	166288615	166375944	58	87387	14
SCN9A-211	-1	166301174	166304089	71913	74828	15
SCN9A-206	-1	166302063	166376001	1	73939	16

5

Suitably, the target nucleic acid may encode an Na_v1.7 protein, in particular mammalian Na_v1.7, such as human Na_v1.7 (See for example tables 2 and 3) which provides the mRNA and pre-mRNA sequences for human, monkey, and pig Na_v1.7 encoding transcripts.

10 In some embodiments, the target nucleic acid is selected from the group consisting of SEQ ID NO: 1, 2, and 3 or naturally occurring variants thereof (e.g. sequences encoding a mammalian Na_v1.7 protein). In some embodiments the target nucleic acid is a transcript variant of SCN9A, such as a transcript variant selected from the group consisting of SEQ ID NOs 4 – 16.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

15 For *in vivo* or *in vitro* application, the oligonucleotide of the invention is typically capable of inhibiting the expression of the target nucleic acid, for example the SCN9A target nucleic acid, in a cell which is expressing the SCN9A target nucleic acid target nucleic acid. The contiguous sequence of nucleobases of the oligonucleotide of the invention is complementary, such as fully complementary to the SCN9A target nucleic acid, as measured across the length of the
20 oligonucleotide optionally excluding nucleotide based linker regions which may link the oligonucleotide to an optional functional group such as a conjugate, or other non-complementary terminal nucleotides (e.g. region D' or D''). The target nucleic acid may, in

some embodiments, be a RNA or DNA, such as a messenger RNA, such as a mature mRNA or a pre-mRNA.

In some embodiments the target nucleic acid is a RNA or DNA which encodes mammalian Nav1.7 protein, such as human SCN9A target, e.g. the human SCN9A pre-mRNA sequence, such as that disclosed as SEQ ID NO 1, or human SCN9A mature mRNA, such as that disclosed as SEQ ID NO 2. Further information on exemplary target nucleic acids is provided in tables 2 and 3.

Table 2. Genome and assembly information for SCN9A across species.

Species	Chr.	Strand	Genomic coordinates Start End		Assembly	NCBI reference sequence* accession number for mRNA
Human	2	Rev	166195185	166376001	GRCh38.p12	ENSG00000169432
Cynomolgus monkey	12	Rev	55071072	55190227	Macaca_fascicularis_5.0	ENSMFAG000000034634
Pig	15	Rev	72745114	72912407	Sscrofa11.1	ENSSSCG000000015913
Rat	3	Rev	52583951	52664209	Rnor_6.0	ENSRNOG000000006639
Mouse	2	Rev	66480080	66634962	GRCm38.p6	ENSMUSG000000075316

Fwd = forward strand. The genome coordinates provide the pre-mRNA sequence (genomic sequence). The NCBI reference provides the mRNA sequence (cDNA sequence).

*The National Center for Biotechnology Information reference sequence database is a comprehensive, integrated, non-redundant, well-annotated set of reference sequences including genomic, transcript, and protein. It is hosted at www.ncbi.nlm.nih.gov/refseq.

Table 3. Exemplary SCN9A target nucleic acid sequences.

Species	RNA type	SEQ ID NO
Human	premRNA	1
Cynomologous monkey	premRNA	2
Pig	premRNA	3

In some embodiments the target nucleic acid is the human SCN10A premRNA transcript, for example a SCN10A target nucleic acid selected from the group consisting of NCBI Genbank references: NM_006514.3 GI: 693073569, NM_001293307.2 GI: 693072645

&NM_001293306.2 GI: 693064349 – hereby incorporated by reference.

Target Sequence

The term "target sequence" as used herein refers to a sequence of nucleotides present in the target nucleic acid which comprises the nucleobase sequence which is complementary to the oligonucleotide of the invention. In some embodiments, the target sequence consists of a region on the target nucleic acid with a nucleobase sequence that is complementary to the contiguous nucleotide sequence of the oligonucleotide of the invention. This region of the target nucleic acid may interchangeably be referred to as the target nucleotide sequence, target sequence or target region. In some embodiments the target sequence is longer than the complementary sequence of a single oligonucleotide, and may, for example represent a preferred region of the target nucleic acid which may be targeted by several oligonucleotides of the invention.

The oligonucleotide of the invention comprises a contiguous nucleotide sequence which is complementary to or hybridizes to the target nucleic acid, such as a target sequence described herein. Advantageously, the contiguous nucleotide sequence of the oligonucleotide of the invention is 100% complementary to the target nucleic acid across at least 10 contiguous bases, more advantageously across at least 12 contiguous bases, more advantageously, the contiguous nucleotide sequence of the oligonucleotide of the invention is 100% complementary to the target nucleic acid across the length of the contiguous nucleotide sequence.

According to the invention, the contiguous nucleotide sequence is between 10 to 30 nucleotides, such as 12 to 30, such as 14 to 20, such as 15 to 18 contiguous nucleotides.

The invention also provides target sequences (sub-sequences) present in SEQ ID NO 1 which may be targeted by the oligonucleotides of the invention. The oligonucleotide of the invention may therefore comprise of a contiguous nucleotide sequence which is at least 90% complementary, advantageously fully complementary to a target sequence (as measured across the length of the contiguous nucleotide sequence).

In some advantageous embodiments of the invention the oligonucleotide of the invention targets both Nav1.7 and Nav1.8 target sequences. A reference human Nav1.8 pre-mRNA sequence is provided herein as SEQ ID NO 651 (see also above SCN10A premRNA transcript information). Compounds which target both Nav1.7 and Nav1.8 are suitably capable of inhibiting the expression of both SCN9A and SCN10A in a cell which is expressing both SCN9A and SCN10A.

Target Sequence List 1

In some embodiments the target sequence is a region of SEQ ID NO 1 selected from the group consisting of 617 - 630; 852 - 868; 963 - 976; 1039 - 1053; 1070 - 1085; 1375 - 1388; 1512 - 1526; 1689 - 1702; 2673 - 2691; 3189 - 3202; 3275 - 3290; 3900 - 3921; 4132 - 4145; 4795 -

4808; 4941 - 4955; 5165 - 5182; 5359 - 5372; 5430 - 5444; 5453 - 5529; 5544 - 5588; 5608 -
5675; 5695 - 5717; 5719 - 5732; 5765 - 5809; 5896 - 5909; 6019 - 6032; 6066 - 6085; 6151 -
6164; 6167 - 6180; 6357 - 6370; 6629 - 6657; 6859 - 6872; 6959 - 6972; 6998 - 7019; 7032 -
7056; 7060 - 7079; 7085 - 7098; 7102 - 7129; 7131 - 7152; 7156 - 7185; 7233 - 7247; 7254 -
5 7271; 7273 - 7295; 7297 - 7317; 7381 - 7412; 7456 - 7499; 7502 - 7522; 7527 - 7561; 7575 -
7592; 8087 - 8100; 8438 - 8454; 8475 - 8490; 8502 - 8515; 8531 - 8572; 8592 - 8610; 8612 -
8635; 8653 - 8677; 8700 - 8715; 8726 - 8741; 9093 - 9106; 9333 - 9346; 9386 - 9399; 9446 -
9463; 9468 - 9481; 9535 - 9550; 9592 - 9606; 10627 - 10643; 10767 - 10780; 11442 - 11458;
11489 - 11502; 11712 - 11725; 11797 - 11810; 11822 - 11843; 11879 - 11901; 12017 - 12030;
10 12302 - 12315; 13542 - 13555; 13740 - 13754; 14186 - 14199; 14451 - 14464; 15059 - 15072;
15354 - 15367; 15747 - 15789; 15800 - 15824; 15851 - 15864; 15869 - 15911; 15931 - 15959;
15987 - 16005; 16019 - 16037; 16039 - 16053; 16066 - 16079; 16136 - 16158; 16245 - 16258;
16304 - 16317; 16486 - 16499; 16680 - 16693; 16753 - 16766; 16962 - 16975; 16983 - 16998;
17032 - 17045; 17146 - 17167; 17536 - 17550; 17574 - 17587; 17634 - 17647; 17660 - 17676;
15 17696 - 17711; 17713 - 17739; 17741 - 17755; 17758 - 17783; 17805 - 17827; 17830 - 17846;
17851 - 17875; 17878 - 17893; 17905 - 17967; 18802 - 18816; 18829 - 18843; 18857 - 18870;
18991 - 19005; 19024 - 19037; 19475 - 19488; 19943 - 19967; 19969 - 19984; 19992 - 20043;
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 180772 - 180806. In some embodiments, the contiguous nucleotide sequence of the
 oligonucleotide of the invention comprises at least 14 contiguous nucleotides which are present
 in one of the above listed target sequences.

Target Sequence List 2

35 In some embodiments the target sequence is a region of SEQ ID NO 1 selected from the group
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136429; 136758 - 136782; 137502 - 137520; 137557 - 137574; 137690 - 137708; 137730 - 137748; 137774 - 137793; 137813 - 137838; 137844 - 137862; 137873 - 137896; 138185 - 138198; 138671 - 138684; 138800 - 138813; 139896 - 139910; 139950 - 139963; 140058 - 140081; 140195 - 140211; 140291 - 140304; 140312 - 140326; 140453 - 140466; 140756 - 5 140769; 141209 - 141222; 141238 - 141255; 141297 - 141312; 141622 - 141639; 142152 - 142174; 142262 - 142281; 142358 - 142371; 142537 - 142559; 142561 - 142583; 142615 - 142637; 142639 - 142681; 142717 - 142730; 143077 - 143090; 143169 - 143182; 143236 - 143266; 143268 - 143283; 143354 - 143368; 143616 - 143646; 144061 - 144074; 144430 - 144458; 144589 - 144603; 144783 - 144796; 144982 - 144995; 145194 - 145208; 145718 - 10 145731; 145737 - 145754; 145770 - 145793; 145907 - 145924; 146150 - 146166; 146220 - 146235; 146238 - 146251; 146600 - 146629; 146695 - 146736; 146846 - 146864; 146987 - 147002; 147054 - 147079; 147087 - 147103; 147111 - 147128; 147144 - 147163; 147171 - 147185; 147222 - 147272; 147282 - 147295; 147297 - 147318; 147727 - 147755; 148194 - 148209; 148302 - 148316; 148752 - 148767; 149049 - 149067; 149195 - 149210; 149237 - 15 149250; 149295 - 149313; 149325 - 149338; 149353 - 149419; 149421 - 149457; 149473 - 149486; 149682 - 149700; 149786 - 149799; 149849 - 149868; 150328 - 150341; 150452 - 150465; 150701 - 150714; 150865 - 150880; 151556 - 151571; 151577 - 151590; 151700 - 151713; 151837 - 151855; 151906 - 151921; 152173 - 152186; 152613 - 152631; 152770 - 152785; 152957 - 152970; 153028 - 153074; 153221 - 153235; 153359 - 153376; 153806 - 20 153819; 153972 - 153986; 153993 - 154006; 154283 - 154296; 154586 - 154602; 154608 - 154621; 154627 - 154641; 154780 - 154796; 154914 - 154927; 155159 - 155172; 155749 - 155762; 155884 - 155900; 156707 - 156721; 156960 - 156976; 156993 - 157018; 157200 - 157216; 157289 - 157306; 157573 - 157591; 158033 - 158046; 158733 - 158747; 158826 - 158842; 159019 - 159032; 159090 - 159107; 159149 - 159162; 159203 - 159225; 159339 - 25 159361; 159882 - 159896; 160203 - 160224; 160434 - 160447; 160513 - 160526; 161476 - 161502; 162507 - 162542; 163573 - 163590; 164410 - 164423; 164923 - 164938; 165090 - 165103; 165465 - 165484; 165967 - 165980; 166254 - 166274; 166504 - 166519; 167830 - 167844; 168140 - 168153; 168545 - 168576; 169037 - 169050; 169288 - 169301; 169542 - 169555; 169725 - 169739; 169760 - 169774; 170045 - 170058; 170257 - 170273; 170552 - 30 170566; 170979 - 170995; 171222 - 171235; 171388 - 171401; 171425 - 171449; 171489 - 171511; 171518 - 171551; 171565 - 171581; 171586 - 171605; 171637 - 171651; 171778 - 171808; 171834 - 171850; 171852 - 171880; 171924 - 171937; 171939 - 171964; 171966 - 171983; 171985 - 171998; 172011 - 172034; 172036 - 172053; 172070 - 172083; 172182 - 172195; 172702 - 172717; 173158 - 173171; 173187 - 173200; 173429 - 173442; 173497 - 35 173510; 173754 - 173767; 173788 - 173801; 173820 - 173835; 173864 - 173881; 173940 - 173953; 174154 - 174167; 174275 - 174288; 174701 - 174740; 174782 - 174795; 174816 - 174829; 175351 - 175364; 175398 - 175412; 175434 - 175447; 175493 - 175506; 175985 -

176026; 176167 - 176219; 176245 - 176285; 176317 - 176348; 176382 - 176402; 176404 - 176423; 176449 - 176469; 176515 - 176555; 176662 - 176678; 176683 - 176708; 176716 - 176735; 176767 - 176801; 176803 - 176816; 176830 - 176846; 176869 - 176915; 176927 - 176948; 176950 - 176981; 176989 - 177008; 177022 - 177047; 177064 - 177078; 177103 - 5 177140; 177181 - 177206; 177235 - 177248; 177253 - 177269; 177282 - 177308; 177349 - 177366; 177419 - 177438; 177476 - 177498; 177594 - 177610; 177631 - 177658; 177795 - 177813; 177866 - 177886; 177928 - 177941; 177943 - 177957; 178012 - 178030; 178218 - 178231; 178268 - 178282; 178781 - 178795; 178809 - 178826; 179174 - 179187; 179213 - 179227; 179287 - 179306; 179358 - 179382; 179500 - 179519; 179696 - 179709; 180302 - 10 180316; 180340 - 180357; 180378 - 180393; 180395 - 180410; 180438 - 180454; 180462 - 180480; 180582 - 180596; 180634 - 180658; 180679 - 180693; 180699 - 180726; and 180753 - 180771. In some embodiments, the contiguous nucleotide sequence of the oligonucleotide of the invention comprises at least 14 contiguous nucleotides which are present in one of the above listed target sequences.

15 Target Sequence List 3

In some embodiments the target sequence is a region of SEQ ID NO 1 selected from the group consisting of 852 - 865 ; 2091 - 2104 ; 2620 - 2633 ; 2675 - 2692 ; 3441 - 3454 ; 3882 - 3921 ; 3970 - 3983 ; 4532 - 4553 ; 4814 - 4827 ; 5068 - 5082 ; 5167 - 5182 ; 5184 - 5198 ; 5430 - 5444 ; 5466 - 5502 ; 5511 - 5529 ; 5544 - 5585 ; 5610 - 5633 ; 5644 - 20 5662 ; 5695 - 5717 ; 6067 - 6085 ; 6087 - 6100 ; 6117 - 6130 ; 6859 - 6873 ; 6998 - 7019 ; 7033 - 7053 ; 7089 - 7121 ; 7131 - 7152 ; 7155 - 7184 ; 7206 - 7221 ; 7254 - 7271 ; 7273 - 7295 ; 7297 - 7315 ; 7381 - 7414 ; 7456 - 7475 ; 7478 - 7499 ; 7509 - 7522 ; 7618 - 7632 ; 8388 - 8401 ; 8508 - 8529 ; 8538 - 8562 ; 8596 - 8610 ; 8612 - 8638 ; 8655 - 8677 ; 8693 - 8715 ; 8944 - 8957 ; 9534 - 9547 ; 9914 - 9928 ; 10068 - 25 10081 ; 10252 - 10265 ; 10363 - 10376 ; 10402 - 10415 ; 10626 - 10640 ; 11437 - 11450 ; 11879 - 11901 ; 11981 - 11994 ; 12145 - 12158 ; 12980 - 12993 ; 13998 - 14011 ; 15098 - 15111 ; 15628 - 15642 ; 15749 - 15792 ; 15801 - 15821 ; 15847 - 15863 ; 15869 - 15911 ; 15931 - 15959 ; 15972 - 15985 ; 16019 - 16037 ; 16039 - 16052 ; 16740 - 16753 ; 17660 - 17676 ; 17696 - 17731 ; 17761 - 17774 ; 17800 - 30 17827 ; 17851 - 17871 ; 17878 - 17896 ; 17906 - 17967 ; 18825 - 18843 ; 19063 - 19080 ; 19821 - 19834 ; 19932 - 19983 ; 20024 - 20039 ; 20045 - 20062 ; 20090 - 20125 ; 20153 - 20183 ; 20196 - 20212 ; 20288 - 20301 ; 20416 - 20435 ; 20481 - 20494 ; 20715 - 20728 ; 20739 - 20756 ; 20808 - 20826 ; 20830 - 20843 ; 20847 - 20874 ; 20892 - 20905 ; 20932 - 20959 ; 21684 - 21697 ; 22764 - 22780 ; 22819 - 35 22836 ; 22856 - 22869 ; 22880 - 22907 ; 22979 - 22992 ; 23370 - 23383 ; 23917 - 23930 ; 25007 - 25020 ; 26048 - 26068 ; 26104 - 26160 ; 26170 - 26200 ; 26224 -

26238 ; 26270 - 26301 ; 26618 - 26635 ; 26843 - 26878 ; 26915 - 26932 ; 26945 -
26958 ; 26961 - 26978 ; 27013 - 27027 ; 27068 - 27085 ; 27218 - 27231 ; 27927 -
27941 ; 28777 - 28795 ; 29103 - 29116 ; 29389 - 29403 ; 29985 - 29998 ; 30360 -
30374 ; 30376 - 30390 ; 30768 - 30782 ; 32173 - 32206 ; 32237 - 32251 ; 32260 -
5 32274 ; 32334 - 32360 ; 32569 - 32583 ; 32597 - 32611 ; 32749 - 32763 ; 33254 -
33268 ; 33299 - 33314 ; 33492 - 33506 ; 34233 - 34247 ; 34360 - 34375 ; 34562 -
34576 ; 34689 - 34703 ; 35106 - 35135 ; 35142 - 35169 ; 35259 - 35275 ; 35280 -
35308 ; 35333 - 35346 ; 35382 - 35470 ; 35477 - 35490 ; 35494 - 35534 ; 35883 -
35896 ; 36784 - 36797 ; 37504 - 37518 ; 39690 - 39704 ; 40005 - 40018 ; 41020 -
10 41037 ; 41749 - 41762 ; 43000 - 43013 ; 43043 - 43061 ; 44274 - 44287 ; 44297 -
44312 ; 44707 - 44720 ; 45664 - 45677 ; 46383 - 46397 ; 46412 - 46439 ; 46690 -
46703 ; 47443 - 47456 ; 47692 - 47707 ; 48415 - 48429 ; 48575 - 48597 ; 48608 -
48628 ; 48637 - 48650 ; 48657 - 48672 ; 48712 - 48728 ; 48798 - 48811 ; 48826 -
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15 51910 ; 52031 - 52044 ; 53317 - 53332 ; 53975 - 53988 ; 54189 - 54210 ; 54303 -
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25 65611 ; 65619 - 65640 ; 65692 - 65712 ; 65714 - 65765 ; 65767 - 65840 ; 65842 -
65894 ; 65920 - 65973 ; 65985 - 66014 ; 66025 - 66042 ; 66074 - 66091 ; 66101 -
66120 ; 66156 - 66182 ; 66216 - 66232 ; 66266 - 66282 ; 66284 - 66301 ; 66324 -
66346 ; 66366 - 66382 ; 66406 - 66423 ; 66440 - 66469 ; 66480 - 66495 ; 67055 -
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30 67294 ; 67310 - 67333 ; 67336 - 67351 ; 67597 - 67616 ; 67754 - 67768 ; 67862 -
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70635 ; 70756 - 70769 ; 71228 - 71241 ; 71564 - 71577 ; 71926 - 71941 ; 73372 -
73386 ; 74239 - 74252 ; 74809 - 74822 ; 74848 - 74880 ; 74890 - 74941 ; 74963 -
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35 76628 ; 76940 - 76953 ; 77233 - 77246 ; 78634 - 78647 ; 78772 - 78825 ; 78867 -
78888 ; 78890 - 78909 ; 78914 - 78940 ; 78955 - 78986 ; 78989 - 79024 ; 79026 -
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81044 ; 81088 - 81101 ; 81166 - 81179 ; 82854 - 82868 ; 83250 - 83263 ; 83621 -
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83950 ; 83986 - 84001 ; 84015 - 84040 ; 84060 - 84073 ; 84075 - 84097 ; 84168 -
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5 84501 ; 84503 - 84518 ; 84534 - 84547 ; 84549 - 84567 ; 84569 - 84583 ; 84653 -
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86978 ; 87641 - 87654 ; 87707 - 87720 ; 87826 - 87839 ; 87845 - 87858 ; 87879 -
87910 ; 88019 - 88059 ; 88602 - 88616 ; 89155 - 89168 ; 89484 - 89497 ; 89866 -
15 89879 ; 90038 - 90051 ; 92157 - 92170 ; 92940 - 92953 ; 93333 - 93348 ; 93404 -
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100492 - 100534 ; 100562 - 100588 ; 100607 - 100627 ; 100653 - 100667 ; 100671 -
100685 ; 102125 - 102138 ; 102391 - 102404 ; 102992 - 103005 ; 104110 - 104128 ;
20 104153 - 104171 ; 104224 - 104243 ; 104336 - 104349 ; 105025 - 105038 ; 105219 -
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107403 ; 107554 - 107567 ; 107801 - 107814 ; 108248 - 108261 ; 108503 - 108517 ;
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25 109427 ; 109935 - 109950 ; 110122 - 110145 ; 110196 - 110210 ; 110366 - 110379 ;
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111520 ; 111626 - 111639 ; 111974 - 111987 ; 112693 - 112706 ; 112899 - 112912 ;
113806 - 113819 ; 114115 - 114128 ; 115700 - 115713 ; 116267 - 116280 ; 116833 -
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30 118652 - 118665 ; 119346 - 119359 ; 120785 - 120798 ; 120858 - 120890 ; 120974 -
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125621 - 125634 ; 126633 - 126646 ; 127044 - 127057 ; 127066 - 127090 ; 127108 -
127130 ; 127196 - 127211 ; 127244 - 127265 ; 127269 - 127296 ; 127322 - 127335 ;
128260 - 128275 ; 128300 - 128318 ; 128339 - 128360 ; 128363 - 128381 ; 128394 -
35 128422 ; 128425 - 128444 ; 128822 - 128848 ; 130000 - 130013 ; 131029 - 131042 ;
131184 - 131197 ; 131926 - 131939 ; 133001 - 133014 ; 133472 - 133493 ; 134969 -
134982 ; 135682 - 135697 ; 136759 - 136791 ; 136794 - 136829 ; 136858 - 136871 ;

137867 - 137883 ; 138425 - 138438 ; 138521 - 138534 ; 138969 - 138983 ; 139291 -
139320 ; 139337 - 139422 ; 139436 - 139471 ; 139515 - 139544 ; 139550 - 139581 ;
140314 - 140327 ; 140582 - 140596 ; 141239 - 141252 ; 142647 - 142660 ; 142816 -
142829 ; 143236 - 143274 ; 144208 - 144246 ; 144250 - 144275 ; 144308 - 144322 ;
5 144326 - 144340 ; 144348 - 144387 ; 144393 - 144415 ; 144431 - 144454 ; 145603 -
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147972 - 147998 ; 148303 - 148316 ; 149483 - 149496 ; 150121 - 150136 ; 151760 -
10 151773 ; 152089 - 152102 ; 152533 - 152546 ; 152616 - 152630 ; 152825 - 152838 ;
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153177 ; 153181 - 153198 ; 153211 - 153253 ; 153255 - 153289 ; 153301 - 153341 ;
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153476 ; 153483 - 153504 ; 153507 - 153532 ; 153577 - 153596 ; 153603 - 153627 ;
15 153629 - 153643 ; 153805 - 153819 ; 154379 - 154401 ; 154483 - 154501 ; 154535 -
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156678 ; 156707 - 156721 ; 156723 - 156753 ; 156777 - 156798 ; 156833 - 156849 ;
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20 157217 ; 157236 - 157289 ; 157293 - 157307 ; 157338 - 157375 ; 157412 - 157426 ;
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157739 ; 158005 - 158018 ; 158258 - 158278 ; 158422 - 158435 ; 158522 - 158545 ;
158694 - 158708 ; 159274 - 159292 ; 159346 - 159360 ; 159590 - 159603 ; 159859 -
159872 ; 159968 - 159981 ; 160208 - 160223 ; 160251 - 160267 ; 161102 - 161115 ;
25 161187 - 161332 ; 161337 - 161386 ; 161388 - 161502 ; 161618 - 161631 ; 162043 -
162056 ; 162561 - 162575 ; 163052 - 163065 ; 163084 - 163097 ; 164109 - 164123 ;
164923 - 164938 ; 164958 - 164980 ; 165017 - 165032 ; 165034 - 165047 ; 165049 -
165063 ; 165065 - 165079 ; 165134 - 165149 ; 165185 - 165224 ; 165467 - 165483 ;
165516 - 165529 ; 165587 - 165604 ; 165608 - 165621 ; 165644 - 165665 ; 165697 -
30 165718 ; 165720 - 165748 ; 165750 - 165774 ; 165777 - 165836 ; 165838 - 165852 ;
165862 - 165946 ; 165948 - 165980 ; 166005 - 166050 ; 166060 - 166102 ; 166122 -
166160 ; 166163 - 166218 ; 166220 - 166239 ; 166254 - 166307 ; 166312 - 166359 ;
166366 - 166391 ; 166508 - 166522 ; 167252 - 167265 ; 167319 - 167332 ; 168224 -
168237 ; 168272 - 168313 ; 168334 - 168348 ; 168356 - 168394 ; 168416 - 168447 ;
35 168477 - 168491 ; 168503 - 168519 ; 168541 - 168579 ; 169037 - 169052 ; 169342 -
169366 ; 169376 - 169400 ; 169411 - 169424 ; 169435 - 169460 ; 169496 - 169517 ;
169519 - 169540 ; 169555 - 169573 ; 169600 - 169629 ; 169631 - 169653 ; 169655 -

169695 ; 169697 - 169722 ; 169729 - 169782 ; 169791 - 169807 ; 169831 - 169847 ;
 169850 - 169883 ; 169898 - 169925 ; 169937 - 169954 ; 169959 - 169980 ; 169982 -
 170005 ; 170007 - 170021 ; 170036 - 170058 ; 170069 - 170097 ; 170105 - 170136 ;
 170138 - 170232 ; 170247 - 170309 ; 170311 - 170347 ; 170350 - 170385 ; 170395 -
 5 170418 ; 170434 - 170466 ; 170469 - 170483 ; 170485 - 170503 ; 170509 - 170532 ;
 170534 - 170562 ; 170568 - 170585 ; 170624 - 170641 ; 170654 - 170675 ; 170685 -
 170709 ; 170712 - 170731 ; 170745 - 170758 ; 170778 - 170791 ; 170859 - 170892 ;
 170948 - 170969 ; 171019 - 171059 ; 171070 - 171086 ; 171090 - 171123 ; 171465 -
 171478 ; 171526 - 171539 ; 171571 - 171584 ; 171645 - 171660 ; 172651 - 172670 ;
 10 172985 - 172999 ; 173795 - 173808 ; 174279 - 174304 ; 174323 - 174355 ; 175105 -
 175123 ; 175143 - 175166 ; 175221 - 175241 ; 175350 - 175364 ; 175493 - 175506 ;
 175707 - 175793 ; 175804 - 175849 ; 175854 - 175941 ; 175944 - 176027 ; 176245 -
 176258 ; 176323 - 176337 ; 176620 - 176636 ; 176719 - 176732 ; 179965 - 179994 ;
 180044 - 180060 ; 180072 - 180104 ; 180136 - 180149 ; 180208 - 180225 ; 180266 -
 15 180280 ; and 180634 - 180647. Oligonucleotides, such as antisense oligonucleotides which
 target these regions (Target Sequence List 3) of SEQ ID NO 1 may further target the human
 SCN10A nucleic acid target. In some embodiments, the contiguous nucleotide sequence of the
 oligonucleotide of the invention comprises at least 14 contiguous nucleotides which are present
 in one of the above listed target sequences.

20 Target Sequence List 4

In some advantageous embodiments the target sequence is a region of SEQ ID NO 1 selected
 from the group consisting of 99525 - 99542 ; 70094 - 70110 ; 133396 - 133411 ; 20666 -
 20682 ; 103244 - 103261 ; 20666 - 20683 ; 103244 - 103262 ; 147238 - 147253 ; 171787 -
 171803 ; 171787 - 171803 ; 147238 - 147253 ; 171788 - 171803 ; 103244 - 103260 ; 103244
 25 - 103262 ; 130009 - 130025 ; 103244 - 103261 ; 98600 - 98616 ; 103244 - 103262 ; 171788
 - 171803 ; 103244 - 103261 ; 70094 - 70110 ; 70094 - 70110 ; 70094 - 70110 ; 70094 -
 70110 ; 70094 - 70110 ; 70094 - 70110 ; 20666 - 20683 ; 97712 - 97728 ;
 75261 - 75277 ; 75260 - 75276 ; 97713 - 97730 ; 75261 - 75277 ; 97712 - 97729 ; 20666 -
 20683 ; 97712 - 97729 ; 20666 - 20683 ; 4426 - 4443 ; 75260 - 75276 ; 97715 - 97731 ;
 30 20666 - 20683 ; 97712 - 97728 ; 4427 - 4443 ; 20666 - 20683 ; 97712 - 97729 ; 89475 -
 89493 ; 99308 - 99324 ; 13076 - 13094 ; 87509 - 87527 ; 103272 - 103290 ; 82676 - 82692 ;
 99526 - 99543 ; 82675 - 82691 ; 87510 - 87528 ; 97704 - 97720 ; 82675 - 82691 ; 89477 -
 89495 ; and 13076 - 13094. In some embodiments, the contiguous nucleotide sequence of the
 oligonucleotide of the invention comprises at least 14 contiguous nucleotides which are present
 35 in one of the above listed target sequences.

Target Sequence List 5

In some advantageous embodiments the target sequence is an exon region of SEQ ID NO 1 selected from the group consisting of E1; E2; E3; E4; E5; E6; E7; E8; E9; E10; E11; E12; E13; E14; E15; E16; E17; E18; E19; E20; E21; E22; E23; E24; E25; E26; and E27.

Target Sequence list 6

- 5 In some advantageous embodiments the target sequence is an intron region of SEQ ID NO 1 selected from the group consisting of I1; I2; I3; I4; I5; I6; I7; I8; I9; I10; I11; I12; I13; I14; I15; I16; I17; I18; I19; I20; I21; I22; I23; I24; I25; and I26.

In some embodiments, the contiguous nucleotide sequence of the oligonucleotide of the invention comprises at least 12 contiguous nucleotides which are present in the target
10 sequence, such as a target sequence selected from those presented in Target Sequence list 1, 2, 3, 4, 5 & 6.

In some embodiments, the contiguous nucleotide sequence of the oligonucleotide of the invention comprises at least 14 contiguous nucleotides which are present in the target sequence, such as a target sequence selected from those presented in Target Sequence list 1,
15 2, 3, 4, 5 & 6. In some embodiments, the contiguous nucleotide sequence of the oligonucleotide of the invention comprises at least 15 contiguous nucleotides which are present in the target sequence, such as a target sequence selected from those presented in Target sequence list 1, 2, 3, 4, 5 & 6.

Advantageous Target Regions

- 20 In some embodiments, the invention provides an oligonucleotide according to the invention which comprises a contiguous nucleotide sequence of at least 12 nucleotides in length which is 100% complementary to a sequence selected from the group consisting of SEQ ID NO 17 – 49.

In some embodiments, the invention provides an oligonucleotide according to the invention which comprises a contiguous nucleotide sequence of at least 14 nucleotides in length which is
25 100% complementary to a sequence selected from the group consisting of SEQ ID NO 17 – 49.

SEQID	Target_seq	Region of SEQ ID No 1		length
		start	end	
17	GAAAATACGATATCCA	16910	16925	16
18	GAAGAGGAATTAAAATATA	64215	64233	19
19	GATTAGTGAAATTTAGTGAA	64574	64593	20
20	TATTTGTAAAAGAGCTGT	70638	70655	18
21	TGGATTTTTTTATGAATGGA	71294	71313	20
22	AAGAGGTGTTTAAATCA	75259	75275	17
23	TGAATGAGTAGTTATATAT	76831	76849	19
24	TGGTTGATAGATCATGA	77336	77352	17

25	TATTATGGAGAAATATACTGT	77664	77684	21
26	TGGTGAATGAAAAGTAAGA	80259	80277	19
27	GAGAATATATGAGAAAATAGTA	81183	81204	22
28	GAATTAGAATTTCAACAGA	87509	87527	19
29	TGTGTAAAGAAAACGAT	89233	89249	17
30	AAGAGATATAGGATCTG	91258	91274	17
31	TGTAAAAAGGTACTTGT	91752	91768	17
32	TTGGGAGTTGATAATGATT	95878	95896	19
33	AATGGTATTAAAACTGAT	97715	97732	18
34	TGTTTACATGATGGTCAT	98983	99000	18
35	TATTTTGTGATGATGTGATCTATT	99064	99087	24
36	ATGAAGTTAATAATGGAC	99356	99373	18
37	TAAGTGGTTAAAATAATCA	99525	99543	19
38	TGGTGTGAGAGTTATGTTT	101191	101209	19
39	TAGAATTAATAATTAAGGAAA	101406	101426	21
40	ATTGAAATGGTTAAGGA	101534	101550	17
41	TGAGAAAAAAAATAATTAA	102373	102392	20
42	TAAGAATTGAGAAATAATGAAGGTTCAAGATCT AGAGGAAATTTGTTTGATAAGATATTAAGCTGT	107237	107302	66
43	TGAAATAGTGATGGTTGT	107586	107603	18
44	TATGTGTAAAATAGATTGTAA	107812	107832	21
45	TTGGTAATAATGTGTGATT	113551	113570	20
46	TGAATTGATTATAAAAAGTAA	117040	117059	20
47	TGATAAATTTGTAAGTGAA	120589	120607	19
48	GATGATTGAGTTTAAAGAA	121347	121365	19
49	ATGATTGGAAAATAAAGA	125835	125852	18

Target Cell

The term a “target cell” as used herein refers to a cell which is expressing the target nucleic acid. In some embodiments the target cell may be *in vivo* or *in vitro*. In some embodiments the target cell is a mammalian cell such as a pig cell or a rodent cell, such as a mouse cell or a rat cell, or a primate cell such as a monkey cell or a human cell.

In some embodiments the target cell may be a dorsal root ganglion cell, such as a C fiber cell, or a somatosensory cell.

For *in vitro* assessment, the target cell may be an established cell line, such as SK-N-AS neuroblastoma cells, which is available from ATCC (CRL-2137), which as illustrated in the examples may be used for *in vitro* screening. Other exemplary target cells include SH-SY5Y cells (also available from ATCC, CRL-2266), or neuronal cells derived from human or pig iPSCs, or primary neurons such as pig primary neurons or human primary neurons (such as primary neurons isolated from dorsal root ganglions) – these may also be used for *in vitro* screening.

Advantageously the target cell expresses the SCN9A target.

Inhibition of the Target

The oligonucleotide of the invention is capable of down-regulating (inhibiting) the expression of human SCN9A in a cell which is expressing human SCN9A (such as the human Na_v1.7 encoded by SEQ ID NO 1). The inhibition of SCN9A results in the inhibition of Na_v1.7 protein in the cell, which may be determined by the protein level of Na_v1.7 or by a Na_v1.7 activity assay.

Therefore, advantageously the oligonucleotide of the invention is capable of down-regulating (inhibiting) the expression of human Na_v1.7 in a cell which is expressing human Na_v1.7 (such as the human Na_v1.7 encoded by SEQ ID NO 1).

In some embodiments the antisense oligonucleotide of the invention is capable of modulating the expression of the target by inhibiting or down-regulating it. Preferably, such modulation produces an inhibition of expression of at least 20% compared to the normal expression level of the target, more preferably at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% inhibition compared to the normal expression level of the target. In some embodiments oligonucleotides of the invention may be capable of inhibiting expression levels of SCN9A mRNA by at least 50% or 60% *in vitro* following gymnotic application of 5 µM oligonucleotide in SK-N-AS neuroblastoma cells, which are available from ATCC (CRL-2137) – see the examples for suitable methodology using gymnotic delivery. In some embodiments compounds of the invention may be capable of inhibiting expression levels of SCN9A protein by at least 70% *in vitro* using 5 µM oligonucleotide to SK-N-AS neuroblastoma cells as described above.

Suitably, the examples provide assays which may be used to measure SCN9A inhibition.

Naturally occurring variant

The term “naturally occurring variant” refers to variants of SCN9A or SCN10A gene or transcripts which originate from the same genetic loci as the target nucleic acid, but may differ for example, by virtue of degeneracy of the genetic code causing a multiplicity of codons encoding the same amino acid, or due to alternative splicing of pre-mRNA, or the presence of polymorphisms, such as single nucleotide polymorphisms (SNPs), and allelic variants. Based on the presence of the sufficient complementary sequence to the oligonucleotide, the oligonucleotide of the invention may therefore target the target nucleic acid and naturally occurring variants thereof.

In some embodiments, the naturally occurring variants have at least 95% such as at least 98% or at least 99% homology to a mammalian SCN9A or SCN10A target nucleic acid, such as a target nucleic acid selected from the group consisting of SEQ ID NO: 1, 2, and 3. In some

embodiments the naturally occurring variants have at least 99% homology to the human SCN9A target nucleic acid, such as that presented as SEQ ID NO: 1.

Modulation of expression

The term “inhibition of expression” as used herein is to be understood as an overall term for an oligonucleotide’s ability to decrease the level of target nucleic acid or target protein when compared to the amount of target nucleic acid or target protein before administration of the oligonucleotide. It will be understood that depending upon the mechanism of action, and antisense oligonucleotide may decrease the level of the target nucleic acid (e.g. via RNaseH cleavage), or may decrease the functionality (or alter the functionality) of the target nucleic acid, e.g. via modulation of splice switching or the pre-RNA.

Modulation, such as inhibition of expression may be determined by reference to a control experiment. It is generally understood that the control is an individual or target cell treated with a saline composition or an individual or target cell treated with a non-targeting oligonucleotide (mock).

One type of modulation is the ability of an oligonucleotide to inhibit, down-regulate, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of the target or target nucleic acid, e.g. by degradation of mRNA or blockage of transcription.

High affinity modified nucleosides

A high affinity modified nucleoside is a modified nucleotide which, when incorporated into the oligonucleotide enhances the affinity of the oligonucleotide for its complementary target, for example as measured by the melting temperature (T^m). A high affinity modified nucleoside of the present invention preferably result in an increase in melting temperature between +0.5 to +12°C, more preferably between +1.5 to +10°C and most preferably between +3 to +8°C per modified nucleoside. Numerous high affinity modified nucleosides are known in the art and include for example, many 2’ substituted nucleosides as well as locked nucleic acids (LNA) (see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213).

Sugar modifications

The oligomer of the invention may comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA.

Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

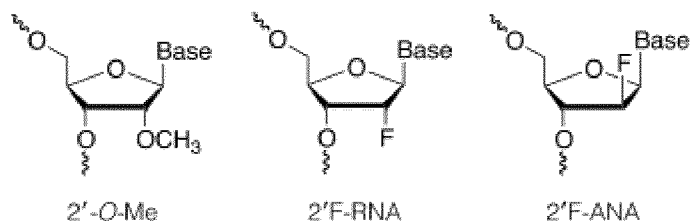
Such modifications include those where the ribose ring structure is modified, e.g. by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (e.g. UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

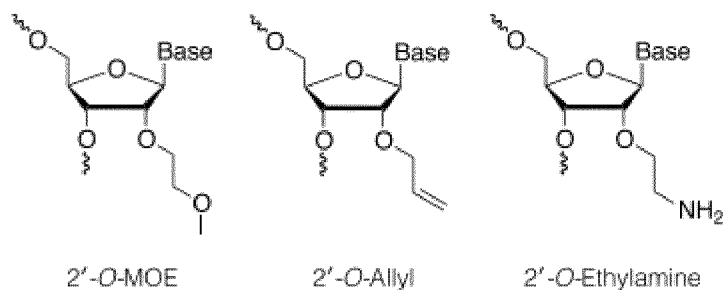
Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions.

2' sugar modified nucleosides

A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or -OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradicle capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2' – 4' biradicle bridged) nucleosides.

Indeed, much focus has been spent on developing 2' sugar substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide. Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213, and Deleavey and Damha, Chemistry and Biology 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.





In relation to the present invention 2' substituted sugar modified nucleosides does not include 2' bridged nucleosides like LNA.

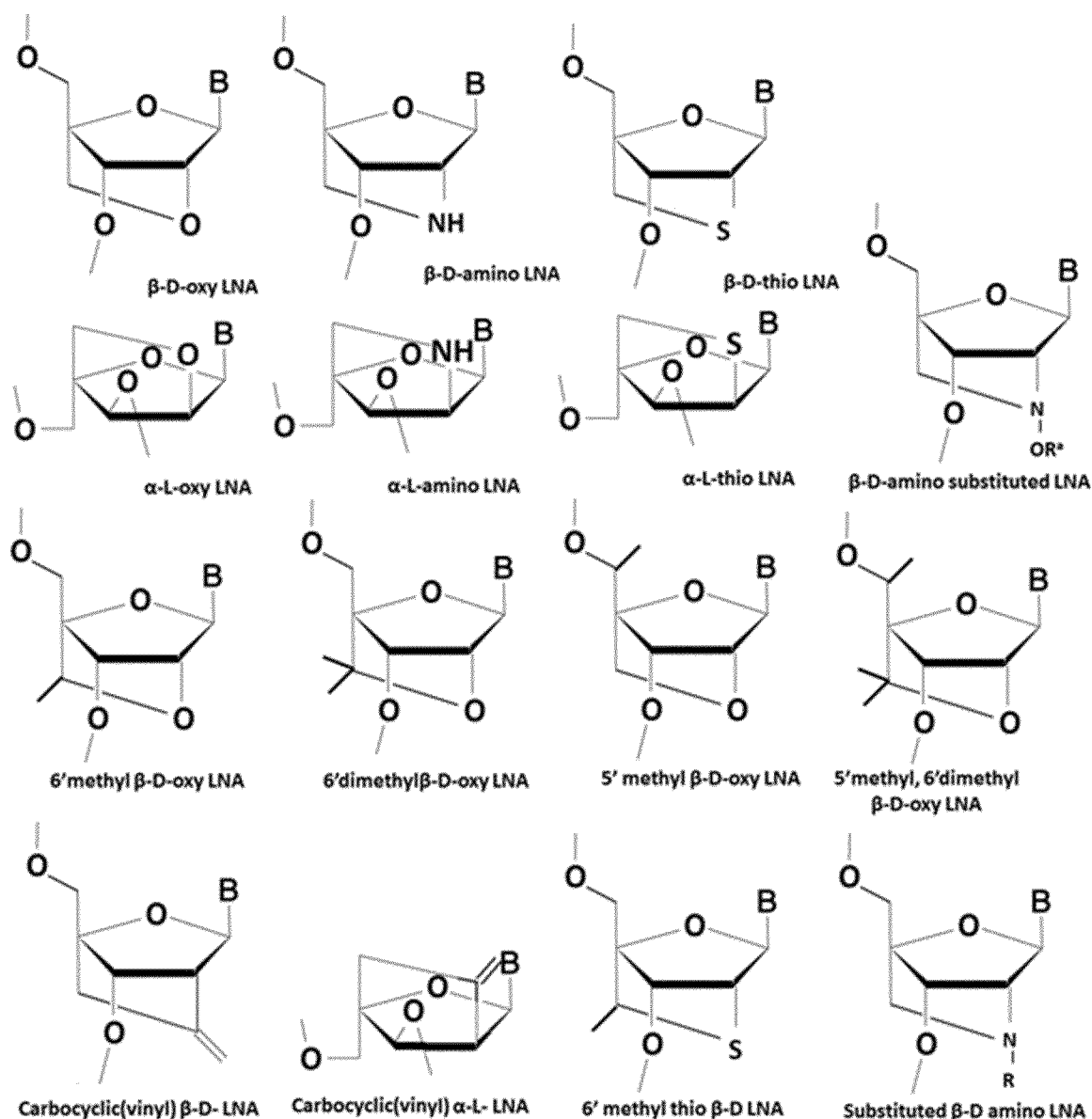
Locked Nucleic Acid Nucleosides (LNA nucleoside)

- 5 A "LNA nucleoside" is a 2'- modified nucleoside which comprises a biradical linking the C2' and C4' of the ribose sugar ring of said nucleoside (also referred to as a "2'- 4' bridge"), which restricts or locks the conformation of the ribose ring. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature. The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the
- 10 LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex.

- Non limiting, exemplary LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352 , WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO
- 15 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita et al., Bioorganic & Med.Chem. Lett. 12, 73-76, Seth et al. J. Org. Chem. 2010, Vol 75(5) pp. 1569-81, and Mitsuoka et al., Nucleic Acids Research 2009, 37(4), 1225-1238, and Wan and Seth, J. Medical Chemistry 2016, 59, 9645-9667.

Further non limiting, exemplary LNA nucleosides are disclosed in Scheme 1.

Scheme 1:



Particular LNA nucleosides are beta-D-oxy-LNA, 6'-methyl-beta-D-oxy LNA, such as (S)-6'-methyl-beta-D-oxy-LNA (ScET) and ENA.

- 5 A particularly advantageous LNA is beta-D-oxy-LNA.

The compounds described herein can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

- 10 The term "asymmetric carbon atom" means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention an asymmetric carbon atom can be of the "R" or "S" configuration.

Pharmaceutically acceptable salts

The term “pharmaceutically acceptable salts” refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, particularly hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein. In addition these salts may be prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins. The compound of formula (I) can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula (I) are the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and methanesulfonic acid.

Protecting group

The term “protecting group”, alone or in combination, signifies a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site. Protecting groups can be removed. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups.

Nuclease mediated degradation

Nuclease mediated degradation refers to an oligonucleotide capable of mediating degradation of a complementary nucleotide sequence when forming a duplex with such a sequence.

In some embodiments, the oligonucleotide may function via nuclease mediated degradation of the target nucleic acid, where the oligonucleotides of the invention are capable of recruiting a nuclease, particularly an endonuclease, preferably endoribonuclease (RNase), such as RNase H. Examples of oligonucleotide designs which operate via nuclease mediated mechanisms are oligonucleotides which typically comprise a region of at least 5 or 6 consecutive DNA nucleosides and are flanked on one side or both sides by affinity enhancing nucleosides, for example gapmers, headmers and tailmers.

RNase H Activity and Recruitment

The RNase H activity of an antisense oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH.

- 5 Typically an oligonucleotide is deemed capable of recruiting RNase H if it, when provided with a complementary target nucleic acid sequence, has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers with phosphorothioate linkages between all
- 10 monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613 (hereby incorporated by reference). For use in determining RNase H activity, recombinant human RNase H1 is available from Lubio Science GmbH, Lucerne, Switzerland.

Gapmer

- The antisense oligonucleotide of the invention, or contiguous nucleotide sequence thereof, may
- 15 be a gapmer, also termed gapmer oligonucleotide or gapmer designs. The antisense gapmers are commonly used to inhibit a target nucleic acid via RNase H mediated degradation. A gapmer oligonucleotide comprises at least three distinct structural regions a 5'-flank, a gap and a 3'-flank, F-G-F' in the '5 -> 3' orientation. The "gap" region (G) comprises a stretch of contiguous DNA nucleotides which enable the oligonucleotide to recruit RNase H. The gap
- 20 region is flanked by a 5' flanking region (F) comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides, and by a 3' flanking region (F') comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides. The one or more sugar modified nucleosides in region F and F' enhance the affinity of the oligonucleotide for the target nucleic acid (*i.e.* are affinity enhancing sugar
- 25 modified nucleosides). In some embodiments, the one or more sugar modified nucleosides in region F and F' are 2' sugar modified nucleosides, such as high affinity 2' sugar modifications, such as independently selected from LNA and 2'-MOE.

- In a gapmer design, the 5' and 3' most nucleosides of the gap region are DNA nucleosides, and are positioned adjacent to a sugar modified nucleoside of the 5' (F) or 3' (F') region respectively.
- 30 The flanks may further defined by having at least one sugar modified nucleoside at the end most distant from the gap region, *i.e.* at the 5' end of the 5' flank and at the 3' end of the 3' flank.

Regions F-G-F' form a contiguous nucleotide sequence. Antisense oligonucleotides of the invention, or the contiguous nucleotide sequence thereof, may comprise a gapmer region of formula F-G-F'.

The overall length of the gapmer design F-G-F' may be, for example 12 to 32 nucleosides, such as 13 to 24, such as 14 to 22 nucleosides, Such as from 14 to 17, such as 16 to 18 nucleosides. By way of example, the gapmer oligonucleotide of the present invention can be represented by the following formulae:

5 F₁₋₈-G₆₋₁₆-F'₁₋₈, such as

F₁₋₈-G₈₋₁₆-F'₂₋₈

with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length.

10 In an aspect of the invention the antisense oligonucleotide or contiguous nucleotide sequence thereof consists of or comprises a gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise or consist of 1-8, such as 2-6, such as 3-4 2' sugar modified nucleosides, wherein there is at least one 2' sugar modified nucleoside positioned at the 3' end of region F (adjacent to a DNA nucleoside of region G), and at least one 2' sugar modified nucleoside positioned at the 5' end of region F' (positioned adjacent to a DNA nucleoside of region G), and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH, such as a region of 6 – 16 DNA nucleosides, such as such as 10 - 15 contiguous DNA nucleosides, such as 10 – 14 contiguous DNA nucleotides, such as 11 – 15 contiguous DNA nucleotides, such as 13 – 15 contiguous DNA nucleotides.

LNA Gapmer

20 An LNA gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of LNA nucleosides. A beta-D-oxy gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of beta-D-oxy LNA nucleosides.

In some embodiments the LNA gapmer is of formula: [LNA]₁₋₅-[region G]-[LNA]₁₋₅, wherein region G is as defined in the Gapmer region G definition.

MOE Gapmers

25 A MOE gapmers is a gapmer wherein regions F and F' consist of MOE nucleosides. In some embodiments the MOE gapmer is of design [MOE]₁₋₈-[Region G]-[MOE]₁₋₈, such as [MOE]₂₋₇-[Region G]₅₋₁₆-[MOE]₂₋₇, such as [MOE]₃₋₆-[Region G]-[MOE]₃₋₆, wherein region G is as defined in the Gapmer definition. MOE gapmers with a 5-10-5 design (MOE-DNA-MOE) have been widely used in the art.

Mixed Wing Gapmer

30 A mixed wing gapmer is an LNA gapmer wherein one or both of region F and F' comprise a 2' substituted nucleoside, such as a 2' substituted nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA

units, 2'-alkoxy-RNA, MOE units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units, such as a MOE nucleosides. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least one LNA nucleoside, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some

5 embodiments wherein at least one of region F and F', or both region F and F' comprise at least two LNA nucleosides, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some mixed wing embodiments, one or both of region F and F' may further comprise one or more DNA nucleosides.

Mixed wing gapmer designs are disclosed in WO2008/049085 and WO2012/109395.

10 ***Alternating Flank Gapmers***

Flanking regions may comprise both LNA and DNA nucleoside and are referred to as "alternating flanks" as they comprise an alternating motif of LNA-DNA-LNA nucleosides.

Gapmers comprising such alternating flanks are referred to as "alternating flank gapmers".

"Alternative flank gapmers" are thus LNA gapmer oligonucleotides where at least one of the

15 flanks (F or F') comprises DNA in addition to the LNA nucleoside(s). In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or both F and F' comprise at least three nucleosides, wherein the 5' and 3' most nucleosides of the F and/or F' region are LNA nucleosides.

20 An alternating flank region may comprise up to 3 contiguous DNA nucleosides, such as 1 to 2 or 1 or 2 or 3 contiguous DNA nucleosides.

Region D' or D'' in an oligonucleotide

The oligonucleotide of the invention may in some embodiments comprise or consist of the contiguous nucleotide sequence of the oligonucleotide which is complementary to the target

25 nucleic acid, such as the gapmer F-G-F', and further 5' and/or 3' nucleosides. The further 5' and/or 3' nucleosides may or may not be fully complementary to the target nucleic acid. Such further 5' and/or 3' nucleosides may be referred to as region D' and D'' herein.

The addition of region D' or D'' may be used for the purpose of joining the contiguous nucleotide sequence, such as the gapmer, to a conjugate moiety or another functional group. When used

30 for joining the contiguous nucleotide sequence with a conjugate moiety it can serve as a biocleavable linker. Alternatively it may be used to provide exonuclease protection or for ease of synthesis or manufacture.

Region D' and D'' can be attached to the 5' end of region F or the 3' end of region F', respectively to generate designs of the following formulas D'-F-G-F', F-G-F'-D'' or

D'-F-G-F'-D''. In this instance the F-G-F' is the gapmer portion of the oligonucleotide and region D' or D'' constitute a separate part of the oligonucleotide.

Region D' or D'' may independently comprise or consist of 1, 2, 3, 4 or 5 additional nucleotides, which may be complementary or non-complementary to the target nucleic acid. The nucleotide adjacent to the F or F' region is not a sugar-modified nucleotide, such as a DNA or RNA or base modified versions of these. The D' or D' region may serve as a nuclease susceptible biocleavable linker (see definition of linkers). In some embodiments the additional 5' and/or 3' end nucleotides are linked with phosphodiester linkages, and are DNA or RNA. Nucleotide based biocleavable linkers suitable for use as region D' or D'' are disclosed in WO2014/076195, which include by way of example a phosphodiester linked DNA dinucleotide. The use of biocleavable linkers in poly-oligonucleotide constructs is disclosed in WO2015/113922, where they are used to link multiple antisense constructs (e.g. gapmer regions) within a single oligonucleotide.

In one embodiment the oligonucleotide of the invention comprises a region D' and/or D'' in addition to the contiguous nucleotide sequence which constitutes the gapmer.

In some embodiments, the oligonucleotide of the present invention can be represented by the following formulae:

F-G-F'; in particular $F_{1-8}-G_{6-16}-F'_{2-8}$

D'-F-G-F', in particular $D'_{1-3}-F_{1-8}-G_{6-16}-F'_{2-8}$

F-G-F'-D'', in particular $F_{1-8}-G_{6-16}-F'_{2-8}-D''_{1-3}$

D'-F-G-F'-D'', in particular $D'_{1-3}-F_{1-8}-G_{6-16}-F'_{2-8}-D''_{1-3}$

In some embodiments the internucleoside linkage positioned between region D' and region F is a phosphodiester linkage. In some embodiments the internucleoside linkage positioned between region F' and region D'' is a phosphodiester linkage.

Conjugate

The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

Conjugation of the oligonucleotide of the invention to one or more non-nucleotide moieties may improve the pharmacology of the oligonucleotide, e.g. by affecting the activity, cellular distribution, cellular uptake or stability of the oligonucleotide. In some embodiments the conjugate moiety modify or enhance the pharmacokinetic properties of the oligonucleotide by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the oligonucleotide. In particular the conjugate may target the oligonucleotide to a specific organ, tissue or cell type and thereby enhance the effectiveness of the oligonucleotide

in that organ, tissue or cell type. At the same time the conjugate may serve to reduce activity of the oligonucleotide in non-target cell types, tissues or organs, e.g. off target activity or activity in non-target cell types, tissues or organs.

In an embodiment, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (e.g. bacterial toxins), vitamins, viral proteins (e.g. capsids) or combinations thereof.

Linkers

A linkage or linker is a connection between two atoms that links one chemical group or segment of interest to another chemical group or segment of interest via one or more covalent bonds.

Conjugate moieties can be attached to the oligonucleotide directly or through a linking moiety (e.g. linker or tether). Linkers serve to covalently connect a third region, e.g. a conjugate moiety (Region C), to a first region, e.g. an oligonucleotide or contiguous nucleotide sequence complementary to the target nucleic acid (region A).

In some embodiments of the invention the conjugate or oligonucleotide conjugate of the invention may optionally, comprise a linker region (second region or region B and/or region Y) which is positioned between the oligonucleotide or contiguous nucleotide sequence complementary to the target nucleic acid (region A or first region) and the conjugate moiety (region C or third region).

Region B refers to biocleavable linkers comprising or consisting of a physiologically labile bond that is cleavable under conditions normally encountered or analogous to those encountered within a mammalian body. Conditions under which physiologically labile linkers undergo chemical transformation (e.g., cleavage) include chemical conditions such as pH, temperature, oxidative or reductive conditions or agents, and salt concentration found in or analogous to those encountered in mammalian cells. Mammalian intracellular conditions also include the presence of enzymatic activity normally present in a mammalian cell such as from proteolytic enzymes or hydrolytic enzymes or nucleases. In one embodiment the biocleavable linker is susceptible to S1 nuclease cleavage. In a preferred embodiment the nuclease susceptible linker comprises between 1 and 10 nucleosides, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 nucleosides, more preferably between 2 and 6 nucleosides and most preferably between 2 and 4 linked nucleosides comprising at least two consecutive phosphodiester linkages, such as at least 3 or 4 or 5 consecutive phosphodiester linkages. Preferably the nucleosides are DNA or RNA. Phosphodiester containing biocleavable linkers are described in more detail in WO 2014/076195 (hereby incorporated by reference) – see also region D' or D'' herein.

Region Y refers to linkers that are not necessarily biocleavable but primarily serve to covalently connect a conjugate moiety (region C or third region), to an oligonucleotide (region A or first region). The region Y linkers may comprise a chain structure or an oligomer of repeating units such as ethylene glycol, amino acid units or amino alkyl groups. The oligonucleotide conjugates of the present invention can be constructed of the following regional elements A-C, A-B-C, A-B-Y-C, A-Y-B-C or A-Y-C. In some embodiments the linker (region Y) is an amino alkyl, such as a C2 – C36 amino alkyl group, including, for example C6 to C12 amino alkyl groups. In a preferred embodiment the linker (region Y) is a C6 amino alkyl group.

Treatment

The term 'treatment' as used herein refers to both treatment of an existing disease (e.g. a disease or disorder as herein referred to), or prevention of a disease, *i.e.* prophylaxis. It will therefore be recognized that treatment as referred to herein may, in some embodiments, be prophylactic.

In some embodiments treatment is performed on a subject who is suffering chronic pain, or is expected to suffer chronic pain (prophylactic treatment).

DETAILED DESCRIPTION OF THE INVENTION

The Oligonucleotides of the Invention

The invention relates to oligonucleotides capable of inhibiting the of voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A or SCN10A, or both SCN9A and SCN10A.

The invention relates to oligonucleotides capable of inhibiting the expression of voltage-gated sodium ion channels, such as Nav1.7 or Nav1.8 or both Nav1.7 or Nav1.8. Oligonucleotides targeting both Nav1.7 and Nav1.8 (or optionally Nav1.9) may be designed by selecting the regions of identity or high sequence similarity between the SCN9A and SCN10A transcripts (or optionally SCN11A). In some embodiments the oligonucleotide of the invention may target both SCN9A and SCN10A transcripts, wherein the contiguous nucleotide sequence of the oligonucleotide is either fully complementary to one of SCN9A and SCN10A transcripts, and has no more than a single mismatch to the other of SCN9A and SCN10A transcript. In some embodiments, the contiguous nucleotide sequence comprises a single mismatch to both SCN9A and SCN10A transcript at the same position in the contiguous nucleotide sequence. In some embodiments it is useful to include a universal base at the site of a mismatch against one of, or both of SCN9A and SCN10A transcripts.

In some embodiments the oligonucleotide of the invention may target both SCN9A and SCN10A transcripts, wherein the contiguous nucleotide sequence of the oligonucleotide is either fully complementary to one of SCN9A and SCN11A transcripts, and has no more than a single

mismatch to the other of SCN9A and SCN11A transcript. In some embodiments, the contiguous nucleotide sequence comprises a single mismatch to both SCN9A and SCN11A transcript at the same position in the contiguous nucleotide sequence. In some embodiments it is useful to include a universal base at the site of a mismatch against one of, or both of SCN9A and SCN11A transcripts.

In some embodiments the oligonucleotide of the invention may target SCN9A and SCN10A and SCN11A transcripts, wherein the contiguous nucleotide sequence of the oligonucleotide is either fully complementary to one of SCN9A, SCN10A and SCN11A transcripts, and has no more than a single mismatch to the others of SCN9A, SCN10A and SCN11A transcripts. The human SCN11A pre-mRNA transcript is disclosed as ENSG00000168356 (Ensembl version ENSG00000168356.11).

The modulation may be achieved by hybridizing to a target nucleic acid encoding the voltage-gated sodium ion channels. The target nucleic acid may be a mammalian SCN9A or SCN10A sequence, such as a sequence selected from the group consisting of SEQ ID NO: 1, 2, and 3.

The oligonucleotide of the invention is an antisense oligonucleotide which targets SCN9A or SCN10A. The antisense oligonucleotide is complementary to a target sequence present in the target nucleic acid. Suitable target regions are disclosed herein (see for example Target Sequence Lists 1, 2, 3, & 4).

Certain illustrated target sequences are SEQ ID NOs 17 – 49.

In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide is at least 90% complementary to, such as fully complementary to an intron region of the SCN9A target nucleic acid sequence such as a target sequence selected I1 – I26 of SEQ ID NO 1.

In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide is at least 90% complementary to, such as fully complementary to an exon region of the SCN9A target nucleic acid sequence such as a target sequence selected E1 – E27 of SEQ ID NO 1.

Contiguous Nucleotide Sequences

In some embodiments, the antisense oligonucleotides of the invention comprises a contiguous nucleotide sequence selected from the group consisting of SEQ ID NO 50 – 641.

In some embodiments, the antisense oligonucleotides of the invention comprises a contiguous nucleotide sequence of at least 12 nucleotides in length which are identical to a sequence selected from the group consisting of SEQ ID NO 50 – 641.

In some embodiments, the antisense oligonucleotides of the invention comprises a contiguous nucleotide sequence of at least 14 nucleotides in length which are identical to a sequence selected from the group consisting of SEQ ID NO 50 – 641.

In determining identity, unless otherwise specified fully identity is meant, and identity of the antisense oligonucleotides of the invention which comprises a contiguous nucleotide sequence which is identical to a sequence selected from the group consisting of SEQ ID NO 50 – 641, is measured across the length of the contiguous nucleotide sequence. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide of the invention comprises a sequence selected from the group consisting of SEQ ID NO 50 – 641.

It will be understood that the antisense oligonucleotide may comprise a modified base where a unmodified base is indicated in the reference sequence – for example a U base may be used in place of a T, and 5-methyl cytosine may be used in place of a C.

SEQ ID	Contiguous Nucleotide Sequence
50	ATGTTTACTATAATCACA
51	GGCATATCATATATCC
52	CCAATTTTTCTTAAATAT
53	TCTCATAATCCTCATAT
54	TATTCTACCCACATTCT
55	AGTATTCTACCCACATT
56	AAGTATTCTACCCACAT
57	TATCTCATATTCCACAAA
58	TTATCTCATATTCCACA
59	GTTATCTCATATTCCAC
60	TTCAATGAAGAAATTTCA
61	GCTCAATTTTCAATTATT
62	TCTAATCTTATTTATCTTTC
63	TCCATAATATTACCTA
64	ATCACTTCAACTTTATAATA
65	TTCATCACTTCAACTTTA
66	TCCTACCTGAATTACC
67	GCTTTTAACACTTTATA
68	CTCCTAATATATAATATACT
69	TCTCCTAATATATAATATA
70	ATATATCTCCTAATATATA
71	ACATATATATCTCCTAATA
72	CTCATATCTACTTATCAT
73	TACTCATATCTACTTATCA
74	TCTACTCATATCTACTTA
75	ACATCTACTCATATCTACT
76	AATTACACCATTCCTCT
77	CCCTTTTAATTACACCAT
78	ACACTATTATACATTCCCA
79	AGCTACACTATTATACAT
80	ACTTCCATATTATTTCCAT

81	TCTCCTTAAATACATCAAAT
82	ATATTACTGTACTCCC
83	ATATTTATACAACAACCTCA
84	TAGTCACCATTTTTTCAT
85	AGAAAATAATTCCTATCCT
86	ATACATGTATCCACTTC
87	TTCCAATATTATTATACA
88	ACCCTTATTTAAATAATTA
89	TCACGTAAATCCCATCT
90	ACGTAAATCCCATC
91	TTCACGTAAATCCCA
92	GGATATCGTATTTTCT
93	TCTGGATATCGTATT
94	GATATATTATCCATCTCA
95	TGATATATTATCCATCT
96	AGCATCTACATTTTAATT
97	TCTTAATCTTATCATTTTA
98	AACTTCTTAATCTTATCA
99	TACAATAATTATCTTCTCA
100	TGCAAATAATACCCTAT
101	CTCTATTCTAAATAAACCTT
102	ACTCTATTCTAAATAAACCC
103	ATGACTCTATTCTAAATA
104	TAAGCATATATTTCCCA
105	TCATTTCCATTAAATCCAA
106	TTTCAATTCATTAAATCC
107	TTTTATCCTACTTCTAC
108	TCCCTCAAATATAAATTC
109	ACTGTTTTCTCTAAACC
110	AGATTCACTACATCCA
111	GCACTCTGATTACATTTCT
112	TATTTAATCACTTTATCTAA

113	ATATTTAATCACTTTATCT
114	ATCAACCACACAATTACTTT
115	TATCAACCACACAATTACTT
116	TTATCAACCACACAATTAC
117	TCAATAAAATTCCTTATACT
118	TCATTTTATTTATTTCAATT
119	TATACACTCTTTCTCTATTTC
120	TGACCATCTTATTCATC
121	CCTGATACTCATTTCCCA
122	TTTCTCTTTATCTTTTATC
123	AAATCAACCCTAAACCC
124	AAAGTACCATTACTCCC
125	TTCATATACTCTTATTTTA
126	CTAATTTTTCATATACTCTT
127	TCTAATTTTTCATATACTC
128	CTCTAATTTTTCATATACT
129	ACATTTTTCCTACAAACTA
130	CTACTATTCCATCATTTTTT
131	CAATTACACCTACAACCTTC
132	TCCAATTACACCTACAAC
133	GCCTTAATCAATTTCTCAA
134	CACTTTCCAATATTACT
135	TTACACTTTCCAATATTAC
136	CATTACACTTTCCAATATTA
137	ACATTACACTTTCCAATA
138	ATATACCCCAATTACTCCA
139	ATACTAGCAATTCATCA
140	ATACCATTAACTATCACC
141	AGATACCATTAACTATCA
142	CCCATCTTCATTATATTA
143	TTCTGATCTCTTATATA
144	ATTCATTACAGGAAATAC

145	TCATTTTCATCAATAACATTA
146	TTGCTTTTTTACTAACA
147	GTTTCATTTCTTTATTAT
148	GCTATTATATTACTTTT
149	GTCCTCTAATCATATCACA
150	TAGTCCTCTAATCATATC
151	TTAGTCCTCTAATCATA
152	ACTTAGTCCTCTAATCA
153	TAAATAAAACAATCCCCA
154	TAATTAATAAAACAATCCC
155	ATACATACCTCTATTATT
156	TCAATACATACCTCTATTA
157	CTCAATACATACCTCTATT
158	GAACTCAATACATACCTC
159	AGAACTCAATACATACC
160	TGAATTTTTATTCCCTTC
161	ACACAATACCATATTTCA
162	TGCTATAATATTTTATCT
163	ACAAACTTTCAATACTCTA
164	TCTTCTACACTATTATTC
165	ATATCTTCTACACTATTATT
166	TATATCTTCTACACTATTA
167	TTATATCTTCTACACTA
168	AGCTCATTTTCCTATAC
169	TACTTTTTTTTCTATCCAA
170	TCTACTTTTTTTTCTATC
171	TTTATTAATTTACTCCTT
172	ATTTTATTAATTTACTCC
173	ACCAATACCATAAATTCCA
174	ATTAATATTTTTTCTCCAT
175	TTTATTAATATTTTTTCTCC
176	TCCTTTTATTAATATTTTTT
177	CCTCCTTTTATTAATATT
178	GCCTCCTTTTATTAATAT
179	TAACATATCTACCATCTC
180	AATCCCTTACCATTATT
181	ACAGCTTCATTTAACTA
182	TTAACCAAATCTATACACT
183	TTAGACTAACCATCCTA
184	TATTAGACTAACCATCC
185	ACCTCATAATACTTTTC
186	TACCTGATAACATCTTT
187	TTACTAATCTAAATACCT
188	TCTCATTTTACTAATCTA
189	TTCTCATTTTACTAATCT

190	AACCAAGTCTATATCCA
191	TCACCTTCATAACTTATC
192	ATTTTAAATTACTCTCCTAT
193	ATATTTTAAATTACTCTCCT
194	AGTACAATTTAACTCCCT
195	ATTATCTATAATATACCTA
196	TCCATAAATCTATTCCAA
197	TTCCATAAATCTATTCCA
198	TTCCATAAATCTATTCC
199	AGCAAATAAATTCCAACAC
200	TCATGCTTCATAATTA
201	CCTTTCCCATTTACAATTT
202	ACATGATACTTAATACC
203	CAACAATATCAATCTTCC
204	TTATTAATATTTCTTCTCA
205	TCAGTTAATCATCTCAC
206	TTGCCATTAAAATTTCC
207	GATGAACAGACCAAAT
208	ATCCATACATCCTAAAAT
209	CTCATCCATACATCCTA
210	GTCCAAATATCATATCAT
211	TGTCCAAATATCATATC
212	ACCATTAATCTCATATT
213	TCACCATTAATCTCATAT
214	CACCATTAATCTCATA
215	ATCAATCAATATTTATTCTT
216	ATACTTTACTTTTCAAATTT
217	TATACTTTACTTTTCAAATTT
218	CTTTATACTTTACTTTTCAA
219	TCTTTATACTTTACTTTTCA
220	CCAATATTCCTATTCTC
221	TGTAACCACTCTTATCAAT
222	AATGTAACCACTCTTATC
223	TTCCAATTTCTATTAAT
224	CATTCCAATTTCTATTA
225	AAATTTTCTAAATTCCCC
226	TTCACTAATCTCAATTTA
227	ACTAAATTTCACTAATCTCA
228	TTATTCACTAAATTTCACT
229	TGCTAAACAATTATACTA
230	AATTATTCATCCATTCTTTC
231	ATCAATTTTTCACATCAATA
232	TTATACCCACTTACTC
233	GTACTTATACCCACTTAC
234	ATGTACTTATACCCACTT

235	TGTACTTATACCCACT
236	AAATGTACTTATACCCAC
237	CATCTAATTTTTCTAATCT
238	TTATAAAACATACACCCA
239	ATTATAAAACATACACCC
240	CTTCTATCAAAAATTCACC
241	CAAAAGTATATATTCCA
242	TACGCAAAAACAATGAC
243	TTACGCAAAAACAATG
244	TACTTACGCAAAAACA
245	CAGCTCTTTTACAAATAT
246	TCTATGATACTTACCT
247	ACACCAATTACTTCTTACC
248	CACACCAATTACTTCTTAC
249	TTACACCAATTACTTCTTA
250	GCTTCACACCAATTACTTC
251	CCTAATGCTTCACACC
252	ACAACCTCCCAATAGTT
253	AAATTTAATTTAAATTTGC
254	ATGCATTATATCAAATCA
255	AAAACACAAGCTTTTCTA
256	TCATCCAATATTTCATCA
257	ATATTACTTTTTATTATCTA
258	GCTAAATTCCTCATCAAAT
259	TGCTAAATTCCTCATCAA
260	ATATGCTAAATTCCTCATCA
261	ATGCTAAATTCCTCATC
262	TATGCTAAATTCCTCAT
263	GAAAATATGCTAAATTCCT
264	TGCAATCTAACTTCATA
265	CTTGATTTAAACACCTCT
266	ACTTGATTTAAACACCT
267	GCTTCTTACTATCTTTTA
268	GTCTTCTTTAATCCATCA
269	CTATATTATATATCCACCT
270	CTCTATATTATATATCCAC
271	TCTCTATATTATATATCCA
272	ATTCTCTATATTATATATCC
273	CCAATTCTCTATATTATAT
274	TCCAATTCTCTATATTATA
275	TCTCCAATTCTCTATATTAT
276	ATCTCCAATTCTCTATATTA
277	AATCTCCAATTCTCTATATT
278	TAAATCTCCAATTCTCTATA
279	GAATTTATCTCCAAACTCA

280	TGTCTACACATATTACC
281	TGATCCCATCTTATAC
282	TATATTTCTCCATAATAC
283	TATTCCTCAATAAACCTA
284	GACTTCCTATTTTACTCA
285	TTTCTCATATATTCTCCC
286	TTTTCTCATATATTCTCC
287	CTATTTTCTCATATATTCT
288	TTTACTATTTTCTCATATAT
289	TACTATTTTCTCATATA
290	AACAAATATTACATACCCT
291	TGCCATTAAATAAATACA
292	TGCCATTCAAAAATACAAT
293	TAATATACTTTTATCATACA
294	ATTACTTTATTCATCTCAT
295	TAATTACTTTATTCATCTCA
296	TTAATTACTTTATTCATCTC
297	TTTAATTACTTTATTCATCT
298	ATTTAATTACTTTATTCATC
299	TTCTATCTTTTCTTTCTTTA
300	CATGCATTTTTTCTTACA
301	GAAATTCTAATTCCTTCT
302	AACATCTGTTGAAATTCT
303	ATTTAATCCCATCATTATTCT
304	TAAGTCCATATCATCAATA
305	ATTAAGTCCATATCATCAA
306	AATTAAGTCCATATCATCA
307	TTTACCTAAAATCATACCA
308	TTATATATCAATCCCCA
309	TTTTATATATCAATCCCC
310	TTTTTATATATCAATCCC
311	CTAAAAAGACTTGTTCT
312	ACTAAAAAGACTTGTTCT
313	CCTTATCTATTATCAC
314	GCCTTATCTATTATCAC
315	TTGCCTTATCTATTATC
316	TCCTTACGCTGTCATCA
317	TAATCCAAATTTCTTCATA
318	CTTTCAAGCCTAATCA
319	TGTTTTCATATAAACCAT
320	GATTATTACATACCTTCCA
321	TATCTTTACCATCATTTAA
322	GTTATCTTTACCATCATT
323	AGACTTACCAAATTTCC
324	GAACATGTTGACTCAC

325	AGTTTTAATACCATTTC
326	CAGTTTTAATACCATTTC
327	ATAATTTATCTTAATTCT
328	TCAATGTTTCCAATCTT
329	CATCTGGTTACATACCACC
330	ATCACAAAATAATTTCCAC
331	CATCACAAAATAATTTCCA
332	TCATCACAAAATAATTTCC
333	TAGATCACATCATCACAA
334	CCTAAATACCTTTCTTTTCA
335	ATACCTAAATACCTTTCTT
336	CCCTAAATAATACCTAAACA
337	TCCACCCTAAATAATACC
338	AGTTAAGTAAATTTCTACA
339	GTCTCTAATATTTCTATA
340	TAGCATTCTATCATCTT
341	CCTAGCATTCTATCTATC
342	GTTTCACATAATTTATTCC
343	TTAGAATAAATTCACG
344	TAATTTCTCAAAAAATTTAA
345	CCTTCATTATTTCTCAATT
346	CACAACCATCACTATTTT
347	TTATTACAATCTATTTTACA
348	CACTCAATTCATCACTTAT
349	ACTCAATTCATCACTTAA
350	TCTCTTTTAAATTCATCT
351	TATCTCTTTTAAATTCATC
352	GCTATCTCTTTTAAATTC
353	GTAATTTATCAATTTCCA
354	AATCTTTTCTTAATCTTTTA
355	GTACAATACCATTACAACA
356	CAGTTTTACTTTTCAATA
357	ATCAATCTACTTAATACA
358	TATTCTTATTTTCATATATA
359	ATATTCTTATTTTCATATA
360	AATGATCAATCACCTTT
361	TTGATCTACTTAATTTTA
362	AGTCCCATAACTAACA
363	TATCACTTATTCATTCATA
364	TTATCCATCTTTTAATTTA
365	ATATCTTTCCATATTTTCA
366	GGTAACAACCTTTTAAATA
367	CTAGTATACAACATCATA
368	ACCTAGTATACAACATC
369	ACCACATTAATTTCTCAAT

370	TTACAACCTTATCTTTTTTA
371	ACAACCTATACCCTAT
372	AGGACAACCTATACCC
373	TGATCTTTCTATCTACAC
374	TTGATCTTTCTATCTACA
375	AGCCTTATTTAATAATC
376	TGCTTTTATTTTCCAATC
377	TGTTTCCATAATATTTCT
378	CCATATACCTTCTCCAT
379	TTTCCATATACCTTCTC
380	TCTTTTCCATATACCTTC
381	CACTATACAAAATCTACCA
382	ACCCTCACTATACAAAAC
383	CACCCTCACTATACAAA
384	AGCACAAATATAAAACCAC
385	TTAACATTATCTTTCCAA
386	CTAGCACTTTAATTTCCA
387	GAATCTCTTCTTAATCT
388	AAATAAATGACTATAACT
389	ACACCTTTCTAAACAATA
390	AGTCTTTAAACCACTTTC
391	ACCAAAATAATTTCAACACC
392	TCCCTCAACCAAATAATTT
393	TCCACCAGATTTTTTCC
394	AAGCTTTCAAACCAAC
395	TTATCCTAAAATACCAT
396	AAGCACCTCATATCTTC
397	TTACCACTCATTTATTTCT
398	AGTTACCACTCATTTAT
399	TACTCTAAAATATCCTTA
400	CAGATTCTTCTTATTCTA
401	GTTCTAATATTCCTCACA
402	CTCTTATCTTCCAATTTTA
403	TCTATAATTTCTTCTTATT
404	CTTCTATAATTTCTTCTTA
405	TCCTTCTATAATTTCTTCTT
406	ATTCCTTCTATAATTTCTT
407	CATTCTTCTATAATTTCT
408	ACATTCTTCTATAATTTCT
409	GCCATATCTCTTAATTTAA
410	AGCCATATCTCTTAATT
411	ACAGCCATATCTCTTAA
412	TAAGTTTCAAATAACCC
413	TCCATTATTTTCCACTTA
414	ACATCCATTATTTTCCAC

415	TCACATCCATTATTTCCA
416	TTCACATCCATTATTTTC
417	TCATTACATCCATTATTT
418	TTATATATTTATCTATTTCA
419	AGCAATACAATCAATACA
420	CCACAATTACCATAACC
421	CACCAAAGATCTACCAA
422	TATTTTCTTACCCTCATT
423	AGTATTTTCTTACCCTCA
424	TAGTATTTTCTTACCCT
425	TTAGTATTTTCTTACCC
426	TTATAATTCCACTTACTTT
427	GTTATAATTCCACTTACT
428	TAGTTATAATTCCACTTA
429	TTTAGTTATAATTCCAC
430	GTTTTCTCAAATATAATT
431	GAATTCTAATACCACCTT
432	ATATACTAACTATTCTCC
433	TTCATTTATCCTTCAAATA
434	TTCATTATTTCAATTCCT
435	TTTAATCCTTTCTTATTTTC
436	CAGTTTTTCTTAAATCCT
437	ATGATCCTATTATTACCA
438	TTGACTAACATTCATAA
439	TTCCATCGCACATTTT
440	ACATAACCTTTTATTTTTTA
441	CATTCTAAATCTTAGTC
442	ATAATCGTCCATCCCTT
443	TCACATAAACTCATCCAA
444	TTCACATAAACTCATCC
445	ACTTATTTACATAAACTC
446	CTTCAAATAACTACAAAG
447	TGTATTCAATTACATACT
448	ACTCTTAACAATTTATTCA
449	TCACTCTTAACAATTTATTC
450	TAACATAATCACTCTTAACA
451	CCAGAACCTATTATTTA
452	ATTATTCAATCCTCTATA
453	TAACCTTCATCACATACT
454	ATCTAACCTTCATCACATAC
455	TCTAACCTTCATCACATA
456	CTCTATCTAACCTTCATC
457	TGACTCTATCTAACCTTC
458	CCTCTTTTATCAACACAATT
459	TCTCCAAATCTTAAATTTTC

460	TTTACTATTTCTCCAAATC
461	TCTTTTACTATTTCTCCAAA
462	CATCTTTTACTATTTCTCCA
463	TCATCTTTTACTATTTCTC
464	CCTCATCTTTTACTATTT
465	AACCTCATCTTTTACTA
466	TTTTTATATCTACTCTCA
467	TTAATAAACATCAATCTCC
468	ATATTTCTTATCTCCATT
469	CATACTGCTCTTTCTA
470	ATGCAAATAAATTCATCA
471	TTTAACTTTCTTACCACAA
472	TTAACTTTCTTACCACA
473	CATATTCATCTCACCTAC
474	TCATATTCATCTCACCTA
475	TTCATATTCATCTCACCT
476	AATTTTCATATTCATCTCAC
477	CTACCTTTTTAATTCTAAAT
478	ACTACCTTTTTAATTCTA
479	TGACTACCTTTTTAATTC
480	TATATTTTTTACCCTT
481	TCAAATATACATCCTTG
482	GTCAAATATACATCCT
483	GGTCAAATATACATCC
484	AGGTCAAATATACATC
485	ACCACATTTATCCAATATA
486	ATAAAAACCAATTTATCCA
487	ATCACAACCACAAAATCA
488	ATAAATATTCTTACCTACA
489	AAGTATAATTTCTTCTA
490	AATTTATAGATTAATAAAT
491	TTTCCACATATTTCTTAC
492	TGTCTATTTCCACATATT
493	TCTTTCAACCTTTTATTTA
494	ATATAAATCACCTGAAAT
495	ATTAATTCCATCTTCTT
496	TCATTAATTCCATCTTCC
497	TGTCATTAATTCCATCTT
498	AACATGTCATTAATTCC
499	CCTTCAACTGAACTTC
500	AGCCATATCTTTTTTATT
501	TAAGCACCTCAAAATATA
502	TTATTCATACTAAACACATA
503	AAAGATCTCATATTCCT
504	TCTCATCTTTAACCATAA

505	TCCCTACTTAAATTATCAA
506	GCAATGTAAAAACATTAA
507	CCCATATTTTTTATTTTACA
508	CCCTTATCTACAAAAATTTA
509	CTGCTTTATTTACATAT
510	ACTGCTTTATTTACATA
511	TCTCAAGTATAACTACA
512	ACTGCTGAGCAGGATCA
512	ACTGCTGAGCAGGATCA
512	ACTGCTGAGCAGGATCA
513	GCTGAGCAGGATCATGA
513	GCTGAGCAGGATCATGA
513	GCTGAGCAGGATCATGA
513	GCTGAGCAGGATCATGA
514	AAAATCCAGCCAGTTCCA
514	AAAATCCAGCCAGTTCCA
514	AAAATCCAGCCAGTTCCA
514	AAAATCCAGCCAGTTCCA
515	ACTGCAATGTACATGTT
515	ACTGCAATGTACATGTT
515	ACTGCAATGTACATGTT
515	ACTGCAATGTACATGTT
515	ACTGCAATGTACATGTT
515	ACTGCAATGTACATGTT
516	TCTATTTGCTTAGCTG
516	TCTATTTGCTTAGCTG
516	TCTATTTGCTTAGCTG
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516	TCTATTTGCTTAGCTG
517	CTATTTGCTTAGCTGTT
517	CTATTTGCTTAGCTGTT
517	CTATTTGCTTAGCTGTT
517	CTATTTGCTTAGCTGTT
517	CTATTTGCTTAGCTGTT
517	CTATTTGCTTAGCTGTT
518	CTGAGCAGGATCATGA
518	CTGAGCAGGATCATGA
518	CTGAGCAGGATCATGA
518	CTGAGCAGGATCATGA
518	CTGAGCAGGATCATGA

519	AAAATCCAGCCAGTTCC
519	AAAATCCAGCCAGTTCC
519	AAAATCCAGCCAGTTCC
519	AAAATCCAGCCAGTTCC
519	AAAATCCAGCCAGTTCC
519	AAAATCCAGCCAGTTCC
520	TCTATTTGCTTAGCTGT
520	TCTATTTGCTTAGCTGT
520	TCTATTTGCTTAGCTGT
520	TCTATTTGCTTAGCTGT
520	TCTATTTGCTTAGCTGT
521	TCTATTTGCTTAGCTGTT
521	TCTATTTGCTTAGCTGTT
521	TCTATTTGCTTAGCTGTT
521	TCTATTTGCTTAGCTGTT
521	TCTATTTGCTTAGCTGTT
522	TGCTGAGCAGGATCAT
522	TGCTGAGCAGGATCAT
522	TGCTGAGCAGGATCAT
522	TGCTGAGCAGGATCAT
523	ACTGCAATGTACATGT
523	ACTGCAATGTACATGT
523	ACTGCAATGTACATGT
523	ACTGCAATGTACATGT
523	ACTGCAATGTACATGT
524	ATTAGGTTCTCTAAT
525	ACTGCAATGTACATG
526	GCAATGTACATGTTAC
527	CAATGTACATGTTAC
528	GTAGATGAACATGACCAG
529	GTAGATGAACATGACCAGG A
530	GTAGATGAACATGACCA
531	GTAGATGAACATGACCAGG
532	TAGATGAACATGACC
533	TAGATGAACATGACCA
534	TAGATGAACATGACCAGG
535	TAGATGAACATGACCAGGA
536	TAGATGAACATGACCAGGA A
537	AGATGAACATGACCAGGA
538	AGATGAACATGACCAGG
539	AGATGAACATGACCAGGAA
540	GATGAACATGACCAGG
541	GATGAACATGACCAGGAA
542	GATGAACATGACCAGGA

543	ATGAACATGACCAGGA
544	TGAACATGACCAGGAA
545	GTGAAGTAGTAGTG
546	ACTTATCTTCTTTTCTGTT
547	ACTTATCTTCTTTTCTGT
548	CTTATCTTCTTTTCTGT
549	CTTATCTTCTTTTCTGTTG
550	CTTATCTTCTTTTCTGTT
551	TTATCTTCTTTTCTGTT
552	TTATCTTCTTTTCTGT
553	TTATCTTCTTTTCTGTTG
554	TATCTTCTTTTCTGTTG
555	ATCTTCTTTTCTGTTG
556	TCCCATGATGCTGAA
557	ACTGCTGAGCAGGATCAT
558	CTGCTGAGCAGGATCAT
559	TGCTGAGCAGGATCATG
560	TGAGCAGGATCATGA
561	TCTCTATCCACTCTCCA
562	CTCTATCCACTCTCCA
563	CTCTATCCACTCTCCAC
564	CTCTATCCACTCTCCACA
565	GGAAGGAGTGGAAGAAGTC G
566	GAAGGAGTGGAAGAAGTCG T
567	GAAGGAGTGGAAGAAGTCG
568	AAGGAGTGGAAGAAGTCG
569	AAGGAGTGGAAGAAGTCGT
570	AGGAGTGGAAGAAGTCG
571	AGGAGTGGAAGAAGTCGT
572	GGAGTGGAAGAAGTCG
573	GGAGTGGAAGAAGTCGT
574	GAGTGGAAGAAGTCGTT
575	GAGTGGAAGAAGTCGTT
576	GAGTGGAAGAAGTCGTTCA T
577	GAGTGGAAGAAGTCG
578	GAGTGGAAGAAGTCGTTCA
579	GAGTGGAAGAAGTCGT
580	AGTGGAAGAAGTCGTTCA
581	AGTGGAAGAAGTCGTTCA
582	AGTGGAAGAAGTCGTTCA G
583	AGTGGAAGAAGTCGT
584	AGTGGAAGAAGTCGTT
585	AGTGGAAGAAGTCGTT

586	GTGGAAGAAGTCGTTT
587	GTGGAAGAAGTCGT
588	GTGGAAGAAGTCGTTTCA
589	GTGGAAGAAGTCGTTTCA
590	GTGGAAGAAGTCGTTTCA
591	GTGGAAGAAGTCGTTTCA T
592	GTGGAAGAAGTCGTT
593	TGGAAGAAGTCGTTTCA G
594	TGGAAGAAGTCGTTCA
595	TGGAAGAAGTCGTTTCA
596	TGGAAGAAGTCGTTT
597	TGGAAGAAGTCGTTTCA
598	TGGAAGAAGTCGTTTCA
599	GGAAGAAGTCGTTCA
600	GGAAGAAGTCGTTTCA
601	GGAAGAAGTCGTTTCA
602	GGAAGAAGTCGTTTCA C
603	GGAAGAAGTCGTTTCA
604	GGAAGAAGTCGTTTCA
605	GAAGAAGTCGTTTCA
606	GAAGAAGTCGTTTCA
607	GAAGAAGTCGTTTCA
608	GAAGAAGTCGTTTCA
609	GAAGAAGTCGTTTCA
610	GAAGAAGTCGTTTCA
611	AAGAAGTCGTTTCA
612	AAGAAGTCGTTTCA
613	AAGAAGTCGTTTCA
614	AAGAAGTCGTTTCA
615	AAGAAGTCGTTTCA
616	AAGAAGTCGTTTCA
617	AAGAAGTCGTTTCA
618	AGAAGTCGTTTCA
619	AGAAGTCGTTTCA
620	AGAAGTCGTTTCA
621	AGAAGTCGTTTCA
622	AGAAGTCGTTTCA
623	AGAAGTCGTTTCA
624	GAAGTCGTTTCA
625	GAAGTCGTTTCA
626	GAAGTCGTTTCA
627	AAGTCGTTTCA
628	AAGTCGTTTCA
629	AGTCGTTTCA

630	AGTCGTTTCATGTGCCA
631	GTCGTTTCATGTGCC
632	TCGTTTCATGTGCCA
633	GGCCAGGATTTTGCCA
634	GGCCAGGATTTTGCC
635	TCAAAGCTCGTGTAG
636	CAAAGCTCGTGTAG

637	AAAGTTCGAAGAGCTG
638	TATTTGCTTAGCTGTT
639	GTAGATGAACATGACC
640	TAGATGAACATGACCAG
641	ATGAACATGACCAGGAA
642	TTCATAAATTTCACTAATC
643	AATGTACTTATACCCA

644	CTTACGCAAAAACAAT
645	ACTTACGCAAAAACAAT
646	TCACACCAATTACTTCTT
647	CTTCACACCAATTACTTCTT
648	TTACTTTATTCATCTCATA
649	TACTTTATTCATCTCATA
650	TTGAACCTTCATTATTC

The invention provides antisense oligonucleotides which comprise a contiguous nucleotide sequence selected from the group consisting of SEQ ID NO 50 – 641.

- 5 The invention provides antisense oligonucleotides which comprise a contiguous nucleotide sequence selected from the group consisting of SEQ ID NO 642 – 650.

The invention provides antisense oligonucleotides which comprise a contiguous nucleotide sequence of at least 12 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 50 – 641; or SEQ ID NO 642 – 650..

- 10 The invention provides antisense oligonucleotides which comprise a contiguous nucleotide sequence of at least 14 contiguous nucleotides which are identical to a sequence selected from the group consisting of SEQ ID NO 50 – 641; or SEQ ID NO 642 – 650.

In some embodiments, with reference to SEQ ID NO 50 – 641, or SEQ ID Nos 642 - 650, T may represent either a T or a U nucleobase, and a C may represent a C or a 5-methylC nucleobase.

- 15 In some embodiments, with reference to SEQ ID NO 50 – 641, or SEQ ID Nos 642 - 650, T is a T nucleobase, A is an A nucleobase, G is a G nucleobase and a C may represent a C or a 5-methylC nucleobase.

In some embodiments the oligonucleotide sequence or contiguous nucleotide sequence of the invention is 100% complementary to a corresponding target nucleic acid region (target

- 20 sequence) present in SEQ ID NO: 1. In some embodiments the oligonucleotide sequence or contiguous nucleotide sequence is 100% complementary to a corresponding target nucleic acid region present in SEQ ID NO: 1 and SEQ ID NO: 2. In some embodiments the oligonucleotide sequence contiguous nucleotide sequence is 100% complementary to a corresponding target nucleic acid region present SEQ ID NO: 1, 2 and 3.

- 25 In some embodiments, the oligonucleotide comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as 100% complementarity, to a corresponding target sequence selected from any region in Target Sequence List 1.

In some embodiments, the oligonucleotide comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as 100% complementarity, to a corresponding target sequence selected from any region in Target Sequence List 2.

5 In some embodiments, the oligonucleotide comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as 100% complementarity, to a corresponding target sequence selected from any region in Target Sequence List 3.

In some embodiments, the oligonucleotide comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as 100% complementarity, to a corresponding target sequence selected from any region in Target Sequence List 4.

10 In some embodiments, the oligonucleotide comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementary, such as 100% complementarity, to a corresponding target sequence selected from SEQ ID NO 17-49.

In one embodiment, the oligonucleotide comprises or consists of a contiguous nucleotide sequence of 12 to 22 nucleotides in length with at least 90% complementary, such as 100% complementarity, to the target sequence of SEQ ID NO 1, selected from the group consisting of
15 99525 - 99542 ; 70094 - 70110 ; 133396 - 133411 ; 20666 - 20682 ; 103244 - 103261 ;
20666 - 20683 ; 103244 - 103262 ; 147238 - 147253 ; 171787 - 171803 ; 171787 - 171803 ;
147238 - 147253 ; 171788 - 171803 ; 103244 - 103260 ; 103244 - 103262 ; 130009 - 130025
; 103244 - 103261 ; 98600 - 98616 ; 103244 - 103262 ; 171788 - 171803 ; 103244 - 103261
20 ; 70094 - 70110 ; 70094 - 70110 ; 70094 - 70110 ; 70094 - 70110 ; 70094 - 70110 ; 70094 -
70110 ; 70094 - 70110 ; 20666 - 20683 ; 97712 - 97728 ; 75261 - 75277 ; 75260 - 75276 ;
97713 - 97730 ; 75261 - 75277 ; 97712 - 97729 ; 20666 - 20683 ; 97712 - 97729 ; 20666 -
20683 ; 4426 - 4443 ; 75260 - 75276 ; 97715 - 97731 ; 20666 - 20683 ; 97712 - 97728 ;
4427 - 4443 ; 20666 - 20683 ; 97712 - 97729 ; 89475 - 89493 ; 99308 - 99324 ; 13076 -
25 13094 ; 87509 - 87527 ; 103272 - 103290 ; 82676 - 82692 ; 99526 - 99543 ; 82675 - 82691 ;
87510 - 87528 ; 97704 - 97720 ; 82675 - 82691 ; 89477 - 89495 ; and 13076 - 13094. Such
oligonucleotides may be a gapmer, such as an LNA gapmer.

In some embodiments, the oligonucleotide of the invention does not comprise a sequence selected from the group consisting of 301, 311, 312, 323, 342, 343, and 394.

30 In some embodiments, the oligonucleotide of the invention does not comprise a sequence of 10 or more contiguous nucleotides which are identical to a sequence selected from the group consisting of 301, 311, 312, 323, 342, 343, and 394.

In some embodiments, the oligonucleotide of the invention does not comprise a sequence of 12 or more contiguous nucleotides which are identical to a sequence selected from the group consisting of 301, 311, 312, 323, 342, 343, and 394.

Mismatches

- 5 Advantageously, the contiguous nucleotide sequence of the oligonucleotide of the invention is full complementary to the target nucleic acid sequence, such as SEQ ID NO 1, such as a targets sequence selected from those disclosed in Target Sequence lists 1, 2, 3 & 4, or SEQ ID NO 17 – 49.

- 10 In some embodiments however, the oligonucleotide of the invention comprises a mismatch between the oligonucleotide and the target nucleic acid. Despite the mismatch, hybridization to the target nucleic acid may still be sufficient to show a desired modulation of SCN9A expression. Reduced binding affinity resulting from a mismatch may advantageously be compensated by increased number of nucleotides in the oligonucleotide and/or an increased number of modified nucleosides capable of increasing the binding affinity to the target, such as
15 2' sugar modified nucleosides, including LNA, present within the oligonucleotide sequence.

- An aspect described in the present application relates to an antisense oligonucleotide of 10 to 30 nucleotides in length which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1. It is generally understood that the contiguous nucleotide sequence is the same
20 length or in some embodiments may be shorter than the antisense oligonucleotide (the sequence of the oligonucleotide may comprise or consist of the contiguous nucleotide sequence).

Oligonucleotide Length

- 25 In some embodiments, the oligonucleotide of the invention comprises or consists of 10 to 30 nucleotides in length, such as from 11 to 28, such as from 10 to 22, such as from 12 to 22, such as from 14 to 20, such as from 15 to 20 such as from 16 to 18 such as from 17 to 20 or 18 to 20 contiguous nucleotides in length. In a preferred embodiment, the oligonucleotide comprises or consists of 17 to 20 nucleotides in length.
- 30 In some embodiments, the oligonucleotide or contiguous nucleotide sequence thereof comprises or consists of 24 or less nucleotides, such as 22 or less nucleotides, such as 20 or less nucleotides, such as 17, 18, 19 or 20 nucleotides. It is to be understood that any range given herein includes the range endpoints. Accordingly, if an oligonucleotide is said to include from 10 to 30 nucleotides, both 10 and 30 nucleotides are included.

In some embodiments, the contiguous nucleotide sequence comprises or consists of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 contiguous nucleotides in length.

Modified Oligonucleotides

- 5 The oligonucleotide of the invention is a modified oligonucleotide – i.e. it comprises modified nucleosides or modified nucleotides, other than unmodified RNA or unmodified DNA.

It is understood that the contiguous nucleobase sequences (motif sequence) can be modified to for example increase nuclease resistance and/or binding affinity to the target nucleic acid.

- 10 The pattern in which the modified nucleosides (such as high affinity modified nucleosides) are incorporated into the oligonucleotide sequence is generally termed oligonucleotide design.

The oligonucleotides of the invention are designed with modified nucleosides and DNA nucleosides. Advantageously, high affinity modified nucleosides are used.

- 15 In an embodiment, the oligonucleotide comprises at least 1 modified nucleoside, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15 or at least 16 modified nucleosides. In an embodiment the oligonucleotide comprises from 1 to 10 modified nucleosides, such as from 2 to 9 modified nucleosides, such as from 3 to 8 modified nucleosides, such as from 4 to 7 modified nucleosides, such as 6 or 7 modified nucleosides. Suitable modifications are described in the “Definitions” section under “modified nucleoside”, “high affinity modified nucleosides”,
20 “sugar modifications”, “2’ sugar modifications” and Locked nucleic acids (LNA)”.

- In an embodiment, the oligonucleotide comprises one or more sugar modified nucleosides, such as 2’ sugar modified nucleosides. Preferably the oligonucleotide of the invention comprise one or more 2’ sugar modified nucleoside independently selected from the group consisting of 2’-O-alkyl-RNA, 2’-O-methyl-RNA, 2’-alkoxy-RNA, 2’-O-methoxyethyl-RNA, 2’-amino-DNA, 2’-fluoro-
25 DNA, arabino nucleic acid (ANA), 2’-fluoro-ANA and LNA nucleosides. It is advantageous if one or more of the modified nucleoside(s) is a locked nucleic acid (LNA).

- In a further embodiment the oligonucleotide or contiguous nucleotide sequence comprises at least one modified internucleoside linkage, such as at least one phosphorothioate internucleoside linkages. Suitable internucleoside modifications are described in the
30 “Definitions” section under “Modified internucleoside linkage”. It is advantageous if at least 75%, such as all, the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages. In some embodiments all the internucleotide linkages in the contiguous sequence of the oligonucleotide are phosphorothioate linkages.

In some embodiments, the oligonucleotide of the invention comprises at least one LNA nucleoside, such as 1, 2, 3, 4, 5, 6, 7, or 8 LNA nucleosides, such as from 2 to 6 LNA nucleosides, such as from 3 to 7 LNA nucleosides, 4 to 8 LNA nucleosides or 3, 4, 5, 6, 7 or 8 LNA nucleosides. In some embodiments, at least 75% of the modified nucleosides in the oligonucleotide are LNA nucleosides, such as 80%, such as 85%, such as 90% of the modified nucleosides are LNA nucleosides. In a still further embodiment all the modified nucleosides in the oligonucleotide are LNA nucleosides. In a further embodiment, the oligonucleotide may comprise both beta-D-oxy-LNA, and one or more of the following LNA nucleosides: thio-LNA, amino-LNA, oxy-LNA, ScET and/or ENA in either the beta-D or alpha-L configurations or combinations thereof. In a further embodiment, all LNA cytosine units are 5-methyl-cytosine. It is advantageous for the nuclease stability of the oligonucleotide or contiguous nucleotide sequence to have at least 1 LNA nucleoside at the 5' end and at least 2 LNA nucleosides at the 3' end of the nucleotide sequence.

In an embodiment of the invention the oligonucleotide of the invention is capable of recruiting RNase H, such as human RNaseH1.

In the current invention an advantageous structural design is a gapmer design as described in the "Definitions" section under for example "Gapmer", "LNA Gapmer", "MOE gapmer" and "Mixed Wing Gapmer" "Alternating Flank Gapmer". The gapmer design includes gapmers with uniform flanks, mixed wing flanks, alternating flanks, and gapbreaker designs. In the present invention it is advantageous if the oligonucleotide of the invention is a gapmer with an F-G-F' design where region F and F' independently comprise 1 - 8 nucleosides, of which 1 - 5 are 2' sugar modified and defines the 5' and 3' end of the F and F' region, and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH. In one embodiment the G region consists of 6 - 16 contiguous DNA nucleosides. In a further embodiment region F and F' each comprise at least one LNA nucleoside.

In all instances the F-G-F' design may further include region D' and/or D'' as described in the "Definitions" section under "Region D' or D'' in an oligonucleotide". In some embodiments the oligonucleotide of the invention has 1, 2 or 3 phosphodiester linked nucleoside units, such as DNA units, at the 5' or 3' end of the gapmer region.

Oligonucleotides

In some embodiments of the invention, the oligonucleotide is selected from the group of oligonucleotide compounds with CMP-ID-NO: 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1

; 98_1; 99_1; 100_1; 101_1; 102_1; 103_1; 104_1; 105_1; 106_1; 107_1; 108_1; 109_1;
; 110_1; 111_1; 112_1; 113_1; 114_1; 115_1; 116_1; 117_1; 118_1; 119_1; 120_1;
121_1; 122_1; 123_1; 124_1; 125_1; 126_1; 127_1; 128_1; 129_1; 130_1; 131_1;
132_1; 133_1; 134_1; 135_1; 136_1; 137_1; 138_1; 139_1; 140_1; 141_1; 142_1;
5 143_1; 144_1; 145_1; 146_1; 147_1; 148_1; 149_1; 150_1; 151_1; 152_1; 153_1;
154_1; 155_1; 156_1; 157_1; 158_1; 159_1; 160_1; 161_1; 162_1; 163_1; 164_1;
165_1; 166_1; 167_1; 168_1; 169_1; 170_1; 171_1; 172_1; 173_1; 174_1; 175_1;
176_1; 177_1; 178_1; 179_1; 180_1; 181_1; 182_1; 183_1; 184_1; 185_1; 186_1;
187_1; 188_1; 189_1; 190_1; 191_1; 192_1; 193_1; 194_1; 195_1; 196_1; 197_1;
10 198_1; 199_1; 200_1; 201_1; 202_1; 203_1; 204_1; 205_1; 206_1; 207_1; 208_1;
209_1; 210_1; 211_1; 212_1; 213_1; 214_1; 215_1; 216_1; 217_1; 218_1; 219_1;
220_1; 221_1; 222_1; 223_1; 224_1; 225_1; 226_1; 227_1; 228_1; 229_1; 230_1;
231_1; 232_1; 233_1; 234_1; 235_1; 236_1; 237_1; 238_1; 239_1; 240_1; 241_1;
242_1; 243_1; 244_1; 245_1; 246_1; 247_1; 248_1; 249_1; 250_1; 251_1; 252_1;
15 253_1; 254_1; 255_1; 256_1; 257_1; 258_1; 259_1; 260_1; 261_1; 262_1; 263_1;
264_1; 265_1; 266_1; 267_1; 268_1; 269_1; 270_1; 271_1; 272_1; 273_1; 274_1;
275_1; 276_1; 277_1; 278_1; 279_1; 280_1; 281_1; 282_1; 283_1; 284_1; 285_1;
286_1; 287_1; 288_1; 289_1; 290_1; 291_1; 292_1; 293_1; 294_1; 295_1; 296_1;
297_1; 298_1; 299_1; 300_1; 301_1; 302_1; 303_1; 304_1; 305_1; 306_1; 307_1;
20 308_1; 309_1; 310_1; 311_1; 312_1; 313_1; 314_1; 315_1; 316_1; 317_1; 318_1;
319_1; 320_1; 321_1; 322_1; 323_1; 324_1; 325_1; 326_1; 327_1; 328_1; 329_1;
330_1; 331_1; 332_1; 333_1; 334_1; 335_1; 336_1; 337_1; 338_1; 339_1; 340_1;
341_1; 342_1; 343_1; 344_1; 345_1; 346_1; 347_1; 348_1; 349_1; 350_1; 351_1;
352_1; 353_1; 354_1; 355_1; 356_1; 357_1; 358_1; 359_1; 360_1; 361_1; 362_1;
25 363_1; 364_1; 365_1; 366_1; 367_1; 368_1; 369_1; 370_1; 371_1; 372_1; 373_1;
374_1; 375_1; 376_1; 377_1; 378_1; 379_1; 380_1; 381_1; 382_1; 383_1; 384_1;
385_1; 386_1; 387_1; 388_1; 389_1; 390_1; 391_1; 392_1; 393_1; 394_1; 395_1;
396_1; 397_1; 398_1; 399_1; 400_1; 401_1; 402_1; 403_1; 404_1; 405_1; 406_1;
407_1; 408_1; 409_1; 410_1; 411_1; 412_1; 413_1; 414_1; 415_1; 416_1; 417_1;
30 418_1; 419_1; 420_1; 421_1; 422_1; 423_1; 424_1; 425_1; 426_1; 427_1; 428_1;
429_1; 430_1; 431_1; 432_1; 433_1; 434_1; 435_1; 436_1; 437_1; 438_1; 439_1;
440_1; 441_1; 442_1; 443_1; 444_1; 445_1; 446_1; 447_1; 448_1; 449_1; 450_1;
451_1; 452_1; 453_1; 454_1; 455_1; 456_1; 457_1; 458_1; 459_1; 460_1; 461_1;
462_1; 463_1; 464_1; 465_1; 466_1; 467_1; 468_1; 469_1; 470_1; 471_1; 472_1;
35 473_1; 474_1; 475_1; 476_1; 477_1; 478_1; 479_1; 480_1; 481_1; 482_1; 483_1;
484_1; 485_1; 486_1; 487_1; 488_1; 489_1; 490_1; 491_1; 492_1; 493_1; 494_1;

495_1 ; 496_1 ; 497_1 ; 498_1 ; 499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ;
 506_1 ; 507_1 ; 508_1 ; 509_1 ; 510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ;
 513_3 ; 513_4 ; 514_1 ; 514_2 ; 514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ;
 515_6 ; 516_1 ; 516_2 ; 516_3 ; 516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ;
 5 517_4 ; 517_5 ; 517_6 ; 517_7 ; 517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ;
 519_1 ; 519_2 ; 519_3 ; 519_4 ; 519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ;
 521_1 ; 521_2 ; 521_3 ; 521_4 ; 521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ;
 523_3 ; 523_4 ; 523_5 ; 524_1 ; 525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ;
 532_1 ; 533_1 ; 534_1 ; 535_1 ; 536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ;
 10 543_1 ; 544_1 ; 545_1 ; 546_1 ; 547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ;
 554_1 ; 555_1 ; 556_1 ; 557_1 ; 558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ;
 565_1 ; 566_1 ; 567_1 ; 568_1 ; 569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ;
 576_1 ; 577_1 ; 578_1 ; 579_1 ; 580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ;
 587_1 ; 588_1 ; 589_1 ; 590_1 ; 591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ;
 15 598_1 ; 599_1 ; 600_1 ; 601_1 ; 602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ;
 609_1 ; 610_1 ; 611_1 ; 612_1 ; 613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ;
 620_1 ; 621_1 ; 622_1 ; 623_1 ; 624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ;
 631_1 ; 632_1 ; 633_1 ; 634_1 ; 635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1 ; and 641_1.

In some embodiments of the invention, the oligonucleotide is selected from the group of
 20 oligonucleotide compounds with CMP-ID-NO: 642_1, 643_1, 644_1, 645_1, 646_1, 647_1,
 648_1, 649_1 and 650_1.

In some embodiments, the invention provides a compound selected from the group consisting
 of CMP-ID-NO: 50_1 - 641_1.

In some embodiments, the invention provides a compound selected from the group consisting
 25 of CMP-ID-NO: 642_1, 643_1, 644_1, 645_1, 646_1, 647_1, 648_1, 649_1 and 650_1.

These compounds are listed in the compound table at the end of the example section and were
 tested for their ability to inhibit SCN9A *in vitro* via gymnotic delivery.

The following compounds gave at least 40% inhibition of SCN9A expression:

51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, 110_1, 65_1,
 30 94_1, 64_1, 57_1, 136_1, 158_1, 159_1, 356_1, 197_1, 132_1, 83_1, 76_1, 130_1, 135_1,
 77_1, 186_1, 105_1, 445_1, 325_1, 265_1, 200_1, 288_1, 346_1, 86_1, 281_1, 339_1, 256_1,
 289_1, 414_1, 286_1, 241_1, 82_1, 475_1, 91_1, 50_1, 97_1, 322_1, 148_1, 443_1, 251_1,
 451_1, 179_1, 466_1, 357_1, 109_1, 472_1, 471_1, 376_1, 413_1, 270_1, 379_1, 416_1,
 311_1, 411_1, 368_1, 333_1, 347_1, 152_1, 89_1, 380_1, 390_1, 429_1, 63_1, 90_1, 415_1,

199_1, 503_1, 476_1, 92_1, 268_1, 371_1, 302_1, 485_1, 205_1, 274_1, 122_1, 419_1,
470_1, 498_1, 156_1, 478_1, 393_1, 312_1, 287_1, 96_1, 226_1, 71_1, 137_1, 365_1, 58_1,
370_1, 280_1, 385_1, 442_1, 134_1, 463_1, 140_1, 440_1, 230_1, 310_1, 479_1, 363_1,
340_1, 495_1, 467_1, 444_1, 418_1, 338_1, 335_1, 496_1, 196_1, 317_1, 341_1, 406_1,
5 330_1, 173_1, 377_1, 474_1, 482_1, 282_1, 266_1, 73_1, 257_1, 342_1, 190_1, 492_1, 87_1,
188_1, 456_1, 372_1, 417_1, 404_1, 239_1, 206_1, 433_1, 486_1, 175_1, 461_1, 56_1,
408_1, 334_1, 504_1, 453_1, 222_1, 410_1, 104_1, 460_1, 439_1, 255_1, 489_1, 203_1,
398_1, 171_1, 407_1, 172_1, 412_1, 321_1, 305_1, 328_1, 120_1, 434_1, 449_1, 350_1,
487_1, 146_1, 420_1, 426_1, 352_1, 150_1, 316_1, 353_1, 469_1, 306_1, 384_1, 155_1,
10 450_1, 279_1, 267_1, 337_1, 184_1, 459_1, 360_1, 75_1, 468_1, 180_1, 245_1, 387_1,
345_1, 98_1, 435_1, 295_1, 369_1, 218_1, 182_1, 448_1, 300_1, 481_1, 427_1, 207_1,
367_1, 240_1, 231_1, 364_1, 355_1, 431_1, 497_1, 397_1, 465_1, 271_1, 502_1, 151_1,
178_1, 499_1, 421_1, 131_1, 309_1, 491_1, 261_1, 121_1, 128_1, 84_1, 304_1, 264_1,
493_1, 185_1, 237_1, 139_1, 441_1, 169_1, 160_1, 102_1, 296_1, 164_1, 362_1, 500_1, and
15 100_1.

The following compounds gave at least 50% inhibition of SCN9A expression:

51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, 110_1, 65_1,
94_1, 64_1, 57_1, 136_1, 158_1, 159_1, 356_1, 197_1, 132_1, 83_1, 76_1, 130_1, 135_1,
77_1, 186_1, 105_1, 445_1, 325_1, 265_1, 200_1, 288_1, 346_1, 86_1, 281_1, 339_1, 256_1,
20 289_1, 414_1, 286_1, 241_1, 82_1, 475_1, 91_1, 50_1, 97_1, 322_1, 148_1, 443_1, 251_1,
451_1, 179_1, 466_1, 357_1, 109_1, 472_1, 471_1, 376_1, 413_1, 270_1, 379_1, 416_1,
311_1, 411_1, 368_1, 333_1, 347_1, 152_1, 89_1, 380_1, 390_1, 429_1, 63_1, 90_1, 415_1,
199_1, 503_1, 476_1, 92_1, 268_1, 371_1, 302_1, 485_1, 205_1, 274_1, 122_1, 419_1,
470_1, 498_1, 156_1, 478_1, 393_1, 312_1, 287_1, 96_1, 226_1, 71_1, 137_1, 365_1, 58_1,
25 370_1, 280_1, 385_1, 442_1, 134_1, 463_1, 140_1, 440_1, 230_1, 310_1, 479_1, 363_1,
340_1, 495_1, 467_1, 444_1, 418_1, 338_1, 335_1, 496_1, 196_1, 317_1, 341_1, 406_1,
330_1, 173_1, 377_1, 474_1, 482_1, 282_1, 266_1, 73_1, 257_1, 342_1, 190_1, 492_1, 87_1,
188_1, 456_1, 372_1, 417_1, 404_1, 239_1, 206_1, 433_1, 486_1, 175_1, 461_1, 56_1,
408_1, 334_1, 504_1, 453_1, 222_1, 410_1, 104_1, 460_1, 439_1, 255_1, 489_1, 203_1,
30 398_1, 171_1, 407_1, 172_1, 412_1, 321_1, 305_1, 328_1, 120_1, 434_1, 449_1, 350_1,
487_1, 146_1, 420_1, 426_1, 352_1, 150_1, 316_1, 353_1, 469_1, 306_1, 384_1, 155_1,
450_1, 279_1, 267_1, 337_1, 184_1, 459_1, 360_1, 75_1, 468_1, 180_1, 245_1, 387_1,
345_1, 98_1, 435_1, 295_1, 369_1, 218_1, 182_1, 448_1, 300_1, 481_1, 427_1, 207_1

The following compounds gave at least 60% inhibition of SCN9A expression:

51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, 110_1, 65_1, 94_1, 64_1, 57_1, 136_1, 158_1, 159_1, 356_1, 197_1, 132_1, 83_1, 76_1, 130_1, 135_1, 77_1, 186_1, 105_1, 445_1, 325_1, 265_1, 200_1, 288_1, 346_1, 86_1, 281_1, 339_1, 256_1, 289_1, 414_1, 286_1, 241_1, 82_1, 475_1, 91_1, 50_1, 97_1, 322_1, 148_1, 443_1, 251_1, 5 451_1, 179_1, 466_1, 357_1, 109_1, 472_1, 471_1, 376_1, 413_1, 270_1, 379_1, 416_1, 311_1, 411_1, 368_1, 333_1, 347_1, 152_1, 89_1, 380_1, 390_1, 429_1, 63_1, 90_1, 415_1, 199_1, 503_1, 476_1, 92_1, 268_1, 371_1, 302_1, 485_1, 205_1, 274_1, 122_1, 419_1, 470_1, 498_1, 156_1, 478_1, 393_1, 312_1, 287_1, 96_1, 226_1, 71_1, 137_1, 365_1, 58_1, 370_1, 280_1, 385_1, 442_1, 134_1, 463_1, 140_1, 440_1, 230_1, 310_1, 479_1, 363_1, 10 340_1, 495_1, 467_1, 444_1, 418_1, 338_1, 335_1, 496_1, 196_1, 317_1, 341_1, 406_1, 330_1, 173_1, 377_1, 474_1, 482_1, 282_1, 266_1, 73_1, 257_1, 342_1, 190_1, 492_1, 87_1, 188_1, 456_1, 372_1, 417_1, 404_1, 239_1, 206_1, 433_1, 486_1, 175_1, 461_1, 56_1, 408_1, 334_1, 504_1, and 453_1.

The following compounds gave at least 70% inhibition of SCN9A expression:

15 51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, 110_1, 65_1, 94_1, 64_1, 57_1, 136_1, 158_1, 159_1, 356_1, 197_1, 132_1, 83_1, 76_1, 130_1, 135_1, 77_1, 186_1, 105_1, 445_1, 325_1, 265_1, 200_1, 288_1, 346_1, 86_1, 281_1, 339_1, 256_1, 289_1, 414_1, 286_1, 241_1, 82_1, 475_1, 91_1, 50_1, 97_1, 322_1, 148_1, 443_1, 251_1, 451_1, 179_1, 466_1, 357_1, 109_1, 472_1, 471_1, 376_1, 413_1, 270_1, 379_1, 416_1, 20 311_1, 411_1, 368_1, 333_1, 347_1, 152_1, 89_1, 380_1, 390_1, 429_1, 63_1, 90_1, 415_1, 199_1, 503_1, 476_1, 92_1, 268_1, 371_1, 302_1, 485_1, 205_1, 274_1,

The following compounds gave at least 80% inhibition of SCN9A expression:

51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, 110_1, 65_1, 94_1, 64_1, 57_1, 136_1, 158_1, 159_1, 356_1, 197_1, 132_1, 83_1, 76_1, 130_1, 135_1, 25 77_1, 186_1, 105_1, 445_1, and 325_1.

The following compounds gave at least 90% inhibition of SCN9A expression:

51_1, 59_1, 127_1, 161_1, 67_1, 106_1, 72_1, 124_1, 163_1, 99_1, 125_1, and 110_1.

In the compounds identified by a compound ID, Capital letters are beta-D-oxy LNA nucleosides, lowercase letters are DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside 30 linkages are phosphorothioate internucleoside linkages.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 50 ; 51 ; 52 ; 53 ; 54 ; 55 ; 56 ; 57 ; 58 ; 59 ; 60 ; 61 ; 62 ; 63 ; 64 ; 65 ; 66 ; 67 ; 68 ; 69 ; 70 ; 71 ; 72 ; 73 ; 74 ; 75 ; 76 ; 77 ; 78 ; 79 ; 80 ; 81 ; 82 ; 83 ; 84

; 85 ; 86 ; 87 ; 88 ; 89 ; 90 ; 91 ; 92 ; 93 ; 94 ; 95 ; 96 ; 97 ; 98 ; 99 ; 100 ; 101 ; 102 ; 103 ; 104 ;
105 ; 106 ; 107 ; 108 ; 109 ; 110 ; 111 ; 112 ; 113 ; 114 ; 115 ; 116 ; 117 ; 118 ; 119 ; 120 ; 121 ;
122 ; 123 ; 124 ; 125 ; 126 ; 127 ; 128 ; 129 ; 130 ; 131 ; 132 ; 133 ; 134 ; 135 ; 136 ; 137 ; 138 ;
139 ; 140 ; 141 ; 142 ; 143 ; 144 ; 145 ; 146 ; 147 ; 148 ; 149 ; 150 ; 151 ; 152 ; 153 ; 154 ; 155 ;
5 156 ; 157 ; 158 ; 159 ; 160 ; 161 ; 162 ; 163 ; 164 ; 165 ; 166 ; 167 ; 168 ; 169 ; 170 ; 171 ; 172 ;
173 ; 174 ; 175 ; 176 ; 177 ; 178 ; 179 ; 180 ; 181 ; 182 ; 183 ; 184 ; 185 ; 186 ; 187 ; 188 ; 189 ;
190 ; 191 ; 192 ; 193 ; 194 ; 195 ; 196 ; 197 ; 198 ; 199 ; 200 ; 201 ; 202 ; 203 ; 204 ; 205 ; 206 ;
207 ; 208 ; 209 ; 210 ; 211 ; 212 ; 213 ; 214 ; 215 ; 216 ; 217 ; 218 ; 219 ; 220 ; 221 ; 222 ; 223 ;
224 ; 225 ; 226 ; 227 ; 228 ; 229 ; 230 ; 231 ; 232 ; 233 ; 234 ; 235 ; 236 ; 237 ; 238 ; 239 ; 240 ;
10 241 ; 242 ; 243 ; 244 ; 245 ; 246 ; 247 ; 248 ; 249 ; 250 ; 251 ; 252 ; 253 ; 254 ; 255 ; 256 ; 257 ;
258 ; 259 ; 260 ; 261 ; 262 ; 263 ; 264 ; 265 ; 266 ; 267 ; 268 ; 269 ; 270 ; 271 ; 272 ; 273 ; 274 ;
275 ; 276 ; 277 ; 278 ; 279 ; 280 ; 281 ; 282 ; 283 ; 284 ; 285 ; 286 ; 287 ; 288 ; 289 ; 290 ; 291 ;
292 ; 293 ; 294 ; 295 ; 296 ; 297 ; 298 ; 299 ; 300 ; 301 ; 302 ; 303 ; 304 ; 305 ; 306 ; 307 ; 308 ;
309 ; 310 ; 311 ; 312 ; 313 ; 314 ; 315 ; 316 ; 317 ; 318 ; 319 ; 320 ; 321 ; 322 ; 323 ; 324 ; 325 ;
15 326 ; 327 ; 328 ; 329 ; 330 ; 331 ; 332 ; 333 ; 334 ; 335 ; 336 ; 337 ; 338 ; 339 ; 340 ; 341 ; 342 ;
343 ; 344 ; 345 ; 346 ; 347 ; 348 ; 349 ; 350 ; 351 ; 352 ; 353 ; 354 ; 355 ; 356 ; 357 ; 358 ; 359 ;
360 ; 361 ; 362 ; 363 ; 364 ; 365 ; 366 ; 367 ; 368 ; 369 ; 370 ; 371 ; 372 ; 373 ; 374 ; 375 ; 376 ;
377 ; 378 ; 379 ; 380 ; 381 ; 382 ; 383 ; 384 ; 385 ; 386 ; 387 ; 388 ; 389 ; 390 ; 391 ; 392 ; 393 ;
394 ; 395 ; 396 ; 397 ; 398 ; 399 ; 400 ; 401 ; 402 ; 403 ; 404 ; 405 ; 406 ; 407 ; 408 ; 409 ; 410 ;
20 411 ; 412 ; 413 ; 414 ; 415 ; 416 ; 417 ; 418 ; 419 ; 420 ; 421 ; 422 ; 423 ; 424 ; 425 ; 426 ; 427 ;
428 ; 429 ; 430 ; 431 ; 432 ; 433 ; 434 ; 435 ; 436 ; 437 ; 438 ; 439 ; 440 ; 441 ; 442 ; 443 ; 444 ;
445 ; 446 ; 447 ; 448 ; 449 ; 450 ; 451 ; 452 ; 453 ; 454 ; 455 ; 456 ; 457 ; 458 ; 459 ; 460 ; 461 ;
462 ; 463 ; 464 ; 465 ; 466 ; 467 ; 468 ; 469 ; 470 ; 471 ; 472 ; 473 ; 474 ; 475 ; 476 ; 477 ; 478 ;
479 ; 480 ; 481 ; 482 ; 483 ; 484 ; 485 ; 486 ; 487 ; 488 ; 489 ; 490 ; 491 ; 492 ; 493 ; 494 ; 495 ;
25 496 ; 497 ; 498 ; 499 ; 500 ; 501 ; 502 ; 503 ; 504 ; 505 ; 506 ; 507 ; 508 ; 509 ; 510 ; 511 ; 512 ;
513 ; 514 ; 515 ; 516 ; 517 ; 518 ; 519 ; 520 ; 521 ; 522 ; 523 ; 524 ; 525 ; 526 ; 527 ; 528 ; 529 ;
530 ; 531 ; 532 ; 533 ; 534 ; 535 ; 536 ; 537 ; 538 ; 539 ; 540 ; 541 ; 542 ; 543 ; 544 ; 545 ; 546 ;
547 ; 548 ; 549 ; 550 ; 551 ; 552 ; 553 ; 554 ; 555 ; 556 ; 557 ; 558 ; 559 ; 560 ; 561 ; 562 ; 563 ;
564 ; 565 ; 566 ; 567 ; 568 ; 569 ; 570 ; 571 ; 572 ; 573 ; 574 ; 575 ; 576 ; 577 ; 578 ; 579 ; 580 ;
30 581 ; 582 ; 583 ; 584 ; 585 ; 586 ; 587 ; 588 ; 589 ; 590 ; 591 ; 592 ; 593 ; 594 ; 595 ; 596 ; 597 ;
598 ; 599 ; 600 ; 601 ; 602 ; 603 ; 604 ; 605 ; 606 ; 607 ; 608 ; 609 ; 610 ; 611 ; 612 ; 613 ; 614 ;
615 ; 616 ; 617 ; 618 ; 619 ; 620 ; 621 ; 622 ; 623 ; 624 ; 625 ; 626 ; 627 ; 628 ; 629 ; 630 ; 631 ;
632 ; 633 ; 634 ; 635 ; 636 ; 637 ; 638 ; 639 ; 640 ; and 641.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide
35 sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected
from the group consisting of SEQ ID NO 642, 643, 644, 645, 646, 647, 648, 649 and 650.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321, 305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155, 450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218, 182, 448, 300, 481, 427, 207, 367, 240, 231, 364, 355, 431, 497, 397, 465, 271, 502, 151, 178, 499, 421, 131, 309, 491, 261, 121, 128, 84, 304, 264, 493, 185, 237, 139, 441, 169, 160, 102, 296, 164, 362, 500, and 100.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321, 305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155, 450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218, 182, 448, 300, 481, 427, and 207.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346,

86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 5 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 504, and 453.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected 10 from the group consisting of SEQ ID NO 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 199, 503, 476, 92, 268, 371, 302, 485, 205, and 274.

15 In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, and 325.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide 20 sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 13 or at least 14 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

25 In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence selected from the group consisting of SEQ ID NOs 512 – 641.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence comprising at least 14 contiguous nucleotides of the selected sequence.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide 30 sequence comprising at least 15 contiguous nucleotides of the selected sequence.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotide sequence which comprises or consists of the selected sequence.

Method of manufacture

In a further aspect, the invention provides methods for manufacturing the oligonucleotides of the invention comprising reacting nucleotide units and thereby forming covalently linked contiguous nucleotide units comprised in the oligonucleotide. Preferably, the method uses phosphoramidite chemistry (see for example Caruthers et al, 1987, Methods in Enzymology vol. 154, pages 287-313). In a further embodiment the method further comprises reacting the contiguous nucleotide sequence with a conjugating moiety (ligand) to covalently attach the conjugate moiety to the oligonucleotide. In a further aspect a method is provided for manufacturing the composition of the invention, comprising mixing the oligonucleotide or conjugated oligonucleotide of the invention with a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

Pharmaceutical salt

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin, Organic Process Research & Development 2000, 4, 427-435 or in Ansel, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457. For example, the pharmaceutically acceptable salt of the compounds provided herein may be a sodium salt.

In a further aspect the invention provides a pharmaceutically acceptable salt of the antisense oligonucleotide or a conjugate thereof. In a preferred embodiment, the pharmaceutically acceptable salt is a sodium or a potassium salt.

Pharmaceutical Composition

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof and a

pharmaceutically acceptable diluent, carrier, salt and/or adjuvant. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS) and pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In some embodiments the pharmaceutically acceptable diluent is sterile phosphate buffered saline or sterile sodium carbonate buffer.

In some embodiments the oligonucleotide of the invention is in the form of a solution in the pharmaceutically acceptable diluent, for example dissolved in PBS or sodium carbonate buffer. The oligonucleotide may be pre-formulated in the solution or in some embodiments may be in the form of a dry powder (e.g. a lyophilized powder) which may be dissolved in the pharmaceutically acceptable diluent prior to administration. Suitably, for example the oligonucleotide may be dissolved in a concentration of 0.1 – 100mg/ml, such as 1 – 10mg/ the pharmaceutically acceptable diluent.

In some embodiments the oligonucleotide of the invention is formulated in a unit dose of between 0.5 – 100mg, such as 1mg – 50mg, or 2 – 25mg.

Oligonucleotides or oligonucleotide conjugates of the invention may be mixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

Pharmaceutical compositions, such as solutions, may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5.

The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

In some embodiments, the oligonucleotide or oligonucleotide conjugate of the invention is a prodrug. In particular with respect to oligonucleotide conjugates the conjugate moiety is cleaved off the oligonucleotide once the prodrug is delivered to the site of action, e.g. the target cell.

Applications

The oligonucleotides of the invention may be utilized as research reagents for, for example, diagnostics, therapeutics and prophylaxis.

In research, such oligonucleotides may be used to specifically modulate the synthesis of Na_v1.7 or in some aspects Na_v1.8 protein in cells (e.g. *in vitro* cell cultures) and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Typically the target modulation is achieved by degrading or inhibiting the mRNA producing the protein, thereby prevent protein formation or by degrading or inhibiting a modulator of the gene or mRNA producing the protein.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

The present invention provides an *in vivo* or *in vitro* method for modulating SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an oligonucleotide of the invention in an effective amount to said cell.

In some embodiments, the target cell, is a mammalian cell in particular a human cell. The target cell may be an *in vitro* cell culture or an *in vivo* cell forming part of a tissue in a mammal. In preferred embodiments the target cell is present in the peripheral nervous system, such as the dorsal root ganglion.

In diagnostics the oligonucleotides may be used to detect and quantitate SCN9A expression in cell and tissues by northern blotting, *in-situ* hybridization or similar techniques.

Therapeutic Applications

The oligonucleotides of the invention, or the conjugates, salts or pharmaceutical compositions of the invention, may be administered to an animal or a human for the prevention or treatment of pain, such as chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain. The oligonucleotides of the invention, or the conjugates, salts or pharmaceutical compositions of the invention may be for use as a local analgesic.

The pain which may be treated by the oligonucleotides of the invention, or the conjugates, salts or pharmaceutical compositions of the invention may be pain wherein the pain signal in the peripheral nervous system. Indications associated with pain with a significant peripheral component include for example, diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia.

Pain which may be prevented, treated or ameliorated using the oligonucleotide, conjugate, composition or salt of the invention may for example be selected from the group consisting of

pain associated with inherited erythromelalgia (EIM), paroxysmal extreme pain disorder (PEPD), trigeminal neuralgia, neurophathic pain, chronic pain, but also general treatment of nociceptive (e.g. decompression of a nerve), neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

- 5 The invention provides for the oligonucleotide, conjugate, composition or salt of the invention for the use for the prevention or for the treatment of pain, such as chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain.

The invention further relates to use of an oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition of the invention for the manufacture of a medicament for the
10 treatment or prevention of pain, such as chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain.

The invention provides for the oligonucleotide, conjugate, composition or salt of the invention for the use as a local analgesic.

The invention provides for the use of the oligonucleotide, conjugate, composition or salt of the
15 invention for manufacture of a local analgesic.

The invention provides for the oligonucleotide, conjugate, composition or salt of the invention for the use for the prevention or for the treatment of pain associated with inherited erythromelalgia (EIM), paroxysmal extreme pain disorder (PEPD), trigeminal neuralgia, neurophathic pain, chronic pain, but also general treatment of nociceptive (e.g. decompression of a nerve),
20 neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

The invention further relates to use of an oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition of the invention for the manufacture of a medicament for the treatment or prevention of pain associated with inherited erythromelalgia (EIM), paroxysmal extreme pain disorder (PEPD), trigeminal neuralgia, neurophathic pain, chronic pain, but also
25 general treatment of nociceptive (e.g. decompression of a nerve), neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

Method of Treatments

The invention provides methods for treating or preventing pain in a subject, such as a human, who is suffering from or is likely to suffer pain, comprising administering a therapeutically or
30 prophylactically effective amount of an oligonucleotide, an oligonucleotide conjugate or a pharmaceutical composition of the invention to a subject who is suffering from or is susceptible to suffering from pain, such as chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain.

By way of example, the method of treatment may be in subjects whose are suffering from an indication selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia.

5 The method of the invention may be for treating and relieving pain, such as pain associated with inherited erythromelalgia (EIM), paroxysmal extreme pain disorder (PEPD), trigeminal neuralgia, neurophathic pain, chronic pain, but also general treatment of nociceptive (e.g. decompression of a nerve), neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

The methods of the invention are preferably employed for treatment or prophylaxis against pain which is mediated by $\text{Na}_v1.7$, or in some aspects, $\text{Na}_v1.7$ and $\text{Na}_v1.8$.

10 Administration

The oligonucleotides or pharmaceutical compositions of the present invention may be administered via parenteral administration.

In some embodiments, the administration route is subcutaneous or intreavenous.

15 In some embodiments the administration route is selected from the group consisting of intravenous, subcutaneous, intra-muscular, intracerebral, epidural, intracerebroventricular intraocular, intrathecal administration, or transforaminal administration).

In some advantageous embodiments, the administration is via intrathecal administration, or epidural administration or transforaminal administration.

20 Advantageously, the oligonucleotide or pharmaceutical compositions of the present invention are administered intrathecally.

The invention also provides for the use of the oligonucleotide of the invention, or conjugate thereof, such as pharmaceutical salts or compositions of the invention, for the manufacture of a medicament for the prevention or treatment of pain wherein the medicament is in a dosage form for intrathecal administration.

25 The invention also provides for the use of the oligonucleotide or oligonucleotide conjugate of the invention as described for the manufacture of a medicament for the manufacture of a medicament for the prevention or treatment of pain wherein the medicament is in a dosage form for intrathecal administration.

30 The invention also provides for the oligonucleotide of the invention, or conjugate thereof, such as pharmaceutical salts or compositions of the invention, for use as a medicament for the prevention or treatment of pain wherein the medicament is in a dosage form for intrathecal administration.

The invention also provides for the oligonucleotide or oligonucleotide conjugate of the invention, for use as a medicament for the prevention or treatment of pain wherein the medicament is in a dosage form for intrathecal administration.

Combination therapies

- 5 In some embodiments the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is for use in a combination treatment with another therapeutic agent. The therapeutic agent can for example be the standard of care for the diseases or disorders described above. In some embodiments the compound of the invention is used in combination with small molecule analgesics which may be administered concurrently or
10 independently of the administration of the compound or compositions of the invention. An advantage of a combination therapy of the compounds of the invention with small molecule analgesics is that small molecule analgesics have a rapid onset of pain relieving activity, typically with a short duration of action (hours – days), whereas the compounds of the invention has a delayed onset of activity (typically a few days or even a week+), but with a long duration
15 of action (weeks – months, e.g. 2+, 3+ or 4 months+).

EMBODIMENTS – the following is a list of exemplary embodiments of the invention.

1. An antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1.
- 20 2. The antisense oligonucleotide of embodiment 2, wherein the contiguous nucleotide sequence is at least 90% complementary, such as 100% complementary to a region of SEQ ID NO 1 selected from the group consisting of the sequences shown in Target Sequence List 1.
3. The antisense oligonucleotide of embodiment 1 or 2 wherein the contiguous nucleotide
25 sequence is at least 90% complementary, such as 100% complementary to a region of SEQ ID NO 1 selected from the group consisting of the sequences shown in Target Sequence List 2.
4. The antisense oligonucleotide of embodiment 1 - 3 wherein the contiguous nucleotide sequence is at least 90% complementary, such as 100% complementary to a region of SEQ
30 ID NO 1 selected from the group consisting of Target Sequence List 3.
5. The antisense oligonucleotide of embodiment 1 - 4 wherein the contiguous nucleotide sequence is at least 90% complementary, such as 100% complementary to a region of SEQ ID NO 1 selected from the group consisting of Target List 4.
6. The antisense oligonucleotide of embodiment 1 - 5, wherein the contiguous nucleotide
35 sequence comprises a sequence which is 100% complementary to at least at least 10

contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 17 - 49.

7. The antisense oligonucleotide of embodiment 1 - 5 wherein the contiguous nucleotide sequence comprises a sequence which is 100% complementary to at least at least 12 contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 17 - 49.
8. The antisense oligonucleotide of embodiment 1 - 6 wherein the contiguous nucleotide sequence comprises a sequence which is 100% complementary to at least at least 14 contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 17 - 49.
9. The antisense oligonucleotide of embodiment 1 - 7 wherein the contiguous nucleotide sequence is 100% complementary to a sequence selected from the group consisting of SEQ ID NO 17 - 49.
10. The antisense oligonucleotide of any one of embodiments 1 – 9, wherein the contiguous nucleotide sequence comprises at least 10 contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 50 – 641, or 642 – 650.
11. The antisense oligonucleotide of any one of embodiments 1 – 9, wherein the contiguous nucleotide sequence comprises at least 12 contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 50 – 641, or 642 – 650.
12. The antisense oligonucleotide of any one of embodiments 1 – 9, wherein the contiguous nucleotide sequence comprises at least 14 contiguous nucleotides present in a sequence selected from the group consisting of SEQ ID NO 50 – 641, or 642 – 650.
13. The antisense oligonucleotide of any one of embodiments 1 – 9, wherein the contiguous nucleotide sequence is a sequence selected from the group consisting of SEQ ID NO 50 – 641, or 642 – 650.
14. The antisense oligonucleotide of any one of embodiments 1 – 13, one or more nucleoside in the contiguous nucleotide sequence is a 2' sugar modified nucleoside.
15. The antisense oligonucleotide of embodiment 14, wherein the one or more 2' sugar modified nucleoside is independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.
16. The antisense oligonucleotide of any one of embodiments 1 - 15, wherein the antisense oligonucleotide or contiguous nucleotide sequence thereof comprises one or more LNA nucleoside.

17. The antisense oligonucleotide of any one of embodiments 1-16, wherein at least one internucleoside linkage in the contiguous nucleotide sequence is a phosphorothioate internucleoside linkages.
18. The antisense oligonucleotide of any one of embodiments 1-17, wherein all the
5 internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.
19. The antisense oligonucleotide of any one of embodiments embodiment 1-18, wherein the oligonucleotide is capable of recruiting RNase H, such as human RNaseH1.
20. The antisense oligonucleotide of any one of embodiments 1 - 19, wherein the antisense
10 oligonucleotide, or contiguous nucleotide sequence thereof, consists or comprises a gapmer, such as a gapmer of formula 5'-F-G-F'-3', wherein region G is a region comprising a contiguous sequence of nucleotides capable of recruiting RNaseH, and regions F and F' each comprise at least one 2' sugar modified nucleoside.
21. The antisense oligonucleotide according to embodiment 20, wherein region G comprises of
15 6 – 16 DNA nucleosides and at least one of region F and F' comprises at least one LNA nucleoside, or both region F and F' comprise at least one LNA nucleoside.
22. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the antisense oligonucleotide is a compound selected from the group consisting of CMP ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ;
20 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ; 103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ; 114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ;
25 125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ; 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ; 147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ; 158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ; 169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ;
30 180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ; 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ; 202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ; 213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ; 224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ;
35 235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ; 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ;

257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ;
268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ;
279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ;
290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ;
5 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ;
312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ;
323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ;
334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ; 343_1 ; 344_1 ;
345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ;
10 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ;
367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ;
378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ;
389_1 ; 390_1 ; 391_1 ; 392_1 ; 393_1 ; 394_1 ; 395_1 ; 396_1 ; 397_1 ; 398_1 ; 399_1 ;
400_1 ; 401_1 ; 402_1 ; 403_1 ; 404_1 ; 405_1 ; 406_1 ; 407_1 ; 408_1 ; 409_1 ; 410_1 ;
15 411_1 ; 412_1 ; 413_1 ; 414_1 ; 415_1 ; 416_1 ; 417_1 ; 418_1 ; 419_1 ; 420_1 ; 421_1 ;
422_1 ; 423_1 ; 424_1 ; 425_1 ; 426_1 ; 427_1 ; 428_1 ; 429_1 ; 430_1 ; 431_1 ; 432_1 ;
433_1 ; 434_1 ; 435_1 ; 436_1 ; 437_1 ; 438_1 ; 439_1 ; 440_1 ; 441_1 ; 442_1 ; 443_1 ;
444_1 ; 445_1 ; 446_1 ; 447_1 ; 448_1 ; 449_1 ; 450_1 ; 451_1 ; 452_1 ; 453_1 ; 454_1 ;
455_1 ; 456_1 ; 457_1 ; 458_1 ; 459_1 ; 460_1 ; 461_1 ; 462_1 ; 463_1 ; 464_1 ; 465_1 ;
20 466_1 ; 467_1 ; 468_1 ; 469_1 ; 470_1 ; 471_1 ; 472_1 ; 473_1 ; 474_1 ; 475_1 ; 476_1 ;
477_1 ; 478_1 ; 479_1 ; 480_1 ; 481_1 ; 482_1 ; 483_1 ; 484_1 ; 485_1 ; 486_1 ; 487_1 ;
488_1 ; 489_1 ; 490_1 ; 491_1 ; 492_1 ; 493_1 ; 494_1 ; 495_1 ; 496_1 ; 497_1 ; 498_1 ;
499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ; 506_1 ; 507_1 ; 508_1 ; 509_1 ;
510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ; 513_3 ; 513_4 ; 514_1 ; 514_2 ;
25 514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ; 515_6 ; 516_1 ; 516_2 ; 516_3 ;
516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ; 517_4 ; 517_5 ; 517_6 ; 517_7 ;
517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ; 519_1 ; 519_2 ; 519_3 ; 519_4 ;
519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ; 521_1 ; 521_2 ; 521_3 ; 521_4 ;
521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ; 523_3 ; 523_4 ; 523_5 ; 524_1 ;
30 525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ; 532_1 ; 533_1 ; 534_1 ; 535_1 ;
536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ; 543_1 ; 544_1 ; 545_1 ; 546_1 ;
547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ; 554_1 ; 555_1 ; 556_1 ; 557_1 ;
558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ; 565_1 ; 566_1 ; 567_1 ; 568_1 ;
569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ; 576_1 ; 577_1 ; 578_1 ; 579_1 ;
35 580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ; 587_1 ; 588_1 ; 589_1 ; 590_1 ;
591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ; 598_1 ; 599_1 ; 600_1 ; 601_1 ;

602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ; 609_1 ; 610_1 ; 611_1 ; 612_1 ;
613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ; 620_1 ; 621_1 ; 622_1 ; 623_1 ;
624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ; 631_1 ; 632_1 ; 633_1 ; 634_1 ;
635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1 ; and 641_1; or 642_1 ; 643_1 ; 644_1 ; 645_1
5 ; 646_1 ; 647_1 ; 648_1 ; 649_1 ; 650_1

23. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the
antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least
10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting
of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356,
10 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256,
289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472,
471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415,
199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312,
287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363,
15 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282,
266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56,
408, 334, 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321,
305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155,
450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218,
20 182, 448, 300, 481, 427, 207, 367, 240, 231, 364, 355, 431, 497, 397, 465, 271, 502, 151,
178, 499, 421, 131, 309, 491, 261, 121, 128, 84, 304, 264, 493, 185, 237, 139, 441, 169,
160, 102, 296, 164, 362, 500, and 100.

24. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the
antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least
25 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting
of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356,
197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256,
289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472,
471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415,
30 199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312,
287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363,
340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282,
266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56,
408, 334, 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321,
35 305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155,

450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218, 182, 448, 300, 481, 427, and 207.

- 5 25. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 10 199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 504, and 453.
- 15 26. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 20 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415, 199, 503, 476, 92, 268, 371, 302, 485, 205, and 274.
- 25 27. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, and 325, such as a compound selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, and 110.
- 30 28. The antisense oligonucleotide according to any one of embodiments 1 – 21, wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of is a compound selected from the group consisting of SEQ ID NOs 512 – 641.
- 35 29. The antisense oligonucleotide according to any one of embodiments 23 – 28 wherein the contiguous nucleotide sequence of the antisense oligonucleotide comprises at least 14 contiguous nucleotides of the selected sequence, or consists of the selected sequence.

30. A conjugate comprising the antisense oligonucleotide according to any one of embodiments 1 – 29, and at least one conjugate moiety covalently attached to said oligonucleotide.
31. A pharmaceutically acceptable salt of the antisense oligonucleotide according to any one of embodiments 1 – 29, or the conjugate according to embodiment 30.
- 5 32. A pharmaceutical composition comprising the antisense oligonucleotide of embodiment 1-29 or the conjugate of embodiment 30 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
33. An *in vivo* or *in vitro* method for modulating SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an antisense oligonucleotide of
10 any one of embodiments 1 -29 or the conjugate of embodiment 30 or the pharmaceutical salt or composition of embodiment 31 or 32 in an effective amount to said cell.
34. A method for treating or preventing pain in a subject such as a human, who is suffering from or is likely to suffer pain, comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of any one of embodiments 1 -29 or the
15 conjugate of embodiment 30 or the pharmaceutical salt or composition of embodiment 31 or 32, such as to prevent or alleviate the pain.
35. The method of embodiment 34, wherein the pain is either
- i) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or
 - 20 ii) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or
 - iii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or
 - 25 iv) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.
36. The oligonucleotide of any one of embodiments 1- 29 or the conjugate according to embodiment 30 or the pharmaceutical salt or composition of embodiment 31 or 32 for use in
30 medicine.
37. The oligonucleotide of any one of embodiments 1 - 29 or the conjugate according to embodiment 30 or the pharmaceutical salt or composition of embodiment 31 or 32 for use in the treatment or prevention or alleviation of pain, such as the pain as defined according to parts i), ii), iii) or iv) of embodiment 35.
- 35 38. The use of an oligonucleotide of any one of embodiments 1 - 29 or the conjugate according to embodiment 30 or the pharmaceutical salt or composition of embodiment 31 or 32, for

the preparation of a medicament for the treatment, prevention or alleviation of pain, such as the pain as defined according to parts I), ii), iii) or iv) of embodiment 35.

5 EXAMPLES

Oligonucleotide synthesis

Compounds are listed in the Compound Table, which also illustrates the nucleobase sequence, complementary target sequence region on SEQ ID NO 1 (start and end), the gapmer design, the T_m (dG), and the level of remaining mRNA in the cells after treatment with the compounds (see Example 1 below)

Oligonucleotide synthesis is generally known in the art. Below is a protocol which may be applied. The oligonucleotides of the present invention may have been produced by slightly varying methods in terms of apparatus, support and concentrations used.

Oligonucleotides are synthesized on uridine universal supports using the phosphoramidite approach on an Oligomaker 48 at 1 μ mol scale. At the end of the synthesis, the oligonucleotides are cleaved from the solid support using aqueous ammonia for 5-16 hours at 60°C. The oligonucleotides are purified by reverse phase HPLC (RP-HPLC) or by solid phase extractions and characterized by UPLC, and the molecular mass is further confirmed by ESI-MS.

Elongation of the oligonucleotide:

The coupling of β -cyanoethyl-phosphoramidites (DNA-A(Bz), DNA- G(ibu), DNA- C(Bz), DNA- T, LNA-5-methyl-C(Bz), LNA-A(Bz), LNA- G(dmf), or LNA-T) is performed by using a solution of 0.1 M of the 5'-O-DMT-protected amidite in acetonitrile and DCI (4,5-dicyanoimidazole) in acetonitrile (0.25 M) as activator. For the final cycle a phosphoramidite with desired modifications can be used, e.g. a C6 linker for attaching a conjugate group or a conjugate group as such. Thiolation for introduction of phosphorothioate linkages is carried out by using xanthane hydride (0.01 M in acetonitrile/pyridine 9:1). Phosphordiester linkages can be introduced using 0.02 M iodine in THF/Pyridine/water 7:2:1. The rest of the reagents are the ones typically used for oligonucleotide synthesis.

For post solid phase synthesis conjugation a commercially available C6 aminolinker phosphoramidite can be used in the last cycle of the solid phase synthesis and after deprotection and cleavage from the solid support the aminolinked deprotected oligonucleotide is isolated. The conjugates are introduced via activation of the functional group using standard synthesis methods.

Purification by RP-HPLC:

The crude compounds are purified by preparative RP-HPLC on a Phenomenex Jupiter C18 10 μ 150x10 mm column. 0.1 M ammonium acetate pH 8 and acetonitrile is used as buffers at a flow rate of 5 mL/min. The collected fractions are lyophilized to give the purified compound typically as a white solid.

Abbreviations:

DCI: 4,5-Dicyanoimidazole

DCM: Dichloromethane

DMF: Dimethylformamide

DMT: 4,4'-Dimethoxytrityl

THF: Tetrahydrofuran

Bz: Benzoyl

Ibu: Isobutyryl

RP-HPLC: Reverse phase high performance liquid chromatography

T_m Assay:

Oligonucleotide and RNA target (phosphate linked, PO) duplexes are diluted to 3 mM in 500 ml RNase-free water and mixed with 500 ml 2x T_m-buffer (200mM NaCl, 0.2mM EDTA, 20mM Naphosphate, pH 7.0). The solution is heated to 95°C for 3 min and then allowed to anneal in room temperature for 30 min. The duplex melting temperatures (T_m) is measured on a Lambda 40 UV/VIS Spectrophotometer equipped with a Peltier temperature programmer PTP6 using PE Templab software (Perkin Elmer). The temperature is ramped up from 20°C to 95°C and then down to 25°C, recording absorption at 260 nm. First derivative and the local maximums of both the melting and annealing are used to assess the duplex T_m.

Example 1: *In vitro* reduction of Nav1.7 in SK-N-AS human cell line using oligonucleotides.

LNA modified oligonucleotides targeting human Nav1.7 were tested for their ability to reduce Nav1.7 mRNA expression in human SK-N-AS neuroblastoma cells acquired from ATCC (CRL-2137). SK-N-AS cells (ECACC - 94092302) were cultured according to the vendor guidelines in Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA) and fetal bovine serum to a final concentration of 10%. Cells were cultured at 37 °C, 5 % CO₂ and 95% humidity in an active evaporation incubator (Thermo C10). Cells were seeded at a density of 9300 cells per well (96-well plate) in 95 μ l of SK-N-AS cell culture medium and left to attach for 24 hours in the incubator. Hereafter, oligos diluted to a final concentration of 5 μ M in PBS (5.0 μ l) were added to the cell cultures from pre-made 96-well dilution plates. The cell culture plates were incubated for 96 hours in the incubator.

After incubation, cells were harvested by removal of media followed by cell lysis and RNA purification using QIAGEN RNeasy 96 Kit (cat 74181), following manufacturers protocol. RNA was diluted 10 fold in water prior to the one-step qPCR reaction. For one-step qPCR reaction qPCR-mix (qScript™ XLT One-Step RT-qPCR ToughMix® Low ROX from QuantaBio, cat.no 95134-500) and QPCR was run as duplex QPCR using assays from Integrated DNA technologies for Nav1.7 (Hs.PT.58.20989243) and GUSB (Hs.PT.58v.27737538).

The reactions were then mixed in a qPCR plate (MICROAMP®optical 384 well, 4309849). After sealing, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a Viia™ 7 system (Applied Biosystems, Thermo), and the following PCR conditions used: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec followed by a temperature decrease of 1.6 °C/sec followed by 60 °C for 45 sec. The data was analyzed using the QuantStudio™ Real_time PCR Software and quantity calculated by the delta delta Ct method ($Quantity = 2^{(-Ct)} * 10000000000$). Quantity is normalized to the calculated quantity for the housekeeping gene assay (GUSB) run in the same well. Relative Target Quantity = $QUANTITY_target / QUANTITY_housekeeping$ (RNA knockdown) was calculated for each well by division with the mean of all PBS-treated wells on the same plate. Normalised Target Quantity = $(Relative Target Quantity / [mean] Relative Target Quantity]_{pbs_wells}) * 100$.

Compounds based on SEQ ID NOs 512 – 641 are being evaluated in the above assay.

The target knock-down data is presented in the following Compound Table:

In the Compound table, motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide.

Design refers to the gapmer design, F-G-F', wherein G is a region of DNA nucleosides, and F and F' are regions of LNA nucleosides.

Oligonucleotide compound represent specific designs of a motif sequence. Capital letters represent beta-D-oxy LNA nucleosides, lowercase letters represent DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

Example 2: *In vitro* reduction of Nav1.8 alone or in combination with reduction of Nav1.7 in modified SK-N-AS human cell line (CRISPR activation of Nav1.8) using oligonucleotides.

Activation of Nav1.8 expression in SK-N-AS cells:

SK-N-AS cells were transduced with lentiviral particles coding for hCMV-Blast-dCas9-VPR (#VCAS11918, Dharmacon) at 0.5 MOI, and selected with Blasticidin at 2 ug/ml for 10 days. SK-N-AS stably expressing dCas9-VPR protein were subsequently engineered to express

Nav1.8 specific sgRNA. Briefly, an expression cassette driven by U6 promoter has been synthesized as a gBlock and then subcloned in PiggyBac vector (#PB511B-1, System Biosciences). The identity of the vector has been Sanger-sequencing validated. Stable integration of the U6 driven cassette expressing Nav1.8 specific sgRNA was obtained with the use of the transposase expression plasmid (#PB210PA-1, System Biosciences) following the manufacturer's instructions. Selection of sgRNA stably expressing cells was obtained in presence of Puromycin at 2 ug/ml for 10 days.

The sgRNA sequence used in Nav1.8 activation is GGCAAGCTGTCACCTCTCTG (SEQ ID NO 652).

The full sequence of the U6 promoter-sgRNA is the following:

GAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGAT
AATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTA
ATAATTTCTTGGGTAGTTTGCAGTTTTAAATTATGTTTTAAATGGACTATCATATGCTTAC
CGTAACTTGAAAGTATTTGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCG
GGCAAGCTGTCACCTCTCTGGTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCC
GTTATCAACTTGAAAAAGTGGCACCAGAGTCGGTGCTTTTTTTT (SEQ ID NO 653).

LNA modified oligonucleotides targeting human Nav1.8 singlehanded or also Nav1.7 as a dual-specific compound were tested for their ability to reduce the expression of their respective mRNA targets in human SK-N-AS neuroblastoma cells acquired from ATCC (CRL-2137). The SK-N-AS cells (ECACC - 94092302) have underwent an activation of transcription of Nav1.8 using CRISPR activation (CRISPRa) as described above. The modified SK-N-AS cells were cultured according to the vendor guidelines for the parent cell line in Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA), fetal bovine serum to a final concentration of 10% along with Blasticidin (2.5µg/ml) and Puromycin (1µg/ml). Cells were cultured at 37 °C, 5 % CO₂ and 95% humidity in an active evaporation incubator (Thermo C10). Cells were seeded at a density of 10,000 cells per well (96-well plate) in 190 ul of SK-N-AS cell culture medium and left to attach for 4 hours in the incubator. Hereafter, oligos were diluted in pre-made 96-well dilution plates to the desired concentration and 10µl hereof was added to the cell culture plate for a final concentration of 10µM. The cell culture plates were incubated for 72 hours in the incubator.

After incubation, cells were harvested by removal of media followed by cell lysis and RNA purification using QIAGEN RNeasy 96 Kit (cat 74181), following manufacturers protocol. RNA was diluted 10 fold in water prior to the one-step qPCR reaction. For one-step qPCR reaction

qPCR-mix (qScript™ XLT One-Step RT-qPCR ToughMix® Low ROX from QuantaBio, cat.no 95134-500) and QPCR was run as duplex QPCR using assays from Integrated DNA technologies for Nav1.7 (Hs.PT.58.20989243), Nav1.8 (Hs.PT.58.23220090) and GUSB (Hs.PT.58v.27737538).

5 Results

This table below lists dual-specific compounds targeting both Nav1.7 (SCN9a) and Nav1.8 (SCN10a)

The effect is here provided as residual target RNA (normalised to GUSB) relative to PBS control.

- 10 The test was performed in regular SK-N-AS cells and in SK-N-AS following CRISPRa of Nav1.8.

Compound	SK-N-AS SCN9a/GUSB	SK-N-AS 1.8 SCN9a/GUSB	SK-N-AS 1.8 SCN10a/GUSB
515_3	0,340	0,423	1,136
526_1	0,238	0,252	0,851
528_1	0,210	0,236	0,468
631_1	0,086	0,142	0,496
632_1	0,032	0,054	0,391
636_1	0,021	0,070	0,286
519_6	0,361	0,490	0,432

Compound Table								
SEQ ID NO	Motif sequence	position on SEQ ID NO: 1		Design	CMP ID NO	Oligonucleotide Compound	dG	SNC9A mRNA % (vs Saline control 100%)
		Start	end					
50	ATGTTTACTATAATCACA	1037	1054	4-10-4	50_1	ATGTttactataatCACA	-21	22,9
51	GGCATATCATATATCC	1779	1794	2-12-2	51_1	GGcatatcatatatCC	-18	4,6
52	CCAATTTTTCTTAAAATAT	3456	3475	3-14-3	52_1	CCAatttttcttaaaaTAT	-19	105,5
53	TCTCATAAATCCTCATAT	4379	4396	2-12-4	53_1	TctcataaatcctcATAT	-20	71,2
54	TATTCTACCCACATTCT	4405	4421	2-13-2	54_1	TAttctaccacattCT	-20	64,6
55	AGTATTCTACCCACATT	4407	4423	2-13-2	55_1	AGtattctaccacaTT	-19	66,8
56	AAGTATTCTACCCACAT	4408	4424	2-12-3	56_1	AAgtattctaccacaCAT	-20	39,5
57	TATCTCATATTCCACAAA	4424	4441	4-12-2	57_1	TATCtcatattccacaAA	-19	13,4
58	TTATCTCATATTCCACA	4426	4442	3-12-2	58_1	TTAtctcatattccaCA	-19	31,6
59	GTTATCTCATATTCCAC	4427	4443	2-12-3	59_1	GTtatctcatattcCAC	-19	5,3
60	TTCATGAAGAAATTTCA	4472	4489	4-7-7	60_1	TTCAtgaagaAATTTCA	-20	95,3
61	GCTCAATTTTCCAATTATT	5276	5294	2-15-2	61_1	GCtcaattttccaattaTT	-20	88,6
62	TCTAATCTTATTTATCTTTC	5302	5321	3-15-2	62_1	TCTaatcttatttatctTC	-19	76,4
63	TCCATAATATTTACCTA	6333	6350	3-13-2	63_1	TCCcataatatttaccTA	-22	28,6
64	ATCACTTCACTTTATAATA	6386	6405	4-12-4	64_1	ATCActtcaactttatAATA	-21	13,0
65	TTCATCACTTCAACTTTA	6391	6408	4-11-3	65_1	TTCAtcacttcaactTTA	-20	11,4
66	TCCTACCTGAATTACC	6468	6483	2-12-2	66_1	TCctacctgaattaCC	-20	77,2
67	GCTTTTAACACTTTATA	6652	6668	4-11-2	67_1	GCTTttaacactttaTA	-19	8,2
68	CTCCTAATATATAATATACT	6839	6858	4-13-3	68_1	CTCCtaatatataatataCT	-21	86,9
69	TCTCCTAATATATAATATA	6841	6859	4-11-4	69_1	TCTCctaatatataaTATA	-21	86,3
70	ATATATCTCCTAATATATA	6846	6864	4-11-4	70_1	ATATatctcctaataTATA	-21	99,7
71	ACATATATATCTCCTAATA	6850	6868	4-11-4	71_1	ACATatataatctcctAATA	-21	31,3
72	CTCATATCTACTTATCAT	6920	6937	4-11-3	72_1	CTCAtatctacttatCAT	-22	9,0
73	TACTCATATCTACTTATCA	6921	6939	3-12-4	73_1	TACtcatatctacttATCA	-22	36,6
74	TCTACTCATATCTACTTA	6924	6941	2-13-3	74_1	TCtactcatatctacTTA	-19	85,3
75	ACATCTACTCATATCTACT	6926	6944	3-13-3	75_1	ACAtctactcatatctACT	-21	48,3
76	AATTACACCATTCTCT	8389	8405	3-10-4	76_1	AATtacaccattcCTCT	-22	17,3
77	CCCTTTTAATTACACCAT	8395	8412	1-13-4	77_1	CccttttaattacaCCAT	-23	18,7
78	ACACTATTATACATTCCCA	9395	9413	3-14-2	78_1	ACActattatacattccCA	-22	83,5
79	AGCTACACTATTATACAT	9400	9417	3-13-2	79_1	AGCtacactattatacAT	-19	98,7
80	ACTTCCATATTATTTCCAT	9421	9440	2-15-3	80_1	ACttccatattattttcCAT	-23	65,2
81	TCTCCTTAAATACATCAAAT	10395	10414	4-12-4	81_1	TCTCcttaaatacatcAAAT	-21	68,9
82	ATATTACTGTACTCCC	10916	10931	1-12-3	82_1	AtattactgtactCCC	-19	22,7
83	ATATTTATACAACAACCTCA	12492	12510	4-11-4	83_1	ATATttataacaacaCTCA	-21	16,5
84	TAGTCACCATTTTTCAT	13016	13032	3-12-2	84_1	TAGtcaccatttttcAT	-19	57,3
85	AGAAAATAATTCCTATCCT	13384	13402	2-14-3	85_1	AGaaaataattcctatCCT	-20	108,7

86	ATACATGTATCCACTTC	15449	15465	1-12-4	86_1	AtacatgtatccaCTTC	-18	21,6
87	TTCCAATATTATTATACA	15461	15478	4-10-4	87_1	TTCCaatattattaTACA	-21	37,7
88	ACCCTTATTTAAATAATTA	15493	15511	4-11-4	88_1	ACCCTtatttaaataATTA	-22	92,5
89	TCACGTAAATCCCATCT	15581	15598	2-14-2	89_1	TCacgttaaatacccatCT	-21	27,6
90	ACGTAAATCCCATC	15582	15596	4-9-2	90_1	ACGTaaatcccaTC	-18	28,7
91	TTCACGTAAATCCCA	15584	15599	1-11-4	91_1	TtcacgttaaataCCCA	-21	22,8
92	GGATATCGTATTTTCT	16909	16924	3-10-3	92_1	GGAtatcgtatttTCT	-19	29,1
93	TCTGGATATCGTATT	16913	16927	5-8-2	93_1	TCTGGatatcgtaTT	-19	98,8
94	GATATATTATCCATCTCA	17171	17188	4-11-3	94_1	GATAtattatccatCTCA	-22	12,0
95	TGATATATTATCCATCT	17173	17189	4-9-4	95_1	TGATatattatccATCT	-21	104,6
96	AGCATCTACATTTTAATT	17339	17356	4-10-4	96_1	AGCActcatatcttTAATT	-21	31,1
97	TCTTAATTCTTATCATTTTA	17606	17625	4-12-4	97_1	TCTTaattcttatcatTTTA	-21	22,9
98	AACTCTTAATTCTTATCA	17611	17629	4-11-4	98_1	AACTtcttaattcttATCA	-21	48,8
99	TACAATAATTATCTTCTCA	19084	19102	4-11-4	99_1	TACAataattatcttCTCA	-22	9,8
100	TGCAAATAATACCCTAT	19281	19297	3-10-4	100_1	TGCaaataataaccCTAT	-22	60,6
101	CTCTATTCTAAATAAACCTT	19713	19732	4-14-2	101_1	CTCTattctaaataaaccTT	-20	69,3
102	ACTCTATTCTAAATAAACCC	19715	19733	4-11-4	102_1	ACTCtattctaaataAACCC	-21	59,8
103	ATGACTCTATTCTAAATA	19719	19736	4-10-4	103_1	ATGActctattctaaATA	-20	70,5
104	TAAGCATATATTTTCCCA	20666	20683	1-14-3	104_1	TaagcatatattttCCCA	-20	41,0
105	TCATTTCCATTAAATCCAA	21212	21230	4-12-3	105_1	TCATttccattaaatcCAA	-22	19,0
106	TTTCATTTCCATTAAATCC	21214	21232	4-12-3	106_1	TTTCatttccattaaaTCC	-22	8,8
107	TTTTATCCTACTTCTAC	22208	22224	1-12-4	107_1	TtttatcctacttCTAC	-18	94,6
108	TCCCTCAAATATAAATTC	22299	22316	4-11-3	108_1	TCCCTcaaataataaTTC	-21	86,8
109	ACTGTTTTCTCTAAACC	23036	23052	2-11-4	109_1	ACTgttttctctaAACC	-20	24,9
110	AGATTCACTACATCCA	24286	24301	3-10-3	110_1	AGAttcactacatCCA	-22	10,8
111	GCACTCTGATTACATTTCT	24422	24441	1-17-2	111_1	GcactctgattacatttCT	-23	62,0
112	TATTTAATCACTTTATCTAA	24503	24522	2-14-4	112_1	TAtttaatcactttatCTAA	-18	102,4
113	ATATTTAATCACTTTATCT	24505	24523	2-13-4	113_1	ATatttaatcactttATCT	-18	125,6
114	ATCAACCACACAATTACTTT	24715	24734	1-15-4	114_1	AtcaaccacacaattaCTTT	-20	72,4
115	TATCAACCACACAATTACTT	24716	24735	2-15-3	115_1	TAtcaaccacacaattaCTT	-21	88,8
116	TTATCAACCACACAATTACT	24718	24736	3-13-3	116_1	TTAtcaaccacacaatTACT	-19	81,8
117	TCAATAAAATTCCTTATACT	25826	25845	2-14-4	117_1	TCaataaaattccttaTACT	-19	99,6
118	TCATTTTATTTATTTCAATT	26537	26556	4-12-4	118_1	TCATtttatttttcaAATT	-19	86,7
119	TATACACTCTTCTCTATTC	26697	26716	2-14-4	119_1	TAtacactcttctctATTC	-22	94,0
120	TGACCATCTTATTCATC	26782	26798	4-10-3	120_1	TGACcatcttattcATC	-21	43,6
121	CCTGATACTCATCCCCA	27287	27303	1-14-2	121_1	CctgatactcattccCA	-21	57,2
122	TTTCTCTTTATCTTTTATC	27498	27516	4-12-3	122_1	TTTCtctttatctttATC	-20	30,1
123	AAATCAACCCTAAACCC	27530	27546	3-10-4	123_1	AAAtcaaccctaaACCC	-22	105,9
124	AAAGTACCATTACTCCC	27603	27620	4-12-2	124_1	AAAGtaccatttactcCC	-23	9,1
125	TTCATATACTCTTATTTTA	27669	27687	4-11-4	125_1	TTCAtatactcttatTTTA	-20	10,5
126	CTAATTTTTCATATACTCTT	27675	27694	1-15-4	126_1	CtaatttttcatataCTCTT	-19	100,5
127	TCTAATTTTTCATATACTC	27677	27695	4-11-4	127_1	TCTAatttttcatataCTC	-21	7,0
128	CTCTAATTTTTCATATACT	27678	27696	3-12-4	128_1	CTCtaatttttcataTACT	-21	57,2
129	ACATTTTTCCTACAACTA	27781	27799	3-12-4	129_1	ACAtttttcctacaaACTA	-22	115,4

130	CTACTATTCCATCATTTTT	28331	28349	4-13-2	130_1	CTACtattccatcatTT	-22	17,3
131	CAATTACACCTACAACCTC	28710	28728	2-13-4	131_1	CAattacacctacaaCTTC	-21	55,7
132	TCCAATTACACCTACAAC	28713	28730	3-11-4	132_1	TCCaattacacctaCAAC	-23	16,5
133	GCCTTAATCAATTTCTCAA	29790	29808	3-14-2	133_1	GCCttaatcaattttctcAA	-22	78,6
134	CACTTTCCAATATTACT	30079	30095	3-11-3	134_1	CACtttccaatattACT	-19	32,1
135	TTACACTTTCCAATATTAC	30080	30098	4-11-4	135_1	TTACactttccaataTTAC	-22	18,0
136	CATTACACTTTCCAATATTA	30081	30100	4-13-3	136_1	CATTacactttccaataTTA	-23	14,3
137	ACATTACACTTTCCAATA	30084	30101	4-10-4	137_1	ACATtacactttccAATA	-21	31,4
138	ATATACCCCAATTACTCCA	30949	30967	1-16-2	138_1	AtataccccaattactcCA	-22	77,5
139	ATACTAGCAATTCATCA	31411	31427	4-9-4	139_1	ATACtagcaattcATCA	-21	58,4
140	ATACCATTAACATCACC	31626	31643	2-12-4	140_1	ATaccattaactatCACC	-22	32,4
141	AGATACCATTAACATCA	31628	31645	4-11-3	141_1	AGATaccattaactaTCA	-22	81,6
142	CCCATCTTCATTATATTA	32138	32155	2-12-4	142_1	CCcatcttcattatATTA	-22	94,9
143	TTCTGATCTCTCTTATA	34051	34067	1-12-4	143_1	TtctgatctctctTATA	-18	76,2
144	ATTTCATTCAAGAAATAC	34107	34124	1-10-7	144_1	AtttcattcagGAAATAC	-19	95,0
145	TCATTTTCATCAATAACATTA	34132	34151	3-15-2	145_1	TCAtttcatcaataacatTA	-18	83,0
146	TTGCTTTTTTACTAACA	34181	34197	4-11-2	146_1	TTGCTtttttactaaCA	-20	45,3
147	GTTTCATTTCTTTATTAT	34206	34223	2-12-4	147_1	GTttcattttctttaTTAT	-19	78,5
148	GCTATTATATTACTTTT	34269	34285	4-9-4	148_1	GCTAttatattacTTTT	-20	23,6
149	GTCCTCTAATCATATCACA	35539	35557	1-15-3	149_1	GtcctctaatacatatcACA	-21	71,5
150	TAGTCCTCTAATCATATC	35542	35559	2-12-4	150_1	TAgtcctctaatacaTATC	-21	46,3
151	TTAGTCCTCTAATCATA	35544	35560	4-10-3	151_1	TTAGtcctctaatacATA	-21	55,1
152	ACTTAGTCCTCTAATCA	35546	35562	4-11-2	152_1	ACTTagtcctctaataCA	-21	27,0
153	TAAATAAAACAATCCCCA	36850	36867	2-12-4	153_1	TAaataaaacaatCCCCA	-21	73,2
154	TAATTAATAAAACAATCCC	36852	36871	2-14-4	154_1	TAattaataaaacaaTCCC	-18	94,5
155	ATACATACCTCTATTATT	38088	38105	4-10-4	155_1	ATACatacctctatTATT	-21	47,1
156	TCAATACATACCTCTATTA	38090	38108	4-11-4	156_1	TCAAtacatacctctATTA	-22	30,7
157	CTCAATACATACCTCTATT	38091	38109	1-14-4	157_1	CtcaatacacacctcTATT	-20	100,7
158	GAACTCAATACATACCTC	38095	38112	4-11-3	158_1	GAACTcaatacacatcCTC	-21	14,4
159	AGAACTCAATACATACC	38097	38113	2-11-4	159_1	AGaactcaatacaTACC	-19	15,4
160	TGAATTTTTATTCCCTTC	42260	42277	2-13-3	160_1	TGaatttttattcccTTC	-19	59,5
161	ACACAATACCATATTTCA	42376	42393	4-10-4	161_1	ACACaataccatattTCA	-22	7,5
162	TGCTATAATATTTTATCT	42912	42929	4-10-4	162_1	TGCTataatattttATCT	-22	65,7
163	ACAAACTTTCAATACTCTA	43082	43100	4-11-4	163_1	ACAAactttcaatacTCTA	-21	9,6
164	TCTTCTACACTATTATTC	43218	43235	2-12-4	164_1	TcttctacactattATTC	-19	60,1
165	ATATCTTCTACACTATTATT	43219	43238	3-13-4	165_1	ATAtcttctacactatTATT	-21	97,4
166	TATATCTTCTACACTATTA	43221	43239	4-11-4	166_1	TATAtcttctacactATTA	-21	93,3
167	TTATATCTTCTACACTA	43224	43240	3-10-4	167_1	TTAtatcttctacACTA	-19	81,7
168	AGCTCATTTTCCTATAC	43713	43729	3-12-2	168_1	AGCtatttttctatAC	-21	67,8
169	TACTTTTTTTCTATCCAA	44082	44100	4-12-3	169_1	TACTtttttttctatcCAA	-22	59,2
170	TCTACTTTTTTTCTATC	44085	44102	2-12-4	170_1	TCtactttttttcTATC	-20	72,4
171	TTTATTAATTTACTCCTT	44846	44863	4-10-4	171_1	TTTAttaatttactCCTT	-21	41,8
172	ATTTTATTAATTTACTCC	44848	44865	4-10-4	172_1	ATTTtattaatttaCTCC	-20	42,1
173	ACCAATACCATAAATTCCA	44868	44886	2-14-3	173_1	ACcaataaccataaattCCA	-22	35,9

174	ATTAATATTTTTCTCCAT	45728	45746	3-12-4	174_1	ATTaatatttttctCCAT	-22	70,9
175	TTTATTAATATTTTTCTCC	45730	45749	3-13-4	175_1	TTTattaatatttttCTCC	-22	39,4
176	TCCTTTTATTAATATTTTT	45734	45753	4-14-2	176_1	TCCTtttattaatatttTT	-20	92,9
177	CCTCCTTTTATTAATATT	45738	45755	4-11-3	177_1	CCTCcttttattaatATT	-22	94,9
178	GCCTCCTTTTATTAATAT	45739	45756	2-13-3	178_1	GCctccttttattaaTAT	-22	55,4
179	TAACATATCTACCATCTC	46470	46487	3-11-4	179_1	TAAcatatctaccaTCTC	-21	24,1
180	AATCCCTTACCATTATT	47155	47171	4-10-3	180_1	AATCccttaccattATT	-21	48,5
181	ACAGCTTCATTTAACTA	48015	48031	4-10-3	181_1	ACAGcttcatttaaCTA	-21	61,0
182	TTAACCAAATCTATACACT	48381	48399	4-11-4	182_1	TTAAccaaatctataCACT	-21	49,8
183	TTAGACTAACCATCCTA	49270	49286	3-11-3	183_1	TTAgactaaccatcCTA	-21	64,0
184	TATTAGACTAACCATCC	49272	49288	4-10-3	184_1	TATTagactaaccaTCC	-22	47,9
185	ACCTCATAATACTTTTC	49305	49321	3-10-4	185_1	ACCtcataatactTTTC	-20	58,1
186	TACCTGATAACATCTTT	49578	49594	4-9-4	186_1	TACCTgataacatCTTT	-22	18,9
187	TTACTAATCTAAATACCT	49590	49607	4-10-4	187_1	TTACtaatctaaatACCT	-20	90,4
188	TCTCATTTTACTAATCTA	49597	49614	4-11-3	188_1	TCTCattttactaatCTA	-21	38,0
189	TTCTCATTTTACTAATCT	49598	49615	3-12-3	189_1	TTCtcatTTtactaaTCT	-19	87,2
190	AACCAAGTCTATATCCA	49655	49671	3-10-4	190_1	AACCaagtctataTCCA	-22	37,6
191	TCACCTTCATAACTTATC	50050	50067	4-11-3	191_1	TCACcttcataacttATC	-21	69,9
192	ATTTTAAATTACTCTCCTAT	50079	50098	4-13-3	192_1	ATTTtaaattactctccTAT	-21	93,0
193	ATATTTTAAATTACTCTCCT	50081	50100	3-14-3	193_1	ATAttttaaattactctCCT	-22	101,6
194	AGTACAATTTAACTCCCT	50396	50413	1-14-3	194_1	AgtacaatttaactcCCT	-21	93,8
195	ATTATCTATAATATACCTA	50755	50773	4-11-4	195_1	ATTAtctataatataCCTA	-22	102,1
196	TCCATAAATCTATTCCAA	50889	50906	4-11-3	196_1	TCCAtaaatctattcCAA	-22	34,6
197	TTCCATAAATCTATTCCA	50890	50907	3-12-3	197_1	TTCcataaatctattCCA	-22	16,2
198	TTTCATAAATCTATTCC	50891	50908	4-10-4	198_1	TTTCcataaatctaTTCC	-22	70,6
199	AGCAAATAAATTCACAC	52815	52833	4-12-3	199_1	AGCAaataaattccaaCAC	-22	28,9
200	TCATGCTTCATAATTA	53336	53352	2-11-4	200_1	TCatgcttcataATTA	-19	21,2
201	CCTTTCCATTACAATTT	53599	53616	1-13-4	201_1	CctttcccattacaATTT	-21	63,4
202	ACATGATACTTAATACC	55294	55310	4-9-4	202_1	ACATgatacttaaTACC	-21	97,9
203	CAACAATATCAATCTTCC	55360	55377	4-10-4	203_1	CAACaatatcaatCTTCC	-21	41,4
204	TTATTAATATTTCTTCTCA	55509	55528	3-14-3	204_1	TTAttaatatttctctTCA	-19	82,5
205	TCAGTTAATCATCTCAC	56328	56344	4-10-3	205_1	TCAGttaatcatctCAC	-21	29,8
206	TTGCCATTAAAATTTC	56848	56864	2-11-4	206_1	TTgccattaaaatTTCC	-19	39,2
207	GATGAACAGACCAAACCT	57524	57540	2-9-6	207_1	GATgaacagacCAAACCT	-20	50,9
208	ATCCATACATCCTAAAAT	57753	57770	4-10-4	208_1	ATCCatacatcctaAAAT	-21	83,7
209	CTCATCCATACATCCTA	57757	57773	1-13-3	209_1	CtcatccatcatcCTA	-21	91,9
210	GTCCAAATATCATATCAT	58334	58351	4-11-3	210_1	GTCCaaatcatatCAT	-22	92,5
211	TGTCCAAATATCATATC	58336	58352	4-9-4	211_1	TGTCCaaatcatTATC	-21	114,5
212	ACCATTAATCTCATATT	58538	58554	4-9-4	212_1	ACCAttaatctcaTATT	-21	61,8
213	TCACCATTAATCTCATAT	58539	58556	4-11-3	213_1	TCACcattaatctcaTAT	-22	78,6
214	CACCATTAATCTCATA	58540	58555	2-10-4	214_1	CAccattaatctCATA	-19	65,7
215	ATCAATCAATATTTATTCTT	58702	58721	3-14-3	215_1	ATCaatcaatatttattCTT	-18	111,2
216	ATACTTTACTTTTCAAATTT	58822	58841	4-14-2	216_1	ATACTttacttttcaaTT	-18	86,5
217	TATACTTTACTTTTCAAATT	58823	58842	4-14-2	217_1	TATActttacttttcaaTT	-18	106,2

218	CTTTATACTTTACTTTTCAA	58826	58845	2-14-4	218_1	CTttatactttactttTCAA	-20	49,3
219	TCTTTATACTTTACTTTTCA	58827	58846	2-16-2	219_1	TCttatactttacttttCA	-19	105,0
220	CCAATATTCCTATTCTC	60635	60651	2-12-3	220_1	CCaatattcctattCTC	-21	75,8
221	TGTAACCACTCTTATCAAT	62608	62626	2-13-4	221_1	TGtaaccactcttatCAAT	-21	92,3
222	AATGTAACCACTCTTATC	62611	62628	2-12-4	222_1	AAtgtaaccactctTATC	-19	40,3
223	TTCCAATTTCTATTAAT	63501	63518	4-10-4	223_1	TTCCaatttcctatTAAT	-22	100,2
224	CATTCCAATTTCTATTA	63503	63520	3-12-3	224_1	CATtccaatttcctaTTA	-21	121,2
225	AAATTTTCTAAATCCCC	63916	63934	1-15-3	225_1	AaattttcctaaattcCCC	-22	90,1
226	TCACTAATCTCAATTTA	64566	64583	4-10-4	226_1	TTCActaatctcaaTTA	-19	31,2
227	ACTAAATTTCACTAATCTCA	64571	64590	1-15-4	227_1	ActaaatttcactaatCTCA	-19	62,4
228	TTATTCACTAAATTTCACT	64578	64596	4-11-4	228_1	TTATtactaaatttCACT	-21	89,1
229	TGCTAAACAATTATACTA	66548	66565	4-12-2	229_1	TGCTaaacaattataCTA	-19	96,5
230	AATTATTCATCCATTCTTC	67741	67760	1-15-4	230_1	AattattcatccatttCTTC	-20	32,5
231	ATCAATTTTTCACATCAATA	68866	68885	4-12-4	231_1	ATCAatttttcacatcAATA	-21	51,1
232	TTATACCCACTTACTC	69491	69506	3-11-2	232_1	TTAtaccacttacTC	-18	102,6
233	GTACTTATACCCACTTAC	69493	69510	1-14-3	233_1	GtacttataccactTAC	-20	101,0
234	ATGTACTTATACCCACTT	69495	69512	1-14-3	234_1	AtgtacttatacccaCTT	-20	95,9
235	TGTACTTATACCCACT	69496	69511	2-12-2	235_1	TGtacttatacccaCT	-19	98,5
236	AAATGTACTTATACCCAC	69497	69514	1-13-4	236_1	AaatgtacttatacCCAC	-20	93,0
237	CATCTAATTTTCTAATCT	69660	69678	4-11-4	237_1	CATCtaatttttctaATCT	-22	58,2
238	TTATAAAACATACACCCA	69755	69772	3-11-4	238_1	TTAtaaaaacatacaCCCA	-22	74,9
239	ATTATAAAACATACACCC	69756	69773	4-10-4	239_1	ATTAtaaaaacatacACCC	-21	39,1
240	CTTCTATCAAAAATTCACC	69800	69818	4-12-3	240_1	CTTCtatcaaaaattcACC	-21	51,1
241	CAAAAGTATATATTCCA	70094	70110	3-8-6	241_1	CAAaagtatatATTCCA	-20	22,6
242	TACGCAAAAACAATGAC	70197	70213	4-7-6	242_1	TACGcaaaaacAATGAC	-20	65,7
243	TTACGCAAAAACAATG	70199	70214	5-5-6	243_1	TTACGcaaaaACAATG	-19	111,1
244	TACTTACGCAAAAACA	70202	70217	5-8-3	244_1	TACTTacgcaaaaACA	-18	99,6
245	CAGCTCTTTTACAAATAT	70637	70654	4-12-2	245_1	CAGCtcttttacaaatAT	-21	48,5
246	TCTATGATACTTACCT	71617	71632	2-10-4	246_1	TCtatgatacttACCT	-19	96,9
247	ACACCAATTACTTCTTACC	71764	71782	1-16-2	247_1	AcaccaattacttcttaCC	-20	101,9
248	CACACCAATTACTTCTTAC	71765	71783	1-15-3	248_1	CacaccaattacttctTAC	-19	98,1
249	TTACACCAATTACTTCTTA	71766	71785	1-17-2	249_1	TtcacaccaattacttctTA	-19	115,8
250	GCTTCACACCAATTACTTC	71769	71787	1-16-2	250_1	GcttcacaccaattactTC	-20	63,0
251	CCTAATGCTTCACACC	71778	71793	1-12-3	251_1	CctaatgcttcacACC	-20	24,0
252	ACAACTCCCAAATAGTT	71808	71824	4-10-3	252_1	ACAActcccaaataGTT	-21	96,1
253	AAATTTAATTAATAATTGC	72045	72062	6-5-7	253_1	AAATTTaattaAAATTGC	-18	112,6
254	ATGCATTATATCAAATCA	72601	72618	4-10-4	254_1	ATGCattatatcaaATCA	-22	92,9
255	AAAACACAAGCTTTCCTA	72626	72643	6-9-3	255_1	AAAACAcagcttttcCTA	-22	41,2
256	TCATCCAATATTCATCA	73726	73742	3-11-3	256_1	TCAtccaatattcaTCA	-20	21,9
257	ATATTACTTTTTATTATCTA	73925	73944	4-12-4	257_1	ATATtactttttattaTCTA	-21	37,0
258	GCTAAATTCCTCATCAAT	74127	74145	2-15-2	258_1	GCtaaattcctcatcaaAT	-20	79,8
259	TGCTAAATTCCTCATCAA	74128	74146	3-13-3	259_1	TGCTaaattcctcatcAAA	-21	70,9
260	ATATGCTAAATTCCTCATCA	74130	74149	1-17-2	260_1	AtatgctaaattcctcatCA	-19	95,2
261	ATGCTAAATTCCTCATC	74131	74147	3-10-4	261_1	ATGctaaattcctCATC	-22	56,8

262	TATGCTAAATTCCTCAT	74132	74148	2-12-3	262_1	TAtgctaaattcctCAT	-18	72,9
263	GAAAATATGCTAAATTCCT	74135	74153	3-10-6	263_1	GAAaatatgctaaATTCCT	-22	85,3
264	TGCAATCTAACTTCATA	74761	74777	3-12-2	264_1	TGCaatctaactcaTA	-18	58,0
265	CTTGATTTAAACACCTCT	75260	75277	2-13-3	265_1	CTtgatttaaacaccTCT	-20	20,9
266	ACTTGATTTAAACACCT	75262	75278	2-12-3	266_1	ACttgatttaaacacCCT	-18	36,6
267	GCTTCTTACTATCTTTTA	75590	75607	3-13-2	267_1	GCTtcttactatctttTA	-21	47,6
268	GTCTTCTTTAATCCATCA	76043	76060	1-13-4	268_1	GtcttctttaatccATCA	-21	29,5
269	CTATATTATATATCCACCT	76205	76223	2-15-2	269_1	CTatattatataatccacCT	-20	97,7
270	CTCTATATTATATATCCAC	76207	76225	3-13-3	270_1	CTCtatattatataatcCAC	-20	25,7
271	TCTCTATATTATATATCCA	76208	76226	2-14-3	271_1	TCtctatattatataCCA	-20	53,9
272	ATTCTCTATATTATATATCC	76209	76228	2-15-3	272_1	ATtctctatattatataTCC	-20	92,3
273	CCAATTCTCTATATTATAT	76213	76231	2-14-3	273_1	CCaattctctatattaTAT	-19	88,5
274	TCCAATTCTCTATATTATA	76214	76232	3-13-3	274_1	TCCaattctctatattATA	-21	30,0
275	TCTCCAATTCTCTATATTAT	76215	76234	2-15-3	275_1	TCtccaattctctatatTAT	-21	62,8
276	ATCTCCAATTCTCTATATTA	76216	76235	1-15-4	276_1	AtctccaattctctatATTA	-20	98,1
277	AATCTCCAATTCTCTATATT	76217	76236	2-14-4	277_1	AAtctccaattctctaTATT	-21	93,8
278	TAAATCTCCAATTCTCTATA	76219	76238	2-16-2	278_1	TAaatctccaattctctaTA	-19	100,0
279	GAATTTATCTCCAAACTCA	76262	76280	3-12-4	279_1	GAAtttatctccaaaCTCA	-22	47,5
280	TGTCTACACATATTACC	76709	76725	2-11-4	280_1	TGtctacacatatTACC	-21	31,7
281	TGATCCCATCTTATAC	77011	77026	3-11-2	281_1	TGAtcccatcttatAC	-18	21,9
282	TATATTTCTCCATAATAC	77663	77680	3-12-3	282_1	TATatttctccataaTAC	-18	36,3
283	TATTCCTCAATAAACCTA	78216	78233	2-12-4	283_1	TAttctcaataaaCCTA	-21	61,6
284	GACTTCCTATTTTACTCA	79981	79998	2-14-2	284_1	GActtctattttactCA	-20	82,6
285	TTTCTCATATATTCTCCC	81181	81198	1-15-2	285_1	TttctcatatattctcCC	-20	81,7
286	TTTTCTCATATATTCTCC	81182	81199	3-12-3	286_1	TTTTctcatatattcTCC	-21	22,6
287	CTATTTTCTCATATATTCT	81184	81202	4-12-3	287_1	CTATtttctcatatatTCT	-22	31,1
288	TTTACTATTTTCTCATATAT	81187	81206	4-12-4	288_1	TTTActatttttctcatATAT	-21	21,4
289	TTACTATTTTCTCATATA	81188	81205	4-10-4	289_1	TTActatttttctcaTATA	-21	22,1
290	AACAAATATTACATACCCT	81401	81419	3-12-4	290_1	AACaaatattacataCCCT	-22	93,8
291	TGCCATTAAATAAATACA	82068	82085	4-10-4	291_1	TGCCattaataaaaTACA	-22	87,4
292	TGCCATTCAAAAATACAAT	82794	82812	3-12-4	292_1	TGCcattcaaaaataCAAT	-21	76,6
293	TAATATACTTTTATCATACA	83724	83743	2-14-4	293_1	TAatatacttttatcaTACA	-18	80,4
294	ATTACTTTATTATCATCTCAT	86909	86927	2-14-3	294_1	ATtactttattcatctCAT	-19	87,1
295	TAATTACTTTATTATCATCTCA	86910	86929	3-14-3	295_1	TAAttactttattcatcTCA	-20	49,2
296	TTAATTACTTTATTATCATCTC	86911	86930	2-15-3	296_1	TTaattactttattcatCTC	-18	60,0
297	TTTAATTACTTTATTATCATCT	86912	86931	4-14-2	297_1	TTTAattactttattcatCT	-19	87,2
298	ATTTAATTACTTTATTATCATC	86913	86932	2-14-4	298_1	ATttaattactttattCATC	-18	101,8
299	TTCTATCTTTTCTTTCTTTA	86984	87003	1-15-4	299_1	TtctatcttttctttcTTTA	-20	107,9
300	CATGCATTTTTTCTTACA	87092	87109	3-13-2	300_1	CATgcattttttctcaCA	-22	50,4
301	GAAATTCTAATTCTTTCT	87504	87521	4-10-4	301_1	GAAAttctaattctTTCT	-18	90,2
302	AACATCTGTTGAAATTCT	87514	87531	2-10-6	302_1	AACatctgttgaAATTCT	-19	29,8
303	ATTTAATCCATCATTATTCT	88639	88658	2-14-4	303_1	ATttaatccatcattaTTCT	-21	74,3
304	TAACCTCATATCATCAATA	89002	89020	4-11-4	304_1	TAACtccatcatcAATA	-21	57,7
305	ATTAACCTCATATCATCAA	89004	89022	4-11-4	305_1	ATTaactccatataTCAA	-22	42,2

306	AATTAACCTCATATCATCA	89005	89023	4-11-4	306_1	AATTaactccatcatCA	-22	46,8
307	TTTACCTAAAATCATACCA	89772	89790	2-13-4	307_1	TTtacctaaaaatcatACCA	-20	61,4
308	TTATATATCAATCCCCA	90811	90827	3-11-3	308_1	TTAtatatcaatccCCA	-22	78,2
309	TTTTATATATCAATCCCC	90812	90829	3-13-2	309_1	TTTTatatatcaatccCC	-20	56,1
310	TTTTTATATATCAATCCC	90813	90830	4-10-4	310_1	TTTTtatatatcaaTCCC	-22	32,6
311	CTAAAAAGACTTGTTCT	91226	91242	4-8-5	311_1	CTAAaaagacttGTTCT	-20	26,3
312	ACTAAAAAGACTTGTTTC	91227	91243	5-8-4	312_1	ACTAAaaagacttGTTTC	-18	31,0
313	CCTTATCTATTATCACC	91516	91532	3-12-2	313_1	CCTtatctattatcaCC	-22	88,1
314	GCCTTATCTATTATCAC	91517	91533	3-12-2	314_1	GCCTtatctattatcAC	-21	97,4
315	TGCTTATCTATTATC	91519	91535	1-12-4	315_1	TgccttatctatTATC	-18	82,9
316	TCCTTACGCTGTCATCA	91540	91556	2-13-2	316_1	TCcttagctgtcatCA	-22	46,4
317	TAATCCAAATTTCTTCATA	91902	91920	3-12-4	317_1	TAAtccaaatttcttCATA	-20	34,9
318	CTTTCAAGCCTAATCA	92437	92452	1-11-4	318_1	CtttcaagcctaATCA	-19	77,5
319	TGTTTTCATATAAACCAT	93022	93039	2-12-4	319_1	TGttttcatataaaCCAT	-20	67,3
320	GATTATTACATACCTTCCA	94318	94336	1-15-3	320_1	GattattacataccttCCA	-22	86,0
321	TATCTTTACCATCATTTAA	94440	94458	4-11-4	321_1	TATCtttaccatcatTTAA	-22	42,1
322	GTTATCTTTACCATCATT	94443	94460	3-11-4	322_1	GTTatctttaccatCATT	-23	23,0
323	AGACTTACCAAATTTCC	95637	95653	4-11-2	323_1	AGACttaccaaatttCC	-21	90,7
324	GAACATGTTGACTCAC	97243	97258	4-8-4	324_1	GAACatgttgacTCAC	-20	61,8
325	AGTTTTAATACCATTTC	97712	97729	3-13-2	325_1	AGTtttaataaccatttCA	-19	20,1
326	CAGTTTTAATACCATTTC	97713	97730	4-12-2	326_1	CAGTtttaataaccattTC	-20	72,1
327	ATAATTTATCCTTAATTCT	98353	98371	3-13-3	327_1	ATAatttatccttaatTCT	-19	65,3
328	TCAATGTTTCCAATCTT	98600	98616	2-12-3	328_1	TCaatgtttccaatCTT	-18	42,4
329	CATCTGGTTACATACCACC	99016	99034	1-16-2	329_1	CatctggttacataccaCC	-23	74,8
330	ATCACAAAATAATTTCCAC	99056	99074	2-13-4	330_1	ATcacaaaataatttCCAC	-19	35,3
331	CATCACAAAATAATTTCCA	99057	99075	2-14-3	331_1	CAtcacaaaataattCCA	-19	74,3
332	TCATCACAAAATAATTTCC	99058	99076	3-14-2	332_1	TCAtcacaaaataattCC	-18	73,0
333	TAGATCATCATCACAA	99068	99085	2-13-3	333_1	TAgatcacatcatcaCAA	-19	26,6
334	CCTAAATACCTTTCTTTCA	100896	100915	1-15-4	334_1	CctaaatcctttcttTTCA	-22	39,6
335	ATACCTAAATACCTTTCTT	100900	100918	4-13-2	335_1	ATACctaaatcctttcTT	-21	34,3
336	CCCTAAATAATACCTAAACA	100938	100957	3-15-2	336_1	CCCTaaataatacctaaaCA	-22	98,9
337	TCCACCCTAAATAATACC	100944	100961	2-14-2	337_1	TCcaccctaaataataCC	-21	47,6
338	AGTTAACTAATTCTACA	101277	101295	3-12-4	338_1	AGTtaacactaattcTACA	-21	34,2
339	GTCTCTAATATTCTATA	101747	101764	3-11-4	339_1	GTCtctaataatttcTATA	-21	21,9
340	TAGCATTCTATCATT	102745	102762	2-12-4	340_1	TAgcattcatctatCATT	-21	32,7
341	CCTAGCATTCTATC	102748	102764	2-12-3	341_1	CCtagcattcatctATC	-21	35,1
342	GTTTCACATAATTTATTCC	103244	103262	1-15-3	342_1	GtttcacataatttatTCC	-19	37,3
343	TTAGAATAAATTCACG	103271	103286	5-5-6	343_1	TTAGAataaaTTCACG	-20	110,8
344	TAATTTCTCAAAAAATTAAA	104848	104867	7-5-8	344_1	TAATTTctcaaaAAATTAA A	-20	103,0
345	CCTTCATTATTCTCAATT	107241	107259	2-13-4	345_1	CCttcattatttctcAATT	-21	48,7
346	CACAACCATCACTATTTTC	107587	107604	4-11-3	346_1	CACAaccatcactatTTC	-22	21,6
347	TTATTACAATCTATTTTACA	107816	107835	4-12-4	347_1	TTATtacaatctattTACA	-21	26,9
348	CACTCAATTCATACTTAT	107902	107920	3-13-3	348_1	CACtcaattccatactTAT	-22	70,5

349	ACTCAATTCATACTTA	107903	107919	2-11-4	349_1	ACtcaattccataCTTA	-20	66,8
350	TCTCTTTTAAATTCAATCT	107954	107972	4-11-4	350_1	TCTCttttaaatcaATCT	-22	44,7
351	TATCTCTTTTAAATTCAATC	107955	107974	4-12-4	351_1	TATCtcttttaaattcAATC	-20	70,9
352	GCTATCTCTTTTAAATTCA	107958	107976	2-13-4	352_1	GCtatctcttttaaaTTCA	-22	46,3
353	GTAATTTATCAATTTCCA	108181	108198	3-11-4	353_1	GTAAtttatcaattTCCA	-22	46,7
354	AATCTTTTCTTAATCTTTTA	113283	113302	4-12-4	354_1	AATCttttcttaattctTTTA	-21	66,3
355	GTACAATACCATTACAACA	113456	113474	4-12-3	355_1	GTACaataccattacaACA	-22	51,2
356	CAGTTTTACTTTTCAATA	113624	113641	4-10-4	356_1	CAGTtttacttttcAATA	-21	15,9
357	ATCAATTCTACTTAATACA	114122	114140	4-11-4	357_1	ATCAattctacttaaTACA	-21	24,7
358	TATTCTTATTTTCATATATA	115013	115032	3-13-4	358_1	TATtcttattttcataTATA	-20	98,0
359	ATATTCTTATTTTCATATA	115015	115033	4-11-4	359_1	ATATtcttattttcaTATA	-21	108,9
360	AATGATCAATCACCCCTT	115389	115405	2-11-4	360_1	AAtgatcaatcacCCTT	-20	48,1
361	TTGATCTACTTAATTTA	117183	117199	5-6-6	361_1	TTGATctacttAATTTA	-21	108,2
362	AGTCCATAACTAACA	117429	117444	4-8-4	362_1	AGTCcctaactAACA	-22	60,2
363	TATCACTTATTCATTGATA	117533	117551	3-12-4	363_1	TATcacttatttcattGATA	-22	32,7
364	TTATCCATCTTTAATTTA	120075	120093	3-12-4	364_1	TTAtccatcttttaaTTTA	-20	51,2
365	ATATCTTTCCATATTTTCA	120837	120856	2-14-4	365_1	ATatctttccatatttTTCA	-22	31,4
366	GGTAACAACTTTTAAATA	122088	122105	4-7-7	366_1	GGTAacaacttTTAAATA	-22	92,3
367	CTAGTATACAACATCATA	122809	122826	4-10-4	367_1	CTAGtatacaacatCATA	-22	51,0
368	ACCTAGTATACAACATC	122812	122828	3-10-4	368_1	ACCTagtatacaaCATC	-21	26,6
369	ACCACATTAAATTCTCAAT	122841	122859	4-11-4	369_1	ACCAcattaaattctCAAT	-23	49,2
370	TTACAACCTTATCTTTTTTA	123014	123033	4-12-4	370_1	TTACaactttatctttTTTA	-21	31,7
371	ACAACCTATACCCTAT	123731	123746	4-9-3	371_1	ACAACctatacccTAT	-21	29,7
372	AGGACAACCTATACCC	123734	123749	1-11-4	372_1	AggacaacctatACCC	-22	38,3
373	TGATCTTTCTATCTACAC	123918	123935	2-13-3	373_1	TGatctttctatctaCAC	-19	113,5
374	TTGATCTTTCTATCTACA	123919	123936	2-13-3	374_1	TTgatctttctatctACA	-18	115,1
375	AGCCTTATTTAATAATC	124037	124053	4-9-4	375_1	AGCCttatttaaatAATC	-21	102,4
376	TGTCTTTATTTTCCAATC	125837	125854	4-12-2	376_1	TGTCTttattttccaaTC	-21	25,3
377	TGTTTCCATAATATTTCT	126386	126403	4-12-2	377_1	TGTTtccataatatttCT	-20	36,0
378	CCATATACCTTCTCCAT	126732	126748	1-13-3	378_1	CcatataccttctcCAT	-21	73,8
379	TTTCCATATACCTTCTC	126735	126751	4-11-2	379_1	TTTCcatataccttcTC	-21	25,9
380	TCTTTTCCATATACCTTC	126737	126754	2-12-4	380_1	TCttttccatatacCTTC	-23	27,7
381	CACTATACAAAACCTACCA	127548	127567	3-15-2	381_1	CACtatacaaaactctacCA	-21	103,7
382	ACCCTCACTATACAAAAC	127555	127572	4-12-2	382_1	ACCCTcactatacaaaaAC	-22	93,9
383	CACCCTCACTATACAAA	127557	127573	4-10-3	383_1	CACCctcactatacaAAA	-22	80,3
384	AGCACAAATATAAAACCAC	128165	128182	3-11-4	384_1	AGCacaataataaaaCCAC	-22	46,9
385	TTAACATTATCTTCCAA	128646	128663	4-10-4	385_1	TTAAcattatctttCCAA	-21	32,0
386	CTAGCACTTTAATTTCCA	130008	130025	1-14-3	386_1	CtagcactttaatttCCA	-21	72,4
387	GAATCTCTTCTTAACCTCT	131220	131237	3-13-2	387_1	GAAtctcttctaactCT	-19	48,6
388	AAATAAATGACTATAACT	132580	132597	6-5-7	388_1	AAATAAatgacTATAACT	-20	102,4
389	ACACCTTTCTAAACAATA	132904	132921	4-10-4	389_1	ACACcttttctaacaATA	-20	85,0
390	AGTCTTTAAACCACTTTC	133059	133076	4-12-2	390_1	AGTCTttaaaccacttTC	-21	28,3
391	ACCAAATAATTTCAACACC	133229	133247	4-13-2	391_1	ACCAaataatttcaacaCC	-22	88,5
392	TCCCTCAACCAAATAATTT	133236	133254	3-13-3	392_1	TCCctcaaccaataaTTT	-22	87,9

393	TCCACCAGATTTTTCC	133396	133411	2-12-2	393_1	TCcaccagatttttCC	-21	30,9
394	AAGCTTTCAAACCAAC	133448	133463	4-10-2	394_1	AAGCtttcaaaccaAC	-18	78,6
395	TTATCCTAAACTACCAT	134579	134596	3-11-4	395_1	TTAtcctaaaaactaCCAT	-22	117,4
396	AAGCACCTCATATCTTC	134917	134933	2-11-4	396_1	AAgcacctcatatCTTC	-21	85,2
397	TTACCACTCATTTATTTCT	135999	136017	4-13-2	397_1	TTACcactcatttatttCT	-22	53,6
398	AGTTACCACTCATTTAT	136003	136019	3-10-4	398_1	AGTtaccactcatTTAT	-21	41,4
399	TACTCTAAAATTATCCTTA	136533	136551	3-12-4	399_1	TACtctaaaattatcCTTA	-20	83,1
400	CAGATTCTTCTTATTCTA	136566	136583	4-12-2	400_1	CAGAttcttcttattcTA	-21	80,9
401	GTTCTAATATTCCTCACA	138079	138096	2-13-3	401_1	GTtctaataattcctcACA	-20	69,8
402	CTCTTATCTTCCAATTTTA	138305	138323	1-15-3	402_1	CtcttatcttccaattTTA	-19	106,3
403	TCTATAATTTCTTCTATTT	139861	139880	4-12-4	403_1	TCTAtaatttcttcttATTT	-21	78,2
404	CTTCTATAATTTCTTCTTA	139864	139882	4-12-3	404_1	CTTCtataatttcttcTTA	-21	38,6
405	TCCTTCTATAATTTCTTCTT	139865	139884	2-16-2	405_1	TCcttctataatttcttcTT	-20	81,4
406	ATTCCTTCTATAATTTCTT	139868	139886	4-12-3	406_1	ATTccttctataatttCTT	-22	35,2
407	CATTCTTCTATAATTTCT	139869	139887	2-13-4	407_1	CAttccttctataatTTCT	-21	41,9
408	ACATTCCTTCTATAATTTCT	139870	139888	4-12-3	408_1	ACATtccttctataatTTC	-21	39,6
409	GCCATATCTCTTAATTTAA	140051	140069	4-13-2	409_1	GCCAtatctcttaatttAA	-22	68,7
410	AGCCATATCTCTTAATT	140054	140070	3-10-4	410_1	AGCcatactcttAATT	-21	40,8
411	ACAGCCATATCTCTTAA	140056	140072	4-10-3	411_1	ACAGccatactctTAA	-22	26,5
412	TAAGTTTCAAATAACCC	140590	140606	4-9-4	412_1	TAAGtttcaaataACCC	-21	42,1
413	TCCATTATTTTCCACTTA	141294	141311	3-13-2	413_1	TCCattattttccactTA	-22	25,5
414	ACATCCATTATTTCCAC	141297	141314	3-12-3	414_1	ACAtccattattttcCAC	-22	22,3
415	TCACATCCATTATTTCCA	141298	141316	2-15-2	415_1	TCacatccattattttcCA	-22	28,7
416	TTCACATCCATTATTTTC	141300	141317	4-10-4	416_1	TTCAcatccattatTTTC	-22	26,2
417	TCATTACATCCATTATTT	141302	141320	4-13-2	417_1	TCATtcacatccattatTT	-21	38,5
418	TTATATATTTATCTATTTCA	141537	141556	4-12-4	418_1	TTATatatttatctatTTCA	-20	33,1
419	AGCAATACAATCAATACA	141785	141802	4-10-4	419_1	AGCAatacaatcaaTACA	-22	30,2
420	CCACAATTACCATAACC	141860	141876	4-11-2	420_1	CCACaattaccataaACC	-23	45,9
421	CACCAAAGATCTACCAA	141996	142012	3-10-4	421_1	CACcaaagatctaCCAA	-22	55,5
422	TATTTTCTTACCCTCATT	142656	142673	1-13-4	422_1	TattttcttaccctCATT	-21	95,0
423	AGTATTTTCTTACCCTCA	142658	142675	1-15-2	423_1	AgtattttcttaccctCA	-20	108,7
424	TAGTATTTTCTTACCCT	142660	142676	1-13-3	424_1	TagtattttcttacCCT	-20	110,1
425	TTAGTATTTTCTTACCC	142661	142677	1-13-3	425_1	TtagtattttcttaCCC	-20	109,3
426	TTATAATTCCACTTACTTT	143602	143620	3-12-4	426_1	TTAtaattccacttaCTTT	-20	46,1
427	GTTATAATTCCACTTACT	143604	143621	4-11-3	427_1	GTTAtaattccacttACT	-21	50,9
428	TAGTTATAATTCCACTTA	143606	143623	3-11-4	428_1	TAGttataattccaCTTA	-21	112,9
429	TTAGTTATAATTCCAC	143609	143625	4-9-4	429_1	TTAgttataattCCAC	-21	28,4
430	GTTTTCTCAAATATAATT	143624	143641	4-7-7	430_1	GTTTTctcaaaTATAATT	-21	109,1
431	GAATTCTAATACCACCTT	144747	144764	3-11-4	431_1	GAAttctaataaccaCCTT	-23	51,4
432	ATATACTAACTATTCTCC	144920	144938	3-12-4	432_1	ATAtactaaactattCTCC	-22	78,0
433	TTCATTTATCCTTCAAATA	145012	145031	4-12-4	433_1	TTCAtttatccttcaaATA	-22	39,2
434	TTCATTATTTCAATTATCCT	145020	145039	4-14-2	434_1	TTCAttatttcatttatCCT	-22	44,3
435	TTTAATCCTTTCTTTATTTT	146253	146272	3-13-4	435_1	TTTaatcctttctttaTTTC	-21	48,9
436	CAGTTTTTCTTTAATCCT	146264	146281	2-13-3	436_1	CAGtttttctttaatCCT	-22	66,5

437	ATGATCCTATTATTACCA	146574	146591	4-12-2	437_1	ATGAtcctattattacCA	-22	62,2
438	TTGACTAACATTTCATAA	147223	147239	4-7-6	438_1	TTGActaacatTCATAA	-21	88,7
439	TTCCATCGCACATTTT	147238	147253	4-9-3	439_1	TTCCatcgcacatTTT	-22	41,2
440	ACATAACCTTTTATTTTTTA	148020	148039	4-12-4	440_1	ACATaaccttttattTTTA	-22	32,5
441	CATTCTAAATCTTAGTC	148085	148101	2-9-6	441_1	CAttctaaatcTTAGTC	-20	58,7
442	ATAATCGTCCATCCCTT	148288	148304	1-12-4	442_1	AtaatcgtccatcCCTT	-23	32,0
443	TCACATAAACTCATCCAA	148809	148826	3-11-4	443_1	TCAcataaactcatCCAA	-22	23,8
444	TTCACATAAACTCATCC	148811	148827	4-9-4	444_1	TTCAcataaactcATCC	-22	33,0
445	ACTTATTTACATAAACTC	148815	148833	4-11-4	445_1	ACTTatttcacataaACTC	-21	20,1
446	CTTCAAATAACTACAAAG	149050	149067	6-5-7	446_1	CTTCAAataacTACAAAG	-23	102,5
447	TGTATTCAATACATACT	149111	149127	3-10-4	447_1	TGTattcattacaTACT	-20	94,2
448	ACTCTTAACAATTTATTCA	149131	149149	4-11-4	448_1	ACTCttaacaatttaTTCA	-21	50,1
449	TCACTCTTAACAATTTATTC	149132	149151	4-12-4	449_1	TCACtcttaacaatttATTC	-22	44,6
450	TAACATAATCACTCTTAACA	149140	149159	4-12-4	450_1	TAAcAtaatcactcttAACA	-20	47,4
451	CCAGAACCTATTATTTA	149630	149646	3-10-4	451_1	CCAgaacctattaTTTA	-21	24,0
452	ATTATTCAATCCTCTATA	149720	149737	2-12-4	452_1	ATtattcaatcctcTATA	-20	64,7
453	TAACCTTCATCACATACT	150502	150519	4-12-2	453_1	TAAccttcacacataCT	-21	40,0
454	ATCTAACCTTCATCACATAC	150503	150522	3-15-2	454_1	ATCtaaccttcacacatAC	-21	70,8
455	TCTAACCTTCATCACATA	150504	150521	2-12-4	455_1	TCtaaccttcacataCATA	-22	74,1
456	CTCTATCTAACCTTCATC	150509	150526	1-13-4	456_1	CtctatctaacctcCATC	-21	38,2
457	TGACTCTATCTAACCTTC	150512	150529	2-14-2	457_1	TGactctatctaacctTC	-19	63,2
458	CCTCTTTTATCAACACAATT	150801	150820	2-14-4	458_1	CCtcttttatcaacacAATT	-22	76,7
459	TCTCAAATCTTAAATTTT	150860	150878	4-13-2	459_1	TCTCcaaactttaaattTC	-19	48,0
460	TTTACTATTTCTCAAATC	150869	150887	3-13-3	460_1	TTTactatttctccaaATC	-19	41,2
461	TCTTTTACTATTTCTCCAAA	150871	150890	2-14-4	461_1	TCttttactatttctcCAAA	-21	39,5
462	CATCTTTTACTATTTCTCCA	150873	150892	2-16-2	462_1	CActtttactatttctcCA	-22	72,6
463	TCATCTTTTACTATTTCTC	150875	150893	3-13-3	463_1	TCAtcttttactatttCTC	-21	32,2
464	CCTCATCTTTTACTATTT	150878	150895	2-12-4	464_1	CCtcatcttttactATTT	-21	62,8
465	AACCTCATCTTTTACTA	150881	150897	4-11-2	465_1	AACCTcatcttttacTA	-20	53,8
466	TTTTATATCTACTCTCA	150908	150925	3-11-4	466_1	TTTttatatctactCTCA	-20	24,6
467	TTAATAAACATCAATCTCC	150999	151017	4-11-4	467_1	TTAAtaaacatcaatCTCC	-21	32,8
468	ATATTTCTATTTCTCCATT	151333	151351	1-14-4	468_1	AtatttctatttctcCATT	-22	48,4
469	CATACTGCTCTTTCTA	151839	151854	1-12-3	469_1	CatactgctctttCTA	-18	46,8
470	ATGCAAATAACTTCATCA	155977	155994	4-11-3	470_1	ATGCaaataacttcaTCA	-21	30,4
471	TTTAACTTTCTTACCACAA	156180	156198	4-11-4	471_1	TTTAactttcttaccACAA	-21	25,3
472	TTAACTTTCTTACCACA	156181	156197	4-9-4	472_1	TTAActttcttacCACA	-21	25,1
473	CATATTATCTCACCTAC	168185	168202	2-12-4	473_1	CAtattcatctcacCTAC	-22	68,5
474	TCATATTATCTCACCTA	168186	168203	3-13-2	474_1	TCAtattcatctcaccTA	-21	36,1
475	TTCATATTATCTCACCT	168187	168204	4-12-2	475_1	TTCAtattcatctcacCT	-22	22,8
476	AATTTTCATATTATCTCAC	168189	168208	4-12-4	476_1	AATTTcatattcatcTCAC	-22	29,0
477	CTACCTTTTTAATTCTAAAT	169169	169188	4-12-4	477_1	CTACctttttaattctAAAT	-21	64,2
478	ACTACCTTTTTAATTCTA	169172	169189	4-11-3	478_1	ACTAcctttttaattCTA	-22	30,7
479	TGACTACCTTTTTAATTC	169174	169191	4-11-3	479_1	TGACtacctttttaaTTC	-21	32,6
480	TATATTTTTTACCCCT	171639	171655	2-12-3	480_1	TAtattttttaccCCT	-21	109,9

481	TCAAATATACATCCTTG	171786	171802	2-9-6	481_1	TCaaatatacaTCCTTG	-21	50,4
482	GTCAAATATACATCCT	171788	171803	4-8-4	482_1	GTCAaatatacaTCCT	-22	36,2
483	GGTCAAATATACATCC	171789	171804	4-8-4	483_1	GGTCAaatatacaATCC	-22	63,6
484	AGGTCAAATATACATC	171790	171805	4-8-4	484_1	AGGTcaaatacaCATC	-20	61,0
485	ACCACATTTATCCAATATA	171913	171931	4-13-2	485_1	ACCACatttatccaataTA	-22	29,8
486	ATAAAAACCACATTTATCCA	171918	171937	2-14-4	486_1	ATaaaaaccacatttaTCCA	-22	39,2
487	ATCACAAACCACAAAATCA	172016	172033	4-11-3	487_1	ATCAcaaccacaaaaTCA	-21	45,0
488	ATAAATATTCTTACCTACA	172043	172061	4-11-4	488_1	ATAAatattctttaccTACA	-21	81,9
489	AAGTATAATTTCTTCTA	172270	172287	4-11-3	489_1	AAGTataatttcttCTA	-21	41,3
490	AATTTATAGATTAATAAAT	173412	173430	7-5-7	490_1	AATTTATagattAATAAAT	-19	105,9
491	TTTCCACATATTTCTAC	173713	173730	2-12-4	491_1	TttccacatatttctCTAC	-22	56,2
492	TGTCTATTTCCACATATT	173719	173736	4-12-2	492_1	TGTCtatttccacataTT	-21	37,6
493	TCTTTCAACCTTTTATTTA	173858	173876	2-13-4	493_1	TCtttcaaccttttaTTTA	-20	58,1
494	ATATAAATCACCTGAAAT	175481	175498	4-7-7	494_1	ATATAaatcacCTGAAAT	-23	82,6
495	ATTAATTCCATCTTCTT	176374	176391	1-13-4	495_1	AttaattccatcttCTT	-21	32,8
496	TCATTAATTCCATCTTCC	176376	176393	3-13-2	496_1	TCAttaattccatcttCC	-22	34,4
497	TGTCATTAATTCCATCTT	176378	176395	2-13-3	497_1	TGtcattaattccatCTT	-20	52,1
498	AACATGTCATTAATTCC	176383	176399	4-9-4	498_1	AACAtgtcatttaaTTCC	-20	30,6
499	CCTTCAACTGAACTTC	176531	176546	2-11-3	499_1	CCttcaactgaacTTC	-19	55,5
500	AGCCATATCTTTTTTATT	177145	177162	3-12-3	500_1	AGCcatatcttttttATT	-21	60,2
501	TAAGCACCTCAAAATATA	177860	177877	2-12-4	501_1	TAagcacctcaaaaTATA	-19	73,2
502	TTATTCATACTAAACACATA	178456	178475	4-12-4	502_1	TTATtcatactaaacaCATA	-21	55,0
503	AAAGATCTCATATTCCT	178779	178795	3-10-4	503_1	AAAgatctcatatTCCT	-20	29,0
504	TCTCATTCTTTAACCATAA	179038	179056	4-12-3	504_1	TCTCattctttaaccaTAA	-22	39,9
505	TCCCTACTTAAATTATCAA	179303	179321	3-12-4	505_1	TCCctacttaaatTCAA	-22	64,8
506	GCAATGTAAAAACATTAA	179500	179517	5-6-7	506_1	GCAATgtaaaaACATTAA	-22	101,2
507	CCCATATTTTTTATTTTACA	179528	179547	2-15-3	507_1	CCcatatTTTTtatttACA	-22	72,1
508	CCCTTATCTACAAAAATTTA	180108	180127	3-14-3	508_1	CCCTtatctacaaaaTTA	-22	79,0
509	CTGCTTTATTTACATAT	180433	180449	3-11-3	509_1	CTGctttatttacaTAT	-19	68,6
510	ACTGCTTTATTTACATA	180434	180450	4-11-2	510_1	ACTGctttatttacaTA	-19	66,9
511	TCTCAAGTATAACTACA	180753	180769	4-9-4	511_1	TCTCaagtataacTACA	-21	63,4
512	ACTGCTGAGCAGGATCA	133475	133491	1-14-2	512_1	ActgctgagcaggatCA	-20	84,7
512	ACTGCTGAGCAGGATCA	133475	133491	1-13-3	512_2	ActgctgagcaggaTCA	-21	90,8
512	ACTGCTGAGCAGGATCA	133475	133491	2-13-2	512_3	ACtgctgagcaggatCA	-22	98,0
513	GCTGAGCAGGATCATGA	133472	133488	1-14-2	513_1	GctgagcaggatcatGA	-20	89,5
513	GCTGAGCAGGATCATGA	133472	133488	1-12-4	513_2	GctgagcaggatcATGA	-22	90,2
513	GCTGAGCAGGATCATGA	133472	133488	1-13-3	513_3	GctgagcaggatcaTGA	-21	91,2
513	GCTGAGCAGGATCATGA	133472	133488	2-13-2	513_4	GCtgagcaggatcatGA	-22	96,8
514	AAAATCCAGCCAGTTCCA	70176	70193	1-15-2	514_1	AaaatccagccagttcCA	-21	70,2
514	AAAATCCAGCCAGTTCCA	70176	70193	2-14-2	514_2	AAaatccagccagttcCA	-22	77,3
514	AAAATCCAGCCAGTTCCA	70176	70193	3-13-2	514_3	AAAatccagccagttcCA	-22	82,0
514	AAAATCCAGCCAGTTCCA	70176	70193	4-12-2	514_4	AAAatccagccagttcCA	-23	82,7
515	ACTGCAATGTACATGTT	176620	176636	1-12-4	515_1	ActgcaatgtacaTGTT	-19	32,7
515	ACTGCAATGTACATGTT	176620	176636	3-12-2	515_2	ACTgcaatgtacatgTT	-19	34,0

515	ACTGCAATGTACATGTT	176620	176636	4-11-2	515_3	ACTGcaatgtacatgTT	-20	37,2
515	ACTGCAATGTACATGTT	176620	176636	2-11-4	515_4	ACtgcaatgtacaTGTT	-20	43,2
515	ACTGCAATGTACATGTT	176620	176636	3-11-3	515_5	ACTgcaatgtacatGTT	-20	45,3
515	ACTGCAATGTACATGTT	176620	176636	3-10-4	515_6	ACTgcaatgtacaTGTT	-22	46,4
516	TCTATTTGCTTAGCTG	41022	41037	1-11-4	516_1	TctatttgcttaGCTG	-20	10,3
516	TCTATTTGCTTAGCTG	41022	41037	1-12-3	516_2	TctatttgcttagCTG	-18	10,4
516	TCTATTTGCTTAGCTG	41022	41037	2-12-2	516_3	TCtatttgcttagcTG	-17	14,3
516	TCTATTTGCTTAGCTG	41022	41037	2-11-3	516_4	TCtatttgcttagCTG	-19	36,2
516	TCTATTTGCTTAGCTG	41022	41037	3-11-2	516_5	TCTatttgcttagcTG	-19	41,6
516	TCTATTTGCTTAGCTG	41022	41037	4-10-2	516_6	TCTAttgcttagcTG	-20	54,1
516	TCTATTTGCTTAGCTG	41022	41037	3-10-3	516_7	TCTatttgcttagCTG	-21	64,6
517	CTATTTGCTTAGCTGTT	41020	41036	1-12-4	517_1	CtatttgcttagcTGTT	-21	6,6
517	CTATTTGCTTAGCTGTT	41020	41036	1-13-3	517_2	CtatttgcttagctGTT	-19	14,4
517	CTATTTGCTTAGCTGTT	41020	41036	2-13-2	517_3	CTatttgcttagctgTT	-19	18,3
517	CTATTTGCTTAGCTGTT	41020	41036	2-12-3	517_4	CTatttgcttagctGTT	-20	18,3
517	CTATTTGCTTAGCTGTT	41020	41036	3-12-2	517_5	CTAttgcttagctgTT	-20	18,7
517	CTATTTGCTTAGCTGTT	41020	41036	4-11-2	517_6	CTAttgcttagctgTT	-21	32,4
517	CTATTTGCTTAGCTGTT	41020	41036	3-11-3	517_7	CTAttgcttagctGTT	-21	46,3
517	CTATTTGCTTAGCTGTT	41020	41036	2-11-4	517_8	CTatttgcttagcTGTT	-22	56,2
518	CTGAGCAGGATCATGA	133472	133487	1-12-3	518_1	CtgagcaggatcaTGA	-19	78,6
518	CTGAGCAGGATCATGA	133472	133487	2-12-2	518_2	CTgagcaggatcatGA	-19	88,3
518	CTGAGCAGGATCATGA	133472	133487	2-11-3	518_3	CTgagcaggatcaTGA	-21	92,1
518	CTGAGCAGGATCATGA	133472	133487	3-11-2	518_4	CTGagcaggatcatGA	-20	92,5
518	CTGAGCAGGATCATGA	133472	133487	2-10-4	518_5	CTgagcaggatcATGA	-22	99,7
518	CTGAGCAGGATCATGA	133472	133487	1-11-4	518_6	CtgagcaggatcATGA	-20	99,9
519	AAAATCCAGCCAGTTCC	70177	70193	1-13-3	519_1	AaaatccagccagtTCC	-21	44,5
519	AAAATCCAGCCAGTTCC	70177	70193	2-13-2	519_2	AAaatccagccagttCC	-21	49,4
519	AAAATCCAGCCAGTTCC	70177	70193	2-12-3	519_3	AAaatccagccagtTCC	-22	62,1
519	AAAATCCAGCCAGTTCC	70177	70193	3-12-2	519_4	AAAatccagccagttCC	-21	63,4
519	AAAATCCAGCCAGTTCC	70177	70193	4-11-2	519_5	AAAatccagccagttCC	-22	71,1
519	AAAATCCAGCCAGTTCC	70177	70193	3-11-3	519_6	AAAatccagccagtTCC	-22	71,9
520	TCTATTTGCTTAGCTGT	41021	41037	1-13-3	520_1	TctatttgcttagcTGT	-20	9,2
520	TCTATTTGCTTAGCTGT	41021	41037	2-13-2	520_2	TCtatttgcttagctGT	-19	12,3
520	TCTATTTGCTTAGCTGT	41021	41037	2-12-3	520_3	TCtatttgcttagcTGT	-21	19,0
520	TCTATTTGCTTAGCTGT	41021	41037	3-12-2	520_4	TCTatttgcttagctGT	-21	47,1
520	TCTATTTGCTTAGCTGT	41021	41037	4-11-2	520_5	TCTAttgcttagctGT	-22	54,6
521	TCTATTTGCTTAGCTGTT	41020	41037	1-14-3	521_1	TctatttgcttagctGTT	-20	7,1
521	TCTATTTGCTTAGCTGTT	41020	41037	2-14-2	521_2	TCtatttgcttagctgTT	-20	14,3
521	TCTATTTGCTTAGCTGTT	41020	41037	2-13-3	521_3	TCtatttgcttagctGTT	-21	24,3
521	TCTATTTGCTTAGCTGTT	41020	41037	3-12-3	521_4	TCTatttgcttagctGTT	-23	54,2
521	TCTATTTGCTTAGCTGTT	41020	41037	1-13-4	521_5	TctatttgcttagcTGTT	-21	60,3
522	TGCTGAGCAGGATCAT	133474	133489	2-12-2	522_1	TGctgagcaggatcAT	-19	71,9
522	TGCTGAGCAGGATCAT	133474	133489	2-11-3	522_2	TGctgagcaggatCAT	-21	76,7
522	TGCTGAGCAGGATCAT	133474	133489	2-10-4	522_3	TGctgagcaggatCAT	-22	88,1

522	TGCTGAGCAGGATCAT	133474	133489	3-11-2	522_4	TGCTgagcaggatcAT	-22	90,2
523	ACTGCAATGTACATGT	176621	176636	2-11-3	523_1	ACTgcaatgtacaTGT	-18	32,0
523	ACTGCAATGTACATGT	176621	176636	4-10-2	523_2	ACTGcaatgtacatGT	-19	33,0
523	ACTGCAATGTACATGT	176621	176636	2-10-4	523_3	ACTgcaatgtacATGT	-19	41,6
523	ACTGCAATGTACATGT	176621	176636	3-10-3	523_4	ACTgcaatgtacaTGT	-20	42,9
523	ACTGCAATGTACATGT	176621	176636	4-8-4	523_5	ACTGcaatgtacATGT	-22	60,7
524	ATTAGGTTCTCTAAT	180266	180280	4-7-4	524_1	ATTAggttctcTAAT	-18	110,1
525	ACTGCAATGTACATG	176622	176636	4-7-4	525_1	ACTGcaatgtaCATG	-20	79,6
526	GCAATGTACATGTTTAC	176617	176633	3-11-3	526_1	GCAatgtacatgttCAC	-21	15,4
527	CAATGTACATGTTTAC	176617	176632	4-8-4	527_1	CAATgtacatgtTCAC	-20	18,2
528	GTAGATGAACATGACCAG	176320	176337	3-12-3	528_1	GTAgtgaacatgacCAG	-22	10,3
529	GTAGATGAACATGACCAGGA	176318	176337	1-16-3	529_1	GtagatgaacatgaccaGGA	-23	32,0
530	GTAGATGAACATGACCA	176321	176337	3-11-3	530_1	GTAgtgaacatgaCCA	-22	10,5
531	GTAGATGAACATGACCAGG	176319	176337	1-14-4	531_1	GtagatgaacatgacCAGG	-23	35,0
532	TAGATGAACATGACC	176322	176336	4-7-4	532_1	TAGAtgaacatGACC	-20	6,4
533	TAGATGAACATGACCA	176321	176336	4-9-3	533_1	TAGAtgaacatgaCCA	-21	5,1
534	TAGATGAACATGACCAGG	176319	176336	3-12-3	534_1	TAGatgaacatgaccAGG	-22	6,7
535	TAGATGAACATGACCAGGA	176318	176336	3-14-2	535_1	TAGatgaacatgaccagGA	-22	20,3
536	TAGATGAACATGACCAGGAA	176317	176336	4-14-2	536_1	TAGAtgaacatgaccaggAA	-23	23,1
537	AGATGAACATGACCAGGA	176318	176335	1-13-4	537_1	AgatgaacatgaccAGGA	-22	9,4
538	AGATGAACATGACCAGG	176319	176335	2-11-4	538_1	AGatgaacatgacCAGG	-22	15,0
539	AGATGAACATGACCAGGAA	176317	176335	2-13-4	539_1	AGatgaacatgaccaGGAA	-23	12,0
540	GATGAACATGACCAGG	176319	176334	4-9-3	540_1	GATGaacatgaccAGG	-22	4,1
541	GATGAACATGACCAGGAA	176317	176334	4-11-3	541_1	GATGaacatgaccagGAA	-23	8,8
542	GATGAACATGACCAGGA	176318	176334	2-11-4	542_1	GATgaacatgaccAGGA	-22	7,5
543	ATGAACATGACCAGGA	176318	176333	3-9-4	543_1	ATGaacatgaccAGGA	-22	9,4
544	TGAACATGACCAGGAA	176317	176332	4-8-4	544_1	TGAACatgaccaGGAA	-22	9,4
545	GTGAAGTAGTAGTG	171984	171997	4-7-3	545_1	GTGAagtagtaGTG	-18	31,4
546	ACTTATCTTCTTTTCTGTT	149422	149441	1-15-4	546_1	ActtatcttcttttcTGTT	-22	104,7
547	ACTTATCTTCTTTTCTGT	149423	149441	1-14-4	547_1	ActtatcttcttttcCTGT	-22	96,4
548	CTTATCTTCTTTTCTGT	149423	149440	1-13-4	548_1	CttatcttcttttcCTGT	-21	90,3
549	CTTATCTTCTTTTCTGTTG	149421	149440	2-15-3	549_1	CTtatcttcttttcctgTTG	-22	96,2
550	CTTATCTTCTTTTCTGTT	149422	149440	1-14-4	550_1	CttatcttcttttcTGTT	-22	102,8
551	TTATCTTCTTTTCTGTT	149422	149439	4-12-2	551_1	TTATcttcttttcctgTT	-20	72,0
552	TTATCTTCTTTTCTGT	149423	149439	1-12-4	552_1	TtatcttcttttcCTGT	-19	101,0
553	TTATCTTCTTTTCTGTTG	149421	149439	4-13-2	553_1	TTATcttcttttcctgtTG	-21	70,7
554	TATCTTCTTTTCTGTTG	149421	149438	3-12-3	554_1	TATcttcttttcctgTTG	-21	71,8
555	ATCTTCTTTTCTGTTG	149421	149437	3-11-3	555_1	ATCttcttttcctgTTG	-20	60,0
556	TCCCATGATGCTGAA	147108	147122	4-9-2	556_1	TCCCatgatgctgAA	-22	61,0
557	ACTGCTGAGCAGGATCAT	133474	133491	1-14-3	557_1	ActgctgagcaggatCAT	-22	98,9
558	CTGCTGAGCAGGATCAT	133474	133490	1-13-3	558_1	CtgctgagcaggatCAT	-22	85,9
559	TGCTGAGCAGGATCATG	133473	133489	2-13-2	559_1	TGctgagcaggatcaTG	-21	88,2
560	TGAGCAGGATCATGA	133472	133486	3-8-4	560_1	TGAgcaggatcATGA	-21	118,1
561	TCTCTATCCACTCTCCA	98920	98936	1-14-2	561_1	TctctatccactctcCA	-21	75,8

562	CTCTATCCACTCTCCA	98920	98935	1-12-3	562_1	CtctatccactctCCA	-23	52,3
563	CTCTATCCACTCTCCAC	98919	98935	1-13-3	563_1	CtctatccactctcCAC	-23	63,8
564	CTCTATCCACTCTCCACA	98918	98935	1-13-4	564_1	CtctatccactctcCACA	-26	35,7
565	GGAAGGAGTGGAAGAAGTCG	98878	98897	2-16-2	565_1	GGaaggagtggaagaagtCG	-22	70,8
566	GAAGGAGTGGAAGAAGTCGT	98877	98896	1-16-3	566_1	GaaggagtggaagaagtCGT	-22	71,6
567	GAAGGAGTGGAAGAAGTCG	98878	98896	3-13-3	567_1	GAAggagtggaagaagTCG	-22	70,7
568	AAGGAGTGGAAGAAGTCG	98878	98895	3-11-4	568_1	AAGgagtggaagaaGTCG	-23	21,2
569	AAGGAGTGGAAGAAGTCGT	98877	98895	2-13-4	569_1	AAGgagtggaagaagTCGT	-23	29,5
570	AGGAGTGGAAGAAGTCG	98878	98894	2-11-4	570_1	AGgagtggaagaaGTCG	-22	23,2
571	AGGAGTGGAAGAAGTCGT	98877	98894	1-13-4	571_1	AggagtggaagaagTCGT	-22	37,9
572	GGAGTGGAAGAAGTCG	98878	98893	4-10-2	572_1	GGAGtggaagaagtCG	-21	40,9
573	GGAGTGGAAGAAGTCGT	98877	98893	3-12-2	573_1	GGAgtggaagaagtcGT	-22	44,1
574	GAGTGGAAGAAGTCGTTC	98875	98892	2-12-4	574_1	GAgtggaagaagtcGTTC	-22	28,0
575	GAGTGGAAGAAGTCGTT	98876	98892	4-11-2	575_1	GAGTggaagaagtcgTT	-22	40,6
576	GAGTGGAAGAAGTCGTTCAT	98873	98892	1-15-4	576_1	GagtggaagaagtcgtTCAT	-23	65,1
577	GAGTGGAAGAAGTCG	98878	98892	4-7-4	577_1	GAGTggaagaaGTCG	-22	99,7
578	GAGTGGAAGAAGTCGTTCA	98874	98892	1-14-4	578_1	GagtggaagaagtcgTTCA	-22	52,8
579	GAGTGGAAGAAGTCGT	98877	98892	3-9-4	579_1	GAGtggaagaagTCGT	-22	71,2
580	AGTGGAAGAAGTCGTTCA	98874	98891	2-12-4	580_1	AGtggaagaagtcgTTCA	-22	38,3
581	AGTGGAAGAAGTCGTTCAT	98873	98891	1-14-4	581_1	AgtggaagaagtcgtTCAT	-22	59,0
582	AGTGGAAGAAGTCGTTCATG	98872	98891	2-16-2	582_1	AGtggaagaagtcgttcaTG	-22	87,1
583	AGTGGAAGAAGTCGT	98877	98891	3-8-4	583_1	AGTggaagaagTCGT	-21	68,1
584	AGTGGAAGAAGTCGTT	98876	98891	3-9-4	584_1	AGTggaagaagtCGTT	-21	32,2
585	AGTGGAAGAAGTCGTTC	98875	98891	3-10-4	585_1	AGTggaagaagtcGTTC	-22	17,6
586	GTGGAAGAAGTCGTTC	98875	98890	3-9-4	586_1	GTGgaagaagtcGTTC	-21	16,6
587	GTGGAAGAAGTCGT	98877	98890	3-7-4	587_1	GTGgaagaagTCGT	-20	73,5
588	GTGGAAGAAGTCGTTCAT	98873	98890	4-12-2	588_1	GTGGaagaagtcgttcAT	-23	48,0
589	GTGGAAGAAGTCGTTCATG	98872	98890	1-14-4	589_1	GtggaagaagtcgttcATG	-22	71,8
590	GTGGAAGAAGTCGTTCATCA	98874	98890	2-11-4	590_1	GTggaagaagtcgTTCA	-22	27,8
591	GTGGAAGAAGTCGTTCATGT	98871	98890	1-16-3	591_1	GtggaagaagtcgttcaTGT	-23	82,0
592	GTGGAAGAAGTCGTT	98876	98890	3-8-4	592_1	GTGgaagaagtCGTT	-21	34,1
593	TGGAAGAAGTCGTTCATGTG	98870	98889	2-16-2	593_1	TGgaagaagtcgttcATG	-22	65,8
594	TGGAAGAAGTCGTTCATCA	98874	98889	4-10-2	594_1	TGGAagaagtcgttcCA	-21	21,3
595	TGGAAGAAGTCGTTCATG	98872	98889	2-12-4	595_1	TGgaagaagtcgttcATG	-22	49,3
596	TGGAAGAAGTCGTTC	98875	98889	4-7-4	596_1	TGGAagaagtcGTTC	-21	86,5
597	TGGAAGAAGTCGTTCAT	98873	98889	3-10-4	597_1	TGgaagaagtcgtTCAT	-22	82,1
598	TGGAAGAAGTCGTTCATGT	98871	98889	3-14-2	598_1	TGgaagaagtcgttcATGT	-22	42,0
599	GGAAGAAGTCGTTCATCA	98874	98888	3-8-4	599_1	GGAagaagtcgTTCA	-20	106,6
600	GGAAGAAGTCGTTCAT	98873	98888	4-9-3	600_1	GGAagaagtcgttcAT	-21	30,3
601	GGAAGAAGTCGTTCATGT	98871	98888	2-13-3	601_1	GGaagaagtcgttcaTGT	-22	34,6
602	GGAAGAAGTCGTTCATGTGC	98869	98888	1-17-2	602_1	GgaagaagtcgttcATGTGC	-23	70,1
603	GGAAGAAGTCGTTCATG	98872	98888	4-10-3	603_1	GGAagaagtcgttcATG	-22	17,9
604	GGAAGAAGTCGTTCATGTG	98870	98888	2-14-3	604_1	GGaagaagtcgttcATGTG	-22	20,3
605	GAAGAAGTCGTTCATGTG	98870	98887	2-12-4	605_1	GAagaagtcgttcATGTG	-22	20,4

606	GAAGAAGTCGTTTCATGTGC	98869	98887	1-15-3	606_1	GaagaagtcgttcgatTGC	-22	52,0
607	GAAGAAGTCGTTTCATGTGCC	98868	98887	1-16-3	607_1	GaagaagtcgttcgatGCC	-25	49,3
608	GAAGAAGTCGTTTCAT	98873	98887	4-7-4	608_1	GAAgaagtcgtTCAT	-19	114,8
609	GAAGAAGTCGTTTCATG	98872	98887	4-8-4	609_1	GAAgaagtcgtTCATG	-21	86,8
610	GAAGAAGTCGTTTCATGT	98871	98887	4-10-3	610_1	GAAgaagtcgttcaTGT	-22	18,5
611	AAGAAGTCGTTTCATGT	98871	98886	4-8-4	611_1	AAGaagtcgttcATGT	-21	59,0
612	AAGAAGTCGTTTCATGTGC	98869	98886	1-13-4	612_1	AagaagtcgttcgatGTGC	-22	33,6
613	AAGAAGTCGTTTCATGTGCCA	98867	98886	1-17-2	613_1	AagaagtcgttcgatgtgcCA	-23	64,9
614	AAGAAGTCGTTTCATG	98872	98886	4-7-4	614_1	AAGaagtcgtTCATG	-19	100,1
615	AAGAAGTCGTTTCAT	98873	98886	4-6-4	615_1	AAGaagtcgtTCAT	-18	95,9
616	AAGAAGTCGTTTCATGTGCC	98868	98886	2-15-2	616_1	AgaagtcgttcgatgtGCC	-23	38,7
617	AAGAAGTCGTTTCATGTG	98870	98886	3-10-4	617_1	AAGaagtcgttcaTGTG	-21	15,7
618	AGAAGTCGTTTCATGTGCC	98868	98885	1-15-2	618_1	AgaagtcgttcgatgtGCC	-22	36,5
619	AGAAGTCGTTTCATGTG	98870	98885	2-10-4	619_1	AGaagtcgttcaTGTG	-20	13,4
620	AGAAGTCGTTTCATGT	98871	98885	4-7-4	620_1	AGAAgtcgttcATGT	-21	59,2
621	AGAAGTCGTTTCATGTGC	98869	98885	3-12-2	621_1	AGAagtcgttcgatGC	-22	8,8
622	AGAAGTCGTTTCATG	98872	98885	4-6-4	622_1	AGAAgtcgtTCATG	-20	93,7
623	AGAAGTCGTTTCATGTGCCA	98867	98885	1-16-2	623_1	AgaagtcgttcgatgtgcCA	-23	43,3
624	GAAGTCGTTTCATGTGCC	98868	98884	1-13-3	624_1	GaagtcgttcgatGCC	-23	18,0
625	GAAGTCGTTTCATGTGCCA	98867	98884	1-15-2	625_1	GaagtcgttcgatgtgcCA	-22	36,7
626	GAAGTCGTTTCATGTGC	98869	98884	4-10-2	626_1	GAAgtcgttcgatGC	-22	9,6
627	AAGTCGTTTCATGTGCC	98868	98883	2-11-3	627_1	AAGtcgttcgatGCC	-22	7,8
628	AAGTCGTTTCATGTGCCA	98867	98883	3-12-2	628_1	AAGtcgttcgatgtgcCA	-22	7,1
629	AGTCGTTTCATGTGCC	98868	98882	1-11-3	629_1	AgtcgttcgatGCC	-21	9,2
630	AGTCGTTTCATGTGCCA	98867	98882	2-12-2	630_1	AGtcgttcgatgtgcCA	-22	12,1
631	GTCGTTTCATGTGCC	98868	98881	1-10-3	631_1	GtcgttcgatGCC	-20	11,5
632	TCGTTTCATGTGCCA	98867	98880	4-8-2	632_1	TCGTtcgatgtgcCA	-21	3,8
633	GGCCAGGATTTTGCCA	98679	98694	1-13-2	633_1	GgccaggattttgcCA	-22	88,1
634	GGCCAGGATTTTGCC	98680	98694	1-12-2	634_1	GgccaggattttgCC	-22	108,7
635	TCAAAGCTCGTGTAG	82684	82698	4-7-4	635_1	TCAAagctcgtGTAG	-21	27,4
636	CAAAGCTCGTGTAG	82684	82697	3-7-4	636_1	CAAagctcgtGTAG	-18	12,9
637	AAAGTTCGAAGAGCTG	71708	71723	4-8-4	637_1	AAAGttcgaagaGCTG	-21	102,9
638	TATTTGCTTAGCTGTT	41020	41035	4-8-4	638_1	TATttgcttagcTGTT	-22	18,1
639	GTAGATGAACATGACC	176322	176337	3-9-4	639_1	GTAgatgaacatGACC	-21	19,8
640	TAGATGAACATGACCAG	176320	176336	4-10-3	640_1	TAGAtgaacatgacCAG	-22	8,1
641	ATGAACATGACCAGGAA	176317	176333	3-10-4	641_1	ATGaacatgaccaGGAA	-21	9,1
642	TTCATAAATTTCACTAATC	64574	64593	4-12-4	642_1	TTCActaaatttcactAATC	-20	20,2
643	AATGTACTTATACCCA	69498	69513	1-11-4	643_1	AatgtacttataCCCA	-20	71,9
644	CTTACGCAAAAACAAT	70200	70215	5-5-6	644_1	CTTACgcaaaaACAAT	-20	84,8
645	ACTTACGCAAAAACAAT	70200	70216	4-8-5	645_1	ACTTAcgcaaaaACAAT	-19	94,9
646	TCACACCAATTACTTCTT	71767	71784	2-13-3	646_1	TCacaccaattacttCTT	-20	43,1
647	CTTCACACCAATTACTTCTT	71767	71786	1-16-3	647_1	CttcacaccaattacttCTT	-22	81,2
648	TTACTTTATTCATCTCATA	86908	86926	3-13-3	648_1	TTActttattcatctcATA	-20	47,0
649	TACTTTATTCATCTCATA	86908	86925	3-13-2	649_1	TACtttattcatctcaTA	-18	80,3

650	TTGAACCTTCATTATTC	107247	107264	4-11-3	650_1	TTGAaccttcattatTTC	-20	20
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CLAIMS

1. An oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 and Nav1.8 in a cell, wherein the contiguous nucleotide sequence is complementary to both human Nav1.7 and human Nav1.8 target nucleic acids.
2. The oligonucleotide of claim 1, wherein the contiguous nucleotide sequence is at least 90% complementary, such as 100% complementary to a region of SEQ ID NO 1, selected from the group consisting of 852 - 865 ; 2091 - 2104 ; 2620 - 2633 ; 2675 - 2692 ; 3441 - 3454 ; 3882 - 3921 ; 3970 - 3983 ; 4532 - 4553 ; 4814 - 4827 ; 5068 - 5082 ; 5167 - 5182 ; 5184 - 5198 ; 5430 - 5444 ; 5466 - 5502 ; 5511 - 5529 ; 5544 - 5585 ; 5610 - 5633 ; 5644 - 5662 ; 5695 - 5717 ; 6067 - 6085 ; 6087 - 6100 ; 6117 - 6130 ; 6859 - 6873 ; 6998 - 7019 ; 7033 - 7053 ; 7089 - 7121 ; 7131 - 7152 ; 7155 - 7184 ; 7206 - 7221 ; 7254 - 7271 ; 7273 - 7295 ; 7297 - 7315 ; 7381 - 7414 ; 7456 - 7475 ; 7478 - 7499 ; 7509 - 7522 ; 7618 - 7632 ; 8388 - 8401 ; 8508 - 8529 ; 8538 - 8562 ; 8596 - 8610 ; 8612 - 8638 ; 8655 - 8677 ; 8693 - 8715 ; 8944 - 8957 ; 9534 - 9547 ; 9914 - 9928 ; 10068 - 10081 ; 10252 - 10265 ; 10363 - 10376 ; 10402 - 10415 ; 10626 - 10640 ; 11437 - 11450 ; 11879 - 11901 ; 11981 - 11994 ; 12145 - 12158 ; 12980 - 12993 ; 13998 - 14011 ; 15098 - 15111 ; 15628 - 15642 ; 15749 - 15792 ; 15801 - 15821 ; 15847 - 15863 ; 15869 - 15911 ; 15931 - 15959 ; 15972 - 15985 ; 16019 - 16037 ; 16039 - 16052 ; 16740 - 16753 ; 17660 - 17676 ; 17696 - 17731 ; 17761 - 17774 ; 17800 - 17827 ; 17851 - 17871 ; 17878 - 17896 ; 17906 - 17967 ; 18825 - 18843 ; 19063 - 19080 ; 19821 - 19834 ; 19932 - 19983 ; 20024 - 20039 ; 20045 - 20062 ; 20090 - 20125 ; 20153 - 20183 ; 20196 - 20212 ; 20288 - 20301 ; 20416 - 20435 ; 20481 - 20494 ; 20715 - 20728 ; 20739 - 20756 ; 20808 - 20826 ; 20830 - 20843 ; 20847 - 20874 ; 20892 - 20905 ; 20932 - 20959 ; 21684 - 21697 ; 22764 - 22780 ; 22819 - 22836 ; 22856 - 22869 ; 22880 - 22907 ; 22979 - 22992 ; 23370 - 23383 ; 23917 - 23930 ; 25007 - 25020 ; 26048 - 26068 ; 26104 - 26160 ; 26170 - 26200 ; 26224 - 26238 ; 26270 - 26301 ; 26618 - 26635 ; 26843 - 26878 ; 26915 - 26932 ; 26945 - 26958 ; 26961 - 26978 ; 27013 - 27027 ; 27068 - 27085 ; 27218 - 27231 ; 27927 - 27941 ; 28777 - 28795 ; 29103 - 29116 ; 29389 - 29403 ; 29985 - 29998 ; 30360 - 30374 ; 30376 - 30390 ; 30768 - 30782 ; 32173 - 32206 ; 32237 - 32251 ; 32260 - 32274 ; 32334 - 32360 ; 32569 - 32583 ; 32597 - 32611 ; 32749 - 32763 ; 33254 - 33268 ; 33299 - 33314 ; 33492 - 33506 ; 34233 - 34247 ; 34360 - 34375 ; 34562 - 34576 ; 34689 - 34703 ; 35106 -

35135 ; 35142 - 35169 ; 35259 - 35275 ; 35280 - 35308 ; 35333 - 35346 ; 35382 -
35470 ; 35477 - 35490 ; 35494 - 35534 ; 35883 - 35896 ; 36784 - 36797 ; 37504 -
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3. The oligonucleotide of any one of claims 1 or 2, wherein the oligonucleotide comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.
4. The oligonucleotide of any one of any one of claims 1 - 3 wherein one or more nucleoside in the contiguous nucleotide sequence is a 2' sugar modified nucleoside.
5. The oligonucleotide of claim 3, wherein the one or more 2' sugar modified nucleoside is independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.
6. The oligonucleotide of any one of claims 1 - 4, wherein the oligonucleotide or contiguous nucleotide sequence thereof comprises one or more LNA nucleoside.
7. The oligonucleotide of any one of claims 1 - 5, wherein at least one internucleoside linkage in the contiguous nucleotide sequence is a phosphorothioate internucleoside linkages.
8. The oligonucleotide according to any one of claims 1 - 6 which is, or forms part of a RNAi agent such as a siRNA or a shRNA.
9. The oligonucleotide according to any one of claims 1 - 6 which is an antisense oligonucleotide.
10. The antisense oligonucleotide of claim 9, wherein all the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.
11. The antisense oligonucleotide of claim 9 or 10, wherein the oligonucleotide is capable of recruiting RNase H, such as human RNaseH1.
12. The antisense oligonucleotide of any one of claims 9 - 11, wherein the antisense oligonucleotide, or contiguous nucleotide sequence thereof, consists or comprises a

gapmer, such as a gapmer of formula 5'-F-G-F'-3', wherein region G is a region comprising a contiguous sequence of nucleotides capable of recruiting RNaseH, and regions F and F' each comprise at least one 2' sugar modified nucleoside.

13. The antisense oligonucleotide according to claim 12, wherein region G comprises of 6 – 16 DNA nucleosides and at least one of region F and F' comprises at least one LNA nucleoside, or both region F and F' comprise at least one LNA nucleoside.
14. An antisense oligonucleotide selected from the group consisting of CMP ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ; 103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ; 114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ; 125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ; 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ; 147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ; 158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ; 169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ; 180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ; 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ; 202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ; 213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ; 224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ; 235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ; 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ; 257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ; 268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ; 279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ; 290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ; 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ; 312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ; 323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ; 334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ; 343_1 ; 344_1 ; 345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ; 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ; 367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ; 378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ; 389_1 ;

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648_1 ; 649_1 and 650_1.

15. A conjugate comprising the oligonucleotide according to any one of claims 1 – 14, and at least one conjugate moiety covalently attached to said oligonucleotide.
16. A pharmaceutically acceptable salt of the antisense oligonucleotide according to any one of claims 1 – 15, or the conjugate according to claim 16.
17. A pharmaceutical composition comprising the antisense oligonucleotide of 1-14 or the conjugate of claim 15, or the salt of claim 16, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

18. An *in vivo* or *in vitro* method for inhibiting SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an antisense oligonucleotide of any one of claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17 in an effective amount to said cell.
19. The method of claim 18, wherein the method is for inhibiting SCN9A and SCN10A expression in a target cell which is expressing SCN9A and SCN10A, said method comprising administering an antisense oligonucleotide of any one of claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17 in an effective amount to said cell.
20. A method for treating or preventing pain in a subject such as a human, who is suffering from or is likely to suffer pain, comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of any one of claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17, such as to prevent or alleviate the pain.
21. The method of claim 20, wherein the pain is either
 - v) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or
 - vi) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or
 - vii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or
 - viii) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.
22. The oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim15 or the pharmaceutical salt or composition of claim 16 or 17 for use in medicine.
23. The oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim 15 or the pharmaceutical salt or composition of claim 16 or 17 for use in the treatment or prevention or alleviation of pain, such as the pain as defined according to parts i), ii), iii) or iv) of claim 21.
24. The use of an oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim 15 or the pharmaceutical salt or composition of claim 16 or 17, for the preparation of a medicament for the treatment, prevention or alleviation of pain, such as the pain as defined according to parts i), ii), iii) or iv) of claim 35.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/066223

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

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

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

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/159595 A2 (REGENERON PHARMACEUTICALS, INC. [US]) 2 October 2014 (2014-10-02) page 37 - page 38 -----	1-24
X	WO 2018/051175 A1 (OLIPASS CORP [KR]) 22 March 2018 (2018-03-22) page 23 -----	1-24
X	WO 02/18637 A2 (IMPERIAL COLLEGE INNOVATIONS LIMITED [GB]) 7 March 2002 (2002-03-07) page 105; claim 29 -----	1-24
A	WO 01/05831 A1 (YALE UNIVERSITY [US]) 25 January 2001 (2001-01-25) claim 37 ----- -/-	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Macchia, Giovanni

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/066223

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