Claims

1. A compound comprising an antisense strand and a sense strand hybridized to form a double-stranded nucleic acid, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand is at least 90% complementary to the human peripheral myelin protein 22 mRNA (SEQ ID NO: 1170), and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.

2. The compound of claim 1, wherein each of the antisense strand and sense strands is 15 to 25 nucleotides in length, the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides, e.g., at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, or 23 contiguous nucleotides, of any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, 645, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1121, 1123, 1126, and 1144, and the nucleotide sequence of the sense strand has no more than two mismatches to the nucleotide sequence of the antisense strand.

3. The compound of any one of claims 1 to 2, wherein the nucleotide sequence of the antisense strand is at least 95% complementary to SEQ ID NO: 1.

4. The compound of any one of claims 1 to 2, wherein the nucleotide sequence of the antisense strand is 100% complementary to SEQ ID NO: 1.

5. The compound of any one of claims 1 to 4, wherein the sense strand is 17 to 23 nucleotides in length, or 19 to 21 nucleotides in length, or 21 to 23 nucleotides in length.

6. The compound of any one of claims 1 to 4, wherein the sense strand is 19 nucleotides in length, or 20 nucleotides in length, or 21 nucleotides in length, or 22 nucleotides in length, or 23 nucleotides in length.

7. The compound of any one of claims 1 to 6, wherein the double-stranded region is 15 to 25 nucleotide pairs in length, e.g., 17 to 23 nucleotide pairs in length, or 19 to 21 nucleotide pairs in length.

8. The compound of any one of claims 1 to 6, wherein the double-stranded region is 19 nucleotide pairs in length, or 20 nucleotide pairs in length, or 21 nucleotide pairs in length.

9. The compound of any one of claims 1 to 8, wherein the nucleotide sequence of the sense strand has no more than one mismatch has no mismatches to the nucleotide sequence of the antisense strand in the double-stranded region.

10. The compound of claim 1 or 2, wherein the antisense strand is (a) 21 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 491, 492, 493, 494, 495, 497, 498, 503, 504, 506, 510, 511, 514, 515, 516, 518, 524, 526, 529, 531, 532, 533, 534, 535, 536, 538, 539, 540, 541, 542, 543, 545, 546, 547, 548, 550, 553, 554, 556, 558, 559, 560, 561, 563, 567, 569, 575, 576, 579, 580, 581, 582, 583, 585, 590, 591, 595, 597, 600, 605, 609, 610, 618, 622, 623, 628, 630, 631, 633, 635, 637, 639, 641, 642, 643, 644, and 645, or (b) 23 nucleotides in length and the nucleotide sequence of the antisense strand is identical to a nucleotide sequence selected from any one of SEQ ID NOs 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1122, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1118, 1126, and 1144.

11. The compound of claim 1 to 2, wherein the double-stranded nucleic acid comprises an antisense strand and sense strand of any of the following pairs of SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 993 and 1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1051 and 1158; SEQ ID NOs: 1069 and 1168; SEQ ID NOs: 993 and 1164; SEQ ID NOs: 1108 and 1156; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1047 and 1160; SEQ ID NOs: 1111 and 1161; SEQ ID NOs: 1066 and 1136; SEQ ID NOs: 1110 and 1122; SEQ ID NOs: 986 and 1142; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1018 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1015 and 1144; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1065 and 1140; SEQ

ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1019 and 1143; SEQ ID NOs: 1000 and 1127; SEQ ID NOs: 1060 and 1138; SEQ ID NOs: 1034 and 1153; SEQ ID NOs: 1088 and 1157; SEQ ID NOs: 1037 and 1154; SEQ ID NOs: 1091 and 1151; SEQ ID NOs: 1045 and 1152; SEQ ID NOs: 1103 and 1155; SEQ ID NOs: 1054 and 1126; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 1065 and 1140; SEQ ID NOs: 1001 and 1129; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1067 and 1141; SEQ ID NOs: 1021 and 1147; SEQ ID NOs: 1077 and 1134; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 997 and 1124; SEQ ID NOs: 1063 and 1130; SEQ ID NOs: 1029 and 1148; SEQ ID NOs: 1056 and 1163; SEQ ID NOs: 1039 and 1113; SEQ ID NOs: 1033 and 1149; SEQ ID NOs: 1031 and 1132; SEQ ID NOs: 1008 and 1139; SEQ ID NOs: 1026 and 1118; SEQ ID NOs: 999 and 1166; SEQ ID NOs: 979 and 1169; SEQ ID NOs: 1098 and 1137; SEQ ID NOs: 1027 and 1135; SEQ ID NOs: 1073 and 1114; SEQ ID NOs: 1078 and 1116; SEQ ID NOs: 981 and 1115; SEQ ID NOs: 1030 and 1159; SEQ ID NOs: 992 and 1146; SEQ ID NOs: 1024 and 1167; SEQ ID NOs: 1007 and 1162; SEQ ID NOs: 978 and 1120; SEQ ID NOs: 1028 and 1131; SEQ ID NOs: 1097 and 1128; SEQ ID NOs: 994 and 1112; SEQ ID NOs: 1086 and 1145; SEQ ID NOs: 977 and 1125; SEQ ID NOs: 1022 and 1117; SEQ ID NOs: 1010 and 1165; SEQ ID NOs: 1071 and 1133; SEQ ID NOs: 1009 and 1150; SEQ ID NOs: 1081 and 1119; SEQ ID NOs: 1029 and 1148; and SEQ ID NOs: 1039 and 1113.

12. The compound of any one of claims 1 to 11, wherein at least one nucleotide of the antisense strand is a modified nucleotide, and / or wherein at least one nucleotide of the sense strand is a modified nucleotide.

13. The compound of claim 12, wherein the modified nucleotide comprises one or more of a modified sugar moiety, a modified internucleotide linkage, and a 5’-terminal modified phosphate group, optionally

(a) wherein the modified nucleotide comprising a modified sugar moiety is selected from a 2’-fluoro nucleotide, a 2’-O-methyl nucleotide, a 2’-O-methoxyethyl nucleotide, and a bicyclic sugar nucleotide, and / or

(b) wherein the modified internucleotide linkage is a phosphorothioate internucleotide linkage, and / or

(c) wherein the first two internucleotide linkages at the 5’ terminus of the sense strand and the last two internucleotide linkages at the 3’ terminus of the sense strand are phosphorothioate

internucleotide linkages, and optionally wherein the first two internucleotide linkages at the 5’ terminus of the antisense strand and the last two internucleotide linkages at the 3’ terminus of the antisense strand are phosphorothioate internucleotide linkages.

14. The compound of claim 13, wherein the covalent linkage of the bicyclic sugar is selected from a 4’-CH(CH_3)-O-2’ linkage, a 4'-(CH_2)$_2$-O-2' linkage, a 4'-CH(CH_2-OMe)-O-2' linkage, 4’-CH_2-N(CH_3)-O-2’ linkage, and 4’-CH_2-N(H)-O-2’ linkage.

15. The compound of claim 13, wherein the 5’-terminal modified phosphate group is a 5’-(E)-vinylphosphonate.

16. The compound of any one of claims 1 to 15, wherein

(i) the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2’-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2’-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2’-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2’-O-methyl nucleotides, and nucleotides 20 and 21 are beta-D-deoxynucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(ii) wherein the antisense strand is 21 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are 2’-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2’-fluoro nucleotides, and nucleotides 20 and 21 are beta-D-deoxy nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 19 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are

2’-fluoro nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, and 18 are 2’-O-methyl nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(iii) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2’-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2’-fluoro nucleotides the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21 are 2’-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2’-O-methyl nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(iv) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2’-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2’-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(v) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand,

nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, and 21 are 2'-fluoronucleotides, nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(vi) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 10, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides and nucleotides 2, 4, 6, 8, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages ,and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 3, 5, 7, 9, 11, 12, 13, 15, 17, 19, and 21 are 2'-fluoro nucleotides, nucleotides 2, 4, 6, 8, 10, 14, 16, 18, and 20 are 2'-O-methyl nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(vii) wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 8, 9, 11, 12, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 10, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleoides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl

nucleotides, nucleotides 7, 9, 11, 13, 15, and 17 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(viii) wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2’-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2’-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(ix) wherein the antisense strand is 23 nucleotides in length and the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, and 23 are 2’-O-methyl nucleotides, nucleotides 2, 6, 14, and 16 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 are 2’-O-methyl nucleotides, nucleotides 7, 9, 10, and 11 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(x) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2’-O-methyl nucleotides,

nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 1 and 2 are 2'-O-methoxyethyl nucleotides, nucleotides 3, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(xi) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2 and 3 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, 19, 20, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(xii) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5' terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2'-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2'-fluoro nucleotides, the first two internucleotide linkages at the 5' terminus and the last two internucleotide linkages at the 3' terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5' terminus of the sense strand, nucleotides 2, 3, 19 and 20 are 2'-O-methoxyethyl nucleotides, nucleotides 1, 4, 6, 8, 12, 14, 16, 18, and 21 are 2'-O-methyl nucleotides, nucleotides 5, 7, 9, 10,

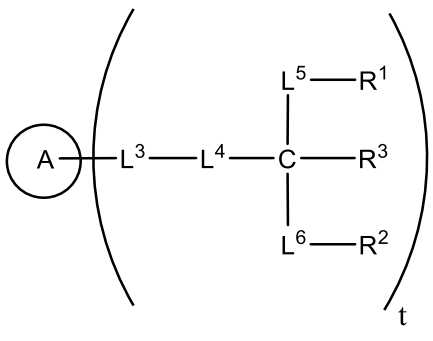
11, 13, 15, and 17 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage, or

(xiii) wherein the antisense strand is 23 nucleotides in length and wherein the nucleotides of the antisense strand are modified such that, counting from the 5’ terminus of the antisense strand, nucleotides 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 22, and 23 are 2’-O-methyl nucleotides, nucleotides 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage; and wherein the sense strand is 21 nucleotides in length and wherein the nucleotides of the sense strand are modified such that, counting from the 5’ terminus of the sense strand, nucleotides 1, 2, 3, and 4 are 2’-O-methoxyethyl nucleotides, nucleotides 6, 8, 12, 14, 16, 18, 19, 20 and 21 are 2’-O-methyl nucleotides, nucleotides 5, 7, 9, 10, 11, 13, 15, and 17 are 2’-fluoro nucleotides, the first two internucleotide linkages at the 5’ terminus and the last two internucleotide linkages at the 3’ terminus are phosphorothioate internucleotide linkages, and each other internucleotide linkage is a phosphodiester internucleotide linkage.

17. The compound of claim 16, wherein the 5’ terminal phosphate group of the antisense strand is a 5’-(E)-vinylphosphonate group.

18. The compound of any one of claims 1 to 17 wherein the compound comprises a ligand covalently linked to one or more of the antisense strand and the sense strand of the double-stranded nucleic acid.

19. The compound of claim 18, wherein the compound has the structure:



(I),

wherein A is the antisense strand and/or the sense strand of the double-stranded nucleic acid;

wherein t is an integer from 1 to 5;

L^3 and L^4 are independently a bond, -N(R^{23})-, -O-, -S-, -C(O)-, -N(R^{23})C(O)-, -C(O)N(R^{24})-, -N(R^{23})C(O)N(R^{24})-, -C(O)O-, -OC(O)-, -N(R^{23})C(O)O-, -OC(O)N(R^{24})-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(R^{25})-O-, -O-P(S)(R^{25})-O-, -O-P(O)($NR^{23}R^{24}$)-N-, -O-P(S)($NR^{23}R^{24}$)-N-, -O-P(O)($NR^{23}R^{24}$)-O-, -O-P(S)($NR^{23}R^{24}$)-O-, -P(O)($NR^{23}R^{24}$)-N-, -P(S)($NR^{23}R^{24}$)-N-, -P(O)($NR^{23}R^{24}$)-O-, -P(S)($NR^{23}R^{24}$)-O-,-S-S-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene;

L^5 is -L^{5A}-L^{5B}-L^{5C}-L^{5D}-L^{5E}-;

L^6 is -L^{6A}-L^{6B}-L^{6C}-L^{6D}-L^{6E}-;

R^1 and R^2 are independently unsubstituted C_1-C_{25} alkyl, wherein at least one of R^1 and R^2 is unsubstituted C_9-C_{19} alkyl;

R^3 is
hydrogen, -NH_2, -OH, -SH, -C(O)H, -C(O)NH_2, -NHC(O)H, -NHC(O)OH, -NHC(O)NH_2, -C(O)OH, -OC(O)H, –N_3, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^{5A}, L^{5B}, L^{5C}, L^{5D}, L^{5E}, L^{6A}, L^{6B}, L^{6C}, L^{6D}, and L^{6E} are independently a
bond, -NH-, -O-, -S-, -C(O)-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, –C(O)NH-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene; and

each R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_{10} alkyl.

20. The compound of claim 19, wherein t is 1 or 2 or 3.

21. The compound of any one of claims 19 to 20, wherein A is the sense strand or wherein A is the antisense strand.

22. The compound of one of claims 19 to 21, wherein each of R^{23}, R^{24} and R^{25} is independently hydrogen or unsubstituted C_1-C_3 alkyl.

23. The compound of one of claims 19 to 22, wherein one L^3 is attached to

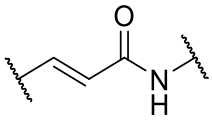
(i) a 3’ carbon of a nucleotide, optionally wherein the 3’ carbon is the 3’ carbon of a 3’ terminal nucleotide, or

(ii) a 5’ carbon of a nucleotide, optionaly wherein the 5’ carbon is the 5’ carbon of a 5’ terminal nucleotide, or

(iii) a 2’ carbon of a nucleotide.

24. The compound of one of claims 19 to 23, wherein L^3 and L^4 are independently a bond, -NH-, -O-, -C(O)-, -C(O)O-, -OC(O)-, -OPO_2-O-, -O-P(O)(S)-O-, -O-P(O)(CH_3)-O-, -O-P(S)(CH_3)-O-, -O-P(O)($N(CH_3)_2$)-N-, -O-P(O)($N(CH_3)_2$)-O-, -O-P(S)($N(CH_3)_2$)-N-, -O-P(S)($N(CH_3)_2$)-O-, - P(O)($N(CH_3)_2$)-N-, -P(O)($N(CH_3)_2$)-O-, -P(S)($N(CH_3)_2$)-N-, -P(S)($N(CH_3)_2$)-O-, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

25. The compound of one of claims 19 to 24, wherein L^3 is

(i) independently , or

(ii) independently -OPO_2-O- or –OP(O)(S)-O-, or

(iii) independently –O-, or

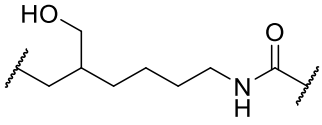
(iv) independently -C(O)-, or

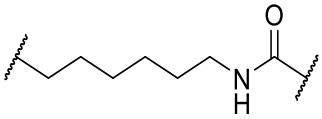
(v) independently -O-P(O)($N(CH_3)_2$)-N-.

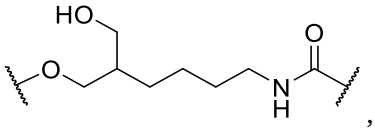
26. The compound of one of claims19 to 30, wherein L^4 is

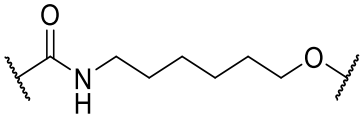
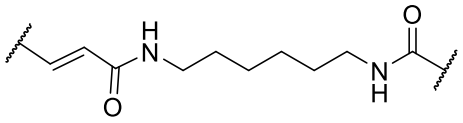
(i) independently substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene, and/or

(ii) independently –L^7-NH-C(O)- or –L^7-C(O)-NH-, wherein L^7 is substituted or unsubstituted alkylene, and /or

(iii) independently , and / or

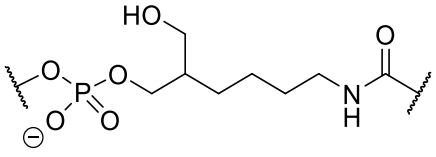
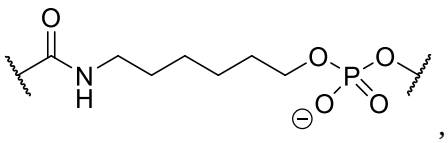
(iv) independently .

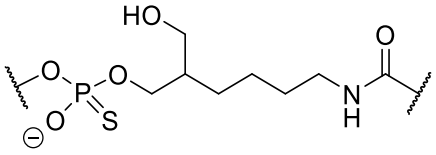
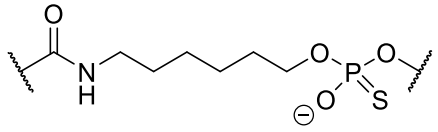
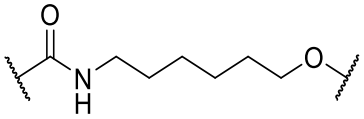
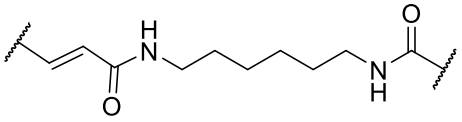
27. The compound of one of claims 19 to 26, wherein –L^3-L^4- is independently –O-L^7-NH-C(O)- or –O-L^7-C(O)-NH-, wherein L^7 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heteroalkenylene, optionally wherein –L^3-L^4- is independently –O-L^7-NH-C(O)-, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene, optionally wherein –L^3-L^4- is independently ,

, or .

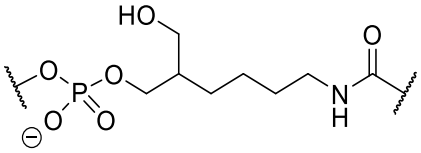
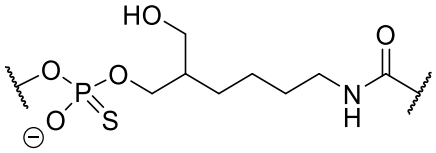
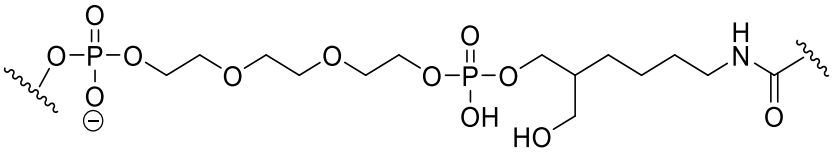
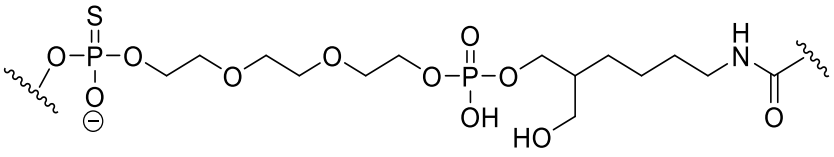
28. The compound of one of claims 19 to 24, wherein –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)-, -OP(O)(S)-O-L^7-NH-C(O)-, -OPO_2-O-L^7-C(O)-NH-or –OP(O)(S)-O-L^7-C(O)-NH-, wherein L^7 is independently substituted or unsubstituted alkylene, optionally wherein –L^3-L^4- is independently -OPO_2-O-L^7-NH-C(O)- or –OP(O)(S)-O-L^7-NH-C(O)-, wherein L^7 is independently substituted or unsubstituted C_5-C_8 alkylene.

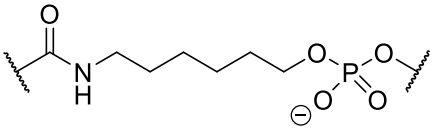
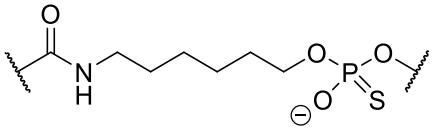
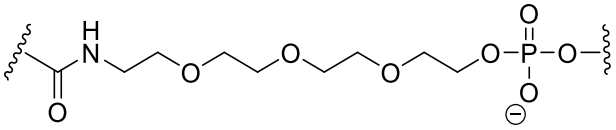
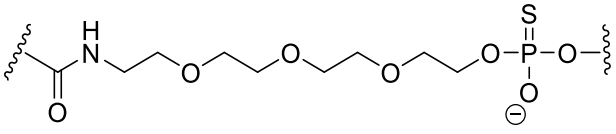
29. The compound of claim 28, wherein –L^3-L^4- is independently

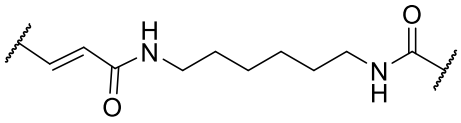
, ,


,

,

, or

.

30. The compound of claim 29, wherein an $-L^3-L^4-$ is

(i) independently

,

,

, or

, and is attached to the 3' carbon of a 3' terminal nucleotide, or

(ii) independently

,

,

, or

and is attached to the 5' carbon of a 5' terminal nucleotide, or

(iii) independently  and is attached to a 2' carbon.

31. The compound of one of claims 17 to 30, wherein R^3 is independently hydrogen.

32. The compound of one of claims 19 to 31, wherein L^6 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

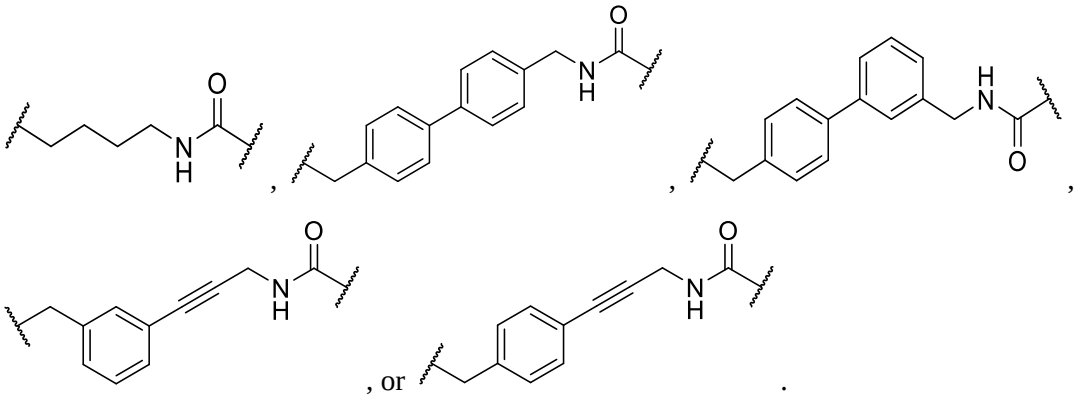
33. The compound of claim 32, wherein

(i) L^6 is independently -NHC(O)-, or

(ii) L^{6A} is independently a bond or unsubstituted alkylene; L^{6B} is independently a bond, -NHC(O)-, or unsubstituted arylene; L^{6C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene; L^{6D} is independently a bond or unsubstituted alkylene; and L^{6E} is independently a bond or -NHC(O)-, or

(iii) L^{6A} is independently a bond or unsubstituted C_1-C_8 alkylene; L^{6B} is independently a bond, -NHC(O)-, or unsubstituted phenylene; L^{6C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene; L^{6D} is independently a bond or unsubstituted C_1-C_8 alkylene; and L^{6E} is independently a bond or -NHC(O)-.

34. The compound of one of claims 19 to 31, wherein L^6 is independently a bond,



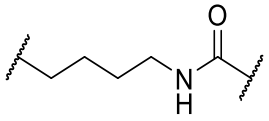
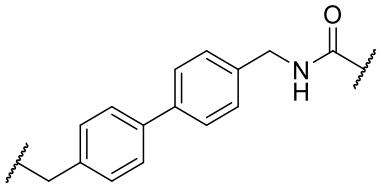
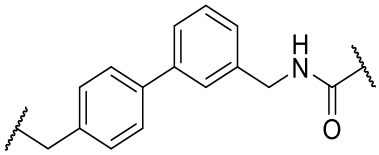
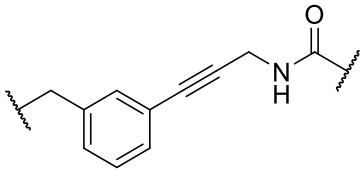
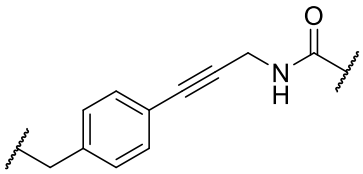
35. The compound of one of claims 19 to 34, wherein

(i) L^5 is independently -NHC(O)-, –C(O)NH-,substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, or

(ii) L^5 is independently -NHC(O)-, or

(iii) L^{5A} is independently a bond or unsubstituted alkylene; L^{5B} is independently a bond, -NHC(O)-, or unsubstituted arylene; L^{5C} is independently a bond, unsubstituted alkylene, or unsubstituted arylene; L^{5D} is independently a bond or unsubstituted alkylene; and L^{5E} is independently a bond or -NHC(O)-, or

(iv) L^{5A} is independently a bond or unsubstituted C_1-C_8 alkylene; L^{5B} is independently a bond, -NHC(O)-, or unsubstituted phenylene; L^{5C} is independently a bond, unsubstituted C_2-C_8 alkynylene, or unsubstituted phenylene; L^{5D} is independently a bond or unsubstituted C_1-C_8 alkylene; and L^{5E} is independently a bond or -NHC(O)-, or

(v) L^5 is independently a bond, , , , , or , or

(vi)R^1 is unsubstituted C_1-C_{17} alkyl, or

(vii)R^1 is unsubstituted C_{11}-C_{17} alkyl, or

(viii) R^1 is unsubstituted C_{13}-C_{17} alkyl, or

(ix) R^1 is unsubstituted C_{14}-C_{15} alkyl, or

(x) R^1 is unsubstituted unbranched C_1-C_{17} alkyl, or

(xi) R^1 is unsubstituted unbranched C_{11}-C_{17} alkyl, or

(xii) R^1 is unsubstituted unbranched C_{13}-C_{17} alkyl, or

(xiii) R^1 is unsubstituted unbranched C_{14}-C_{15} alkyl, or

(xiv) R^1 is unsubstituted unbranched saturated C_1-C_{17} alkyl, or

(xv)R^1 is unsubstituted unbranched saturated C_{11}-C_{17} alkyl, or

(xvi) R^1 is unsubstituted unbranched saturated C_{13}-C_{17} alkyl, or

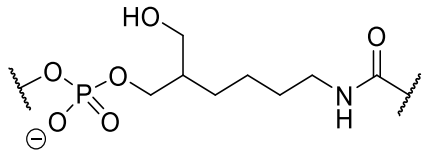
(xvii) R^1 is unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

36. The compound of one of claims 17 to 0, wherein R^2 is unsubstituted C_1-C_{17} alkyl or unsubstituted C_{11}-C_{17} alkyl or unsubstituted C_{13}-C_{17} alkyl or unsubstituted C_{14}-C_{15} alkyl or unsubstituted unbranched C_1-C_{17} alkyl or unsubstituted unbranched C_{11}-C_{17} alkyl or unsubstituted unbranched C_{13}-C_{17} alkyl or unsubstituted unbranched C_{14}-C_{15} alkyl or unsubstituted unbranched saturated C_1-C_{17} alkyl or unsubstituted unbranched saturated C_{11}-C_{17} alkyl or unsubstituted unbranched saturated C_{13}-C_{17} alkyl or unsubstituted unbranched saturated C_{14}-C_{15} alkyl.

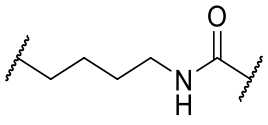
37. The compound of any one of claims 17 to 36, wherein the ligand is covalently linked to the antisense strand or wherein the ligand is covalently linked to the sense strand.

38. The compound of claim 19, wherein

(i) -L^3-L^4-

is 

, the phosphate group of -L^3-L^4- is attached to the 3' carbon of the 3' terminal nucleotide of the sense strand,

L^6 is 

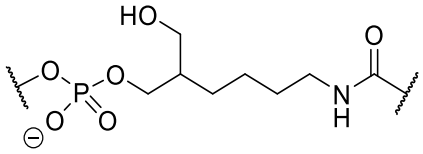
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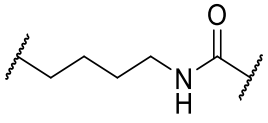
L^5 is -NHC(O)-,

R^3 is hydrogen,

R^1 is unsubstituted unbranched C_{15} alkyl, and

R^2 is unsubstituted unbranched C_{15} alkyl, or

(ii) $-L^3-L^4-$ is , the phosphate group of $-L^3-L^4-$ to the 3' carbon of the 3' terminal nucleotide of the sense strand,

L^6 is ,

L^5 is -NHC(O)-,

R^3 is hydrogen,

R^1 is unsubstituted unbranched C_{13} alkyl, and

R^2 is unsubstituted unbranched C_{13} alkyl.

39. The compound of claim 19, wherein the compound is selected from any one of DT-000544, DT-000545, DT-000546, DT-000620, DT-000621, DT-000622, DT-000623, DT-000624, DT-000625, DT-000626, DT-000627, DT-000628, DT-000811, DT-000812, DT-000945, DT-000959, DT-000960, DT-000961, DT-000962, DT-000963, DT-000964, DT-000965, DT-000966, DT-000967, DT-001037, DT-001038, DT-001039, DT-001044, DT-001045, DT-001046, DT-001047, DT-001048, DT-001049, DT-001050, DT-001051, DT-001052, DT-001053, DT-001054, DT-001055, DT-001056, DT-001057, DT-001058, DT-001059, DT-001060, DT-001061, DT-001109, DT-001110, DT-001111, DT-001112, DT-001113, DT-001114, DT-001115, DT-001116, DT-001117, DT-001118, DT-001119, DT-001120, DT-001121, DT-001122, DT-001123, DT-001124, DT-001125, DT-001126, DT-001127, DT-001128, DT-001129, DT-001130, DT-001131, DT-001132, DT-001145, DT-001146, DT-001147, DT-001148, DT-001149, DT-001150, DT-001151, DT-001152, DT-001153, DT-001154, DT-001155, DT-001156, DT-001157, DT-001158, DT-001159, DT-001160, DT-001161, DT-001162, DT-001163, DT-001164, DT-001176, DT-001177, DT-001178, DT-001179, DT-001180, DT-001181, DT-001182, DT-001183, DT-001184, DT-001185, DT-001186, DT-001187, DT-001188, DT-001189, DT-001190, DT-001191, DT-001192, DT-001193, DT-001194, DT-001195, DT-001196, DT-001197, DT-001198, DT-

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40. The compound of claim 19, wherein the compound is DT-000623 or DT-000812 or DT-001246 or DT-001247 or DT-001250 or DT-001251 or DT-001252 or DT-001253 or DT-001254 or DT-001255 or DT-001256 or DT-001257.

41. A pharmaceutical composition comprising the compound of any one of claims 1 to 40.

42. Use of the compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for use in a method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a cell, comprising contacting the cell with a compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41, thereby inhibiting the expression of PMP22 mRNA in the cell, optionally wherein the cell is a peripheral nerve cell, optionally wherein the cell is *in vitro*.

43. Use of the compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for use in a method of inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA in a subject, wherein an effective amount of a compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 is to be administered to the subject, thereby inhibiting the expression of peripheral myelin protein 22 (PMP22) mRNA, optionally wherein the expression of PMP22 mRNA is inhibited in a peripheral nerve of the subject, optionally

wherein the peripheral nerve is one or more of a sciatic nerve, a brachial plexus nerve, a tibial nerve, a peroneal nerve, a femoral nerve, a lateral femoral cutaneous nerve, and a spinal accessory nerve.

44. Use of the compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for use in a method for increasing myelination and/or slowing the loss of myelination in a subject, wherein an effective amount of a compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 is to be administered to the subject.

45. The use of any one of claims 43 to 44, wherein the subject has a peripheral demyelinating disease, in particular wherein the peripheral demyelinating disease is Charcot-Marie-Tooth disease (CMT), more particularly wherein the CMT is Charcot-Marie-Tooth disease Type 1A (CMT1A).

46. Use of the compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 in manufacturing of a medicament for treating Charcot-Marie-Tooth disease (CMT), in particular wherein the Charcot-Marie-Tooth disease is Charcot-Marie-Tooth disease Type 1A (CMT1A).

47. The use of claim 46, wherein the administration improves or slows the progression of one or more clinical indicators of CMT1A in the subject, wherein the one or more clinical indicators is selected from:

a. distal muscle weakness;
b. distal musculature atrophy;
c. reduced deep tendon reflexes;
d. distal sensory impairment;
e. reduced nerve conduction velocity;
f. reduced compound muscle action potential;
g. reduced sensory nerve action potential;
h. increased calf muscle fat fraction;
i. elevated plasma neurofilament light (NfL); and/or
j. elevated plasma tramsmembrane protease serine 5 (TMPRSS55).

48. The compound of any one of claims 1 to 40 or the pharmaceutical composition of claim 41 for use in therapy.