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(54) **RNAI AGENTS TARGETING CIDEB AND RELATED METHODS**

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(57) **ABSTRACT**

Provided herein are, inter alia, agents (e.g., RNAi agents, dsRNA agents) comprising a sense strand and an antisense strand targeting CIDEB (e.g., hCIDEB); and methods of manufacturing and pharmaceutical compositions comprising the same. Further provided herein are methods of utilizing the agents (e.g., RNAi agents, dsRNA agents) including, e.g., methods of inhibiting or decreasing CIDEB expression (e.g., mRNA expression), methods of treating CIDEB associated diseases, and methods of treating liver diseases (e.g., MASH).

Specification includes a Sequence Listing.

RNAI AGENTS TARGETING CIDE B AND RELATED METHODS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Ser. No.: 63/555,164, filed Feb. 19, 2024, U.S. Ser. No. 63/635,269, filed Apr. 17, 2024, and U.S. Ser. No. 63/707,351, filed Oct. 15, 2024, the entire contents of each of which is incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on May 5, 2025, is named 62801.53US01 Sequence Listing.xml and is 6,883,805 bytes in size.

1. FIELD

[0003] This disclosure relates to RNAi agents (e.g., double stranded RNA (dsRNA) agents comprising a sense strand and an antisense strand) targeting cell death inducing DNA fragmentation factor alpha like effector B (CIDE B). The disclosure further relates to pharmaceutical compositions comprising the same; and methods of utilizing the same, including, e.g., methods of treating CIDE B associated diseases (e.g., liver diseases).

2. BACKGROUND

[0004] The CIDE (cell death inducing DNA fragmentation factor alpha like effector) protein family is a family of lipid droplet-associated proteins. There are three members of the CIDE protein family, CIDEA, CIDE B, and CIDE C. Each of the CIDE proteins comprises a common CIDE-N domain and a CIDE-C domain, which varies between each of the members. The tissue expression pattern of each CIDE protein differs but is correlative with their association with lipid droplets—CIDEA and CIDE C are primarily expressed in adipose tissue, while CIDE B is highly expressed in the liver. The association of CIDE proteins with lipid droplets can be a direct physical interaction with the surface of the lipid droplet, as well as an association with other lipid droplet proteins, such as perilipin.

3. SUMMARY

[0005] Provided herein are, inter alia, agents (e.g., RNAi agents, dsRNA agents) comprising a sense strand and an antisense strand targeting CIDE B (e.g., hCIDE B); and methods of manufacturing and pharmaceutical compositions comprising the same. Further provided herein are methods of utilizing the agents (e.g., RNAi agents, dsRNA agents) including, e.g., methods of inhibiting or decreasing CIDE B expression (e.g., mRNA expression), methods of treating CIDE B associated diseases, and methods of treating liver diseases (e.g., metabolic dysfunction-associated steatohepatitis (MASH)).

[0006] Accordingly, in one aspect provided herein are double stranded ribonucleic acid (dsRNA) agents for inhibiting expression of cell death inducing DNA fragmentation factor alpha like effector (CIDE B) (e.g., human CIDE B (hCIDE B)), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the antisense

strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0007] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0008] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0009] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0010] In some embodiments, (a) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172; (b) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132; (c) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173; or (d) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138.

[0011] In some embodiments, (a) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172; (b) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ

more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of dsRNA agent 480; or (c) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of dsRNA agent 409; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of dsRNA agent 409.

[0023] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 479; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 479; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 481; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 481; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 482; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 482; (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 480; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 480; or (e) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 409; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 409.

[0024] In one aspect, provided herein are dsRNA agents for inhibiting expression of CIDEB (e.g., hCIDEB), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., 3 (e.g., 0, 1, 2, or 3))) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1230-1280, 1240-1290, 1250-1300, 1240-1270, 1240-1280, 1235-1270, 1245-1265, 1247-1267, 1252-1272, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 1920-1970, 1930-1970, 1930-1965, 1940-1970, 1940-1965, 1937-1957, 1942-1962, 1938-1958, 1943-1963, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1; wherein the nucleotide sequence of the antisense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21, 22, or 23) contiguous nucleotides of and differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., 2 or 3)) nucleotides from the nucleotide sequence of the corresponding complementary nucleotide sequence of SEQ ID NO: 2.

[0025] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the antisense strands set

forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0026] In some embodiments, the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0027] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1220-1270, 1230-1280, 1240-1290, 1250-1300, 1240-1270, 1240-1280, 1235-1270, 1245-1265, 1247-1267, 1252-1272, 1915-1966, 1920-1970, 1930-1970, 1930-1965, 1940-1970, 1940-1965, 1937-1957, 1942-1962, 1938-1958, 1943-1963, of SEQ ID NO: 1.

[0028] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1220-1270, 1230-1280, 1240-1290, 1250-1300, 1240-1270, 1240-1280, 1235-1270, 1245-1265, 1247-1267, 1252-1272, and wherein the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315 or 321.

[0029] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1915-1966, 1920-1970, 1930-1970, 1930-1965, 1940-1970, 1940-1965, 1937-1957, 1942-1962, 1938-1958, 1943-1963, and wherein the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 355 or 356.

[0030] In one aspect, provided herein are dsRNA agent for inhibiting expression of CIDEB (e.g., hCIDEB), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the antisense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21, 22, or 23) contiguous nucleotides of and differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0031] In some embodiments, the nucleotide sequence of the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0032] In some embodiments, the nucleotide sequence of the antisense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21, 22, or 23) contiguous nucleotides of and differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and wherein the nucleotide sequence of the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0048] For the sake of clarity, it is noted that the following embodiments are applicable to any of the foregoing aspects as if individually recited directly following each aspect.

[0049] In some embodiments, the sense strand comprises at least one modified nucleotide and/or the antisense strand comprises at least one modified nucleotide. In some embodiments, at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the sense strand and/or antisense strand are modified. In some embodiments, all of the nucleotides in the sense strand and/or antisense strand are modified. In some embodiments, all of the nucleotides in the sense strand and the antisense strand are modified.

[0050] In some embodiments, at least one of the modified nucleotides comprises a modified sugar (e.g., ribose moiety).

[0051] In some embodiments, (a) the sense strand comprises at least one 2'-O-methyl and/or the antisense strand comprises at least one 2'-O-methyl and/or (b) the sense strand comprises at least one 2'-deoxy-2'-fluoro and/or the antisense strand comprises at least one 2'-deoxy-2'-fluoro.

[0052] In some embodiments, (a) the sense strand comprises at least one 2'-O-methyl and at least one 2'-deoxy-2'-fluoro; and the antisense strand comprises at least one 2'-O-methyl and at least one 2'-deoxy-2'-fluoro.

[0053] In some embodiments, at least one of the modified nucleotides comprises a modified nucleobase.

[0054] In some embodiments, the sense strand comprises at least one vinyl-phosphonate and/or the antisense strand comprises at least one vinyl-phosphonate. In some embodiments, the antisense strand comprises a 5' vinyl-phosphonate. In some embodiments, the sense strand comprises at least one vinyl-phosphonate-2'-O-methyl (e.g., vinyl-phosphonate-2'-O-methyluridine) and/or the antisense strand comprises at least one vinyl-phosphonate-2'-O-methyl (e.g., vinyl-phosphonate-2'-O-methyluridine) (e.g., wherein the antisense strand comprises at least one vinyl-phosphonate-2'-O-methyl (e.g., vinyl-phosphonate-2'-O-methyluridine). In some embodiments, the antisense strand comprises a 5' vinyl-phosphonate-2'-O-methyl (e.g., vinyl-phosphonate-2'-O-methyluridine).

[0055] In some embodiments, the sense strand comprises at least one modified internucleoside linkage and/or the antisense strand comprises at least one modified internucleoside linkage.

[0056] In some embodiments, the sense strand comprises at least one phosphorothioate and/or the antisense strand comprises at least one phosphorothioate.

[0057] In some embodiments, the sense strand comprises at least one phosphorothioate and the antisense strand comprises at least one phosphorothioate.

[0058] In some embodiments, each of the antisense strand and the sense strand are not more than 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, or 15 nucleotides in length. In some embodiments, the antisense strand comprises from about 15-30, 16-30, 17-30, 18-30, 19-30 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 36-30, 27-30, 28-30-, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides; and/or the sense strand comprises from about 15-30, 16-30, 17-30, 18-30, 19-30 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 36-30, 27-30, 28-30-, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides. In some embodiments, antisense strand comprises from about 19-23 nucleotides; and/or the sense strand comprises from about 19-23 nucleotides. In some embodiments, antisense strand comprises or

consists of about 23 nucleotides; and/or the sense strand comprises or consists of about 21 nucleotides.

[0059] In some embodiments, the sense strand and/or the antisense strand comprises a 3' and/or 5' overhang of 1, 2, or 3 nucleotides. In some embodiments, the antisense strand comprises a 3' overhang of 1, 2, or 3 nucleotides (e.g., 2 nucleotides). In some embodiments, the antisense strand comprises a 3' overhang of 2 nucleotides.

[0060] In some embodiments, the double stranded region is from about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-20, 19-21, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, 23-24, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotide pairs in length. In some embodiments, the double stranded region is from about 19-23 or 19-21 nucleotide pairs in length. In some embodiments, the double stranded region is about 21 nucleotide pairs in length.

[0061] In some embodiments, the sense strand and the antisense strand are part of a single nucleic acid molecule (e.g., wherein a hairpin loop is between the sense strand and the antisense strand of the single nucleic acid molecule).

[0062] In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (i.e., connected only through the double stranded region).

[0063] In some embodiments, the nucleotide sequence of the antisense strand consists of 23 nucleotides; the nucleotide sequence of the sense strand consists of 21 nucleotides; the double stranded region is 21 nucleotide pairs in length; the antisense strand comprises a 3' overhang of 2 nucleotides; the antisense strand comprises a 5' vinyl-phosphonate-2'-O-methyl (e.g., vinyl-phosphonate-2'-O-methyluridine), at least one 2'-O-methyl, at least one 2'-deoxy-2'-fluoro and at least one phosphorothioate; and the sense strand comprises at least one 2'-O-methyl, at least one 2'-deoxy-2'-fluoro and at least one phosphorothioate.

[0064] In one aspect, provided herein are conjugates comprising a dsRNA agent described herein and a heterologous moiety.

[0065] In some embodiments, the heterologous moiety is a peptide, protein, carbohydrate, lipid, polymer, or small molecule.

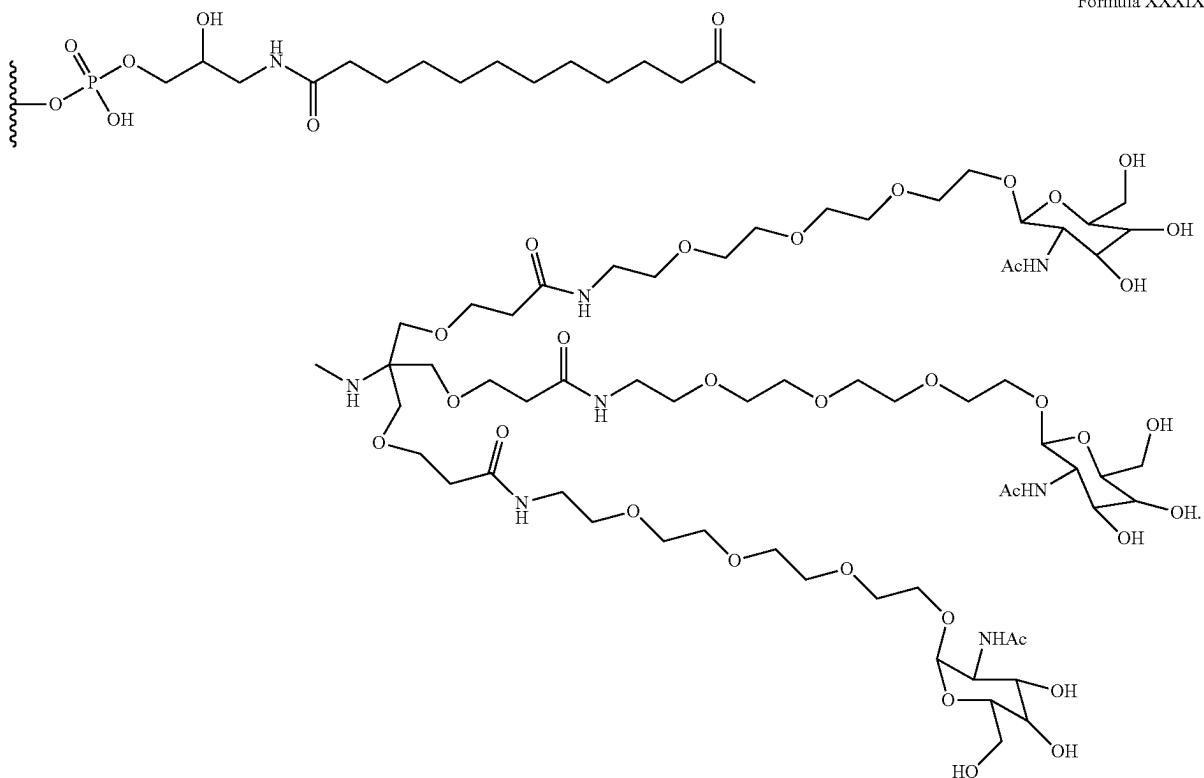
[0066] In some embodiments, the heterologous moiety is carbohydrate. In some embodiments, the heterologous moiety comprises one or more GalNac. In some embodiments, the GalNac is triantennary GalNac.

[0067] In some embodiments, the heterologous moiety is a targeting moiety. In some embodiments, the targeting moiety specifically binds to a moiety expressed by hepatocytes (e.g., on the surface of the hepatocytes). In some embodiments, the targeting moiety comprises GalNac. In some embodiments, the GalNac is triantennary GalNac. In some embodiments, the targeting moiety directs the agent to hepatocytes through specific binding to the asialoglycoprotein receptor (e.g., expressed on the surface of hepatocytes).

[0068] In some embodiments, the heterologous moiety is attached to the dsRNA agent via a linker.

[0069] In some embodiments, the linker comprises triethylene glycol (TEG). In some embodiments, the heterologous moiety comprises GalNac and the linker is TEG. In some embodiments, the heterologous moiety comprises triantennary GalNac and the linker is TEG.

[0070] In some embodiments, the heterologous moiety and linker comprises Formula XXXIX below:



[0071] In some embodiments, the heterologous moiety attached to the 3' end of the sense and/or antisense strand and/or the 5' end of the sense and/or antisense strand, and/or at an internal site of the sense and/or antisense strand. In some embodiments, the heterologous moiety attached to the 3' end of the sense strand.

[0072] In some embodiments, the conjugate is set forth in Table 11.

[0073] In some embodiments, (a) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1193; (b) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1193; (c) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1194; (d) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5)

nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense

strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1195; or (e) the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1196.

[0074] In some embodiments, (a) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1193; (b) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1193; (c) the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1194; (d) the nucleotide sequence of the antisense

dendrimer, a cationic delivery system, or a hydrogel. In some embodiments the lipid-based delivery system is a lipid nanoparticle (LNP), liposome, lipoplex, nanoliposome, an exosome, or a micelle.

[0083] In one aspect, provided herein are cells (or population of cells) comprising a dsRNA agent described herein, a conjugate described herein, a vector described herein, or a carrier described herein.

[0084] In one aspect, provided herein are pharmaceutical compositions comprising a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a cell (or population of cells) described herein, and a pharmaceutically acceptable excipient.

[0085] In one aspect, provided herein are kits comprising a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein.

[0086] In one aspect, provided herein are methods of delivering a dsRNA, conjugate, vector, carrier, or pharmaceutical composition to a cell, the method comprising introducing into a cell a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein, to thereby deliver the dsRNA, conjugate, vector, carrier, or pharmaceutical composition into the cell. In some embodiments, the cell is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments the cell is a subject (e.g., a human subject).

[0087] In one aspect, provided herein are methods of delivering a dsRNA, conjugate, vector, carrier, cell, or pharmaceutical composition to a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein, to thereby deliver the dsRNA, conjugate, vector, carrier, cell, or pharmaceutical composition to the subject.

[0088] In one aspect, provided herein are methods of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell, the method comprising delivering into the cell a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell.

[0089] In one aspect, provided herein are methods of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject.

[0090] In one aspect, provided herein are methods of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical

composition described herein, to thereby treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0091] In some embodiments, the treating, ameliorating, or preventing of the CIDEB (e.g., hCIDEB) associated disease is mediated (at least in part) through the by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0092] In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

[0093] In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0094] In one aspect, provided herein are methods of treating, ameliorate, or preventing a liver disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the liver disease in the subject.

[0095] In some embodiments, the treating, ameliorating, or preventing of the liver disease is mediated (at least in part) through the by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0096] In some embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. In some embodiments, the liver disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0097] In one aspect, provided herein are methods of diagnosing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the one or more somatic mutation indicates that the subject has a CIDEB (e.g., hCIDEB) associated disease.

[0098] In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is a liver disease. In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0099] In one aspect, provided herein are methods of diagnosing a liver disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the one or more somatic mutation indicates that the subject has a liver disease.

[0100] In some embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. In some embodiments, the liver disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0101] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of the one or more somatic CIDEB mutation in the DNA.

[0102] In some embodiments, the method further comprises administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if a CIDEB somatic mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein.

[0103] In one aspect, provided herein are methods of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the subject is selected for administration of the inhibitory nucleic acid molecule if the one or more somatic mutation is present.

[0104] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of the one or more somatic CIDEB mutation in the DNA.

[0105] In some embodiments, the method further comprises administering to the subject the inhibitory nucleic acid molecule if the subject is selected.

[0106] In some embodiments, the inhibitory nucleic acid molecule comprises a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein.

[0107] In one aspect, provided herein are methods of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, and (c) administering to the subject an inhibitory nucleic acid that inhibits expression of CIDEB if the one or more CIDEB somatic mutation is detected in the DNA, RNA, or protein.

[0108] In some embodiments, the CIDEB (e.g., hCIDEB) associated disease is a liver disease. In some embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

[0109] In some embodiments, the liver disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0110] In some embodiments, the treating, ameliorating, or preventing of the CIDEB (e.g., hCIDEB) associated disease is mediated (at least in part) through the by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0111] In one aspect, provided herein are methods of treating, ameliorating, or preventing a liver disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, and (c) administering to the subject an inhibitory nucleic acid that inhibits expression of CIDEB if the one or more CIDEB somatic mutation is detected in the DNA, RNA, or protein.

[0112] In some embodiments, the liver disease is fatty liver, liver inflammation, NASH, NAFLD, obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, cirrhosis, MASLD, MASH, MetALD, SLD, or cryptogenic SLD. In some embodiments, the liver disease is liver fibrosis, cirrhosis, liver failure, jaundice, AFLD, obesity-induced metabolic syndrome, insulin insensitivity, or type-2 diabetes.

[0113] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of the one or more somatic CIDEB mutation in the DNA.

[0114] In some embodiments, the inhibitory nucleic acid molecule comprises a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein.

[0115] In some embodiments, the treating, ameliorating, or preventing of the liver disease is mediated (at least in part) through the by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0116] In one aspect, provided herein are in vitro methods of screening a sample from a subject for one or more somatic CIDEB mutation, the method comprising (a) isolating and purifying DNA, RNA, or protein from a sample obtained from the subject; and (b) detecting the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein.

[0117] In some embodiments, the sample is a blood, tissue, or cell sample. In some embodiments, the sample is biopsy. In some embodiments, the sample is a liver biopsy.

[0118] In some embodiments, at least one of the one or more somatic mutation is a loss of function mutation. In some embodiments, at least one of the one or more somatic mutation is a gain of function mutation.

[0119] In some embodiments, the subject is a human.

[0120] In one aspect, provided herein are dsRNA agents described herein, conjugates described herein, vectors described herein, carriers described herein, cells (or populations of cells) described herein, or pharmaceutical compositions described herein for use in a method of treating,

ameliorating, or preventing a CIDEB associated disease (e.g., a CIDEB associated disease described herein) in a subject.

[0121] In one aspect, provided herein are dsRNA agents described herein, conjugates described herein, vectors described herein, carriers described herein, cells (or populations of cells) described herein, or pharmaceutical compositions described herein for use in a method of treating, ameliorating, or preventing a liver disease (e.g., a liver disease described herein) in a subject.

[0122] In one aspect, provided herein are uses of a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein for the manufacture of a medicament for the treatment, amelioration, or prevention of a CIDEB associated disease (e.g., a CIDEB associated disease described herein) in a subject.

[0123] In one aspect, provided herein are uses of a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell (or population of cells) described herein, or a pharmaceutical composition described herein for the manufacture of a medicament for the treatment, amelioration, or prevention of a liver disease (e.g., a liver disease described herein) in a subject.

4. DETAILED DESCRIPTION

[0124] The inventors have further discovered, inter alia, RNAi agents that inhibit expression of CIDEB (e.g., hCIDEB). As such, the RNAi agents described herein are useful for the treatment of CIDEB mediated diseases such as liver diseases (e.g., fatty liver disease, liver inflammation, MASH). As such, the current disclosure provides RNAi agents (e.g., dsRNAi agents comprising a sense strand and an antisense strand) capable of inhibiting CIDEB expression (e.g., in a cell, in a cell in a subject); and their use in, inter alia, pharmaceutical compositions, and methods of treating diseases (e.g., liver diseases).

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4.1 Definitions

[0125] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0126] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed.

[0127] In this application, the use of the singular includes the plural unless specifically stated otherwise. For example, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Furthermore, use of the term "including" as well as other forms, such as "include," "includes," and "included," is not limiting.

[0128] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and "consisting essentially of" are also provided.

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[0129] The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0130] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[0131] The terms “about” or “comprising essentially of” refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of “about” or “comprising essentially of” should be assumed to be within an acceptable error range for that particular value or composition.

[0132] As used herein, the term “administering” refers to the physical introduction of an agent, e.g., a therapeutic agent (or a precursor of the therapeutic agent that is metabolized or altered within the body of the subject to produce the therapeutic agent *in vivo*) to a subject, using any of the various methods and delivery systems known to those skilled in the art. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods. Administration includes administration to a subject by a third party; as well as self-administration by the subject.

[0133] As used herein, the term “agent” is used generically to describe any macro or micro molecule. Exemplary moieties include, but are not limited polypeptides, proteins, peptides, polynucleotides (e.g., DNA, RNA), small molecules, carbohydrates, lipids, synthetic polymers (e.g., polymers of PEG).

[0134] As used herein, the term “antisense strand” refers to an RNA molecule (e.g., part of an RNAi agent (e.g., described herein), part of a dsRNA agent (e.g., described herein)) that comprises a region of complementarity comprising a nucleotide sequence that is at least partially (e.g., substantially, fully) complementary to a target nucleic acid sequence (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)).

[0135] As used herein, the term “bicyclic sugar” refers to a modified sugar (e.g., ribose) moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In some embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In some embodiments, the furanosyl sugar moiety is a ribosyl moiety.

[0136] As used herein, the term “bicyclic nucleoside” (“BNA”) is a nucleoside comprising a bicyclic sugar.

[0137] As used herein, the term “blunt end” refers to a dsRNA molecule that does not contain any unpaired nucleotides at the end (e.g., 3' terminus, 5' terminus) of the dsRNA

molecule (i.e., no nucleotide overhang(s)). The dsRNA molecule can have, for example, a blunt end at the 3' end, 5' end, or both the 3' and 5' end of the molecule.

[0138] As used herein, the term “CIDEB” or “cell death inducing DNA fragmentation factor alpha like effector” refers to the lipid droplet-associated protein primarily expressed in the liver and functions, e.g., to promote unicellular lipid droplet formation by mediating lipid droplet fusion. The mRNA sequence of a reference hCIDEB gene is set forth in SEQ ID NO: 1 (NCBI Ref.: NM_014430.4). The amino acid sequence of a reference hCIDEB protein is set forth in SEQ ID NO: 3 (NCBI Ref.: NP_055245). The term CIDEB includes naturally occurring variants of CIDEB. CIDEB gene and mRNA sequences of e.g., human, mouse, rat, non-human primate (e.g., rhesus macaque, *Macaca fascicularis* (cynomolgus monkey)), are readily available through publicly available databases, including, e.g., GenBank, UniProt, OMIM, and the *Macaca* genome project web site.

[0139] As used herein, the term “complementary” in reference to a first nucleotide sequence (e.g., a sense strand or a target mRNA) in relation to a second nucleotide sequence (e.g., an antisense strand), refers to the ability of a nucleic acid molecule comprising the first nucleotide sequence to hybridize to a nucleic acid molecule comprising the second nucleotide sequence and form a double stranded region (through base pair hydrogen bonds) under suitable *in vivo* or *vitro* conditions (e.g., under certain standard conditions, under mammalian (e.g., human) physiological conditions). A person of ordinary skill in the art would be able to select the set of conditions most appropriate for a hybridization test. Complementary sequences include, e.g., Watson-Crick base pairs. For example, complementary nucleobase pairs include adenine (A) and thymine (T); adenine (A) and uracil (U); and cytosine (C) and guanine (G). Complementary nucleobase pairs include natural and modified nucleotides, and nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. As such, determinations of complementarity (as described herein) are independent of nucleotide chemical modifications (e.g., as described herein). For example, (C) and 5-methyl cytosine (mC) are both complementary to (G).

[0140] As used herein, the term “conjugation” refers to chemical conjugation of an agent (e.g., a nucleic acid molecule) with a moiety (e.g., carbohydrate, small molecule, polypeptide, polynucleotide, lipid, synthetic polymer (e.g., polymers of polyethylene glycol (PEG)), etc.). The moiety can be directly connected to the agent (e.g., nucleic acid molecule) or indirectly connected through a linker, e.g., as described herein. Chemical conjugation methods are well known in the art, as are commercially available conjugation reagents and kits, with detailed instructions for their use readily available from the commercial suppliers.

[0141] As used herein, the term “differing by no more than X nucleotides” in reference to a nucleotide sequence means that the nucleotide sequence comprises no more than X (wherein X is a specified number (e.g., 3, 2, 1, 0)) nucleotide variations relative to a reference sequence. For example, the phrase “wherein the nucleotide sequence of the antisense strand differs by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: X” means that the nucleotide sequence comprises no more than 3 nucleotide variations relative to the nucleotide sequence set forth in the cited SEQ ID NO: X.

[0142] As used herein, the term “disease” refers to any abnormal condition that impairs physiological function. The term is used broadly to encompass any disorder, illness, abnormality, pathology, sickness, condition, or syndrome in which physiological function is impaired, irrespective of the nature of the etiology. The term disease includes infection (e.g., a viral, bacterial, fungal, protozoal infection). The term disease includes other conditions caused by an infection.

[0143] As used herein, the term “double stranded RNA agent” or “dsRNA agent” refers to a complex of two RNA molecules comprising a double stranded region comprising two anti-parallel and at least partially (e.g., substantially, fully) complementary nucleic acid sequences that form the double stranded region. For example, in some embodiments, the dsRNA agent comprises a sense strand and an antisense strand.

[0144] The terms “DNA” and “polydeoxyribonucleotide” are used interchangeably herein and refer to macromolecules that include multiple deoxyribonucleotides that are polymerized via phosphodiester bonds. Deoxyribonucleotides are nucleotides in which the sugar is deoxyribose.

[0145] As used herein, the term “fully complementary” means that in a hybridized pair of a first nucleic acid molecule and a second nucleic acid molecule, 100% (all), of the bases in a contiguous sequence of the first nucleic acid molecule will hybridize with the same number of bases in a contiguous sequence of the second nucleic acid molecule. The contiguous sequence may comprise all or a part of the first and/or second nucleic acid molecule.

[0146] As used herein, the term “heterologous,” when used to describe a first element in reference to a second element means that the first element and second element do not exist in nature disposed as described. For example, a nucleic acid molecule comprising a “heterologous moiety” means a nucleic acid molecule that is joined to a moiety (e.g., carbohydrate, small molecule, polypeptide, polynucleotide, lipid, synthetic polymer (e.g., polymers of PEG), etc.) that is not joined to the nucleic acid molecule in nature.

[0147] As used herein, the term “isolated” with reference to a polypeptide, protein, or polynucleotide refers to a polypeptide, protein, or polynucleotide that is substantially free of other cellular components with which it is associated in the natural state.

[0148] As used herein, the term “nucleotide variation,” “variant nucleotide,” or use of the term “variation” and the like in reference to a nucleotide or nucleic acid sequence refers to a nucleic acid molecule that comprises at least one substitution, addition, deletion, or inversion of one or more nucleotide compared to a reference nucleic acid molecule. As used herein, the term “variant” or “variation” with reference to a peptide or protein refers to a peptide or protein that comprises at least one substitution, addition, deletion, or inversion of an amino acid residue compared to a reference peptide or protein.

[0149] As used herein, the term “modified agent” refers to any agent (or any component thereof (e.g., any nucleic acid molecule thereof)) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) that comprises one or more modified nucleotide (as defined herein).

[0150] As used herein, the term “modified nucleotide,” “nucleotide modification,” or use of the term “modification” and the like in reference to a nucleotide or nucleic acid sequence refers to a nucleotide comprising a chemical

modification, e.g., a modified sugar moiety, a modified nucleobase, and/or a modified internucleoside linkage, or any combination thereof. Exemplary modifications are provided herein, see, e.g., §§ 4.3, 4.3.1. In certain embodiments of the instant disclosure, inclusion of a deoxynucleotide—which is acknowledged as a naturally occurring form of nucleotide—if present within an RNAi agent or component thereof (e.g., described herein, e.g., a sense strand, an antisense strand, a dsRNA agent) is considered to constitute a modified nucleotide.

[0151] As used herein, the term “moiety” is used generically to describe any macro or micro molecule that can be operably connected to a protein described herein. Exemplary moieties include, but are not limited small molecules, polypeptides, polynucleotides (e.g., DNA, RNA), carbohydrates, lipids, synthetic polymers (e.g., polymers of PEG).

[0152] As used herein, the term “nucleotide overhang” refers to at least one unpaired nucleotide that extends from the double stranded region of a nucleic acid molecule (e.g., a dsRNA molecule (e.g., a dsRNA molecule described herein)). For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang.

[0153] As used herein, the term, “non-complementary nucleotide mismatch” refers to a nucleotide within a region of complementarity (as described herein) that is not complementary to the corresponding nucleotide in the target nucleic acid molecule.

[0154] As used herein, the term “operably connected” refers to the linkage of two moieties in a functional relationship. For example, a polypeptide is operably connected to another polypeptide when they are linked (either directly or indirectly via a peptide linker) in frame such that both polypeptides are functional (e.g., a fusion protein described herein). Or for example, a transcription regulatory polynucleotide e.g., a promoter, enhancer, or other expression control element is operably linked to a polynucleotide that encodes a protein if it affects the transcription of the polynucleotide that encodes the protein. The term “operably connected” can also refer to the conjugation of a moiety to e.g., a polynucleotide or polypeptide (e.g., the conjugation of a PEG polymer to a protein).

[0155] As used herein, “partially complementary” means that in a hybridized pair of a first nucleic acid molecule and a second nucleic acid molecule, at least 70%, but not all, of the bases in a contiguous sequence of the first nucleic acid molecule will hybridize with the same number of bases in a contiguous sequence of the second nucleic acid molecule. The contiguous sequence may comprise all or a part of a first or second nucleic acid molecule.

[0156] The determination of “percent identity” between two sequences (e.g., protein (amino acid sequences) or polynucleotide (nucleic acid sequences)) can be accomplished using a mathematical algorithm. Determinations of identity (as described herein) are independent of nucleotide chemical modifications (e.g., as described herein). For example, (mC) is identical to (C) for the purposes of determining identity. A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87:2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90:5873-5877, each of which is herein incorporated by reference in its entirety. Such an algorithm is incorporated into the NBLAST and XBLAST programs of

Altschul S F et al., (1990) J Mol Biol 215:403, which is herein incorporated by reference in its entirety. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, e.g., for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecule described herein. BLAST protein searches can be performed with the XBLAST program parameters set, e.g., to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul S F et al., (1997) Nuc Acids Res 25:3389-3402, which is herein incorporated by reference in its entirety. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (e.g., of XBLAST and NBLAST) can be used (see, e.g., National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another specific, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17, which is herein incorporated by reference in its entirety. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[0157] As used herein, the term “pharmaceutical composition” means a composition that is suitable for administration to an animal, e.g., a human subject, and comprises a therapeutic agent and a pharmaceutically acceptable carrier or diluent. A “pharmaceutically acceptable carrier or diluent” means a substance intended for use in contact with the tissues of human beings and/or non-human animals, and without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable therapeutic benefit/risk ratio.

[0158] The terms “nucleic acid molecule” and “polynucleotide” are used interchangeably herein and refer to a polymer of DNA or RNA. The nucleic acid molecule can be single-stranded or double-stranded; contain natural, non-natural, or altered nucleotides; and contain a natural, non-natural, or altered internucleoside linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified nucleic acid molecule. Nucleic acid molecules include, but are not limited to, all nucleic acid molecules which are obtained by any means available in the art, including, without limitation, recombinant means, e.g., the cloning of nucleic acid molecules from a recombinant library or a cell genome, using ordinary cloning technology and polymerase chain reaction, and the like, and by synthetic means. The skilled artisan will appreciate that, except where otherwise noted, nucleic acid sequences set forth in the instant application will recite thymidine (T) in a representative DNA sequence but where the sequence represents RNA (e.g., mRNA), the thymidines (Ts) would be substituted for uracils (Us). Thus, any of the RNA polynucleotides

encoded by a DNA identified by a particular sequence identification number may also comprise the corresponding RNA (e.g., mRNA) sequence encoded by the DNA, where each thymidine (T) of the DNA sequence is substituted with uracil (U).

[0159] As used herein, the term “plurality” means 2 or more (e.g., 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 9 or more, or 10 or more).

[0160] As used herein, the terms “protein” and “polypeptide” refers to a polymer of at least 2 (e.g., at least 5) amino acids linked by a peptide bond. The term “polypeptide” does not denote a specific length of the polymer chain of amino acids. It is common in the art to refer to shorter polymers of amino acids (e.g., approximately 2-50 amino acids) as peptides; and to refer to longer polymers of amino acids (e.g., approximately over 50 amino acids) as polypeptides. However, the terms “peptide” and “polypeptide” and “protein” are used interchangeably herein. In some embodiments, the protein is folded into its three-dimensional structure. Where proteins are contemplated herein, it should be understood that proteins folded into their three-dimensional structure are also provided herein.

[0161] As used herein, the term “region of complementarity” refers to a portion of a first nucleic acid molecule comprising a nucleotide sequence that is at least partially complementary to the nucleotide sequence of at least a portion of a second nucleic acid molecule.

[0162] The terms “RNA” and “polyribonucleotide” are used interchangeably herein and refer to macromolecules that include multiple ribonucleotides that are polymerized via phosphodiester bonds. Ribonucleotides are nucleotides in which the sugar is ribose. RNA may contain modified nucleotides; and contain natural, non-natural, or altered internucleoside linkages, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified nucleic acid molecule.

[0163] As used herein, the term “RNAi agent” refers to an agent that contains one or more RNA molecules which can mediate the targeted cleavage of an RNA molecule (e.g., an mRNA molecule) via an RNA-induced silencing complex (RISC) pathway. The RNAi agent, is thereby capable of e.g., modulating, e.g., inhibiting, the expression of a target gene (e.g., CIDEB) in a cell, e.g., a cell within a subject, such as a mammalian subject. In some embodiments, the RNAi agent is a dsRNA agent comprising a sense strand and an antisense strand that form a double stranded region, wherein optionally the sense strand and the antisense strand each independently comprise or consist of from about 19-23 nucleotides.

[0164] As used herein, the term “sense strand” refers to an RNA molecule (e.g., part of an RNAi agent (e.g., described herein), part of a dsRNA agent (e.g., described herein)) that comprises a region that is at least partially (e.g., substantially, fully) complementary to a region of the antisense strand (as defined herein). The sense strand is often referred to as such with reference to the orientation of the sequence of the sense strand being the same with respect to a target RNA (e.g., mRNA sequence).

[0165] As used herein, the term “subject” includes any animal, such as a human or other animal. In some embodiments, the subject is a vertebrate animal (e.g., mammal, bird, fish, reptile, or amphibian). In some embodiments, the subject is a human. In some embodiments, the method

subject is a non-human mammal. In some embodiments, the subject is a non-human mammal such as a non-human primate (e.g., monkeys, apes), ungulate (e.g., cattle, buffalo, sheep, goat, pig, camel, llama, alpaca, deer, horses, donkeys), carnivore (e.g., dog, cat), rodent (e.g., rat, mouse), or lagomorph (e.g., rabbit). In some embodiments, the subject is a bird, such as a member of the avian taxa Galliformes (e.g., chickens, turkeys, pheasants, quail), Anseriformes (e.g., ducks, geese), Palcaognathac (e.g., ostriches, emus), Columbiformes (e.g., pigeons, doves), or Psittaciformes (e.g., parrots).

[0166] As used herein, “substantially complementary” means that in a hybridized pair of a first nucleic acid molecule and a second nucleic acid molecule, at least 85%, but not all, of the bases in a contiguous sequence of the first nucleic acid molecule will hybridize with the same number of bases in a contiguous sequence of the second nucleic acid molecule. The contiguous sequence may comprise all or a part of a first or second nucleic acid molecule.

[0167] In some embodiments, the term “substantially all” means at least 95%, 96%, 97%, 98% or 99%, e.g., of the subject of said sentence. The term “substantially all” preferably excludes 100%. For example, in some embodiments, the term “substantially all of the nucleotides in the sense strand and/or antisense strand are modified” means that at least 95%, 96%, 97%, 98% or 99% of said nucleotides are modified. For example, in some embodiments, the term “substantially all of the nucleotides of the agent are modified” means that at least 95%, 96%, 97%, 98% or 99% of said nucleotides are modified. For example, in some embodiments, the term “substantially all of the nucleotides of the agent are unmodified” means that at least 95%, 96%, 97%, 98% or 99% of said nucleotides are unmodified. For example, in some embodiments the term “wherein the dsRNA agent is in the sodium salt form, sodium ions are present in the composition comprising the dsRNA agent as counterions for substantially all of the phosphodiester or phosphorothioate groups present in the dsRNA agent” means that wherein the dsRNA agent is in the sodium salt form, sodium ions are present in the composition comprising the dsRNA agent as counterions for at least 95%, 96%, 97%, 98% or 99% of the phosphodiester or phosphorothioate groups present in the dsRNA agent.

[0168] As used herein, the term “target nucleic acid sequence” refers to a contiguous portion of the nucleotide sequence of a nucleic acid sequence (e.g., an mRNA molecule formed during the transcription of a target gene (e.g., CIDEB)). In some embodiments, the target nucleic acid sequence is an mRNA molecule formed during the transcription of a target gene (e.g., CIDEB)). In some embodiments, the target nucleic acid molecule comprises an mRNA that is a product of RNA processing of a primary transcription product. The target portion of the sequence (e.g., mRNA) will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during

the transcription of a CIDEB gene. In one embodiment, the target sequence is within the protein coding region of CIDEB.

[0169] As used herein, the term “therapeutically effective amount” of a therapeutic agent refers to any amount of the therapeutic agent that, when used alone or in combination with another therapeutic agent, improves a disease condition, e.g., protects a subject against the onset of a disease (or infection); improves a symptom of disease or infection, e.g., decreases severity of disease or infection symptoms, decreases frequency or duration of disease or infection symptoms, increases disease or infection symptom-free periods; prevents or reduces impairment or disability due to the disease or infection; or promotes disease (or infection) regression. The ability of a therapeutic agent to improve a disease condition can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in in vitro assays.

[0170] As used herein, the terms “treat,” “treating,” “treatment,” and the like refer to reducing or ameliorating a disease and/or symptom(s) associated therewith or obtaining a desired pharmacologic and/or physiologic effect. It will be appreciated that, although not precluded, treating a disease does not require that the disease, or symptom(s) associated therewith be completely eliminated. In some embodiments, the effect is therapeutic, i.e., without limitation, the effect partially or completely reduces, diminishes, abrogates, abates, alleviates, decreases the intensity of, or cures a disease and/or adverse symptom attributable to the disease. In some embodiments, the effect is preventative, i.e., the effect protects or prevents an occurrence or reoccurrence of a disease. To this end, the presently disclosed methods comprise administering a therapeutically effective amount of a compositions as described herein.

4.2 RNAi Agents

[0171] Provided herein are, inter alia, agents (e.g., RNAi agents, dsRNA agents), useful in, inter alia, inhibiting expression of cell death inducing DFFA like effector B (CIDEB) (e.g., human CIDEB (hCIDEB)) (e.g., within a cell, e.g., within a cell in a subject, e.g., a mammalian subject, e.g., a human subject) (e.g., through the degradation of CIDEB (e.g., hCIDEB) mRNA).

[0172] CIDEB is a lipid droplet-associated protein primarily expressed in the liver and functions, e.g., to promote unilobular lipid droplet formation by mediating lipid droplet fusion. The mRNA sequence of a reference hCIDEB gene is set forth in SEQ ID NO: 1 (NCBI Ref.: NM_014430.4). The reverse complement sequence of the hCIDEB mRNA is set forth in SEQ ID NO: 2. The amino acid sequence of a reference hCIDEB protein is set forth in SEQ ID NO: 3 (NCBI Ref.: NP_055245). See Table 1, herein.

TABLE 1

<u>The mRNA and Amino Acid Sequence of a Reference hCIDEb Protein.</u>		SEQ ID NO
Description	Amino Acid Sequence	SEQ ID NO
hCIDEb mRNA	CCCUUCCGGUUGGAGCCAGCCUGCGACGCCCUCCAGAGCAAGGUUGACUGC	1
NCBI Ref.: NM_014430.4	GUGGUAGGGGGCCACAGCAAGCGAAGCAAGCACGAUGGGGCUCAC	
	CAGCCGGCCACCCCGCGCCCCGUGCCGCCCCGAGCCCCAGCGGGCGCC	
	CCGGACGGCAGGGUGCCAGCGCAGCUGGUAGCAGCGGAGCAUCAGCCCAGAA	
	AGGAAGACACGAAAGCGGUAGAGUCUCCAGGCUCAGGUGGGCGGGCGGC	
	GUGGACCGGCAGCGGUAGCCAGCUGGGCAUAGCGGUUCCUCCACAG	
	GUGGGGUAGACGGCGCCGGGACGGCGAGCAACAGGGGCCAGCCA	
	GACCGCCAGCAGCAGCAGGGCGGGGGCAGGGCCGGCUCGCAGCCGAGG	
	CGCCAGGAAGGGCGGGGUAGCUCGAGGGCAGCGCUCGGCUGAGCAG	
	GCCCGUGAGCAGCACGCUCCGUACAUUGCUGAGCGCCACACGUAGUA	
	CACCGCCUUGCAGCCGCCUUGGCCAGCGGCCAGGGCUCGCGGUAG	
	GAAGGCCACAAGAGCGCGUGAGCGAGCACCGGCCCGUGCGCAG	
	CGCCAGGGUGCAGCACAGCAGGGCGCCAGCGGUAGGCCAGCGAGG	
	CCGCAGCCGCCAACGUCCACACCAGCAAGCGGUUGGCCAGGCAGCCC	
	CAGCAGCGCCGCAGCAGCAGGAAGGCUGUGCCUGGGCCCGCGAAGU	
	CUUCCAGCUCAGCAGGUUCGUUCCUGGGGACGUAGCAGACCGA	
	CAUCCUUCUGGUCCUACAGGACACAGAAAAAGUGGGGAAGCUGGGG	
	GACCCUACAAGGAUCCUUGCGAGGAAAGCAGGGAUUGGUUCAUUUGA	
	GGGUUUUACUGUCAGUGAGAGUCUAGCUCUCCAUAGCUCGUCAUCA	
	CGGUGCAACUAGAAAUCAGAGCUGGGGACACAGGGCACAGAAGCUAAA	
	GUCUGAUGGCAUCAAAAGGCAUCCUUGGCCCAAUUCAACUUCUGUCA	
	CGUCCACUUAUCGCCAAAAGGAGAAAAGUGAGAGAAGAUGACCUAAGU	
	GUGACUGCAGCAGCAGGUCCUGGAAAAGAAGCAGAGCAGUGAGCCA	
	GCCCCUCCUCCGACCAAGGAGGAAGGGAGAGCAGCCCCAGCACAGGA	
	GAGAACCACCCAGCCAGAAGGUUCCAGGGAAAGGAACUCUCCGUCCAC	
	CAUGGAGUACCUUCUCAGCUCUGAACCCCAGUGACUUACUAGGUACAGU	
	AUCUAAUAUAAGCUCGGAGUUGUGACGGAGGGCUGGUACAGCUCC	
	ACCACCCCCAGCGACCUUUCGUGUCUGUACACAAGCGGACCAUCG	
	GAAAGGCCUGACAGCUGCCACCCGCCAGAGCUGGUACGCAAAAGCAUU	
	GGAGACCCUACUGCUGAAUGGAGUGGUACUACCCUUGGUAGAGGAGGA	
	UGGAACUGCAGUGACAGUGAGGACUUCUUCUCCAGCUGCUGGAGGAUGA	
	CACGUGCCUGAUGGGUUGUAGCUGUCCUGGUACAGCUGGUAGGCCUACAAG	
	GAGUGGAGUGCUGUCAUAUGGCCUGGGACGGGAGAGGCCAAGCAG	
	CAAGGACAUUCGGCAUUCGUCAAGGUACAUUCCACGGGUCCUACAG	
	AGACCUUCUUGGCAUGUCAAGGUACAUUCCACGGGUCCUACAG	
	CUCUAGAGUUGUGACUUUCAAGGACUUGGCCAAAGAAAGUACUCAG	
	GGAGACCCUACUGCUGAAUGGAGUGGUACUACCCUUGGUAGAGGAGGA	
	GUUGCUGGGAAUUUCUCCACCCUUCGUCAUCCAGUUGGGGGCUGA	
	GCAGUGGAGCAGAAGGGCGCCUCCAUUCUACUAAGGGGUCCUAG	
	CUUCUGCCCCAGAAUCAUCCACCGGUCCACUGCAAAGACUAGAC	
	AGCAUCAAAUUCAGGACUUCUGUACAGGUACAGGUACAGGUAAACCCACC	
	CAAUUCCCCACUGGUCCUUGACUGACAGGUACAGGUACAGGUACUUCAGCA	
	UAACGCCUACAUCCAAGGUACUAAACCCUACCUUGAAGAAUGCUGUUC	
	UUUCCUAGCCACUUUCUGGCCUCCACUUGGCCUGAAAGGCCAAGAU	
	CAAGAUGUCCCCCAGGCAUCUUGAUCCAGCCUGACUGCUGUACAU	
	UAUUCCCCUACCAAGGUCCUCCUGUCCUAAACUCCCCAGCAUACUGAU	
	GACAGCCCCUACUGUACUUUACCUUGAGACUGCUUCAUACCCUCC	
	CUAAACUAACAAAAACAUUCCAAUAAAAAUCAAAAUUUACCAC	
	UAA	
Reverse Complement of hCIDEb mRNA	UUAGUGGUAAAUAUUGUAUUUUUUAUUGGAAUUGUUUUUGUAGUU GAGGGGAAGGGUAUGAAGACAGAUCUCAAGGUAAAGUCAGAGAGGGCU GUCAUCAGUACAGCAGUACGGCUGGGGAUAGCAAGUGGUAGGGGA UUAGAUGUAGCAGCAGUACGGCUGGGGAUAGGUAGGGGA AAAGAACAGCAUUCUUCAGGUAGGGGUAAAGACUUGGGAUUGUGAGCG UUAGCUGAAAGGUUCUGUACAGGGGGAUACAGAGGAAGUGGGAAA UUGGUGGGGUUAUCUAGCCUGUACUGUCCUGGUAGGGGGAAA GCUGUCAUAGCUUUGCAGUGGGUCCUGGUAGGAUAGAUUUCUGGGGAG AAGCUCAGAGCCCCUUAUGAGGAUUGGGGGCCUUCUUCUGCUGCCAC UGCUCAGCCCCUCCACUGUACAGCAGGGGGGGGGAAA AACAUAAUGGCCAGGGCCUUCAGGUACAGGGGGGUCCAAACGAAGGAGC UCCCGUGAGUACUUUCUUCUGGCCAGGUACUUGGUAGGUACAGGAGC GAGUAGAGCCGUAGAAUGGGGUUUGACAUUCAGGUCCAGCAAAGAGG UCUCGAGGGUUUUCGUUACACGUCAAGGUAAUCGGGGGAUUC UUGCUGUGCUUUGGGCCUUCUCCCGUCCAGGGCAUUAUGACAGCACU CUCCUUGUAGGGGUCCACGUCCAGGUAGGUACUCCACACCAUCAGGC GUGUCAUCCUCCAGCAGGUAGGUAGGUACUCCACAGGUACUGGU CCAUCUCCUCCACGUACAGGGGUUAGCACUUCAGCAGUAGGGUC UCCCAUAGGUUGGUAGCAGGUCCUCCUGGGGGGUCCAGCUGU UUCGGGAUGGUCCGUUGUGAUACAGACAGCGAAAGGUCCUGGGGU GGUGGGCUGAGGUCCAGACCCUCCGUCCAAACUCCGAGGUCAUUAUUA	2

TABLE 1-continued

The mRNA and Amino Acid Sequence of a Reference hCIDEB Protein.		SEQ ID NO
Description	Amino Acid Sequence	
	GAAUCUGACCUGAGUAAGUCAUGGGGUUCAGAGCUGAGAGGUACUCC AUGGGGACCGGAGAGUUCCUUCCUGGAACUUCCUGGGCUGGGGGUU CUCUCCUGUGCUGGGGCUGCUUUCCUUCUCCUCCUUGGUCCGGAGGAGG GGCUGGCUCACUGCCUCAUUUUCCAGAGCUGCCUGCCAGU CACACUAGGUCAUCUUCUUCUACACUUUUCCUCCUUUUGCCGAUAGU ACGUGACAGAGAUGUGAUGGGCAGGGGAUGGUCCCCUAGGCCAUCAA GACUUUAGCUUCUGGUGCGCUGGUCCAGCUCUGAUUUCAGUUGCAG CCGUGAUGGACAGUUGCAUGGGAAGCUGAGACUCUACUGACAGUGAAA CCCUCAAAUGAACACAACAUCCUGCUUUCCUGCCAAGGAUCUUGUAGG GUCCCCCACGUUCCCCACUUUUUCCUGUGUCCUGUAGGCCAGAAGG AUGUCGGCUGCUACCGUCCCCCAGGGAACGAGACACUGCUGAGCUGG AAGACUUUCGGGGCCACAGGCACAGCCUUCUGCUGCUGGGCGCUG CUGGGCUGCCUGGCAACGGCUUCUGGUUGGGAGCUUUGGGGGCUGG CGGCUGCUGCACGGGGCGACCGCUGGCCACGCCUUGUGCUGCCACCG GCGCUGGCCGACGGCGGGCUGCUGCUCACGCCGCUUUGUGGCC UUCCUGACCCCGAGGCCUGGGCAGGGCCACGGGGCUGCAAGGGG GUGUACUACGUGUGCGCUCAGCAUGUACGCCAGCGUGCUGCUCACCC GGCCUGCUAGCCUGCAGGCCUGCUCCUGCAGUACCCGCCUUCCUG GCGCCUCGGCUGCGCAGCCGGCCUUGGCCCGCCUGCUGCUGCG GUCUGGUUGCCGGCCUGUUGCUCGCCGUCCCGGCCGCUACCCG CACCUUGGGAGGGACCGCGCUAUGCUGCCACCGCUUGCCGG CACGCCGCCACCUGAGCCUGGAGACUCUGACCCGUUUCGUGCUU CCUUUCGGGUAGUCUGGUUGCCUGCUACAGCGUGACGUGGCCACGG CGGGGCGCCCGCUGGGGUCCCGGGCUGCCGACGGGGCGCGGGGGCG CUGGUAGGCGCCAUCUGGUUGCCUUGCUCUGGGCCCCUAC CACGCAUCUACCUUCUGCAGGGGUUGCGCAGCGCUGGUCCACCG GGG	
hCIDE _B Protein	MEYLSALNPSDLRSVSNISSFGRRVWTSAPPQPQRPFVRCDHKRTIR	3
NCBI Ref.:	KGLTAATRQELLAKELETLLNGVLTLVLEEDTAVDSEDFPQLLEDD	
NP_055245	TCLMVLQSGQSWSPTRSGVLSTYGLGRERPKHSKDIARFTFDVYKQNPR DLFGSLNVKATFYGLYSMSCDFQGLGPKVILRELLRWSTTLLQGLGHM LLGISSTLRHAVEGAEQWQQKGRLHSY	

[0173] In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises one or more RNA molecule. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises an antisense strand. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises a sense strand. In some embodiments, the agent comprises one or more single stranded RNA (ssRNA) molecules. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises a dsRNA agent.

[0174] In some embodiments, the agent (e.g., RNAi agent) comprises a dsRNA agent comprising a sense strand and an antisense strand. In some embodiments, the agent (e.g., RNAi agent) comprises a dsRNA agent comprising a sense strand and an antisense strand that form a double stranded region. In some embodiments, the agent (e.g., RNAi agent) comprises a dsRNA agent comprising a sense strand and an antisense strand that hybridize to form a double stranded region. In some embodiments, the sense strand and the antisense strand are part of a single nucleic acid molecule (e.g., a single nucleic acid molecule comprising a hairpin loop). In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules.

4.2.1 Antisense Strand

4.2.1.1 Targeting Region

[0175] As described above, antisense strands (e.g., described herein) comprise a region of complementarity that comprises a nucleotide sequence that is at least partially

(e.g., substantially, fully) complementary to the nucleotide sequence of a target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity is at least substantially complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity is fully complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)).

[0176] In some embodiments, the nucleotide sequence of the region of complementarity is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). For example, the nucleotide sequence of the region of complementarity may be at least 70% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). The nucleotide sequence of the region of complementarity may be at least 75% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). The nucleotide sequence of the region of complementarity may be at least 80% complementary to the

nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). The nucleotide sequence of the region of complementarity may be at least 85% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA)), a portion of a target mRNA (e.g., a CIDEB mRNA)). The nucleotide sequence of the region of complementarity may be at least 90% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). The nucleotide sequence of the region of complementarity may be at least 95% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity is at least 95%, 96%, 97%, 98%, 99%, or 100% (e.g., in some embodiments, preferably at least 95%, more preferably at least 98%) complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity is 100% complementary to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)).

[0177] In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of one or more non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)). In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 5 (e.g., 4, 3, 2, 1, or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 3 (e.g., 2, 1, or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 2 (e.g., 1 or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 1 (e.g., 0) non-complementary nucleotide mismatch relative to the nucleotide sequence of the target nucleic acid molecule. In some embodiments, the nucleotide sequence of the region of complementarity comprises 0 non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule. In some embodiments, the region of complementarity comprises one or more (e.g., 2, 3, or more) non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule, wherein the one or more non-complementary

nucleotide mismatches are within the last 5 (e.g., 4, 3, 2, or 1) nucleotides from either the 5'- and/or 3'-end of the region of complementarity. In some embodiments, the region of complementarity comprises at least one but not more than 3 non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule, wherein the one or more non-complementary nucleotide mismatches are within the last 5 (e.g., 4, 3, 2, or 1) nucleotides from either the 5'- and/or 3'-end of the region of complementarity. In some embodiments, the region of complementarity comprises one or more (e.g., 2, 3, or more) non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule, wherein the one or more non-complementary nucleotide mismatches are within the last 3 (e.g., 2 or 1) nucleotides from either the 5'- and/or 3'-end of the region of complementarity. In some embodiments, the region of complementarity comprises at least one but not more than 3 non-complementary nucleotide mismatches relative to the nucleotide sequence of the target nucleic acid molecule, wherein the one or more non-complementary nucleotide mismatches are within the last 3 (e.g., 2 or 1) nucleotides from either the 5'- and/or 3'-end of the region of complementarity. Methods known in the art and described herein can be utilized to evaluate the effect of any non-complementary mismatches between an antisense strand and a target nucleic acid molecule on functional properties (e.g., inhibition of expression of the target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA))).

[0178] In some embodiments, the region of complementarity comprises or consists of from about 15-30 nucleotides, e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides. In some embodiments, the region of complementarity comprises from about 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 nucleotides. In some embodiments, the region of complementarity comprises from about 19-21 (e.g., 19-20) nucleotides. In some embodiments, the region of complementarity comprises or consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 19, 20, 21, 22, or 23 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 19 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 20 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 21 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 22 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 23 nucleotides. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

[0179] In some embodiments, the target nucleic acid molecule is part (e.g., a contiguous portion) of a larger nucleic

acid molecule. For example, in some embodiments, the target nucleic acid molecule is a portion (e.g., a contiguous portion) of a target mRNA (e.g., a CIDEB mRNA). In some embodiments, the target nucleic acid molecule is a contiguous nucleotide sequence of a target mRNA (e.g., a CIDEB mRNA) of sufficient length to allow it to be a substrate for cleavage directed by an RNAi agent (e.g., an RNAi agent described herein, e.g., a dsRNA agent (e.g., described herein)) (i.e., cleavage through a RISC pathway).

[0180] In some embodiments, the target nucleic acid molecule is a target mRNA (e.g., a CIDEB mRNA). In some embodiments, the target nucleic acid molecule is at least a portion (e.g., a portion) of a target mRNA (e.g., a CIDEB mRNA). In some embodiments, the target nucleic acid molecule is at least a portion (e.g., a portion) of an mRNA (e.g., a CIDEB mRNA) formed in the expression of a target gene (e.g., a mammalian, primate, human, non-human primate, mouse, and/or rat gene) (e.g., a CIDEB gene). In some embodiments, the target nucleic acid molecule is at least a portion (e.g., a portion) of a CIDEB (e.g., hCIDEB) mRNA. In some embodiments, the target nucleic acid molecule is at least a portion (e.g., a portion) of an mRNA formed in the expression of a CIDEB (e.g., hCIDEB) gene. In some embodiments, the target nucleic acid molecule comprises at least a portion (e.g., a portion) of the nucleotide sequence set forth in SEQ ID NO: 1 (or a variant or fragment thereof). In some embodiments, the target nucleic acid molecule comprises at least a portion (e.g., a portion) of an mRNA encoding a target protein. In some embodiments, the target nucleic acid molecule comprises at least a portion (e.g., a portion) of an mRNA encoding a CIDEB (e.g., hCIDEB) protein. In some embodiments, the target nucleic acid molecule comprises at least a portion (e.g., a portion) of an mRNA sequence encoding a protein comprising the amino acid sequence set forth in SEQ ID NO: 3 (or a variant or fragment thereof).

[0181] In some embodiments, the target nucleic acid molecule comprises or consists of from about 19-30 nucleotides, e.g., 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, 23-24, 23-23, 23-22, 23-21, 23-20, 23-19, 23-18, 23-17, 23-16, 23-15, 23-14, 23-13, 23-12, 23-11, 23-10, 23-9, 23-8, 23-7, 23-6, 23-5, 23-4, 23-3, 23-2, 23-1, 23-0, 22-31, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 22-22, 22-21, 22-20, 22-19, 22-18, 22-17, 22-16, 22-15, 22-14, 22-13, 22-12, 22-11, 22-10, 22-9, 22-8, 22-7, 22-6, 22-5, 22-4, 22-3, 22-2, 22-1, 22-0, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 21-21, 21-20, 21-19, 21-18, 21-17, 21-16, 21-15, 21-14, 21-13, 21-12, 21-11, 21-10, 21-9, 21-8, 21-7, 21-6, 21-5, 21-4, 21-3, 21-2, 21-1, 21-0, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 20-20, 20-19, 20-18, 20-17, 20-16, 20-15, 20-14, 20-13, 20-12, 20-11, 20-10, 20-9, 20-8, 20-7, 20-6, 20-5, 20-4, 20-3, 20-2, 20-1, 20-0, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 19-19, 19-18, 19-17, 19-16, 19-15, 19-14, 19-13, 19-12, 19-11, 19-10, 19-9, 19-8, 19-7, 19-6, 19-5, 19-4, 19-3, 19-2, 19-1, 19-0, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 18-19, 18-18, 18-17, 18-16, 18-15, 18-14, 18-13, 18-12, 18-11, 18-10, 18-9, 18-8, 18-7, 18-6, 18-5, 18-4, 18-3, 18-2, 18-1, 18-0, 17-30, 17-29, 17-28, 17-27, 17-26, 17-25, 17-24, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 17-17, 17-16, 17-15, 17-14, 17-13, 17-12, 17-11, 17-10, 17-9, 17-8, 17-7, 17-6, 17-5, 17-4, 17-3, 17-2, 17-1, 17-0, 16-30, 16-29, 16-28, 16-27, 16-26, 16-25, 16-24, 16-23, 16-22, 16-21, 16-20, 16-19, 16-18, 16-17, 16-16, 16-15, 16-14, 16-13, 16-12, 16-11, 16-10, 16-9, 16-8, 16-7, 16-6, 16-5, 16-4, 16-3, 16-2, 16-1, 16-0, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 15-15, 15-14, 15-13, 15-12, 15-11, 15-10, 15-9, 15-8, 15-7, 15-6, 15-5, 15-4, 15-3, 15-2, 15-1, 15-0, 14-30, 14-29, 14-28, 14-27, 14-26, 14-25, 14-24, 14-23, 14-22, 14-21, 14-20, 14-19, 14-18, 14-17, 14-16, 14-15, 14-14, 14-13, 14-12, 14-11, 14-10, 14-9, 14-8, 14-7, 14-6, 14-5, 14-4, 14-3, 14-2, 14-1, 14-0, 13-30, 13-29, 13-28, 13-27, 13-26, 13-25, 13-24, 13-23, 13-22, 13-21, 13-20, 13-19, 13-18, 13-17, 13-16, 13-15, 13-14, 13-13, 13-12, 13-11, 13-10, 13-9, 13-8, 13-7, 13-6, 13-5, 13-4, 13-3, 13-2, 13-1, 13-0, 12-30, 12-29, 12-28, 12-27, 12-26, 12-25, 12-24, 12-23, 12-22, 12-21, 12-20, 12-19, 12-18, 12-17, 12-16, 12-15, 12-14, 12-13, 12-12, 12-11, 12-10, 12-9, 12-8, 12-7, 12-6, 12-5, 12-4, 12-3, 12-2, 12-1, 12-0, 11-30, 11-29, 11-28, 11-27, 11-26, 11-25, 11-24, 11-23, 11-22, 11-21, 11-20, 11-19, 11-18, 11-17, 11-16, 11-15, 11-14, 11-13, 11-12, 11-11, 11-10, 11-9, 11-8, 11-7, 11-6, 11-5, 11-4, 11-3, 11-2, 11-1, 11-0, 10-30, 10-29, 10-28, 10-27, 10-26, 10-25, 10-24, 10-23, 10-22, 10-21, 10-20, 10-19, 10-18, 10-17, 10-16, 10-15, 10-14, 10-13, 10-12, 10-11, 10-10, 10-9, 10-8, 10-7, 10-6, 10-5, 10-4, 10-3, 10-2, 10-1, 10-0, 9-30, 9-29, 9-28, 9-27, 9-26, 9-25, 9-24, 9-23, 9-22, 9-21, 9-20, 9-19, 9-18, 9-17, 9-16, 9-15, 9-14, 9-13, 9-12, 9-11, 9-10, 9-9, 9-8, 9-7, 9-6, 9-5, 9-4, 9-3, 9-2, 9-1, 9-0, 8-30, 8-29, 8-28, 8-27, 8-26, 8-25, 8-24, 8-23, 8-22, 8-21, 8-20, 8-19, 8-18, 8-17, 8-16, 8-15, 8-14, 8-13, 8-12, 8-11, 8-10, 8-9, 8-8, 8-7, 8-6, 8-5, 8-4, 8-3, 8-2, 8-1, 8-0, 7-30, 7-29, 7-28, 7-27, 7-26, 7-25, 7-24, 7-23, 7-22, 7-21, 7-20, 7-19, 7-18, 7-17, 7-16, 7-15, 7-14, 7-13, 7-12, 7-11, 7-10, 7-9, 7-8, 7-7, 7-6, 7-5, 7-4, 7-3, 7-2, 7-1, 7-0, 6-30, 6-29, 6-28, 6-27, 6-26, 6-25, 6-24, 6-23, 6-22, 6-21, 6-20, 6-19, 6-18, 6-17, 6-16, 6-15, 6-14, 6-13, 6-12, 6-11, 6-10, 6-9, 6-8, 6-7, 6-6, 6-5, 6-4, 6-3, 6-2, 6-1, 6-0, 5-30, 5-29, 5-28, 5-27, 5-26, 5-25, 5-24, 5-23, 5-22, 5-21, 5-20, 5-19, 5-18, 5-17, 5-16, 5-15, 5-14, 5-13, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 5-5, 5-4, 5-3, 5-2, 5-1, 5-0, 4-30, 4-29, 4-28, 4-27, 4-26, 4-25, 4-24, 4-23, 4-22, 4-21, 4-20, 4-19, 4-18, 4-17, 4-16, 4-15, 4-14, 4-13, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 4-4, 4-3, 4-2, 4-1, 4-0, 3-30, 3-29, 3-28, 3-27, 3-26, 3-25, 3-24, 3-23, 3-22, 3-21, 3-20, 3-19, 3-18, 3-17, 3-16, 3-15, 3-14, 3-13, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 3-3, 3-2, 3-1, 3-0, 2-30, 2-29, 2-28, 2-27, 2-26, 2-25, 2-24, 2-23, 2-22, 2-21, 2-20, 2-19, 2-18, 2-17, 2-16, 2-15, 2-14, 2-13, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 2-2, 2-1, 2-0, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1-1, 1-0, 0-30, 0-29, 0-28, 0-27, 0-26, 0-25, 0-24, 0-23, 0-22, 0-21, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.

4.2.1.2 Overall Length

[0182] In some embodiments, the antisense strand comprises or consists of from about 15-30 nucleotides (e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 15-15, 15-14, 15-13, 15-12, 15-11, 15-10, 15-9, 15-8, 15-7, 15-6, 15-5, 15-4, 15-3, 15-2, 15-1, 15-0, 14-30, 14-29, 14-28, 14-27, 14-26, 14-25, 14-24, 14-23, 14-22, 14-21, 14-20, 14-19, 14-18, 14-17, 14-16, 14-15, 14-14, 14-13, 14-12, 14-11, 14-10, 14-9, 14-8, 14-7, 14-6, 14-5, 14-4, 14-3, 14-2, 14-1, 14-0, 13-30, 13-29, 13-28, 13-27, 13-26, 13-25, 13-24, 13-23, 13-22, 13-21, 13-20, 13-19, 13-18, 13-17, 13-16, 13-15, 13-14, 13-13, 13-12, 13-11, 13-10, 13-9, 13-8, 13-7, 13-6, 13-5, 13-4, 13-3, 13-2, 13-1, 13-0, 12-30, 12-29, 12-28, 12-27, 12-26, 12-25, 12-24, 12-23, 12-22, 12-21, 12-20, 12-19, 12-18, 12-17, 12-16, 12-15, 12-14, 12-13, 12-12, 12-11, 12-10, 12-9, 12-8, 12-7, 12-6, 12-5, 12-4, 12-3, 12-2, 12-1, 12-0, 11-30, 11-29, 11-28, 11-27, 11-26, 11-25, 11-24, 11-23, 11-22, 11-21, 11-20, 11-19, 11-18, 11-17, 11-16, 11-15, 11-14, 11-13, 11-12, 11-11, 11-10, 11-9, 11-8, 11-7, 11-6, 11-5, 11-4, 11-3, 11-2, 11-1, 11-0, 10-30, 10-29, 10-28, 10-27, 10-26, 10-25, 10-24, 10-23, 10-22, 10-21, 10-20, 10-19, 10-18, 10-17, 10-16, 10-15, 10-14, 10-13, 10-12, 10-11, 10-10, 10-9, 10-8, 10-7, 10-6, 10-5, 10-4, 10-3, 10-2, 10-1, 10-0, 9-30, 9-29, 9-28, 9-27, 9-26, 9-25, 9-24, 9-23, 9-22, 9-21, 9-20, 9-19, 9-18, 9-17, 9-16, 9-15, 9-14, 9-13, 9-12, 9-11, 9-10, 9-9, 9-8, 9-7, 9-6, 9-5, 9-4, 9-3, 9-2, 9-1, 9-0, 8-30, 8-29, 8-28, 8-27, 8-26, 8-25, 8-24, 8-23, 8-22, 8-21, 8-20, 8-19, 8-18, 8-17, 8-16, 8-15, 8-14, 8-13, 8-12, 8-11, 8-10, 8-9, 8-8, 8-7, 8-6, 8-5, 8-4, 8-3, 8-2, 8-1, 8-0, 7-30, 7-29, 7-28, 7-27, 7-26, 7-25, 7-24, 7-23, 7-22, 7-21, 7-20, 7-19, 7-18, 7-17, 7-16, 7-15, 7-14, 7-13, 7-12, 7-11, 7-10, 7-9, 7-8, 7-7, 7-6, 7-5, 7-4, 7-3, 7-2, 7-1, 7-0, 6-30, 6-29, 6-28, 6-27, 6-26, 6-25, 6-24, 6-23, 6-22, 6-21, 6-20, 6-19, 6-18, 6-17, 6-16, 6-15, 6-14, 6-13, 6-12, 6-11, 6-10, 6-9, 6-8, 6-7, 6-6, 6-5, 6-4, 6-3, 6-2, 6-1, 6-0, 5-30, 5-29, 5-28, 5-27, 5-26, 5-25, 5-24, 5-23, 5-22, 5-21, 5-20, 5-19, 5-18, 5-17, 5-16, 5-15, 5-14, 5-13, 5-12, 5-11, 5-10, 5-9, 5-8, 5-7, 5-6, 5-5, 5-4, 5-3, 5-2, 5-1, 5-0, 4-30, 4-29, 4-28, 4-27, 4-26, 4-25, 4-24, 4-23, 4-22, 4-21, 4-20, 4-19, 4-18, 4-17, 4-16, 4-15, 4-14, 4-13, 4-12, 4-11, 4-10, 4-9, 4-8, 4-7, 4-6, 4-5, 4-4, 4-3, 4-2, 4-1, 4-0, 3-30, 3-29, 3-28, 3-27, 3-26, 3-25, 3-24, 3-23, 3-22, 3-21, 3-20, 3-19, 3-18, 3-17, 3-16, 3-15, 3-14, 3-13, 3-12, 3-11, 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 3-3, 3-2, 3-1, 3-0, 2-30, 2-29, 2-28, 2-27, 2-26, 2-25, 2-24, 2-23, 2-22, 2-21, 2-20, 2-19, 2-18, 2-17, 2-16, 2-15, 2-14, 2-13, 2-12, 2-11, 2-10, 2-9, 2-8, 2-7, 2-6, 2-5, 2-4, 2-3, 2-2, 2-1, 2-0, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2, 1-1, 1-0, 0-30, 0-29, 0-28, 0-27, 0-26, 0-25, 0-24, 0-23, 0-22, 0-21, 0-20, 0-19, 0-18, 0-17, 0-16, 0-15, 0-14, 0-13, 0-12, 0-11, 0-10, 0-9, 0-8, 0-7, 0-6, 0-5, 0-4, 0-3, 0-2, 0-1, 0-0.

4.2.1.3 Exemplary Antisense Strands

[0184] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0185] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the antisense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 0 (e.g., 0) nucleotides from the antisense strand set forth in Table 2 or Table 3.

some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the antisense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 1 (e.g., 0 or 1) nucleotide from the antisense strand set forth in Table 2 or Table 3.

[0186] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0187] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0188] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0189] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23)))

contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0190] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0191] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0192] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0193] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2,

3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0194] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0195] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least

98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0196] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0197] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0198] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0199] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some

embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0200] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

[0201] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0202] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356.

[0203] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321,

355, 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356.

[0204] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356.

[0205] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356.

[0206] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, or 356 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0207] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth

in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191.

[0208] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191.

[0209] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the anti-

sense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191.

[0210] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191.

[0211] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062, 1188, 1189, 1190, or 1191 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0212] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 315.

[0213] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 315.

[0214] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some

embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315.

[0215] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 315.

[0216] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0217] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 315. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315.

[0218] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315.

In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315.

[0219] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315.

[0220] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0221] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 321.

[0222] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 321.

[0223] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321.

[0224] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 321.

[0225] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIIDEB mRNA transcript targeted by the select antisense strand.

[0226] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321.

[0227] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321.

[0228] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 321. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321.

[0229] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIIDEB mRNA transcript targeted by the select antisense strand.

[0230] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 355. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355.

[0231] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide

sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 355.

[0232] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 355.

[0233] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355.

[0234] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 355.

[0235] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides

from the nucleotide sequence set forth in SEQ ID NO: 355 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0236] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355.

[0237] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 355. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355.

[0238] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0239] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 356.

[0240] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence

set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 356.

[0241] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356.

[0242] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 356.

[0243] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0244] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the antisense

strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 356. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356.

[0245] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356.

[0246] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 356. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356.

[0247] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0248] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodi-

ments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1188.

[0249] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1188.

[0250] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188.

[0251] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1188.

[0252] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0253] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 1188. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188.

[0254] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188.

[0255] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1188. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188.

[0256] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0257] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2,

3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1190.

[0258] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1190.

[0259] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190.

[0260] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1190.

[0261] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the

antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0262] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 1190. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190.

[0263] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190.

[0264] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1190. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190.

[0265] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1190 and further comprising additional nucleotide sequences (e.g.,

comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0266] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1191.

[0267] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1191.

[0268] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191.

[0269] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the

nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1191.

[0270] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0271] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 1191. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191.

[0272] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191.

[0273] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1191. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191.

[0274] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted

by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1191 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0275] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1189.

[0276] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1189.

[0277] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to

the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189.

[0278] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1189.

[0279] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0280] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 1189. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189.

[0281] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189.

[0282] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set

forth in any one of SEQ ID NOS: 1189. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189.

[0283] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1189 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0284] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1062.

[0285] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1062.

[0286] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO:

1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062.

[0287] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1062.

[0288] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides an antisense strand wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0289] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in SEQ ID NO: 1062. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062.

[0290] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062. In some embodiments, the antisense strand comprises from about

21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062.

[0291] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 1062. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062.

[0292] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1062 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0293] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0294] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the antisense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the antisense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 differing by no more than 1 (e.g., 0 or 1) nucleotide from the antisense strand of any one of dsRNA agents 1-482.

[0295] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0296] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0297] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0298] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense

strands of any one of dsRNA agents 1-482. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0299] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0300] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482.

[0301] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0302] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

481, or 482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0303] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 1 (e.g., 0 or 1) nucleotide from the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0304] In some embodiments, the nucleotide sequence of the antisense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is at least 97%, identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is at least 98% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the

nucleotide sequence of the antisense strand is at least 99% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand is 100% identical to the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0305] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0306] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. As such, the disclosure further provides antisense strands wherein the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0307] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0308] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides

from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the antisense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0309] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0310] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the antisense strands. The disclosure further provides antisense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select antisense strand.

[0311] It is to be understood, that although the antisense strands set forth in Table 2 or Table 3 are not described as being modified (e.g., comprising chemically modified nucleotides), conjugated, etc., the disclosure includes any antisense strand set forth in Table 2 or Table 3 that is unmodified, unconjugated, modified (e.g., as described herein), or conjugated (e.g., as described herein).

4.2.2 Sense Strand

4.2.2.1 Antisense Strand Complementarity

[0312] As described above, sense strands (e.g., described herein) comprise a region of complementarity that comprises a nucleotide sequence that is at least partially (e.g., substantially, fully) complementary to the nucleotide sequence of at least a portion of an antisense strand. As such, pairs of sense and antisense strands can hybridize to form a double stranded region (e.g., under conditions in which the pairs will be used).

[0313] In some embodiments, the nucleotide sequence of the region of complementarity is at least substantially complementary to the nucleotide sequence of at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity is

fully complementary to the nucleotide sequence of at least a portion of an antisense strand.

[0314] In some embodiments, the nucleotide sequence of the region of complementarity is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to the nucleotide sequence of at least a portion of an antisense strand. For example, the nucleotide sequence of the region of complementarity may be at least 70% complementary to the nucleotide sequence of at least a portion of an antisense strand. The nucleotide sequence of the region of complementarity may be at least 75% complementary to the nucleotide sequence of at least a portion of an antisense strand. The nucleotide sequence of the region of complementarity may be at least 80% complementary to the nucleotide sequence of at least a portion of an antisense strand. The nucleotide sequence of the region of complementarity may be at least 85% complementary to the nucleotide sequence of at least a portion of an antisense strand. The nucleotide sequence of the region of complementarity may be at least 90% complementary to the nucleotide sequence of at least a portion of an antisense strand. The nucleotide sequence of the region of complementarity may be at least 95% complementary to the nucleotide sequence of at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to the nucleotide sequence of at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity is at least 95%, 96%, 97%, 98%, 99%, or 100% complementary to the nucleotide sequence of at least a portion of an antisense strand.

[0315] In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of one or more non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 5 (e.g., 4, 3, 2, 1, or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 3 (e.g., 2, 1, or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 2 (e.g., 1 or 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity comprises or consists of no more than 1 (e.g., 0) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the nucleotide sequence of the region of complementarity comprises 0 non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand. In some embodiments, the region of complementarity comprises one or more (e.g., 2, 3, or more) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand, wherein the one or more non-complementary nucleotide mismatch is within the last 5 (e.g., 4, 3, 2, or 1)

nucleotides from either the 5'- and/or 3'-end of the region of complementarity. In some embodiments, the region of complementarity comprises at least one but not more than 3 (e.g., 1, 2, or 3) non-complementary nucleotide mismatches relative to the nucleotide sequence of the at least a portion of an antisense strand, wherein the one or more non-complementary nucleotide mismatch is within the last 5 (e.g., 4, 3, 2, or 1) nucleotides from either the 5'- and/or 3'-end of the region of complementarity.

[0316] In some embodiments, the region of complementarity comprises from about 15-30 nucleotides, e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides. In some embodiments, the region of complementarity comprises from about 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 nucleotides. In some embodiments, the region of complementarity comprises from about 19-21 (e.g., 19-20) nucleotides. In some embodiments, the region of complementarity comprises or consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 19, 20, or 21 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 19 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 20 nucleotides. In some embodiments, the region of complementarity comprises or consists of about 21 nucleotides. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

4.2.2.2 Overall Length

[0317] In some embodiments, the sense strand comprises or consists of from about 15-30 nucleotides (e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides). In some embodiments, the sense strand comprises or consists of from about 18-25 nucleotides (e.g., 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 nucleotides). In some embodiments, the sense strand comprises or consists of from about 19-25 nucleotide (e.g., 19-20, 19-21, 19-22, 19-23, 19-24, 19-25, 20-21, 20-22, 20-23, 20-24, 20-25, 21-22, 21-23, 21-24, 21-25, 22-23, 22-24, 22-25, 23-24, 23-25, 24-25 nucleotides). In some embodiments, the sense strand comprises or consists of from about 15-30, 16-30, 17-30, 18-30, 19-30 20-30, 21-30, 22-30, 23-30, 24-30, 25-30, 36-30, 27-30, 28-30-, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides.

[0318] In some embodiments, the sense strand comprises or consists of not more than about 15, 16, 17, 18, 19, 20, 21,

22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides. In some embodiments, the sense strand comprises or consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides. In some embodiments, the sense strand comprises or consists of about 19, 20, 21, 22, 23 nucleotides. In some embodiments, the sense strand comprises or consists of about 19, 20, 21 nucleotides. In some embodiments, the sense strand comprises or consists of about 20 nucleotides. In some embodiments, the sense strand comprises or consists of about 21 nucleotides. In some embodiments, the sense strand comprises or consists of about 21 nucleotides. In some embodiments, the sense strand comprises or consists of about 23 nucleotides. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

4.2.2.3 Exemplary Sense Strands

[0319] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0320] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the sense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 1 (e.g., 0 or 1) nucleotide from the sense strand set forth in Table 2 or Table 3.

[0321] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands set forth in Table

2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0322] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0323] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0324] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0325] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing

by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0326] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in Table 2 or Table 3. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0327] Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, the disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0328] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0329] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodi-

ments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0330] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0331] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0332] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0333] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0334] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0335] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0336] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous

(e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0337] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173.

[0338] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173.

[0339] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in any one of

SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173.

[0340] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173.

[0341] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 132, 138, 172, or 173 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0342] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 132, 138, 172, or 173 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0343] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 315, 321, 355, 356. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192 differing by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192.

[0344] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192.

[0345] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192.

[0346] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in any one of SEQ ID NOS: 786, 792, 827, or 1192 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0347] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 132.

[0348] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set

forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 132.

[0349] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132.

[0350] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 132.

[0351] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0352] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29,

30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 132. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132.

[0353] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132.

[0354] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132.

[0355] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0356] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand differs by

no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 138.

[0357] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 138.

[0358] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138.

[0359] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 138.

[0360] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0361] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 138. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138.

[0362] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138.

[0363] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138.

[0364] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0365] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g.,

0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 172.

[0366] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 172.

[0367] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172.

[0368] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 172.

[0369] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172 and further comprising additional nucleotide sequences (e.g., comprising

ing from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIIDEB mRNA transcript targeted by the select sense strand.

[0370] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 172. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172.

[0371] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172.

[0372] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172.

[0373] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIIDEB mRNA transcript identical to the select sense strand.

[0374] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 173.

[0375] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 173.

[0376] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173.

[0377] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 173.

[0378] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an

sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0379] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 173. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173.

[0380] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173.

[0381] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173.

[0382] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173 and further comprising additional nucleotide sequences (e.g., compris-

ing from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0383] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 786.

[0384] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 786.

[0385] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786.

[0386] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide

sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 786.

[0387] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0388] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 786. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786.

[0389] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786.

[0390] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786.

[0391] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further pro-

vides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0392] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1192.

[0393] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 1192.

[0394] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide

sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192.

[0395] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1192.

[0396] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0397] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 1192. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192.

[0398] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192.

[0399] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192. In some embodiments, the nucleotide

sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192.

[0400] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1192 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0401] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 792.

[0402] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 792.

[0403] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in

SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792.

[0404] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 792.

[0405] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0406] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792.

[0407] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792.

[0408] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792.

[0409] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 792 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0410] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 827.

[0411] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827 differing by no more than 1 (e.g., 0 or 1) nucleotide from nucleotide sequence set forth in SEQ ID NO: 827.

[0412] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some

embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827.

[0413] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 827.

[0414] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides an sense strand wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0415] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in SEQ ID NO: 827. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827.

[0416] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide

sequence set forth in SEQ ID NO: 827. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827.

[0417] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827.

[0418] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 827 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0419] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0420] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the sense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 differing by no more than 1 (e.g., 0 or 1) nucleotide from the sense strand of any one of dsRNA agents 1-482.

[0421] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand is at least 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0422] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0423] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0424] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides

differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0425] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0426] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0427] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0428] In some embodiments, the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the sense strand comprises at least 21 (e.g., 22, 23,

24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the sense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 1-482.

[0429] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0430] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the sense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 1 (e.g., 0 or 1) nucleotide from the sense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0431] In some embodiments, the nucleotide sequence of the sense strand is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480,

481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0432] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the nucleotide sequence of the sense strand consists of the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0433] Table 2 or Table 3 further identifies the target nucleic acid molecule within the cited reference CIDEB mRNA transcript (SEQ ID NO: 1) targeted by each of the sense strands. As such, the disclosure further provides sense strands wherein the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., no more than 3 (e.g., 0, 1, 2, or 3))) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially complementary to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript targeted by the select sense strand.

[0434] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleo-

tides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0435] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of any one of dsRNA 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0436] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0437] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1. In some embodiments, the sense strand comprises at least 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90,

68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1.

[0438] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198,

2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1.

[0439] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, the disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0440] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1. In some embodiments, the sense strand comprises at least 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1.

[0441] In some embodiments, the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23,

17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1932-1968, or 1943-1963 of SEQ ID NO: 1. In some embodiments, the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1932-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1. In some embodiments, the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1.

[0442] As described above, Table 2 or Table 3 further identifies the target nucleic acid molecule within the reference CIDEB mRNA transcript at least partially identical to each of the sense strands. As such, the disclosure further provides sense strands comprising at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1 and further comprising additional nucleotide sequences (e.g., comprising from about 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3, or 1-2 nucleotides) at least partially identical to the region contiguous (e.g., either at the 3' end, the 5' end, or both the 3' and 5' end) of the CIDEB mRNA transcript identical to the select sense strand.

[0443] It is to be understood, that although the sense strands are not described as being modified (e.g., comprising chemically modified nucleotides), conjugated, etc., the disclosure includes any sense strand that is unmodified, unconjugated, modified (e.g., as described herein), or conjugated (e.g., as described herein).

4.2.3 dsRNA Agents

[0444] In some embodiments, the agent (e.g., RNAi agent) comprises a dsRNA agent comprising an antisense strand (e.g., described herein, e.g., described in § 4.2.1) and a sense strand (e.g., described herein, e.g., described in § 4.2.2) that hybridize to form a double stranded region (e.g., under conditions in which the dsRNA will be used (e.g., under physiological (e.g., mammalian, e.g., human) conditions within a cell)).

[0445] As described above, antisense strands (e.g., described herein) comprise a region of complementarity that comprises a nucleotide sequence that is at least partially (e.g., substantially, fully) complementary to the nucleotide sequence of a target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA), a portion of a target mRNA (e.g., a CIDEB mRNA)); and the sense strands comprise a region of complementarity that comprises a nucleotide sequence that is at least partially (e.g., substantially, fully) complementary to the nucleotide sequence of at least a portion of an antisense strand.

4.2.3.1 Single & Multiple Nucleic Acid Molecules

[0446] As described herein, and known in the art, the sense strand and the antisense strand can be part of a single larger nucleic acid molecule (connected as a single stranded nucleic acid molecule) or separate nucleic acid molecules (only connected through the double stranded region). In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules. In some embodiments, sense strand and the antisense strand are part of a single larger nucleic acid molecule.

[0447] In embodiments wherein the sense and antisense strands are part of a single nucleic acid molecule, the nucleic acid molecule may comprise a hairpin loop between the antisense strand and the sense strand to allow for formation of the double stranded region. In some embodiments, the hairpin loop comprises at least 1 (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 23, 25 or more) unpaired nucleotides (non-complementary nucleotide mismatches). In some embodiments, the hairpin loop comprises at least one but less than 25, 23, 20, 10, 9, 8, 7, 6, 5, 4, 3, or 2 unpaired nucleotides (non-complementary nucleotide mismatches). In some embodiments, the hairpin loop comprises about 25, 23, 20, 9, 8, 7, 6, 5, 4, 3, or 1 unpaired nucleotide (non-complementary nucleotide mismatch).

[0448] Without wishing to be bound by theory, in embodiments wherein the sense strand and the antisense strand are part of a single nucleic acid molecule, after introduction into a suitable cell (e.g., a mammalian cell, e.g., a human cell), the nucleic acid molecule may be cleaved into a dsRNA molecule wherein the two strands of the dsRNA molecule are no longer part of the same nucleic acid molecule e.g., by a Type III endonuclease (e.g., Dicer) (see, e.g., Sharp et al. (2001) *Genes Dev.* 15:485, the entire contents of which are incorporated by herein by reference for all purposes).

4.2.3.2 Length of Double Stranded Region

[0449] In some embodiments, the double stranded region is about 15-30 base pairs in length (e.g., 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20,

20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length). In some embodiments, the double stranded region is about 18-25 base pairs in length (e.g., 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-25, 20-24, 20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length (e.g., 19-21 base pairs in length)). In some embodiments, the double stranded region is about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-20, 19-21, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, 23-24, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In some embodiments, the double stranded region is about 19-21 (e.g., 19-20) base pairs in length.

[0450] In some embodiments, the double stranded region is not more than about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 base pairs in length. In some embodiments, the double stranded region is about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 base pairs in length. In some embodiments, the double stranded region is about 19, 20, or 21 base pairs in length. In some embodiments, the double stranded region is about 19 base pairs in length. In some embodiments, the double stranded region is about 20 base pairs in length. In some embodiments, the double stranded region is about 21 base pairs in length. In some embodiments, the double stranded region is about 23 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

4.2.3.3 Nucleotide Overhangs & Blunt Ends

[0451] In some embodiments, the dsRNA agent comprises one or more (e.g., 1 or 2) nucleotide overhang. As is clear from the disclosure, but for the sake of clarity, the nucleotides of a nucleotide overhang can include one or more a modified (e.g., chemically modified) nucleotide (e.g., described herein, e.g., described in §§ 4.3, 4.3.1).

[0452] In some embodiments, the nucleotide overhang comprises from about 1-5 nucleotides, e.g., 1-4, 1-3, 1-2, 2-5, 2-4, 2-3, 3-5, 3-4, 4-5 nucleotides. In some embodiments, the nucleotide overhang comprises or consists of about 1, 2, 3, 4, or 5 nucleotides. In some embodiments, the nucleotide overhang comprises or consists of about 1 nucleotide. In some embodiments, the nucleotide overhang comprises or consists of about 2 nucleotides.

[0453] The nucleotide overhang(s) can be on the sense strand, the antisense strand, or both the sense strand and the antisense strand. In some embodiments, the sense strand comprises a nucleotide overhang. In some embodiments, the antisense strand comprises a nucleotide overhang. In some embodiments, the sense strand and the antisense strand both comprise a nucleotide overhang.

[0454] Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end, or both the 5'-end, 3'-end of an antisense or sense strand. In some embodiments, the sense strand comprises a nucleotide overhang at the 5'-end. In some embodiments, the sense strand comprises a nucleotide overhang at the 3'-end. In some embodiments, the sense strand comprises a nucleotide overhang at the 5'-end and the 3'-end. In some embodiments, the antisense strand com-

prises a nucleotide overhang at the 5'-end. In some embodiments, the antisense strand comprises a nucleotide overhang at the 3'-end. In some embodiments, the antisense strand comprises a nucleotide overhang at the 5'-end and the 3'-end. In some embodiments, the antisense strand comprises a nucleotide overhang at the 3'-end; and the sense strand comprises a nucleotide overhang at the 3'-end. In some embodiments, the antisense strand comprises a nucleotide overhang at the 5'-end; and the sense strand comprises a nucleotide overhang at the 5'-end.

[0455] In some embodiments, the dsRNA agent comprises one or more blunt end. In some embodiments, the dsRNA agent comprises a blunt end at the end of the agent comprising the 3' end of the sense strand and the 5' end of the antisense strand. In some embodiments, the dsRNA agent comprises a blunt end at the end of the agent comprising the 5' end of the sense strand and the 3' end of the antisense strand. In some embodiments, both ends of the dsRNA agent are blunt ends.

4.2.3.4 Exemplary Structural Combinations of Sense & Antisense Strands

[0456] In some embodiments, the antisense strand and the sense strand contain the same number of nucleotides. In some embodiments, the antisense strand and the sense strand contain different numbers of nucleotides. In some embodiments, the nucleotide sequence of the sense strand is from about 1-5, 1-3, or 1-2 nucleotides shorter than the nucleotide sequence of the antisense strand. In some embodiments, the nucleotide sequence of the sense strand is about 1, 2, 3, 4, or 5 nucleotides shorter than the nucleotide sequence of the antisense strand. In some embodiments, the nucleotide sequence of the sense strand is about 2 nucleotides shorter than the nucleotide sequence of the antisense strand. In some embodiments, the nucleotide sequence of the antisense strand is from about 1-5, 1-3, or 1-2 nucleotides shorter than the nucleotide sequence of the sense strand. In some embodiments, the nucleotide sequence of the antisense strand is about 1, 2, 3, 4, or 5 nucleotides shorter than the nucleotide sequence of the sense strand. In some embodiments, the nucleotide sequence of the antisense strand is about 2 nucleotides shorter than the nucleotide sequence of the sense strand.

[0457] In some embodiments, the sense strand comprises or consists of 21 nucleotides. In some embodiments, the antisense strand comprises or consists of 23 nucleotides. In some embodiments, the sense strand comprises or consists of 21 nucleotides; and the antisense strand comprises or consists of 23 nucleotides. In some embodiments, the double stranded region comprises or consists of 21 nucleotides. In some embodiments, the antisense strand comprises a 2-nucleotide overhang at the 3' end. In some embodiments, the 5' end of the antisense strand and 3' end of the sense strand form a blunt end. In some embodiments, the sense strand comprises or consists of 21 nucleotides; the antisense strand comprises or consists of 23 nucleotides; the double stranded region comprises or consists of 21 nucleotides; the antisense strand comprises a 2-nucleotide overhang at the 3' end; and the 5' end of the antisense strand and 3' end of the sense strand form a blunt end.

[0458] In some embodiments, the sense strand comprises or consists of 19 nucleotides. In some embodiments, the antisense strand comprises or consists of 21 nucleotides. In some embodiments, the sense strand comprises or consists

of 19 nucleotides; and the antisense strand comprises or consists of 21 nucleotides. In some embodiments, the double stranded region comprises or consists of 19 nucleotides. In some embodiments, the antisense strand comprises a 2-nucleotide overhang at the 3' end. In some embodiments, the 5' end of the antisense strand and 3' end of the sense strand form a blunt end. In some embodiments, the sense strand comprises or consists of 19 nucleotides; the antisense strand comprises or consists of 21 nucleotides; the double stranded region comprises or consists of 19 nucleotides; the antisense strand comprises a 2-nucleotide overhang at the 3' end; and the 5' end of the antisense strand and 3' end of the sense strand form a blunt end.

[0459] In some embodiments, the sense strand comprises or consists of 21 nucleotides. In some embodiments, the antisense strand comprises or consists of 21 nucleotides. In some embodiments, the sense strand comprises or consists of 21 nucleotides; and the antisense strand comprises or consists of 21 nucleotides. In some embodiments, the double stranded region comprises or consists of 19 nucleotides. In some embodiments, the antisense strand comprises a 2-nucleotide overhang at the 3' end. In some embodiments, the sense strand comprises a 2-nucleotide overhang at the 3' end. In some embodiments, the sense strand comprises or consists of 21 nucleotides; the antisense strand comprises or consists of 21 nucleotides; the double stranded region comprises or consists of 19 nucleotides; the antisense strand comprises a 2-nucleotide overhang at the 3' end; and the sense strand comprises a 2-nucleotide overhang at the 3' end.

[0460] In some embodiments, the sense strand comprises or consists of 20 nucleotides. In some embodiments, the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the sense strand comprises or consists of 20 nucleotides; and the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the double stranded region comprises or consists of 20 nucleotides. In some embodiments, the sense strand comprises a 1-nucleotide overhang at the 5' end. In some embodiments, the 5' end of the antisense strand and 3' end of the sense strand form a blunt end. In some embodiments, the sense strand comprises or consists of 20 nucleotides; the antisense strand comprises or consists of 19 nucleotides; the double stranded region comprises or consists of 20 nucleotides; the sense strand comprises a 1-nucleotide overhang at the 5' end; and the 5' end of the antisense strand and 3' end of the sense strand form a blunt end.

[0461] In some embodiments, the sense strand comprises or consists of 21 nucleotides. In some embodiments, the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the sense strand comprises or consists of 21 nucleotides; and the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the double stranded region comprises or consists of 19 nucleotides. In some embodiments, the sense strand comprises a 1-nucleotide overhang at the 3' end. In some embodiments, the sense strand comprises a 1-nucleotide overhang at the 5' end. In some embodiments, the sense strand comprises or consists of 21 nucleotides; the antisense strand comprises or consists of 19 nucleotides; the double stranded region comprises or consists of 19 nucleotides; the sense strand comprises a 1-nucleotide overhang at the 3' end; and the sense strand comprises a 1-nucleotide overhang at the 5' end.

[0462] In some embodiments, the sense strand comprises or consists of 24 nucleotides. In some embodiments, the

antisense strand comprises or consists of 23 nucleotides. In some embodiments, the sense strand comprises or consists of 24 nucleotides; and the antisense strand comprises or consists of 23 nucleotides. In some embodiments, the double stranded region comprises or consists of 21 nucleotides. In some embodiments, the antisense strand comprises a 2-nucleotide overhang at the 3' end. In some embodiments, the sense strand comprises a 3-nucleotide overhang at the 3' end. In some embodiments, the sense strand comprises or consists of 24 nucleotides; the antisense strand comprises or consists of 23 nucleotides; the double stranded region comprises or consists of 21 nucleotides; the antisense strand comprises a 2-nucleotide overhang at the 3' end; and the sense strand comprises a 3-nucleotide overhang at the 3' end.

[0463] In some embodiments, the sense strand comprises or consists of 19 nucleotides. In some embodiments, the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the sense strand comprises or consists of 19 nucleotides; and the antisense strand comprises or consists of 19 nucleotides. In some embodiments, the double stranded region comprises or consists of 19 nucleotides. In some embodiments, the 5' end of the antisense strand (and 3' end of the sense strand) form a blunt end. In some embodiments, the 3' end of the antisense strand (and 5' end of the sense strand) form a blunt end. In some embodiments, the sense strand comprises or consists of 19 nucleotides; the antisense strand comprises or consists of 19 nucleotides; the double stranded region comprises or consists of 19 nucleotides; the 5' end of the antisense strand (and 3' end of the sense strand) form a blunt end; and the 3' end of the antisense strand (and 5' end of the sense strand) form a blunt end.

[0464] In some embodiments, the antisense strand and the sense strand are part of the same larger nucleic acid molecule, wherein the nucleic acid molecule comprises or consists of 44 nucleotides, the antisense portion comprises or consists of 21 nucleotides, the sense strand portion of the nucleic acid molecule comprises 19 nucleotides, the double stranded region comprises or consists of 19 nucleotides, the antisense strand comprises a 2-nucleotide overhang at the 3' end, and the intervening nucleotide sequence between the antisense strand and the sense strand comprises or consists of 4 unpaired nucleotides that create a hairpin loop.

4.2.3.5 Exemplary Antisense Strands & Sense Strands

[0465] In some embodiments, the antisense strand is an antisense strand described herein. In some embodiments, the sense strand is a sense strand described herein. In some embodiments, the antisense strand is an antisense strand described in § 4.2.1. In some embodiments, the sense strand is a sense strand described in § 4.2.2. In some embodiments, the antisense strand is an antisense strand described in § 4.2.1; and the sense strand is a sense strand described in § 4.2.2. It is to be understood that any sense strand described herein (e.g., in § 4.2.2); and be utilized in combination with any antisense strand in a dsRNA agent described herein (e.g., in § 4.2.1). For the sake of clarity, the entire contents of in §§ 4.2.1 and § 4.2.2, are incorporated by reference into the instant section in § 4.2.3.5.

[0466] In some embodiments, the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3; and the nucleotide sequence of the antisense strand differs by no

[0473] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand set forth in Table 2 or Table 3; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in Table 2 or Table 3.

[0474] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of any one of any one of the antisense strands set forth in Table 2 or Table 3; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of any one of the sense strands set forth in Table 2 or Table 3.

[0475] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,

25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises at least 19 (e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises at least 23 (e.g., 24, 25, 26, 27, 28, 29, 30 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises at least 21 (e.g., 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3.

[0476] In some embodiments, the antisense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3; and the sense strand comprises from about 15-23 (e.g., 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 15-16, 16-22, 16-20, 16-19, 16-18, 16-17, 17-23, 17-22, 17-21, 17-20, 17-19, 17-18, 18-23, 18-22, 18-21, 18-20, 18-19, 19-23, 19-22, 19-21, 19-20,

forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the sense strand comprises from about 19-23 (e.g., 19-22, 19-21, 19-20, 20-23, 20-22, 20-21, 21-23, 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the antisense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the sense strand comprises from about 21-23 (e.g., 21-22, 22-23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

(e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the antisense strand comprises or consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the sense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the antisense strand comprises or consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the sense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192. In some embodiments, the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the sense strand comprises or consists of about 19 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0488] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0489] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of any one of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0490] In some embodiments, the antisense strand comprises at least 15 (e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23))) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the antisense strands set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; and the

[0526] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356 differing

by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 173.

[0527] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173.

[0528] In some embodiments, the antisense strand consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the sense strand consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand consists of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the sense strand consists of 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the sense strand consists of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the sense strand consists of at about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 356; and the sense strand consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3)

[0589] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of

the antisense strand set forth in SEQ ID NO: 1190 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 786 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 786.

[0590] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 786.

[0591] In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the antisense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the anti-sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence set forth in SEQ ID NO: 786.

[0592] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1188 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786 differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the nucleotide sequence set forth in SEQ ID NO: 786. In some embodiments, the nucleotide sequence

than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0618] In some embodiments, the antisense strand comprises or consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of at about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or

482; and the sense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the sense strand comprises or consists of about 19 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0619] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the antisense strand set forth in any one of the dsRNA agents 169, 129, 170, 175, 134, 204, 218, 135, 238, 167, 137, 233, 148, 152, 130, 166, 136, 149, 151, or 172; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in the corresponding (the same) dsRNA agent.

[0620] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence of the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; and the nucleotide sequence of the sense strand comprises or consists of the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0621] In some embodiments, the dsRNA agent is any one of dsRNA agents 1-482. In specific embodiments the dsRNA agent is any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482. In specific embodiments the dsRNA agent is dsRNA agent 129. In specific embodiments the dsRNA agent is dsRNA agent 135. In specific embodiments the dsRNA agent is dsRNA agent 169. In specific embodiments the dsRNA agent is dsRNA agent 170. In specific embodiments the dsRNA agent is dsRNA agent 409. In specific embodiments the dsRNA agent is dsRNA agent 479. In specific embodiments the dsRNA agent is dsRNA agent 480. In specific embodiments the dsRNA agent is dsRNA agent 481. In specific embodiments the dsRNA agent is dsRNA agent 482.

[0622] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of

2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1; and the antisense strand comprises or consists of at about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170, 2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 19 contiguous nucleotides

differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2.

[0625] In some embodiments, the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21, 22, or 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises at least 19 (e.g., 20, 21) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises at least 19 (e.g., 20, 21, 22, or 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises at least 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises at least 21 (e.g., 22 or 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises at least 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises at least 21 (e.g., 22 or 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises at least 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-

comprises or consists of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 19, 20, 21, 22, 23 (e.g., 21)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 21, 22, 23 (e.g., 23)) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23, 24, 25, 26, 27, 28, 29, 30 (e.g., 23) contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 23 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2.

1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from nucleotides 1225-1285, 1235-1275, 1240-1270, 1245-1265, 1227-1287, 1237-1277, 1242-1272, 1247-1267, 1231-1291, 1241-1261, 1246-1276, 1251-1271, 1235-1295, 1245-1265, 1250-1280, 1255-1275, 1353-1411, 1363-1381, 1368-1396, 1373-1391, 1762-1820, 1772-1810, 1757-1805, 1782-1800, 1912-1972, 1922-1942, 1927-1957, 1932-1952, 1922-1982, 1932-1972, 1937-1967, 1942-1962, 1923-1983, 1933-1973, 1938-1968, or 1943-1963 of SEQ ID NO: 1; and the antisense strand comprises or consists of about 19 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises or consists of about 21 contiguous nucleotides differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding complementary nucleotide sequence of SEQ ID NO: 2.

4.2.3.6 Exemplary dsRNA Agents

[0628] The nucleotide sequence of exemplary unmodified dsRNA agents comprising a sense and antisense strand (e.g., suitable for targeting hCIDEB, suitable for inhibiting hCIDEB expression)) are set forth in Table 2. More specifically, Table 2 sets forth the nucleotide sequence of exemplary sense strands, antisense strands, and dsRNA agent pairs of sense and antisense strands. It is to be understood that while the sense and antisense strands are set forth in pairs in Table 2, the disclosure encompasses dsRNA agents comprising any sense strand and any antisense set forth in Table 2 (e.g., that are at least partially complementary (e.g., as could be determined by a person of ordinary skill in the art)). It is to be understood that while the nucleotide sequence of the sense strands and antisense strands in Table 2 are set forth as unmodified (not containing any modified nucleotides), the disclosure encompasses the sense and antisense sense strands set forth in Table 2 comprising one or more modified nucleotide (e.g., as described herein).

TABLE 2

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense Agent Sequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence	Antisense Sequence	SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence
1 AGAGCAAGC CGAAGGCAA GCA	4	63-83	UGCUUGCCUU187	61-83	CCAGAGCAAG	370	CGGAAGGCAA GCA
2 AAGCCGAAG GCAAGCACG AUA	5	68-88	UAUCGUGCUU188	66-88	GCAAGCCGAA	371	GGCAAGCACG AUG
3 AGCCGAAGG CAAGCACGA UGA	6	69-89	UCAUCGUGCU189	67-89	CAAGCCGAAG	372	GCAAGCACGA UGG
4 CCGAAGGCA AGCACGAUG GCA	7	71-91	UGCCAUCGUG190	69-91	AGCCGAAGGC	373	AAGCACGAUG GCG

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense Agent Sequence	SEQ ID	Range in NO NM_014430.4	Antisense SEQ Sequence	ID	Range in NO NM_014430.4	mRNA Target	SEQ ID	SEQ NO
5	CGAAGGCAA GCACGAUGG CGA	8	72-92	UCGCCAUUCGU191 GUUUGCCUUC GGC		70-92	GCCGAAGGCA AGCACGAUGG CGC	374	
6	GGCAAGCAC GAUGGCCU CAA	9	76-96	UUGAGCGCCA192 UCGUGCUUGC CUU		74-96	AAGGCAAGCA CGAUGGCCU CAC	375	
7	GCAAGCACG AUGGCGCUC ACA	10	77-97	UGUGAGCGCC193 AUCGUGCUUG CCU		75-97	AGGCAAGCAC GAUGGCCU ACC	376	
8	CAAGCACGA UGGCCUCA CCA	11	78-98	UGGUGAGCGC194 CAUCGUGCUU GCC		76-98	GGCAAGCACG AUGGCGCUC CCA	377	
9	AAGCACGAU GGGCUCAC CAA	12	79-99	UUGGUGAGCG195 CCAUCGUGCU UGC		77-99	GCAAGCACGA UGGCGCUCAC CAG	378	
10	ACGAUGGCG CUCACCAGC CGA	13	83-103	UCGGCUGGUG196 AGCGCCAUUCG UGC		81-103	GCACGAUGGC GCUCACCAGC CGG	379	
11	CCCCGCAGC CGUGCCAGC GUA	14	143-163	UACGCUGGCA197 CGGCUGCGGG GCG		141-163	CGCCCCGAG CCGUGCCAGC GUC	380	
12	GCAGCCUG CCAGCGUCA CGA	15	147-167	UCGUGACGCU198 GGCACGGCUG CGG		145-167	CCGCAGCCGU GCCAGCGUCA CGC	381	
13	CAGCCGUGC CAGCGUCAC GCA	16	148-168	UGCGUGACGC199 UGGCACGGCU GCG		146-168	CGCAGCCUG CCAGCGUCAC GCU	382	
14	AGCCGUGCC ACGGUCACG CUA	17	149-169	UAGCGUGACG200 CUGGCACGGC UGC		147-169	GCAGCCGUGC CAGCGUCACG CUG	383	
15	GCCGUGCCA GCGUCACGC UGA	18	150-170	UCAGCGUGAC201 GCUGGCACGG CUG		148-170	CAGCCGUGCC AGCGUCACGC UGU	384	
16	CGUGCCAGC GUACCGCUG UAA	19	152-172	UUACAGCGUG202 ACGCUGGCAC GGC		150-172	GCCGUGCCAG CGUCACCGUG UAG	385	
17	GCCAGCGUC ACCGCUGUAG CAA	20	155-175	UUGCUACAGC203 GUGACGCGUG CAC		153-175	GUGCCAGCGU CACCGUGUAG CAG	386	
18	CCAGCGUCA CGCUGUAGC AGA	21	156-176	UCUGCUACAG204 CGUGACGCG GCA		154-176	UGCCAGCGUC ACGCUGUAGC AGC	387	
19	CAGCGUCAC GCGUGUAGCA GCA	22	157-177	UGCUGCUACA205 GCGUGACGCU GGC		155-177	GCCAGCGUCA CGCUGUAGCA GCC	388	
20	GCGUCACGC UGUAGCAGC CGA	23	159-179	UCGGCUGCUA206 CAGCGUGACG CUG		157-179	CAGCGUCACG CUGUAGCAGC CGA	389	
21	CGUCACGCC GUAGCAGCC GAA	24	160-180	UUCGGCUGCU207 ACAGCGUGAC GCU		158-180	AGCGUCACGC UGUAGCAGCC GAG	390	

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Sense SEQ Range in 5' to 3'	Antisense Sequence ID	Range in Target NO NM_014430.4	mRNA Target ID	SEQ Sequence NO	
22	GUACACGUG UAGCAGCCG AGA	25	161-181	UCUCGGCUGC208	159-181	GCGUCACGCC GUAGCAGCCG AGC	391		
23	CACGCUGUA GCAGCCGAG CAA	26	163-183	UUGCUCGGCU209	161-183	GUCACGCUGU AGCAGCCGAG CAU	392		
24	ACGCUGUAG CAGCCGAGC AUA	27	164-184	UAUGCUCGGC210	162-184	UCACGCUGUA GCAGCCGAGC AUC	393		
25	GCUGUAGCA GCCGAGCAU CAA	28	166-186	UUUGAUGCUCG211	164-186	ACGCUGUAGC AGCCGAGCAU CAG	394		
26	AGCCGAGCA UCAGCCCCGA AAA	29	174-194	UUUUUCGGGCU212	172-194	GCAGCCGAGC AUCAGCCCGA AAG	395		
27	CGAGCAUCA GCCCGAAAG GAA	30	177-197	UUCCUUUCGG213	175-197	GCCGAGCAUC AGCCCGAAAG GAA	396		
28	CAGCCCGAA AGGAAGCAC GAA	31	184-204	UUCGUGCUUC214	182-204	AUCAGCCCGA AAGGAAGCAC GAA	397		
29	AGCCCGAAA GGAAGCACG AAA	32	185-205	UUUCGUGCUU215	183-205	UCAGCCCGAA AGGAAGCACG AAA	398		
30	GCCCCGAAAG GAAGCACGA AAA	33	186-206	UUUUUCGUGCU216	184-206	CAGCCCGAAA GGAAGCACGA AAG	399		
31	CGGGCGGCG GGACCGCGCG ACA	34	234-254	UGUCGCCGGU217	232-254	GGCGGGCGGC UGGACCGCGC ACG	400		
32	GGGGCGUG GACCGGCAG CGA	35	235-255	UCCUGCGCCGG218	233-255	GCGGGGGCGU GGACCGGCAG CGG	401		
33	GCGGCGUGG ACCGGCAGC GGA	36	236-256	UCCGUCGCCG219	234-256	CGGCGGGCGUG GACCGGCAGC GGG	402		
34	GUGGACCGG CGACGGGUG GCA	37	241-261	UGCCACCCGU220	239-261	GCGUGGACCG GCGACGGGUG GCA	403		
35	UGGACCCGGC GACGGGUGG CAA	38	242-262	UUGGCCACCCG221	240-262	CGUGGACCGG CGACGGGUGG CAC	404		
36	GGACCGGGCG ACGGGUGGC ACA	39	243-263	UGUGGCCACCC222	241-263	GUGGACCGGGC GACGGGUGGC ACA	405		
37	GACCGGGCGA CGGGUGGCA CAA	40	244-264	UUGUGGCCACC223	242-264	UGGACCGGGCG ACGGGUGGCA CAG	406		
38	CGGCGACGG GUGGCACAG CUA	41	247-267	UAGCUGUGGCC224	245-267	ACCGGCGACG GGUGGCACAG CUG	407		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense SEQ Sequence ID 5' to 3' NO NM_014430.4	mRNA Target ID	SEQ Sequence NO			
39	GCGACGGGU GCCACAGCU GGA	42	249-269	UCCAGCUGUG225 CCACCCGUCG CCG	247-269	CGGCGACGGG UGGCACAGCU GGC	408		
40	GGUGGCACA GCUGGCAUA CGA	43	255-275	UCGUUAUGCCA226 GCUGUGGCCAC CCG	253-275	CGGGUGGCAC AGCUGGCAUA CGC	409		
41	GUGGCACAG CUGGCAUAC GCA	44	256-276	UGCGUAUGCC227 AGCUGUGCCA CCC	254-276	GGGUGGCACA GCUGGCAUAC GCG	410		
42	UGGCACAGC UGGCAUACG CGA	45	257-277	UCGCGUAUGC228 CAGCUGUGCC ACC	255-277	GGUGGCACAG CUGGCAUACG CGG	411		
43	CCUCCACAG GUGGCGGU GAA	46	280-300	UUCUACCGCC229 ACCUGUGGAG GGA	278-300	UCCCUCCACA GGUGGCGGU GAC	412		
44	UCCACAGGU GGCGGUAGA CGA	47	282-302	UCGUCUACCG230 CCACCUUGGG AGG	280-302	CCUCCACAGG UGGCGGUAGA CGG	413		
45	CACAGGUGG CGGUAGACG GCA	48	284-304	UGCCGUCUAC231 CGCCACCUGU GGA	282-304	UCCACAGGUG GCGGUAGACG GCG	414		
46	GUGGCGGU GACGGCGC CGA	49	289-309	UCGGCCGCCG232 UCUACCGCCA CCU	287-309	AGGUGGCGGU AGACGGCGC CGG	415		
47	CGGCCGGGA CGGCGAGCA ACA	50	303-323	UGUUGUCUCGC233 CGUCCCGGCC GCC	301-323	GGCGGCCGGG ACGGCGAGCA ACA	416		
48	GGCCGGGAC GCCGAGCAA CAA	51	304-324	UUGUUGCUCUG234 CCGUCCCCGGC CGC	302-324	GGGGCCGGGA CGGCAGACAA CAG	417		
49	CUGGCCUAC AUGCUGAGC GCA	52	449-469	UGCGCUCAGC235 AUGUACGCCA GCG	447-469	CGCUGGCGUA CAUGCUGAGC GCG	418		
50	UGGCGUACA UGCUGAGCG CGA	53	450-470	UCGCGCUCAG236 CAUGUACGCC AGC	448-470	GCUGGCGUAC AUGCUGAGCG CGC	419		
51	GGCGUACAU GCUGAGCGC GCA	54	451-471	UGCGCGCUCA237 GCAUGUACGC CAG	449-471	CUGGCGUACA UGCUGAGCGC GCA	420		
52	GCGUACAU CUGAGCGC CAA	55	452-472	UUGCGCGCUC238 AGCAUGUACG CCA	450-472	UGGCGUACAU GCUGAGCGC CAC	421		
53	GCUGAGCGC GCACACGUA GUA	56	460-480	UACUACGUGU239 GCGCGCUCAG CAU	458-480	AUGCUGAGCG CGCACACGUA GUA	422		
54	CUGAGCGCG CACACGUAG UAA	57	461-481	UUACUACGUG240 UGCGCGCUC GCA	459-481	UGCUGAGCGC GCACACGUAG UAC	423		
55	GAGCGCGCA CACGUAGUA CAA	58	463-483	UUGUACUACG241 UGUGCGCGCU CAG	461-483	CUGAGCGCGC ACACGUAGUA CAC	424		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense Agent Sequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Sense SEQ Range in Sequence 5' to 3'	Antisense SEQ ID	Range in Target Sequence 5' to 3' NO NM_014430.4	mRNA SEQ ID	Target Sequence NO	
56	CGCGCACAC GUAGUACAC CGA	59	466-486	UCGGUGUACU242 ACGUGUGCGC GCU	464-486	AGCGCGCACA CGUAGUACAC CGC	425		
57	GCGCACACG UAGUACACC GCA	60	467-487	UGCGGUGUAC243 UACGUGUGCG CGC	465-487	GCGCGCACAC GUAGUACACC GCC	426		
58	CGCACACGU AGUACACCG CCA	61	468-488	UGGCGGUGUA244 CUACGUGUGC GCG	466-488	CGCGCACACG UAGUACACCG CCU	427		
59	GCACACGUA GUACACCGC CUA	62	469-489	UAGGCGGUGU245 ACUACGUGUG CGC	467-489	GCGCACACGU AGUACACCGC CUU	428		
60	CACACGUAG UACACCGCC UUA	63	470-490	UAAGGGCGUG246 UACUACGUGU GCG	468-490	CGCACACGU GUACACCGCC UUG	429		
61	ACACGUAGU ACACCGCCU UGA	64	471-491	UCAAGGCGGU247 GUACUACGUG UGC	469-491	GCACACGUAG UACACCGCCU UGC	430		
62	ACGUAGUAC ACCGCCUUG CAA	65	473-493	UUGCAAGGCG248 GUGUACUACG UGU	471-493	ACACGUAGUA CACCGCCUUG CAG	431		
63	CGUAGUACA CCGCCUUGC AGA	66	474-494	UCUGCAAGGC249 GGUGUACUAC GUG	472-494	CACGUAGUAC ACCGCCUUGC AGC	432		
64	GUAGUACAC CGCCUUGCA GCA	67	475-495	UGCUGCAAGG250 CGGUGUACUA CGU	473-495	ACGUAGUACA CCGCCUUGCA GCC	433		
65	GCCUGCCGG GUCAGGAAG GCA	68	515-535	UGCCUUCCUG251 ACCCGGCAGG CCU	513-535	AGGCCUGCCG GGUCAGGAAG GCC	434		
66	CAGGAAGGC CACAAAGAG CGA	69	526-546	UGGCUCUUUG252 UGGCCUUCCU GAC	524-546	GUCAGGAAGG CCACAAAGAG CGG	435		
67	GGAAGGCCA CAAAGAGCG GCA	70	528-548	UGCCGCUUU253 UGUGGCCUUC CUG	526-548	CAGGAAGGCC ACAAAGAGCG GCG	436		
68	GAAGGCCAC AAAGAGCGG CGA	71	529-549	UCGCCGCUU254 UUGUGGCCUU CCU	527-549	AGGAAGGCCA CAAAGAGCGG CGU	437		
69	AAGGCCACA AAGAGCGG GUA	72	530-550	UACGCCGCU255 UUUGUGGCCU UCC	528-550	GGAAGGCCAC AAAGAGCGG GUG	438		
70	AGGCCACAA AGAGCGCG UGA	73	531-551	UCACGCCGU256 CUUUGUGGCC UUC	529-551	GAAGGCCACA AAGAGCGCG UGA	439		
71	GGCCACAAA GAGCGCGU GAA	74	532-552	UUCACGCCG257 UCUUUGUGGC CUU	530-552	AAGGCCACAA AGAGCGCGU GAG	440		
72	CCACAAAGA GCGCGUGA GCA	75	534-554	UGCUCACGCC258 GCUUUUGUG GCC	532-554	GGCCACAAAG AGCGCGUGA GCA	441		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in NO NM_014430.4	Antisense SEQ Sequence	ID	Range in NO NM_014430.4	mRNA Target	SEQ ID	SEQ NO
73	CACAAAGAG CGCGUGAG CAA	76	535-555	UUGCUCACGC259	533-555	GCCACAAAGA 442			
				CGCUCUUUGU GGC		GCGGCGUGAG CAG			
74	AGCACCGCG CCGUCGGCC AGA	77	557-577	UCUGGCCGAC260	555-577	GCAGCACCGC 443			
				GGCGCGGUGC UGC		GCCGUCGGCC AGC			
75	CGCGCCGUC GGCCAGCGC CAA	78	562-582	UUGGCGCUGG261	560-582	ACCGCGCCGU 444			
				CCGACGGCGC GGU		CGGCCAGCGC CAG			
76	GCGCCGUCG GCCAGGCC AGA	79	563-583	UCUGGCGCUG262	561-583	CCGCGCCGUC 445			
				GCCGACGGCG CGG		GGCCAGCGC AGG			
77	CAGCACAAAG CGUGGCCGC CAA	80	586-606	UUGGCGGCCA263	584-606	UGCAGCACAA 446			
				CGCUUUGUGCU GCA		GCGUGGCCGC CAG			
78	AGCACAAAGC GUGGCCGCC AGA	81	587-607	UCUGGCGGCC264	585-607	GCAGCACAAAG 447			
				ACGCUUUGUGC UGC		CGUGGCCGCC AGC			
79	GCACAAGCG UGGCCGCCA GCA	82	588-608	UGCUGGCGGC265	586-608	CAGCACAAAGC 448			
				CACGCUUUGUG CUG		GUGGCCGCCA GCG			
80	CAAGCGUGG CCGCCAGCG GUA	83	591-611	UACCGCUGGC266	589-611	CACAAGCGUG 449			
				GCCCACGCUU GUG		GCCGCCAGCG GUC			
81	AAGCGUGGC CGCCAGCGG UCA	84	592-612	UGACCGCUGG267	590-612	ACAAGCGUGG 450			
				CGGCCACGCU UGU		CCGCCAGCGG UCG			
82	AGCGUGGCC GCCAGCGGU CGA	85	593-613	UCGACCGCUG268	591-613	CAAGCGUGGC 451			
				GCGGCCACGC UUG		CGCCAGCGGU CGC			
83	GCGUGGCCG CCAGCGUC GCA	86	594-614	UGCGACCGCU269	592-614	AAGCGUGGCC 452			
				GGCGGCCACG CUU		GCCAGCGUC GCC			
84	GGCUGUGGCC UGUGGCCCG CGA	87	697-717	UCGCGGGCCA270	695-717	AAGGCUGUGC 453			
				CAGGCACAGC CUU		CUGUGGCCCG CGA			
85	GCCUGUGGC CCCGGAAGU CUA	88	703-723	UAGACUUCGC271	701-723	GUGCCUGUGG 454			
				GGGCCACAGG CAC		CCCGGAAGU CUU			
86	CUGUGGCC GCGAAGUC UCA	89	705-725	UGAAGACUUC272	703-725	GCCUGUGGCC 455			
				GCGGGCCACA GGC		CGCGAAGUC UCC			
87	GCCCCGCAA GCUUCCAG CUA	90	710-730	UAGCUGGAAG273	708-730	UGGCCCGCGA 456			
				ACUUUCGCGG CCA		AGUCUUCAGC CUC			
88	CCCGCGAAAG UCUUCCAGC UCA	91	711-731	UGAGCUGGAA274	709-731	GGCCCGCGAA 457			
				GACUUUCGCG GCC		GUCUUCCAGC UCA			
89	CCGCGAAAGU CUUCCAGCU CAA	92	712-732	UUGAGCUGGA275	710-732	GCCCCGCGAAAG 458			
				AGACUUUCGCG GGC		UCUUCCAGCU CAG			

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense SEQ Sequence	ID	Range in 5' to 3' NO NM_014430.4	mRNA Target	SEQ ID	SEQ NO
90	UCCAGCUCA GCAGUGUCU CGA	93	723-743	UCGAGACACU276 GCUGAGCUGG AAG	721-743	CUUCCAGCUC AGCAGUGUCU CGU	459		
91	CAGCUCAGC AGUGUCUCG UUA	94	725-745	UAACGAGACA277 CUGCUGAGCU GGA	723-745	UCCAGCUCAG CAGUGUCUCG UUC	460		
92	GCGCACCAAG AACCUAAAG UCA	95	944-964	UGACUUUAGC278 UUCUGGUGCG CUG	942-964	CAGCGCACCA GAAGCUAAAG UCU	461		
93	CAGAAGCUA AAGCUUUGA UGA	96	950-970	UCAUCAAGAC279 UUUAGCUUC GGU	948-970	ACCAGAACU AAAGCUUUGA UGC	462		
94	AGAAGCUAA AGCUUUGAU GCA	97	951-971	UGCAUCAAGA280 CUUAGCUUC UGG	949-971	CCAGAACU AAGCUUUGAU GCC	463		
95	GAAGCUAAA GCUUUGAUG CCA	98	952-972	UGGCAUCAAG281 ACUUUAGCUU CUG	950-972	CAGAACU AGCUUUGAUG CCA	464		
96	AAGCUAAAG UCUUGAUGC CAA	99	953-973	UUGGCAUCAA282 GACUUUAGCU UCU	951-973	AGAACU GCUUUGAUGC CAU	465		
97	GCUAAAGUC UUGAUGCCA UCA	100	955-975	UGAUGGCAUC283 AAGACUUUAG CUU	953-975	AAGCU CUUGAUGCCA UCA	466		
98	GAUGCCAUC AAAGGACAU CCA	101	966-986	UGGAUGGUCC284 UUGAUGGCAU CAA	964-986	UUGAUGCCA CAAAGGACAU CCC	467		
99	AUGCCAUC AAGGACAU CCA	102	967-987	UGGGAUGGUCC285 UUUGAUGGCA UCA	965-987	UGAACU AAAGGACAU CCU	468		
100	GCACAUAAA GGACAUCCC UGA	103	969-989	UCAGGGGAUGU286 CCUUUGAUGG CAU	967-989	AUGCCAUC AGGACAUCCC UGC	469		
101	CAUCUCUGU CACGUCCAC UAA	104	998-1018	UUAGUGGACG287 UGACAGAGAU GUG	996-1018	CACAU UCACGUCCAC UAA	470		
102	AUCUCUGUC ACGUCCACU AAA	105	999-1019	UUUAGUGGAC288 GUGACAGAGA UGU	997-1019	ACAUC CACGUCCACU AAU	471		
103	UCUCUGUCA CGUCCACUA AUA	106	1000-1020	UAUUAGUGGA289 CGUGACAGAG AUG	998-1020	CAUC ACGUCCACUA AUC	472		
104	CUCUGUCAC GUCCACUA UCA	107	1001-1021	UGAUUAGUGG290 ACGUGACAGA GAU	999-1021	AUC CGUCCACUA UCG	473		
105	UCUGUCACG UCCACUA CGA	108	1002-1022	UCGAUUAGUG291 GACGUGACAG AGA	1000-1022	UCUC GUCCACUA CGG	474		
106	CUGUCACGU CCACUA GGA	109	1003-1023	UCCGAUUAGU292 GGACGUGACA GAG	1001-1023	CUC UCCACUA GGC	475		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense	SEQ		Antisense	SEQ		mRNA	SEQ	
Agent	Sequence	ID	Range in	Sequence	ID	Range in	Target	ID	
	ID 5' to 3'	NO NM_014430.4	5' to 3'	NO NM_014430.4	Sequence	Range	Target	NO	
107	UGUCACGUC	110	1004-1024	UGCCGAUUAG	293	1002-1024	UCUGUCACGU	476	
	CACUAAUCG			UGGACGUGAC			CCACUAAUCG		
	GCA			AGA			GCA		
108	GUCA	111	1005-1025	GUCCGAUUA	294	1003-1025	CUGUCACGUC	477	
	GUCA			GUGGACGUGA			CACUAAUCGG		
	CAA			CAG			CAA		
109	UCACGUCCA	112	1006-1026	UUUGCCGAUU	295	1004-1026	UGUCACGUCC	478	
	CUAAUCGGC			AGUGGACGUG			ACUAAUCGGC		
	AAA			ACA			AAA		
110	CACGUCCAC	113	1007-1027	UUUUGCCGAU	296	1005-1027	GUCACGUCCA	479	
	UAAUCGGCA			UAGUGGACGU			CUAAUCGGCA		
	AAA			GAC			AAA		
111	CGUCCACUA	114	1009-1029	UCUUUUGCCG	297	1007-1029	CACGUCCACU	480	
	AUCGGCAAA			AUUAGUGGAC			AAUCGGCAAA		
	AGA			GUG			AGG		
112	GUCCACUAA	115	1010-1030	UCUUUUUGCC	298	1008-1030	ACGUCCACUA	481	
	UCGGCAAAA			GAUUAGUGGA			AUCGGCAAAA		
	GGA			CGU			GGA		
113	UCCACAUAA	116	1011-1031	UUCUUUUUGC	299	1009-1031	CGUCCACUAA	482	
	CGGC			CGAUUAGUGG			UCGGCAAAAG		
	GAA			ACG			GAG		
114	CCACUAAUC	117	1012-1032	UCUCCUUUUG	300	1010-1032	GUCCACUAAU	483	
	GGCAAAAGG			CCGAUUAGUG			CGGC		
	AGA			GAC			AAAGG		
115	CACUAAUCG	118	1013-1033	UUCUCCUUU	301	1011-1033	UCCACUAAUC	484	
	GCAAAAGGA			GCCGAUUAGU			GGCAAAAGGA		
	GAA			GGA			GAA		
116	ACUAAUCGG	119	1014-1034	UUUCUCCUUU	302	1012-1034	CCACUAAUCG	485	
	CAAAAGGAG			UGCCGAUUAG			GGCAAAAGGAG		
	AAA			UGG			AAA		
117	GAGAAGAUG	120	1040-1060	UCACACUUAG	303	1038-1060	GAGAAGAAGAU	486	
	ACCUAAGUG			GUCAUCUUCU			GACCUAAGUG		
	UGA			CUC			UGA		
118	UCCUCCGAC	121	1110-1130	UCUUCUCCU	304	1108-1130	CCUCCUCCGA	487	
	CAAGGAGGA			UGGUCCGGAGG			CCAAGGAGGA		
	AGA			AGG			AGG		
119	CCAGGGAAAG	122	1176-1196	UCCGGAGAGU	305	1174-1196	UCCAGGGAAAG	488	
	GAACUCUCC			UCCUUCCUG			GGAACUCUCC		
	GGA			GAA			GGU		
120	CAGGGAAAG	123	1177-1197	UACCGGAGAG	306	1175-1197	UCCAGGGAAAG	489	
	AACUCUCG			UUCCUUCCU			GAACUCUCG		
	GUA			GGA			GUC		
121	AGGAACUCU	124	1183-1203	UUGGUGGACC	307	1181-1203	GAAGGAACUC	490	
	CCGGUCCAC			GGAGAGAUCC			UCCGGUCCAC		
	CAA			UUC			CAU		
122	GGAACUCUC	125	1184-1204	UAUGGUGGAC	308	1182-1204	AAGGAACUCU	491	
	CGGUCCACC			CGGAGAGUUC			CCGGUCCACC		
	AUA			CUU			AUG		
123	ACUCUCGG	126	1187-1207	UUCCAUGGUG	309	1185-1207	GAACUCUCGG	492	
	UCCACCAUG			GACCGGAGAG			GUCCACCAUG		
	GAA			UUC			GAG		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense Sequence Range in 5' to 3' NO NM_014430.4	mRNA Target ID	SEQ ID	NO		
124	CUCGGGUCC	127	1190-1210	UUACUCCAUG310	1188-1210	CUCUCCGGUC	493		
	ACCAUGGAG			GUGGACCGGA		CACCAUGGAG			
	UAA			GAG		UAC			
125	UGAACCCCCA	128	1221-1241	UGAGUAAGUC311	1219-1241	UCUGAACCCC	494		
	GUGACUUAC			ACUGGGGUUC		AGUGACUUAC			
	UCA			AGA		UCA			
126	GUGACUUAC	129	1230-1250	UUACUGACCU312	1228-1250	CAGUGACUUA	495		
	UCAGGUCAG			GAGUAAGUCA		CUCAGGUCAG			
	UAA			CUG		UAU			
127	GACUUACUC	130	1232-1252	UGAUACUGAC313	1230-1252	GUGACUUACU	496		
	AGGUCAGUA			CUGAGUAAGU		CAGGUCAGUA			
	UCA			CAC		UCU			
128	CUUACUCAG	131	1234-1254	UUAGAUACUG314	1232-1254	GACUUACUCA	497		
	GUCAGUAUC			ACCUGAGUAA		GGUCAGUAUC			
	UAA			GUC		UAA			
129	CAGUAUCUA	132	1245-1265	UCGAGCUUAU315	1243-1265	GUCAGUAUCU	498		
	AUUAUAAGCU			AUUAGAUACU		AAUUAUAAGCU			
	CGA			GAC		CGG			
130	GUACUCAAU	133	1247-1267	UUCCGAGCUU316	1245-1267	CAGUAUCUAA	499		
	AUAAGCUCG			AUAAUAGUA		UAUAAGCUCG			
	GAA			CUG		GAG			
131	UAUCUAAA	134	1248-1268	UCUCCGAGCU317	1246-1268	AGUAUCUAAU	500		
	UAAGCUCGG			UAUAUUAAGAU		AUAAGCUCGG			
	AGA			ACU		AGU			
132	AUCUAAAUAU	135	1249-1269	UACUCCGAGC318	1247-1269	GUACUAAAUAU	501		
	AAGCUCGGGA			UUUAUAUAGA		UAAGCUCGGGA			
	GUA			UAC		GUU			
133	UCUAAAUAUA	136	1250-1270	UAAUCUCCGAG319	1248-1270	UAUCUAAAUAU	502		
	AGCUCGGAG			CUUUAUAUAG		AAGCUCGGAG			
	UUA			AUA		UUU			
134	CUAAAUAUA	137	1251-1271	UAAAACUCCGA320	1249-1271	AUCUAAAUAUA	503		
	GCUCGGAGU			GUUUUAUAUA		AGCUCGGAGU			
	UUA			GAU		UUG			
135	UAAAUAUAAG	138	1252-1272	UCAAACUCCG321	1250-1272	UCUAAAUAUA	504		
	CUCGGAGUU			AGCUUUAUAU		GCUCGGAGUU			
	UGA			AGA		UGG			
136	AUAAAAGCU	139	1254-1274	UCCCAAACUC322	1252-1274	UAAAUAUAAGC	505		
	CGGAGUUUG			CGAGCUUUA		UCGGAGUUUG			
	GAA			UUA		GAC			
137	UAAAAGCUC	140	1255-1275	UGUCCAAACU323	1253-1275	AAUAAAAGCU	506		
	GGAGUUUGG			CCGAGCUUAU		CGGAGUUUGG			
	ACA			AUU		ACG			
138	AUAAGCUCG	141	1256-1276	UCGUCCAAAC324	1254-1276	AUAUAAGCUC	507		
	GAGUUUGGA			UCCGAGCUUA		GGAGUUUGGA			
	CGA			UAU		CGG			
139	GCUCGGAGU	142	1260-1280	UCUCUCCGUCC325	1258-1280	AAGCUCGGAG	508		
	UUGGACCGGA			AAACUCCGAG		UUUGGACCGGA			
	GGA			CUU		GGG			
140	GGAGUUUGG	143	1264-1284	UAGACCCUCC326	1262-1284	UCGGAGUUUG	509		
	ACGGAGGGU			GUCCAAACUC		GACGGAGGGU			
	CUA			CGA		CUG			

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Sense SEQ Range in 5' to 3'	Antisense Sequence ID	Range in Target NO NM_014430.4	mRNA ID	SEQ Sequence	Target ID NO
141	CACCCAGC GACCUUCC GUA	144	1299-1319	UACGGAAAGG327 UCGCUGGGGU GGU	1297-1319	ACCACCCAG CGACCUUCC GUG	510		
142	GUCUGUGAU CAAAAGCGG ACA	145	1319-1339	UGUCCGCUUG328 UGAUCACAGA CAC	1317-1339	GUGUCUGUGA UCACAAGCGG ACC	511		
143	UCUGUGAU ACAAGCGGA CCA	146	1320-1340	UGGUCCGCUU329 GUGAUCACAG ACA	1318-1340	UGUCUGUGAU CACAAGCGGA CCA	512		
144	CUGUGAUCA CAAGCGGAC CAA	147	1321-1341	UUGGUCCGCU330 UGUGAUCACA GAC	1319-1341	GUCUGUGAU ACAAGCGGAC CAU	513		
145	UGUGAUCA AAGCGGACC AUA	148	1322-1342	UAUGGUCCGC331 UUGUGAUCAC AGA	1320-1342	UCUGUGAUCA CAAGCGGACC AUC	514		
146	GUGAUCACA AGCGGACCA UCA	149	1323-1343	UGAUGGUCCG332 CUUGUGAUC CAG	1321-1343	CUGUGAUAC AAGCGGACCA UCC	515		
147	AGGAGCUGC UAGCCAAAG CAA	150	1371-1391	UUGCUUUGGC333 UAGCAGCUCC UGG	1369-1391	CCAGGAGCUG CUAGCCAAAG CAU	516		
148	AGCUGCUAG CCAAAGCAU UGA	151	1374-1394	UCAAUGCUUU334 GGCUAGCAGC UCC	1372-1394	GGAGCUGCUA GCCAAAGCAU UGG	517		
149	CUGCUAGCC AAAGCAUUG GAA	152	1376-1396	UUCCAAUGCU335 UUGGCUAGCA GCU	1374-1396	AGCUGCUAGC CAAAGCAUUG GAG	518		
150	UGCUAGCCA AAGCAUUGG AGA	153	1377-1397	UCUCCAAUGC336 UUUGGCUAGC AGC	1375-1397	GCUGCUAGCC AAAGCAUUGG AGA	519		
151	CUAGCCAAA GCAUUGGAG ACA	154	1379-1399	UGUCUCCAAU337 GCUUUGGCUA GCA	1377-1399	UGCUAGCCAA AGCAUUGGAG ACC	520		
152	UAGCCAAAG CAUUGGAGA CCA	155	1380-1400	UGGUCUCCAA338 UGCUUUGGC AGC	1378-1400	GCUAGCCAAA GCAUUGGAGA CCC	521		
153	GGAGCUCCU UCGUUGGAC CUA	156	1729-1749	UAGGUCCAAC339 GAAGGAGCUC CCU	1727-1749	AGGGAGCUCC UUCGUUGGAC CUC	522		
154	GAGCUCCUU CGUUGGACC UCA	157	1730-1750	UGAGGUCCA340 CGAAGGAGCU CCC	1728-1750	GGGAGCUCCU UCGUUGGACC UCC	523		
155	AGCUCCUUC GUUGGACCU CCA	158	1731-1751	UGGAGGUCCA341 ACGAAGGAGC UCC	1729-1751	GGAGCUCCUU CGUUGGACCU CCA	524		
156	AGGCCUUGG CCAU AUGUU GCA	159	1762-1782	UGCAACAUAU342 GGCCCAGGCC UUG	1760-1782	CAAGGCCUUGG GCCAU AUGUU GCU	525		
157	GCCUGGGCC AUAUGUUGC UGA	160	1764-1784	UCAGCAACAU343 AUGGCCAGG CCU	1762-1784	AGGCCUGGGC CAUAUGUUGC UGG	526		

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense Sequence Range in 5' to 3' NO NM_014430.4	mRNA ID	Target Sequence	SEQ ID	Target ID	NO
158	CUGGGCCAU	161	1766-1786	UCCCAGCAAC344	1764-1786	GCCUGGGCCA	527		
	AUGUUGCUG			AUAUGGCCA		UAUGUUGCUG			
	GGA			GGC		GGA			
159	UGGGCCAU	162	1767-1787	UUCCCAGCAA345	1765-1787	CCUGGGCCAU	528		
	UGUUGCGUG			CAUAUGGCC		AUGUUGCUGG			
	GAA			AGG		GAA			
160	AUGUUGCUG	163	1775-1795	UGAGGGAAAUU346	1773-1795	AUAUGUUGCU	529		
	GGAAUUUCC			CCCAGCAACA		GGGAAUUUCC			
	UCA			UAU		UCC			
161	CUGGGAAAU	164	1781-1801	UAGGGGUGGAG347	1779-1801	UGCUGGGAAU	530		
	UCCUCCACC			GAAAUUCCCA		UUCCUCCACC			
	CUA			GCA		CUU			
162	UUCCUCCAC	165	1789-1809	UCAUGACGAA348	1787-1809	AUUUUCUCCA	531		
	CCUUCGUCA			GGGUGGGAGGA		CCCUUCGUCA			
	UGA			AAU		UGC			
163	AAGGGCCGC	166	1838-1858	UUAGGGAAUUGG349	1836-1858	AGAAGGGCCG	532		
	CUCCAUUCC			AGGC GGCCU		CCUCCAUUCC			
	UAA			UCU		UAC			
164	GGCCGCCUC	167	1841-1861	UUAGUAGGAA350	1839-1861	AGGGCCGCCU	533		
	CAUUCUAC			UGGAGGGCGC		CCAUUCUAC			
	UAA			CCU		UAA			
165	ACUGCAAAG	168	1904-1924	UGCUGUCAUA351	1902-1924	CCACUGCAAA	534		
	ACUAUGACA			GCUUUGCAG		GACUAUGACA			
	GCA			UGG		GCA			
166	CAGCAUCAA	169	1920-1940	UGGUCCUGAA352	1918-1940	GACAGCAUCA	535		
	AUUCAGGA			AUUUGAUGCU		AAUUUCAGGA			
	CCA			GUC		CCU			
167	UCAGGACCU	170	1932-1952	UGUACUGUCU353	1930-1952	UUUCAGGACC	536		
	GCAGACAGU			GCAGGUCCUG		UGCAGACAGU			
	ACA			AAA		ACA			
168	GCAGACAGU	171	1941-1961	UAUUCUAGCCU354	1939-1961	CUGCAGACAG	537		
	ACAGGCUAG			GUACUGUCUG		UACAGGCUAG			
	AUA			CAG		AUA			
169	CAGACAGUA	172	1942-1962	UUAUCUAGCC355	1940-1962	UGCAGACAGU	538		
	CAGGCUAGA			UGUACUGUCU		ACAGGCUAGA			
	UAA			GCA		UAA			
170	AGACAGUAC	173	1943-1963	UUUAUCUAGC356	1941-1963	GCAGACAGUA	539		
	AGGCUAGAU			CUGUACUGUC		CAGGCUAGAU			
	AAA			UGC		AAC			
171	UCCCCACUUG	174	2087-2107	UGCCUUUCAG357	2085-2107	CCUCCCACUU	540		
	CCCUGAAAG			GGCAAGUGGG		GCCCGUGAAAG			
	GCA			AGG		GCC			
172	CUGCUGCUA	175	2148-2168	UGGGAUUAGA358	2146-2168	GACUGCUGCU	541		
	CAUCUAUAC			UGUAGCAGCA		ACAUCUAUAC			
	CCA			GUC		CCC			
173	UGCUGCUAC	176	2149-2169	UGGGGAUUAG359	2147-2169	ACUGCUGCUA	542		
	AUCUAAUCC			AUGUAGCAGC		CAUCUAUCC			
	CCA			AGU		CCU			
174	GCUGCUACA	177	2150-2170	UAGGGGAUUA360	2148-2170	CUGCUGCUAC	543		
	UCUAAUCCC			GAUGUAGCAG		AUCUAAUCCC			
	CUA			CAG		CUA			

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense Sequence 5' to 3'	SEQ ID	Range in Target NO NM_014430.4	mRNA ID	SEQ NO	
175	ACAUCAUAU	178	2156-2176	UAAUUGGUAGG361	2154-2176	CUACAUCAA	544		
	CCCUUACCA			GGAAUAGAUG		UCCCCUACCA			
	AUA			UAG		AUG			
176	AUCUAAAUC	179	2158-2178	UGCAUUGGU362	2156-2178	ACAUCUAUC	545		
	CCUACCAAU			GGGGAUUAGA		CCCUACCAAU			
	GCA			UGU		GCC			
177	CCCCUACCA	180	2165-2185	UACAGGAGGC363	2163-2185	AUCCCCUACC	546		
	AUGCCUCCU			AUUGGUAGGG		AAUGCCUCCU			
	GUA			GAU		GUC			
178	CCCUACCAA	181	2166-2186	UGACAGGAGG364	2164-2186	UCCCCUACCA	547		
	UGCCUCUG			CAUUGGUAGG		AUGCCUCUG			
	UCA			GGA		UCC			
179	ACCAAUGCC	182	2170-2190	UUAGGGACAG365	2168-2190	CUACCAAUGC	548		
	UCCUGUCCC			GAGGCAUUGG		CUCCUGUCCC			
	UAA			UAG		UAA			
180	CCAAUGCCU	183	2171-2191	UUUAGGGACA366	2169-2191	UACCAAUGCC	549		
	CCUGUCCCU			GGAGGCAUUG		UCCUGUCCCU			
	AAA			GUU		AAA			
181	AUGCCUCCU	184	2174-2194	UAGUUUAGGG367	2172-2194	CAAUGCCUCC	550		
	GUCCCUAAA			ACAGGAGGCA		UGUCCCCUAAA			
	CUA			UUG		CUC			
182	UGCCUCUG	185	2175-2195	UGAGUUUAGG368	2173-2195	AAUGCCUCCU	551		
	UCCCUCUAC			GACAGGAGGC		GUCCCCUAAA			
	UCA			AUU		UCC			
183	UACUGAUGA	186	2202-2222	UAGAGAGGGC369	2200-2222	CAUACUGAUG	552		
	CAGCCCUCU			UGUCAUCAGU		ACAGCCCUCU			
	CUA			AUG		CUG			
184	AGCUCAGCA	553	726-746	UGAACCGAGAC602	724-746	CCAGCUCAGC	1132		
	GUGUCUCGU			ACUGCUGAGC		AGUGUCUCGU			
	UCA			UGG		UCC			
185	GCUCAGCAG	554	727-747	UGGAACCGAGA603	725-747	CAGCUCAGCA	1133		
	UGUCUCGUU			CACUGCUGAG		GUGUCUCGUU			
	CCA			CUG		CCC			
186	GGACGGUAG	555	752-772	UAUGUCGGUC604	750-772	GGGGACGGUA	1134		
	CAGACCGAC			UGCUACCGUC		GCAGACCGAC			
	AUA			CCC		AUC			
187	ACGGUAGCA	556	754-774	UGGAUGUCGG605	752-774	GGACGGUAGC	1135		
	GACCGACAU			UCUGCUACCG		AGACCGACAU			
	CCA			UCC		CCU			
188	CGGUAGCAG	557	755-775	UAGGAUGUCG606	753-775	GACGGUAGCA	1136		
	ACCGACAU			GUCUGCUACC		GACCGACAU			
	CUA			GUC		CUU			
189	AGCAGACCG	558	759-779	UCAGAAGGAU607	757-779	GUAGCAGACC	1137		
	ACAUCCUUC			GUCGGUCUGC		GACAUCCUUC			
	UGA			UAC		UGG			
190	GCAGACCGA	559	760-780	UCCAGAAGGA608	758-780	UAGCAGACCG	1138		
	CAUCCUUC			UGUCGGUCUG		ACAUCCUUC			
	GGA			CUA		GGG			
191	UCCAUGCAA	560	894-914	UGUGAUGGAC609	892-914	CUUCCAUGCA	1139		
	CUGUCCAU			AGUUGCAUGG		ACUGUCCAU			
	ACA			AAG		ACG			

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Antisense SEQ Range in 5' to 3' NO NM_014430.4	mRNA Target SEQ ID	SEQ NO			
192	CCAUCAAC UGUCCAUC CGA	561	895-915	UCGUGAUGGA610 CAGUUGCAUG GAA	893-915	UUCCAUGCAA 1140 CUGUCCAUC CGG			
193	CAUGCAAC GUCCAUCAC GGA	562	896-916	UCCGUGAUGG611 ACAGUUGCAU GGA	894-916	UCCAUGCAAC 1141 UGUCCAUCAC GGC			
194	AACUGUCCA UCACGGCUG CAA	563	901-921	UUGCAGCCGU612 GAUGGACAGU UGC	989-921	GCAACUGUCC 1142 AUCACGGCUG CAA			
195	ACUGUCCAU CACGGCUGC AAA	564	902-922	UUUGCAGCCG613 UGAUGGACAG UUG	900-922	CAACUGUCCA 1143 UCACGGCUGC AAC			
196	GUCCAUCAC GCCUGCAAC UGA	565	905-925	UCAGUUGCAG614 CCGUGAUGGA CAG	903-925	CUGUCCAUC 1144 CGGCUGCAAC UGA			
197	AUCACGGCU GCAACUGAA AUA	566	909-929	UAUUUCAGUU615 GCAGCCGUGA UGG	907-929	CCAUCACGGC 1145 UGCAACUGAA AUC			
198	UGGGACACA GCGCACCA AAA	567	935-955	UUUCUGGUGC616 GCUGUGUCCC AGC	933-955	GCUGGGACAC 1146 AGCGCACCA AAG			
199	GACACAGCG CACCAGAAG CUA	568	938-958	UAGCUUCUGG617 UGCGCUGUGU CCC	936-958	GGGACACAGC 1147 GCACCAGAAG CUA			
200	ACAGCGCAC CAGAACUA AAA	569	941-961	UUUUAGCUUC618 UGGUGCGCUG UGU	939-961	ACACAGCGCA 1148 CCAGAACUA AAG			
201	GCCACAUUC UACGGGCUC A	570	1659-1677	UGAGCCCCGU619 GAAUGUGGCC U	1659-1679	AAGCCACAUU 1149 CUACGGGCUC U			
202	GAAAGUACU CAGGGAGCU A	571	1715-1733	UAGCUCCCCUG620 AGUACUUUCU U	1715-1735	AAGAAAGUAC 1150 UCAGGGAGCU C			
203	GUCUAUACC CUUACCUGA A	572	2033-2051	UUCAGGUAAG621 GGUUAUAGACU U	2033-2053	AAGUCUAUAC 1151 CCUUACCUGA A			
204	GCUGCUAGC CAAAGCAAU A	573	1373-1391	UAAAUGCUUUG622 GCUAGCAGCU C	1373-1393	GAGCUGCUAG 1152 CCAAAGCAAU G			
205	GGAGUGGAG UGCUGUCAU A	574	1534-1552	UAUGACAGCA623 CUCCACUCU U	1534-1554	AAGGAGUGGA 1153 GUGCUGUCAU A			
206	GGCCAAGAU CAAGAUGUC A	575	2102-2120	UGACAUUUUG624 AUCUUGGCC U	2102-2122	AAGGCCAAGA 1154 UCAAGAUGUC C			
207	CUUGAGAAC UGUCUUCAU A	576	2228-2246	UAUGAAAGACA625 GAUCUCAAGU U	2228-2248	ACCUUGAGAU 1155 CUGUCUUCAU ACC			
208	CUUGAGAAC UGUCUUCAU A	576	2228-2246	UAUGAAAGACA626 GAUCUCAAGG U	2228-2248	UUACCUUGAG 1156 AUCUGUCUUC AUA			

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAs	Sense AgentSequence	SEQ ID	Range in ID 5' to 3' NO NM_014430.4	Sense Sequence	Antisense SEQ ID	Range in 5' to 3' NO NM_014430.4	mRNA Target	SEQ ID	NO
209	CCUCAACU AACAAAAAC A	577	2254-2272	UGUUUUUGUU627	2254-2274	CCCCUCAAAC	1157	UAACAAAAAC A	
210	CUCAAACUA ACAAAAACA A	578	2255-2273	UUGUUUUUGU628	2255-2275	CCCCUCAAACU	1158	AACAAAAACA U	
211	CAAACUAA AAAAACAU A	579	2257-2275	UAAUGUUUUU629	2257-2277	CUCAAACUAA	1159	CAAAACAUU U	
212	CUAACAAA ACAUUCCA A	580	2261-2279	UUGGAAAUGU630	2261-2281	AACUAACAAA	1160	AACAUUCCA A	
213	CAAAAACA UUCCAAUA A	581	2265-2283	UUUAUUUGGAA631	2265-2285	AACAAAAACA	1161	UUUCCAAUAA A	
214	CCAAUAAA AUAUCAAAU A	582	2276-2294	UUUUUUGAU632	2276-2296	UUCCAAUAAA	1162	AAUAUCAAAU A	
215	CAAUAAAA UAUCAAAUA A	583	2277-2295	UUUUUUGUA633	2277-2297	UCCAAUAAAA	1163	AUAUCAAAUA U	
216	CCAAAGCA UGGAGACCC A	584	1381-1399	UGGGUCUCCA634	1381-1401	AGCCAAAGCA	1164	UUGGAGACCC U	
217	CAGGUCA AUCUAAU A	585	1238-1256	UAAUUAUAGAU635	1238-1258	CUCAGGUAG	1165	UAUCUAAU A	
218	AUGUCAAAG CCACAUUC A	586	1651-1669	UAGAAUUGGG636	1651-1671	GAAUGUCAAA	1166	GCCACAUUC A	
219	GCUCUACUC UAUGAGUUG A	587	1673-1691	UCAACUCUA637	1673-1693	GGGCUCUACU	1167	CUAUGAGUUG U	
220	CUAUGAGUU GUGACUUUC A	588	1681-1699	UGAAAGUCAC638	1681-1701	CUCUAUGAGU	1168	UGUGACUUUC A	
221	UAUGAGUUG UGACUUUCA A	589	1682-1700	UUGAAAGUCA639	1682-1702	UCUAUGAGUU	1169	GUGACUUUCA A	
222	GGCCCAAAG AAAGUACUC A	590	1707-1725	UGAGUACUUU640	1707-1727	UUGGCCAAA	1170	GAAAGUACUC A	
223	GCCAU AUG UGCUGGGAA A	591	1768-1786	UUUCCCAGCA641	1768-1788	GGGCCAU AUG	1171	UUGCUGGGAA U	
224	CCCACUGCA AAGACUAUG A	592	1899-1979	UCAUAGUCUU642	1899-1981	GACCCACUGC	1172	AAAGACUAUG A	
225	GACUAUGAC AGCAUCAAA A	593	1910-1928	UUUUGAUGCU643	1910-1930	AAGACUAUGA	1173	CAGCAUCAAA U	

TABLE 2-continued

Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO NM_014430.4	Range in NO	Sense SEQ 594	Antisense SEQ 1912-1930	ID	Range in NO NM_014430.4	mRNA Target Sequence	SEQ ID NO	
226 CUAUGACAG CAUCAAAU A	594	1912-1930	UAUUUUGAUG644	1912-1932	GACUAUGACA	1174	GCAUCAAAU U		
227 CUGAAGAAU GCUGUUCUU A	595	2047-2065	UAAGAACAGC645	2047-2067	ACCUGAAGAA	1175	UGCUGUUCUU U		
228 CUGAAGAAU GCUGUUCUU A	595	2047-2065	UAAGAACAGC646	2047-2067	ACCUGAAGAA	1176	UGCUGUUCUU U		
229 CCUGAAAGG CCAAGAUCA A	596	2095-2113	UUGAUCUUGG647	2095-2115	GCCCUGAAAG	1177	GCCAAGAUCA A		
230 CCUGAAAGG CCAAGAUCA A	596	2095-2113	UUGAUCUUGG648	2095-2115	GCCCUGAAAG	1178	GCCAAGAUCA A		
231 GACUGCUGC UACAUCUAA A	597	2144-2162	UUUAGAUGUA649	2144-2164	CUGACUGCUG	1179	CUACAUCAA U		
232 AGGUCAGUA UCUAAUAAA A	598	1239-1257	UUUAUUAUAGA650	1239-1259	UCAGGUCAGU	1180	AUCUAAUAAA A		
233 GGAAUUUCC UCCACCCUU A	599	1782-1800	UAAGGGUGGA651	1782-1802	UGGGAAUUC	1181	CUCCACCCUU C		
234 GAUUCACCU UUGACGUGU A	600	1597-1615	UACACGUCAA652	1597-1617	CCGAUUCACC	1182	UUUGACGUGU A		
235 GAGGAUGAC ACGUGCCUG A	601	1479-1497	UCAGGCACGU653	1479-1499	UGGAGGAUGA	1183	CACGUGCCUG A		
236 CUCUAUGAG UUGUGACUU A	602	1679-1697	UAAGUCACAA654	1679-1699	UACUCUAUGA	1184	GUUGUGACUU U		
237 AGAGGGAGGA UGGAACUGC A	603	1430-1448	UGCAGGUCCA655	1430-1450	CUAGAGGGAGG	1185	AUGGAACUGC A		
238 GAUUCACCU UUGACGUGU A	600	1597-1615	UACACGUCAA656	1597-1617	CCGAUUCACC	1186	UUUGACGUGU A		
239 UCAGGUCAAG UAUCUAAA A	601	1237-1255	UUUUUAGAUA657	1237-1257	ACUCAGGUCA	1187	GUAUCAAUA U		

[0629] The nucleotide sequence of exemplary modified versions of the dsRNA agents set forth in Table 2 are set forth in Table 3. More specifically, Table 3 sets forth the nucleotide sequence of exemplary sense strands, antisense strands, and dsRNA agent pairs of sense and antisense strands. It is to be understood that while the sense and antisense strands are set forth in pairs in Table 3, the disclosure encompasses dsRNA agents comprising any sense strand and any antisense set forth in Table 3 (e.g., that

are at least partially complementary (e.g., as could be determined by a person of ordinary skill in the art)). It is to be understood that while the nucleotide sequence of the sense strands and antisense strands in Table 3 are set forth as modified (i.e., contain at least one modified nucleotide), the disclosure encompasses the sense and antisense sense strands set forth in Table 3 comprising other nucleotide modifications (e.g., as described herein) or that are unmodified.

TABLE 3

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
240 asgsagcaA fgCfcFcfA aggcaagca	658	63-83	(vinu)sGfs cuuGfcCfUf ucggCfuUfg cucusgsg	893	61-83	CCAGAGCAAG CCGAAGGCAA GCA	370
241 asasgcgA faGfGfCfa agcacgaua	659	68-88	(vinu)sAfs ucgUfgCfUf ugcuCfuUfg gcuusgsc	894	66-88	GCAAGCCGAA GGCAAGCACG AUG	371
242 asgsccgA fgGfCfAfa gcacgauga	660	69-89	(vinu)sCfs aucGfuGfCf uuucCfuUfc ggcususg	895	67-89	CAAGCCGAAG GCAAGCACGA UGG	372
243 cscsgaaG fcAfAfGfc acgauggca	661	71-91	(vinu)sGfs ccaUfcGfUf gcuuGfcCfu ucggscsu	896	69-91	AGCCGAAGGC AAGCACGAUG GCG	373
244 csgsaaggC faAfGfCfa cgauggcga	662	72-92	(vinu)sCfs gccAfUfcGfGf ugcuUfgCfc uucgsgsc	897	70-92	GCCGAAGGCA AGCACGAUUG CGC	374
245 gsgscaagC faCfGfAf fu ggccucaaa	663	76-96	(vinu)sUfs gagCfCfCf aucGfgCfu ugccsusu	898	74-96	AAGCCAAGCA CGAUGGCCU CAC	375
246 gcscaagcA fcGfAfUfg cgccucaca	664	77-97	(vinu)sGfs ugaGfcGfCf caucGfuUfc uugcscsu	899	75-97	AGCCAAGCAC GAUGGCGCUC ACC	376
247 csasagaAC fgAfUfgCf cgccucacca	665	78-98	(vinu)sGfs gugAfCfGfCf ccauCfgUfg cuugscsc	900	76-98	GGCAAGCACG AUGGCGCUCA CCA	377
248 asasgcacG faUfGfGfc gcucaccaa	666	79-99	(vinu)sUfs gguGfaGfCf gccaUfcGfu gcuusgsc	901	77-99	GCAAGCACGA UGGCGCUCAC CAG	378
249 ascsgaugG fcGfCfUfc accagccga	667	83-103	(vinu)sCfs ggcUfgGfUf gagcGfcCfa ucgusgsc	902	81-103	GCACGAUGGC GCUCACCAGC CGG	379
250 cscscggcA fgCfcFcfu gccagcgua	668	143-163	(vinu)sAfs cgcUfgGfCf acggCfuGfc ggggscsg	903	141-163	CGCCCCGCAG CCGUGGCCAGC GUC	380
251 gscsagccG fuGfCfCfa gecucacga	669	147-167	(vinu)sCfs gugAfCfGfCf ugCcAfCfGfg cugcsgsg	904	145-167	CCGCAGCCGU GCCAGCGUCA CGC	381
252 csasgccgU fgCfcfAf g cguacacga	670	148-168	(vinu)sGfs cguGfaCfGf cuggCfaCfg gcuugscsg	905	146-168	CGCAGCCGUG CCAGCGCUCAC GCU	382
253 asgscgguG fcCfAfGfc gucacgaua	671	149-169	(vinu)sAfs gcgUfgAfcCf gcugGfcAfC ggcusgsc	906	147-169	GCAGCCGUGC CAGCGUCACG CUG	383

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence 5' to 3'	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
254 gscscgugC fcAfGfCfg ucacgcuga	672	150-170	(vinu)sCfs agcGfuGfAf cgcuGfgCfa cgccsug	907	148-170	CAGCCGUGCC AGGGUCACGC UGU	384
255 csgsugccA fgCfGfUfc acgcuguaa	673	152-172	(vinu)sUfs acaGfcGfUf gacgCfuGfg cacgsgsc	908	150-172	GCCGUGGCCAG CGUCACGCUG UAG	385
256 gscscagcG fuCfAfCfg cuguagcaa	674	155-175	(vinu)sUfs gcuAfcaGfGf cgugAfcaGfc uggcsasc	909	153-175	GUGCAGCGU CACGCUGUAG CAG	386
257 cscsagcguC fcAfCfGfc uguagcaga	675	156-176	(vinu)sCfs ugcUfaCfAf gcuGuGfaCfg cuggscsa	910	154-176	UGCCAGCGUC ACGCUGUAGC AGC	387
258 csasgcguC faCfGfCfu guagcagca	676	157-177	(vinu)sGfs cugCfuAfCf agcgUfgafc gcugsgsc	911	155-177	GCCAGCGUCA CGCUGUAGCA GCC	388
259 gscsgucaC fgCfUfcfu agcagccga	677	159-179	(vinu)sCfs ggcUfgCfUf acagCfgUfg acgcsug	912	157-179	CAGCGUCACG CUGUAGCAGC CGA	389
260 csgsucacG fcUfGfUfa gcagccgaa	678	160-180	(vinu)sUfs cgGfuGfCf uacaGfcGfu gacgscsu	913	158-180	AGCGUCACGC UGUAGCAGCC GAG	390
261 gsuscaaggC fuGfUfAfg cagccgaga	679	161-181	(vinu)sCfs ucgGfcUfGf cuacAfgCfg ugacsgsc	914	159-181	GCCUCACCCU GUAGCAGCCG AGC	391
262 csascgcuG fuAfGfCfa gccgagcaa	680	163-183	(vinu)sUfs gcuCfgGfCf ugcuAfcaGfg cgugscasc	915	161-183	GUCACGCUGU AGCAGCCGAG CAU	392
263 ascsgcugU faGfCfAfg ccgagcaua	681	164-184	(vinu)sAfs ugcUfcGfGf cugcUfaCfa gcuGusgsa	916	162-184	UCACGCUGUA GCAGCCGAGC AUC	393
264 gscsuguaG fcAfGfCfc gagcaucaa	682	166-186	(vinu)sUfs gauGfcUfCf ggcuGfcUfa cagcsgsu	917	164-186	ACGCUGUAGC AGCCGAGCAU CAG	394
265 asgscggagaG fcAfUfcfa gcccgaaaa	683	174-194	(vinu)sUfs uucGfgGfCf ugauGfcUfc ggcugscsc	918	172-194	GCAGCCGAGC AUCAAGCCGA AAG	395
266 csgsagcaU fcAfGfCfc cgaaggaa	684	177-197	(vinu)sUfs ccuUfuCfGf ggcuGfaUfg cugcsgsc	919	175-197	GCCGAGCAUC AGCCGAGAAAG GAA	396
267 csasgccG faAfAfGfg aagcacgaa	685	184-204	(vinu)sUfs cguGfcUfUf ccuuUfcGfg gcugscas	920	182-204	AUCAGCCCCGA AAGGAAGCAC GAA	397

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence 5' to 3'	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
268 asgscccgA faAfGfGfa agcacaaa	686	185-205	(vinu)sUfs ucgUfgCfUF uccuUfuCfG ggcuusgsa	921	183-205	UCAGCCCGAA AGGAAGCACG AAA	398
269 gscscggA faGfGfAfa gcacgaaaa	687	186-206	(vinu)sUfs uucGfuGfCf uuccUfuUfc gggcsusg	922	184-206	CAGCCCGAAA GGAAGCACGA AAG	399
270 csgsgcggC fgUfGfGfa ccggcgaca	688	234-254	(vinu)sGfs ucgCfcGfGf uccaCfGfCfc gccgscsc	923	232-254	GGCGGCCGGCG UGGACCGGGCG ACG	400
271 gsgscggcG fuGfGfAfc cgccgacga	689	235-255	(vinu)sCfs gucGfcCfGf guccAfcGfc cgccsgsc	924	233-255	GCGCGGGCGU GGACCGGGCGA CGG	401
272 gscsgggcgU fgGfAfCfc ggcgacgga	690	236-256	(vinu)sCfs cguCfGfCfCf ggucCfGfCfG cccgscsng	925	234-256	CGGCGGGCGUG 402 GACCGGGCGAC GGG	
273 gsusggacc fgGfCfGfa cgggguggca	691	241-261	(vinu)sGfs ccaCfcCfGf ucgcCfGfGfu ccacsgsc	926	239-261	GCGUGGGACCG 403 GCGACGGGUG GCA	
274 usgsgaccG fgCfGfAfc ggguggcaa	692	242-262	(vinu)sUfs gccAfcCfCfCf gucgCfcGfg uccascsng	927	240-262	CGUGGACCGG 404 CGACGGGUGG CAC	
275 gsgsacccG fcGfAfCfc gguggcaca	693	243-263	(vinu)sGfs ugcCfaCfCfCf cgucGfcCfc guccsasc	928	241-263	GUGGACCCGC 405 GACGGGUGGC ACA	
276 gsasccggC fgAfCfGfg guggcaca	694	244-264	(vinu)sUfs gugCfcAfCfCf cceuCfGfCfc ggucscsa	929	242-264	UGGACCGGGCG 406 ACGGGUGGCA CAG	
277 csgsgcgacA fgGfGfUfg gcacagcua	695	247-267	(vinu)sAfs gcuGfuGfCfCf caccCfGfUfc gccgsgsu	930	245-267	ACCGGCGACG 407 GGUGGCACAG CUG	
278 gscsgacgG fgUfGfGfc acagcugga	696	249-269	(vinu)sCfs caqCfuGfUF gccaCfcCfG ucgcscsng	931	247-269	CGGCGACGGG 408 UGGCACAGCU GGC	
279 gsgsuggcA fcAfGfCfu ggcauacga	697	255-275	(vinu)sCfs guaUfgCfCfCf agcuGfuGfc caccscsng	932	253-275	CGGGUGGCAC 409 AGCUGGGCAUA CGC	
280 gsusggcaC faGfCfUfg gcauacgca	698	256-276	(vinu)sGfs cguAfufCfCf cagcUfgUfg ccacscsc	933	254-276	GGGUGGGACA 410 GCUGGCAUAC GCG	
281 usgsgcacA fgCfUfGfg cauacgca	699	257-277	(vinu)sCfs gcgUfaUfGfCf ccagCfuGfu gccascsc	934	255-277	GGUGGGCACAG 411 CUGGCAUACG CGG	

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NO	Sense Sequence NM_014430.4	Antisense Range in 5' to 3'	SEQ ID NO	mRNA Target Sequence NM_014430.4	SEQ ID NO
282 cscsuccaC faGfGfUfg cggguaagaa	700	280-300	(vinu)sUfs cuuCfcGfCf caccUfgUfg gaggsgsa	935	278-300	UCCCCUCCACA GGUGGCGGUAGAC	412
283 uscscacaG fgUfGfGfc gguagacga	701	282-302	(vinu)sCfs gucUfaCfCf gcacaCfcUfg uggasgsg	936	280-302	CCUCACACAGG UGGCGGUAGACCGG	413
284 csascaggU fggfCfGfg uagacggca	702	284-304	(vinu)sGfs ccgUfcUfAf ccgcCfaCfc ugugsgsa	937	282-304	UCCACAGGUG GCGGUAGACG GCG	414
285 gsusggcgG fuAfGfAfc ggccggccga	703	289-309	(vinu)sCfs ggcCfgcfc gucuAfcCfg ccacscsu	938	287-309	AGGUGGCCGGU AGACGGCGGC CGG	415
286 csgsgcgcG fgAfCfGfg cgagcaaca	704	303-323	(vinu)sGfs uugCfuCfGf ccguCfcCfg gccgscsc	939	301-323	GGCGGCCGGG ACGGCGAGCA ACA	416
287 gsgsccggG faCfGfGfc gagcaacaa	705	304-324	(vinu)sUfs guuGfcUfcf gccgUfcCfc ggccsgsc	940	302-324	GCGGCCGGGA CGGCGAGCAA CAG	417
288 csusggcgU faCfAfUfg cugagcgca	706	449-469	(vinu)sGfs cgcUfcAfGf caugUfaCfg ccagscsg	941	447-469	CGCUGGCCUA CAUGCUGAGC GCG	418
289 usgsgcguaA fcAfUfGfc ugagcgca	707	450-470	(vinu)sCfs gcgCfuCfAf gcauGfuAfc gccaasgsc	942	448-470	GCUUGCCUAC AUGCUGAGCG CGC	419
290 gsgscguacA faUfGfCfu gagcgcgca	708	451-471	(vinu)sGfs cgcGfcUfCf agcaUfgUfa cgccsasg	943	449-471	CUGGCGUACAU UGCUGAGCGC GCA	420
291 gscsguacA fuGfCfUfg agcgcgca	709	452-472	(vinu)sUfs gcgCfgcUfUf cagcAfUfgfu acgcscsa	944	450-472	UGGCGUACAU GCUGAGCGC GAC	421
292 gscsugagC fgCfGfCfa cacguagua	710	460-480	(vinu)sAfs cuuCfjUfGf ugcgCfgcfu cagcsasu	945	458-480	AUGCUGAGCG CGCACACGUAGUA	422
293 csusgagcG fcGfCfAfc accguagua	711	461-481	(vinu)sUfs acuAfcGfUf gugcGfcGfc ucagscsa	946	459-481	UGCUGAGCGC GCACACGUAG UAC	423
294 gsasgcgcG fcAfCfAfc guaguacaa	712	463-483	(vinu)sUfs guaCfuAfCf guguGfcGfc gcucsasg	947	461-483	CUGAGCGCGC ACACGUAGAC CAC	424
295 csgscgcaC faCfGfUfa guacaccga	713	466-486	(vinu)sCfs gguGfuAfCf uaCgUfgUfg cgccscsu	948	464-486	AGCGCGCACAC GUAGUACAC CGC	425

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
296 gscsgcacA fcGfUfAf g uacaccgca	714	467-487	(vinu)sGfs cggUfgUfAf cuacGfuGfu gcgcsgsc	949	465-487	GCGGCCACAC GUAGUACACC GCC	426
297 csgscacaC fgUfAfGfu acaccgcca	715	468-488	(vinu)sGfs gcgGfuGfUf acuaCfUfUg ugCGscsg	950	466-488	CGCGCACACG UAGUACACCG CCU	427
298 gscsacacG fuAfGfUfa caccgcua	716	469-489	(vinu)sAfs ggcGfgUfGf uacuAfGfu gugcsgsc	951	467-489	GCGCACACGU AGUACACCGC CUU	428
299 csascacgU faGfUfAfCfc accgccuu	717	470-490	(vinu)sAfs aggCfGfUf guacUfaCfU ugugscsg	952	468-490	CGCACACGUA GUACACCGCC UUG	429
300 ascsacguA fgUfAfCfa ccgcccua	718	471-491	(vinu)sCfs aagGfcGfGf uguiaCfUfc gugusgsc	953	469-491	GCACACGUAG UACACCGCCU UGC	430
301 ascsguagU faCfAfCfc gccuugcaa	719	473-493	(vinu)sUfs gcaAfGfCfc ggugUfaCfu acgusgsu	954	471-493	ACACGUAGUA CACGCCUUG CAG	431
302 csgsuaguA fcAfCfCfUf ccuugcaga	720	474-494	(vinu)sCfs ugcAfaGfGf cgguGfuUfc uacgsusg	955	472-494	CACGUAGUAC ACCGCCUUGC AGC	432
303 gsusaguac faCfCfGfC cuuugcaga	721	475-495	(vinu)sGfs cuuCfaAfGf gcgGufgUfa cuacsgsu	956	473-495	ACGUAGUACA CGGCCUUGCA GCC	433
304 gscscugcC fgGfGfUfc aggaaggca	722	515-535	(vinu)sGfs ccuUfcCfUf gaccCfUfCfc aggcscsu	957	513-535	AGGCCUGCCG GGUCAGGAAG GCC	434
305 csasggaaG fgCfCfAfCfc aaagagcga	723	526-546	(vinu)sCfs gcuCfuUfUf guggCfUfUf ccugsasc	958	524-546	GUCAGGAAGG CCACAAAGAG CGG	435
306 gsgsaaggC fcAfCfAfAfa agagcggca	724	528-548	(vinu)sGfs ccgCfUfCfUf uuuguGfgCfc uuuccsusg	959	526-548	CAGGAAGGCC ACAAAAGAGCG GCG	436
307 gsasaggcC faCfAfAfAfa gagcggcga	725	529-549	(vinu)sCfs gccGfcUfCfc uuuggUfgGfc cuucscsu	960	527-549	AGGAAGGCCA CAAAGAGCGG CGU	437
308 asasggccA fcAfAfAfAfg agcggcgua	726	530-550	(vinu)sAfs cgcCfUfCfUf cuuuGfuGfg ccuuscs	961	528-550	GGAAGGCCAC AAAGAGCGGC GUG	438
309 asgsgcacaC faAfAfGfa gcgccguga	727	531-551	(vinu)sCfs acgCfcGfCf cuuuUfgUfg gcccususc	962	529-551	GAAGGCCACA AAGAGCGGC UGA	439

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence 5' to 3'	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
310 gsgscacA faAfGfAf gccgugaa	728	532-552	(vinu)sUfs cacGfcCfGf cucuUfuGfu ggccsusu	963	530-552	AAGGCCACAA AGAGCGGCGU GAG	440
311 cscsacaaA fgAfGfCf gcgugagca	729	534-554	(vinu)sGfs cucAfcGfCf cgcuCfuUfu guggscsc	964	532-554	GGCCACAAAG AGCGGCGUGA GCA	441
312 csascaaAG faGfCfGf cgugagcaa	730	535-555	(vinu)sUfs gcuCfaCfGf ccgcUfcUfu ugugsgsc	965	533-555	GCCACAAAGA GCGCGUGAG CAG	442
313 asgscaccG fcGfCfCf ucggccaga	731	557-577	(vinu)sCfs uggCfcGfAf cgccGfcGfg ugcusgs	966	555-577	GCAGCACCGC GCCGUCGGCC AGC	443
314 csgscgcccG fuCfGfGfc cagcgccaa	732	562-582	(vinu)sUfs ggcGfcUfGf gcggAfcCfGf cgcgsgsu	967	560-582	ACCGCGCCGU CGGCAGCGC CAG	444
315 gcsrgccgU fcGfGfCfc agcgccaga	733	563-583	(vinu)sCfs uggCfgeCfUf ggccGfaCfGf ggcgsgs	968	561-583	CCGCGCCGUC GGCCAGGCC AGG	445
316 csasgcacA faGfCfGfu ggccgcca	734	586-606	(vinu)sUfs ggcGfgCfCf acgcUfuGfu gcugscsa	969	584-606	UGCAGCACAA GCGUGGCCGC CAG	446
317 asgscacaaA fgCfGfUfg gccgcca	735	587-607	(vinu)sCfs uggCfgeCfCf caCgCfuUfg ugcusgs	970	585-607	GCAGCACAAAG CGUGGCCGCC AGC	447
318 gscsacaaAG fcGfUfGfg ccgcccaga	736	588-608	(vinu)sGfs cugGfcGfGf ccacGfcUfu gugcsusg	971	586-608	CAGCACAAAG GUGGCCGCCA GCG	448
319 csasagcgU fgGfCfCfG ccaagcgua	737	591-611	(vinu)sAfs ccgCfuGfGf cgccCfaCfGf cuugsgus	972	589-611	CACAAGCGUG GCCGCCAGCG GUC	449
320 asasgcguG fgCfCfGfc cagcgguca	738	592-612	(vinu)sGfs accGfcUfGf gcccGfcAfc gcuusgsu	973	590-612	ACAAGCGUGG CCCCAGCGG UCG	450
321 asgscguggG fcCfGfCfc agcgguca	739	593-613	(vinu)sCfs gacCfgeCfUf ggccGfcCfa cgcuusgs	974	591-613	CAAGCGUGGC CGCCAGCGU CGC	451
322 gscsguggC fcGfCfCfa ggggucgca	740	594-614	(vinu)sGfs cgaCfcGfCf uggeGfgCfc acgcususu	975	592-614	AAGCGUGGCC GCCAGCGGUC GCC	452
323 gsgscugugG fcCfUfGfu ggccccgaga	741	697-717	(vinu)sCfs gcgGfgCfCf acagGfcAfc agccsusu	976	695-717	AAGGCUGUGC CUGUGGCCCG CGA	453

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence	Antisense SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO
324 gscscuguG fgCfcFcfGf cgaagucua	742	703-723	(vinu)sAfs gacUfuCfGf cgggCfcAfC aggcsasc	977	701-723	GUGCCUGUGG CCCGCGAAGU CUU	454
325 csusugggC fcCfGfCfG aagucuuca	743	705-725	(vinu)sGfs aagAfcUfUf cgcgGfgCfc acagsgsc	978	703-725	GCCUGUGGCC CGCGAAGUCU UCC	455
326 gscscgcG faAfGfUfc uuccagcua	744	710-730	(vinu)sAfs gcuGfgAfAf gacuUfcGfc gggcscsa	979	708-730	UGGCCCGCGA AGUCUUCCAG CUC	456
327 cscscgcgA faGfUfCfu uccagcua	745	711-731	(vinu)sGfs agcUfgGfAf agacUfuCfG cgggscsc	980	709-731	GGCCCGCGAA GUCUUCCAGC UCA	457
328 cscscgcgA fgUfCfUfu ccagcuaaa	746	712-732	(vinu)sUfs gagCfuGfGf aaqaCfuUfc gcggspsc	981	710-732	GCCCCGCGAAG UCUUCCAGCU CAG	458
329 uscscagcU fcAfGfCfa gugucucga	747	723-743	(vinu)sCfs gagAfcAfCf ugcuGfaGfc uggasasg	982	721-743	CUUCCAGCUC AGCAGUGUCU CGU	459
330 csasgcucA fgCfAfGfu gucucguua	748	725-745	(vinu)sAfs acgAfgAfCf acugCfuGfa gcugsgsa	983	723-745	UCCAGCUCAG CAGUGUCUCG UUC	460
331 gscscgcacC faGfAfAfG cuaaaguca	749	944-964	(vinu)sGfs acuUfuAfGf cuucUfgGfu gchgcsusg	984	942-964	CAGCCCACCA GAAGCUAAAG UCU	461
332 csasgaagC fuAfAfAfG ucuugauga	750	950-970	(vinu)sCfs aucAfaGfAf cuuuAfgCfu ucugsgsu	985	948-970	ACCAGAACGU AAAGCUUUGA UGC	462
333 asgsaagcU faAfAfGfu cuugaugca	751	951-971	(vinu)sGfs cauCfaAfGf acuuUfaGfc uucusgsg	986	949-971	CCAGAACUA AAGCUUUGAU GCC	463
334 gsasagcuaA faAfGfUfc uugaugcca	752	952-972	(vinu)sGfs gcaUfcAfAf gacuUfuAfG cuucsusg	987	950-972	CAGAACUA AGUCUUGAUG CCA	464
335 asasgcuaA faGfUfCfu ugaugccaa	753	953-973	(vinu)sUfs ggcAfufAf agacUfuUfa gcuuscsu	988	951-973	AGAACUAAA GUCUUGAUGC CAU	465
336 gscsuaaaG fuCfUfUfg augccauca	754	955-975	(vinu)sGfs augGfcAfUf caagAfcUfu uagcsusu	989	953-975	AAGCUAAAGU CUUGAUGCCA UCA	466
337 gsasugccA fuCfAfAfa ggacaucca	755	966-986	(vinu)sGfs gauGfuCfCf uuugAfufGf caucsasa	990	964-986	UUGAUGCCAU CAAAGGACAU CCC	467

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NM_014430.4	Sense Sequence 45' to 3'	Antisense Sequence 5' to 3'	SEQ ID NO	Range in NM_014430.4	mRNA Target Sequence	SEQ ID NO	
338 asusgcuaU fcAfaFafg gacauccca	756	967-987	(vinu)sGfs ggaUfgUfcf cuuuGfaUfg gcauscsa	991 965-987	UGAUGCCAUC AAAGGACAUC CCU	468			
339 gscscaucA faAfGfGfa caucccuga	757	969-989	(vinu)sCfs aggGfaUffGf uccuUfuGfa uggcsasu	992 967-989	AUGCCAUCAA AGGACAUCCC UGC	469			
340 csasucucU fgUfcAfC guccacuaaa	758	998-1018	(vinu)sUfs aguGfgAfCf gugaCfaGfa gaugusug	993 996-1018	CACAUUCUG UCACGUCCAC UAA	470			
341 asuscucuG fuCfAfCf uccacuaaaa	759	999-1019	(vinu)sUfs uagUfgGfAf cgugAfcAfg agausgsu	994 997-1019	ACAUUCUGU CACGUCCACU AAU	471			
342 uscsucugU fcAfCfGfu ccacuaaaa	760	1000-1020	(vinu)sAfs uuuGfuGfGf acquGfaCfa gagasusg	995 998-1020	CAUCUCUGUC ACGUCCACUA AUC	472			
343 csuscuguC faCfGfUfc cacuaauca	761	1001-1021	(vinu)sGfs auuAfgUfGf gacgUfgAfc agagsasu	996 999-1021	AUCUCUGUCA CGUCCACUAA UCG	473			
344 uscsugucA fcGfUfCfc acuaaucgca	762	1002-1022	(vinu)sCfs gauUfaGfUf ggacGfuGfa cagasgsa	997 1000-1022	UCUCUGUCAC GUCCACUAAU CGG	474			
345 csusgucaC fgUfcAfCfa cuaaucgga	763	1003-1023	(vinu)sCfs cgaUfuAfGf uggaCfgUfg acagsasg	998 1001-1023	CUCUCUCACG UCCACUAAUC GGC	475			
346 usgsucacG fuCfCfAfC uaauucggca	764	1004-1024	(vinu)sGfs ccgAfUfAf guggAfcGfu gacagsasg	999 1002-1024	UCUGUCACGU CCACUAAUCG GCA	476			
347 gsuscacgU fcCfAfCfu aaucggcaa	765	1005-1025	(vinu)sUfs gccGfaUfUf agugGfaCfg ugacsasg	1000 1003-1025	CUGUCACGUC CACUAAUCGG CAA	477			
348 uscsacguC fcAfCfUfa aucggcaaa	766	1006-1026	(vinu)sUfs ugcCfgAfUf uaguGfgAfc gugascsa	1001 1004-1026	UGUCACGUCC ACUAUUCGGC AAA	478			
349 csascgucc faCfUfAfa ucggcaaaa	767	1007-1027	(vinu)sUfs uugCfcGfAf uuagUfgGfa cgugsasc	1002 1005-1027	GUCACGUCCA CUAACGGCA AAA	479			
350 csgsucacaC fuAfAfUfc ggcaaaaaga	768	1009-1029	(vinu)sCfs uuuUfgCfCf gauuAfgUfg gaugusug	1003 1007-1029	CACGUCCACU AAUCGGCAAA AGG	480			
351 gsusccacU faAfUfCf gcaaaaagga	769	1010-1030	(vinu)sCfs cuuUfuGfCf cgauUfaGfu ggacsgsu	1004 1008-1030	ACGUCCACUA AUCGGCAAAA GGA	481			

TABLE 3-continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in Sequence NM_014430.4	Antisense SEQ 5' to 3'	ID NO	Range in Target Sequence NM_014430.4	mRNA ID	SEQ NO
352 uscscacuA	770	1011-1031	(vinu)sUfs faUfCfGfg caaaaggaa	1005 ccuUfuUfGf ccgaUfuAfg uggascsq	1009-1031	CGUCCACUAA UCGGCAAAAG GAG	482
353 cscsacuaA	771	1012-1032	(vinu)sCfs fuCfGfGfc aaaaggaga	1006 uccUfuUfUf gcccAfuUfa guggsasc	1010-1032	GUCCACUAAU CGGCAAAAGG AGA	483
354 csascuauU	772	1013-1033	(vinu)sUfs fcGfGfCfa aaaggagaa	1007 cucCfuUfUf ugccGfaUfu agugsgsa	1011-1033	UCCACUAUAC GGCAAAAGGA GAA	484
355 ascsuuauC	773	1014-1034	(vinu)sUfs fgGfCfAfa aaggagaaa	1008 ucuCfcUfUf uugcCfAgfu uaugusgsq	1012-1034	CCACUAAUCG GCAAAAGGAG AAA	485
356 gsasgaagA	774	1040-1060	(vinu)sCfs fuGfAfCfc uaaguguga	1009 acaCfuUfAf ggucAfuUfu ucucsusc	1038-1060	GAGAGAAGAU GACCUAAGUG UGA	486
357 uscscuccG	775	1110-1130	(vinu)sCfs faCfCfAfa ggagagaga	1010 uucCfuCfc uuggUfcGfg aggasgsq	1108-1130	CCUCCUCCGA CCAAGGAGGA AGG	487
358 cscsagggA	776	1176-1196	(vinu)sCfs faGfGfAfa cucuccggaa	1011 cgGAgfGfGf uuccUfuCfc cuggsasa	1174-1196	UUCCAGGGAA GGAACUCUCC GGU	488
359 csasgggAA	777	1177-1197	(vinu)sAfs fgGfAfAfc ucuccggua	1012 ccgGfaGfAf guuucCfuUfc ccugsgsa	1175-1197	UCCAGGGAAAG GAACUCUCG GUC	489
360 asgsgaacU	778	1183-1203	(vinu)sUfs fcUfCfCfG guccaccaa	1013 gguGfgAfCf cggaGfaGfu uccususc	1181-1203	GAAGGAACUC UCCGGUCCAC CAU	490
361 gsgsaacuC	779	1184-1204	(vinu)sAfs fuCfCfGfg uccaccaa	1014 uggUfgGfAf ccggAfgAfg uuccsusu	1182-1204	AAGGAACUCU CCGGUCCACC AUG	491
362 ascsucuccC	780	1187-1207	(vinu)sUfs fgGfUfCfc accaggaa	1015 ccaUfgGfUF ggacCfGfA gagususc	1185-1207	GAACUCUCCG GUCCACCAUG GAG	492
363 csusccggU	781	1190-1210	(vinu)sUfs fcCfAfCfc augguaguaa	1016 acuCfcAfUf ggugGfaCfc ggagsasq	1188-1210	CUCUCGGUC CACCAUGGAG UAC	493
364 usgsaaccc	782	1221-1241	(vinu)sGfs fcAfGfUfg acuuacuca	1017 aguAfaGfUf cacuGfgGfg uucasgsa	1219-1241	UCUGAACCCC AGUGACUAC UCA	494
365 gsusgacuU	783	1230-1250	(vinu)sUfs faCfUfCfa ggucaguua	1018 acuGfaCfc ugagUfaAfg ucacsusg	1228-1250	CAGUGACUUA CUCAGGUCAG UAU	495

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in Sequence NM_014430.4	Antisense SEQ Range in Sequence 5' to 3'	mRNA Target ID NO	SEQ ID NO	Range in Sequence NM_014430.4	Antisense SEQ Range in Sequence 5' to 3'
366 gsascuuuaC fuCfAfGfg ucaguauca	784	1232-1252	(vinu)sGfs 1019 auaCfuGfAf ccugAfgUfa agucsasc	1230-1252	GUGACUUACU 496 CAGGUCAGUA UCU		
367 csusuacuC faGfGfUfc aguaucuaa	785	1234-1254	(vinu)sUfs 1020 agaUfaCfUF gaccUfgAfg uaagsusc	1232-1254	GACUUACUCA 497 GGUCAGUAUC UAA		
368 csasguauC fuAfAfUfa uaagcucuga	786	1245-1265	(vinu)sCfs 1021 gagCfuUfAf uaauuAfgAfu acugsasc	1243-1265	GUCAGUAUCU 498 AAUAAAAGCU CGG		
369 gsusaucuA faUfAfUfa agcucggaa	787	1247-1267	(vinu)sUfs 1022 ccgAfgCfUF uaauaUfuAfg auacsusg	1245-1267	CAGUAUCUAA 499 UAUAAGCUCG GAG		
370 usasucuaA fuAfUfAfa gcucggaga	788	1248-1268	(vinu)sCfs 1023 uccGfaGfCf uuauuAfuUfa gauascsu	1246-1268	AGUAUCUAAU 500 AUAAAGCUCGG AGU		
371 asuscuuaU faUfAfAfg cucggagua	789	1249-1269	(vinu)sAfs 1024 cucCfgAfGf cuuaUfaUfu agausasc	1247-1269	GUAUCUAAUA 501 UAAGCUCGGA GUU		
372 uscsuuaauA fuAfAfGfc ucggaguuua	790	1250-1270	(vinu)sAfs 1025 acuCfcGfAf gcuuAfuUfu uagasusa	1248-1270	UAUCUAAUAU 502 AAGCUCGGAG UUU		
373 csusaauaaU faAfGfCfu cgaggauuuua	791	1251-1271	(vinu)sAfs 1026 aacUfcCfGf agcuUfaUfa uuagsasu	1249-1271	AUCUAAUAAUA 503 AGCUCGGAGU UUG		
374 usasauauA faGfCfUfc ggaguuuuga	792	1252-1272	(vinu)sCfs 1027 aaaCfuCfCf gagcUfuUfu auuasgsa	1250-1272	UCUAAUAAUA 504 GCUCGGAGUU UGG		
375 asusauaaG fcUfCfGfg aguuuggaa	793	1254-1274	(vinu)sUfs 1028 ccaAfaCfUF ccgaGfcUfu auaususa	1252-1274	UAAAUAUAGC 505 UCCGAGUUUG GAC		
376 usasuaagC fuCfGfGfa guuuggaca	794	1255-1275	(vinu)sGfs 1029 uccAfaAfCf uccgAfgCfu uaauasusu	1253-1275	AAUAAAAGCU 506 CGGAGUUUGG ACG		
377 asusaagcU fcGfGfAfg uuuggacga	795	1256-1276	(vinu)sCfs 1030 gucCfaAfAf cuccGfaGfc uuauasasu	1254-1276	AUAAAAGCUC 507 GGAGUUUGGA CGG		
378 gscsucggA fgUfUfUfg gacggagga	796	1260-1280	(vinu)sCfs 1031 cucCfgUfCf caaaCfuCfc gagcsusu	1258-1280	AAGCUCGGAG 508 UUUGGACCGGA GGG		
379 gsgsaguuU fgGfAfCfg gagggucua	797	1264-1284	(vinu)sAfs 1032 gacCfcUfCf cgucCfaAfa cuccsgsa	1262-1284	UCGGAGUUUG 509 GACGGAGGGU CUG		

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NO	Sense Sequence NM_014430.4	Antisense Range in 5' to 3'	SEQ ID NO	Range in Target NO	mRNA Sequence NM_014430.4	SEQ ID NO	
380 csasccccA	798	1299-1319	(vinu)sAfs	1033	1297-1319	ACCACCCAG	510		
fgCfGfAfC			cgGAfAfGf			CGACCUUUCC			
cuuuccgua			guGcGfuGfG			GUG			
			ggugsgsu						
381 gsuscuGuG	799	1319-1339	(vinu)sGfs	1034	1317-1339	GUGUCUGUGA	511		
faUfCfAfC			uccGfcUfUf			UCACAAGCGG			
aagcggaca			gugaUfcAfC			ACC			
			agacsaSc						
382 uscsugugA	800	1320-1340	(vinu)sGfs	1035	1318-1340	UGUCUGUGAU	512		
fuCfAfCfA			gucCfGcfUf			CACAAGCGGA			
agcggacca			ugugAfufcfa			CCA			
			cagascsa						
383 csusuguaU	801	1321-1341	(vinu)sUfs	1036	1319-1341	GUCUGUGAUC	513		
fcAfCfAfA			gguCfcGfCf			ACAAGCGGAC			
gccccacaa			uuugGfaUfc			CAU			
			acagsasc						
384 usgsugauC	802	1322-1342	(vinu)sAfs	1037	1320-1342	UCUGUGAUCA	514		
faCfAfAfG			uggUfcCfGf			CAAGCGGACC			
cggaccatt			cuugUfgafu			AUC			
			cacagsa						
385 gsusgaucA	803	1323-1343	(vinu)sGfs	1038	1321-1343	CUGUGAUAC	515		
fcAfAfGfc			augGfuCfcf			AAGCGGACCA			
ggaccatt			gcuuGfuGfa			UCC			
			ucacsasg						
386 asgsgagcU	804	1371-1391	(vinu)sUfs	1039	1369-1391	CCAGGAGCUG	516		
fgCfUfAfG			gcuUfuGfGf			CUAGCCAAG			
ccaaagcaa			cuagCfaGfc			CAU			
			uccusgsg						
387 asgscugcU	805	1374-1394	(vinu)sCfs	1040	1372-1394	GGAGCUGCUA	517		
faGfCfCfa			aaUGfcUfUf			GCCAAGCAU			
aagcauuga			uggcUfaGfc			UGG			
			agcuscsc						
388 csusgcuaG	806	1376-1396	(vinu)sUfs	1041	1374-1396	AGCUGCUAGC	518		
fcCfAfAfa			ccaAfufcfc			CAAAGCAUUG			
gcauuggaa			uuugGfcUfa			GAG			
			gcagscsu						
389 usgscuagC	807	1377-1397	(vinu)sCfs	1042	1375-1397	GCUGCUAGCC	519		
fcAfAfAfG			uccAfaUfGf			AAAGCAUUGG			
cauuggaga			cuuuGfgCfu			AGA			
			agcasgsc						
390 csusagccA	808	1379-1399	(vinu)sGfs	1043	1377-1399	UGCUGAGCAA	520		
faAfGfCfa			ucuCfcAfAf			AGCAUUGGAG			
uuggagaca			ugcUfuGfg			ACC			
			cuagscsa						
391 usasgcAa	809	1380-1400	(vinu)sGfs	1044	1378-1400	GCUAGCCAAA	521		
faGfCfAf			gucUfcCfAf			GCAUUGGAGA			
uggagacca			augcUfuUfg			CCC			
			gcuasgsc						
392 gsgsagcuC	810	1729-1749	(vinu)sAfs	1045	1727-1749	AGGGAGCUCC	522		
fcUfUfcfg			gguCfcAfAf			UUCGUUGGAC			
uggaccua			cgaaGfgAfG			CUC			
			cuccscsu						
393 gsasgcucc	811	1730-1750	(vinu)sGfs	1046	1728-1750	GGGAGCUCCU	523		
fuUfCfGfu			aggUfcCfAf			UCGUUGGACC			
uggaccua			acgaAfGfGa			UCC			
			gcucscsc						

TABLE 3-continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.						
dsRNAsense AgentSequence ID 5' to 3'	SEQ NO	Range in Sequence NM_014430.4	Antisense SEQ Range in Sequence 5' to 3'	mRNA Target ID NO	SEQ NO	
394 asgscuccuU fuCfGfuFu ggaccucca	812	1731-1751	(vinu)sGfs 1047 gagGfuCfCf aacgAfaGfg agcuscsc	1729-1751	GGAGCUCCUU CGUUGGACCU CCA	524
395 asgsgccuG fgGfCfcfa uauguuugca	813	1762-1782	(vinu)sGfs 1048 caaCfaUfAf uggcCfcAfg gccususg	1760-1782	CAAGGCCUGG GCCAUUAUGUU GCU	525
396 gscscuggG fcCfAfUfa uguugcuga	814	1764-1784	(vinu)sCfs 1049 agcAfaCfAf uaugGfcCfc aggcscsu	1762-1784	AGGCCUGGGC CAAU AUGU UGC UGG	526
397 csusgggcC faUfAfUfg uuggcuggga	815	1766-1786	(vinu)sCfs 1050 ccaGfcAfAf cauaUfgGfc ccagsgsc	1764-1786	GCCUGGGCCA UAUGU UGCUG GGA	527
398 usgsgggcA fuAfUfGfu ugcugggaa	816	1767-1787	(vinu)sUfs 1051 cccAfgCfAf acauAfuUfg cccasgsg	1765-1787	CCUGGGCCAU AUGU UGCUGG GAA	528
399 asusguugC fuGfGfCfa auuuccuca	817	1775-1795	(vinu)sGfs 1052 aggAfaAfUf ucccAfgCfa acausasu	1773-1795	AUAUGU UGCU GGGAAU UUCC UCC	529
400 csusgggaA fuUfUfcfc uccaccua	818	1781-1801	(vinu)sAfs 1053 gggUfgGfAf ggaaAfUfc ccagscsa	1779-1801	UGCUGGGAAU UUCCUCCACC CUU	530
401 ususccucC faCfcfcfu ucguauga	819	1789-1809	(vinu)sCfs 1054 augAfcGfAf agggUfgGfa ggaasasu	1787-1809	AUUUCCUCCA CCCUUCGUCA UGC	531
402 asasgggcC fgCfcfUfc cauuccuaa	820	1838-1858	(vinu)sUfs 1055 aggAfaUfGf gaggCfGfFc ccuuscsu	1836-1858	AGAAGGGCCC CCUCCAUUCC UAC	532
403 gsgsccgcC fuCfCfAf fu uccuacuaa	821	1841-1861	(vinu)sUfs 1056 aguAfgGfAf auggAfgGfc ggccscsu	1839-1861	AGGGCCGCCU CCAUUCUAC UAA	533
404 ascsugcaA faGfAfUfu augacagca	822	1904-1924	(vinu)sGfs 1057 cuqUfcAfUf agucUfuUfg cagusgs	1902-1924	CCACUGCAA GACUAUGACA GCA	534
405 csasgcauC faAfAfUfu ucaggacca	823	1920-1940	(vinu)sGfs 1058 gucCfuGfAf aaauUfgAfU gcugsusc	1918-1940	GACAGCAUCA AAUUCAGGA CCU	535
406 uscsaggaC fcUfGfCfa gacaguaca	824	1932-1952	(vinu)sGfs 1059 uacUfgUfCf ugcaGfgUfc cugasasa	1930-1952	UUUCAGGACC UGCAGACAGU ACA	536
407 gscsagacA fgUfAfCfa ggcuagaua	825	1941-1961	(vinu)sAfs 1060 ucuAfgCfCf uguaCfuGfu cugcsasg	1939-1961	CUGCAGACAG UACAGGCUAG AUA	537

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in Sequence NM_014430.4	Antisense SEQ 5' to 3'	ID NO	Range in Target Sequence NM_014430.4	mRNA ID	SEQ NO
408 csasgacaG fuAfCfAfg gcuagauaa	826	1942-1962	(vinu)sUfs 1061 aucUfaGfCf cuguAfcUfg ucugscsa	1940-1962	UGCAGACAGU ACAGGCUAGA UAA	538	
409 asgsacagU faCfAfGfg cuagauaaa	827	1943-1963	(vinu)sUfs 1062 uauCfuAfGf ccugUfafcu gucusgsc	1941-1963	GCAGACAGUA CAGGCUAGAU AAC	539	
410 uscsccacU fuGfCfCfc ugaaaggca	828	2087-2107	(vinu)sGfs 1063 ccuUfucfAf gggcAfaGfu gggasgsg	2085-2107	CCUCCCACUU GCCUGAAAG GCC	540	
411 csusgcugC fuAfCfAfu cuaauccca	829	2148-2168	(vinu)sGfs 1064 ggaUfuAfGf auguAfgCfa gcagsusc	2146-2168	GACUGCUGCU ACAUCUAUC CCC	541	
412 usgscugcU faCfAfUfc uaaauccca	830	2149-2169	(vinu)sGfs 1065 gggAfufAf gaugUfaGfc agcasgsu	2147-2169	ACUGCUGCUA CAUCUAUCC CCU	542	
413 gscsugcuA fcAfUfcfu aauccccua	831	2150-2170	(vinu)sAfs 1066 gggGfaUfUF agauGfuAfg cagcsasg	2148-2170	CUGCUGCUAC AUCUAUCC CUA	543	
414 ascsaucuA faUfcfCfc cuaccaaaua	832	2156-2176	(vinu)sAfs 1067 uugGfuAfGf gggaUfuUfg augusasg	2154-2176	CUACAUUA UCCCCUACCA AUG	544	
415 asuscuauA fcCfCfCfu accaaugca	833	2158-2178	(vinu)sGfs 1068 cauUfgGfUF agggGfaUfu agausgsu	2156-2178	ACAUUA CCCCUACAU GCC	545	
416 cscsccuaC fcAfAfUfg ccuccugua	834	2165-2185	(vinu)sAfs 1069 cagGfaGfGf cauuGfgUfa ggggasas	2163-2185	AUCCCCUAC AAUGCCUCC GUC	546	
417 cscscuacc faAfUfGfc cuccuguca	835	2166-2186	(vinu)sGfs 1070 acaGfgafGf gcauUfgGfu aggsgsas	2164-2186	UCCCCUACCA AUCCCUCCUG UCC	547	
418 ascscaauG fcCfUfcfCfc ugucccuua	836	2170-2190	(vinu)sUfs 1071 aggGfaCfAf ggagGfcAfu uggusasg	2168-2190	CUACCAAUGC CUCCUGUCCC UAA	548	
419 cscsaaugC fcUfCfCfu gucccuaaa	837	2171-2191	(vinu)sUfs 1072 uagGfgafCf aggaGfgCfa uuggsusa	2169-2191	UACCAAUGCC UCCUGUCCCU AAA	549	
420 asusgccuC fcUfGfUfc ccuaaacua	838	2174-2194	(vinu)sAfs 1073 guuUfaGfGf gacaGfgAfg gcaususg	2172-2194	CAAUGCCUCC UGUCCCCUAAA CUC	550	
421 usgscuccC fuGfUfCfc cuaaacuca	839	2175-2195	(vinu)sGfs 1074 aguUfuAfGf ggacAfgGfa ggcasusu	2173-2195	AAUGCCUCCU GUCCCUAAAC UCC	551	

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.						
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NO	Sense Sequence NM_014430.4	Antisense Sequence 5' to 3'	SEQ ID NO	mRNA Target Sequence NM_014430.4
422 usascugaU fgAfCfAfg ccucucua	840	2202-2222	(vinu)sAfs 1075 gagAfgGfGf cuguCfaUfc aguasusg	2200-2222	CAUACUGAUG ACAGCCCUCU CUG	552
423 asgscucaG fcAfGfUfg ucucguuca	841	726-746	(vinu)sGfs 1076 aacGfaGfAf cacuGfcUfg agcugsgg	724-746	CCAGCUCAGC AGUGUCUCGU UCC	1132
424 gscsucagC faGfUfgfu cucguucca	842	727-747	(vinu)sGfs 1077 gaaCfGafGf acacUfgCfu gagcsusg	725-747	CAGCUCAGCA GUGUCUCGUU CCC	1133
425 gsgsacggU faGfCfAfg accgacaua	843	752-772	(vinu)sAfs 1078 uguCfGfUf cugcUfaCfc guccscsc	750-772	GGGGACGGUA GCAGACCGAC AUC	1134
426 ascsgguuG fcAfGfAfc cgacaucca	844	754-774	(vinu)sGfs 1079 gauGfuCfGf gucuGfcUfa ccguscsc	752-774	GGACGGUAGC AGACCGACAU CCU	1135
427 csgsguagC faGfAfCfc gacaucua	845	755-775	(vinu)sAfs 1080 ggaUfgUfcf ggucUfgCfu accgsusc	753-775	GACGGUAGCA GACCGACAUC CUU	1136
428 asgscagaC fcGfAfCfa uccuucuga	846	759-779	(vinu)sCfs 1081 agaAfgGfAf ugucGfgUfc ugcusasc	757-779	GUAGCAGACC GACAUCCUUC UGG	1137
429 gscsagacC fgAfCfAfu ccuucugga	847	760-780	(vinu)sCfs 1082 caqAfaGfGf auguCfGfCfu cugcsusa	758-780	UACAGACCG ACAUCCUUUC GGG	1138
430 uscscaugC faAfCfUfg uccaucaca	848	894-914	(vinu)sGfs 1083 ugaUfgGfAf caguUfgCfa uggasasg	892-914	CUUCCAUGCA ACUGUCCAUC ACG	1139
431 cscsaugcA faCfUfgfu ccaucacga	849	895-915	(vinu)sCfs 1084 guqAfufGf acagUfuGfc auggsasa	893-915	UUCCAUGCAA CUGUCCAUC CGG	1140
432 csasugcaA fcUfgfUfc caucacgga	850	896-916	(vinu)sCfs 1085 cguGfaUfgf gacaGfuUfg caugsgsa	894-916	UCCAUGCAAC UGUCCAUCAC GGC	1141
433 asascuguC fcAfUfcfa cggcugcaa	851	901-921	(vinu)sUfs 1086 gcaGfCfGf ugauGfgAfC aguusgsc	989-921	GCAACUGUCC AUACACGGCUG CAA	1142
434 ascsugucC faUfcfAfc ggcugcaa	852	902-922	(vinu)sUfs 1087 ugcAfgCfCf gugaUfgGfa cagususg	900-922	CAACUGUCCA UCACACGGCUG AAC	1143
435 gsusccauC faCfGfGfc ugcaacuga	853	905-925	(vinu)sCfs 1088 aguUfgCfAf gccgUfgAfU ggacsasg	903-925	CUGUCCAUC CGGCUGCAAC UGA	1144

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NO	Sense Sequence NM_014430.4	Antisense Range in 5' to 3'	SEQ ID NO	mRNA Target Sequence NM_014430.4	SEQ ID NO
436 asuscacgG fcUfGfcfa acugaaaa	854	909-929	(vinu)sAfs uuuCfaGfUF ugcaGfcCfg ugausgsg	1089	907-929	CCAUACACGGC UGCAACUGAA AUC	1145
437 usgsggacA fcAfGfcfg caccagaaa	855	935-955	(vinu)sUfs ucuGfgUfGf cgcuGfuGfu cccasgsc	1090	933-955	GCUGGGACAC AGCGCACAG AAG	1146
438 gsascacaG fcGfcAfC cagaagcua	856	938-958	(vinu)sAfs gcuUfcUfGf gugcGfcUfg ugucscsc	1091	936-958	GGGACACAGC GCACCAGAAG CUA	1147
439 asc sagcgc faCfcAfC aagcuaaaa	857	941-961	(vinu)sUfs uuuGfcUfUF cuggUfgCfg cugusgsu	1092	939-961	ACACAGCGCA CCAGAACUA AAG	1148
440 gscscaCfa UfUfCfuac gggcuca	858	1659-1677	(vinu)sGfs agcCfcGfUF agaaUfgUfg gcsusu	1093	1659-1679	AAGCCACAUU CUACGGGCUC U	1149
441 gsasaaGfu AfCfcUfcag ggagcua	859	1715-1733	(vinu)sAfs gcuCfcCfUF gaguAfcUfu ucsusu	1094	1715-1735	AAGAAAGUAC UCAGGGAGCU C	1150
442 gsuscuAfu AfCfcfcuu accugaa	860	2033-2051	(vinu)sUfs cagGfuAfAf ggguAfuAfg acsusu	1095	2033-2053	AAGCUAUAC CCUUACCUGA A	1151
443 gscsugCfu AfGfcFccaa agcaaua	861	1373-1391	(vinu)sAfs augCfuUfUF ggcuAfgCfa gcsusc	1096	1373-1393	GAGCUGCUAG CCAAAGCAUU G	1152
444 gsgsagUfg GfAfGfugc ugucaua	862	1534-1552	(vinu)sAfs ugaCfaGfCf acucCfaCfu ccsusu	1097	1534-1554	AAGGAGUGGA GUGCUGUCAU A	1153
445 gsgsccAfa GfAfUfccaa gauguca	863	2102-2120	(vinu)sGfs acaUfcUfUF gaucUfuGfg ccsusu	1098	2102-2122	AAGGCCAAGA UCAAGAUGUC C	1154
446 csusugAfg AfUfCfugu cuucaua	864	2228-2246	(vinu)sAfs ugaAfAfCf agauCfuCfa agsusu	1099	2228-2248	ACCUUGAGAU CUGUCUUCAU ACC	1155
447 csusugAfg AfUfCfugu cuucaua	864	2228-2246	(vinu)sAfs ugaAfAfCf agauCfuCfa agsusu	1100	2228-2248	UUACCUUGAG AUCUGUCUUC AUA	1156
448 cscsucAfa AfCfcUfaac aaaaaca	865	2254-2272	(vinu)sGfs uuuUfuGfUF uaguUfuGfa ggsgsg	1101	2254-2274	CCCCUCAAAC UAACAAAAAC A	1157
449 csuscaAfa CfUfAfaca aaaaacaa	866	2255-2273	(vinu)sUfs guuUfuUfGf uuagUfuUfg agsgsg	1102	2255-2275	CCCUAAACU AACAAAAACA U	1158

TABLE 3-continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ NO	Range in ID	Sense Sequence	Antisense SEQ ID	Range in Target NO	mRNA ID	SEQ NO
450 csasaaaCfu AfAfCfaaa aacauua	867	2257-2275	(vinu)sAfs 1103 augUfuUfUF uguuAfgUfu ugseasg	1103 1103 1103 1103	2257-2277 CAAAAACAUU U U	CUCAAACUAA 1159	
451 csusaaaCfa AfAfAfaca uuuccaa	868	2261-2279	(vinu)sUfs 1104 ggaAfaUfGf uuuuUfgUfu agsusu	1104 1104 1104 1104	2261-2281 AACAUUCCAA A A	AACUAACAAA 1160	
452 csasaaaAfa CfAfUfuuc caauaaa	869	2265-2283	(vinu)sUfs 1105 uauUfgGfAf aaugUfuUfu ugseusu	1105 1105 1105 1105	2265-2285 UUUCCAAUAA A A	AACAAAAAAC 1161	
453 cscsaaaUfa AfAfAfaua ucaaaaua	870	2276-2294	(vinu)sAfs 1106 uuuGfaUfAf uuuuUfaUfu ggssasa	1106 1106 1106 1106	2276-2296 AAUAUCAAAU A A	UUCCAAUAAA 1162	
454 csasauAfa AfAfAfaua caaaauaa	871	2277-2295	(vinu)sUfs 1107 auuUfgAfUf auuuUfuAfu ugsgsa	1107 1107 1107 1107	2277-2297 AUAUCAAAUA U U	UCCAAUAAA 1163	
455 cscsaaaAfg CfAfUfugg agaccca	872	1381-1399	(vinu)sGfs 1108 gguCfuCfc aaugCfuUfu ggseusu	1108 1108 1108 1108	1381-1401 UUGGAGACCC U U	AGCCAAAGCA 1164	
456 csasggUfc AfGfUfauc uaaauua	873	1238-1256	(vinu)sAfs 1109 uauUfaGfAf uacuGfaCfc ugseusu	1109 1109 1109 1109	1238-1258 UAUCUAAUAU A A	CUCAGGUCA 1165	
457 asusguCfa AfAfGfcca cauucua	874	1651-1669	(vinu)sAfs 1110 gaaUfgUfGf gcuuUfgAfc aususc	1110 1110 1110 1110	1651-1671 GCCACAUUC A A	GAAUGUCAAA 1166	
458 gscsucUfa CfUfCfuau gaguuga	875	1673-1691	(vinu)sCfs 1111 aacUfcAfUf agagUfaGfa gcsusu	1111 1111 1111 1111	1673-1693 CUAUGAGUUG U U	GGGCUCUACU 1167	
459 csusauGfa GfUfUfugg acuuuca	876	1681-1699	(vinu)sGfs 1112 aaaGfuCfcAf caacUfcAfU agsasg	1112 1112 1112 1112	1681-1701 UGUGACUUUC A A	CUCUAUGAGU 1168	
460 usasugAfg UfUfGfuga cuuucaa	877	1682-1700	(vinu)sUfs 1113 gaaAfgUfCf acaaCfuCfa uaesgsa	1113 1113 1113 1113	1682-1702 GUGACUUUCA A A	UCUAUGAGUU 1169	
461 gsgscccCfa AfAfGfaaa guacuca	878	1707-1725	(vinu)sGfs 1114 aguAfcUfUF ucuuUfgGfg ccsusu	1114 1114 1114 1114	1707-1727 GAAAGUACUC A A	UUGGCCCAAA 1170	
462 gscscaUfa UfGfUfugc ugaaa	879	1768-1786	(vinu)sUfs 1115 uccCfaGfCf aacaUfaUfg gcsusu	1115 1115 1115 1115	1768-1788 UGGCUGGGAA U U	GGGCCAUUAUG 1171	
463 cscscaCfu GfCfAfaag acuauga	880	1899-1979	(vinu)sCfs 1116 auaGfuCfcUf uugcAfgUfg ggsusu	1116 1116 1116 1116	1899-1981 AAAGACUAUG A A	GACCCACUGC 1172	

TABLE 3-continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.							
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in Sequence NM_014430.4	Antisense SEQ 5' to 3'	ID NO	Range in Target Sequence NM_014430.4	mRNA ID	SEQ NO
464 gsascuAfu GfAfCfagc aucaaaaa	881	1910-1928	(vinu)sUfs 1117 uugAfuGfCf ugucAfuAfg ucsusu	1117	1910-1930	AAGACUAUGA 1173 CAGCAUCAAA U	
465 csusauGfa CfAfGfcau caaauua	882	1912-1930	(vinu)sAfs 1118 auuUfgAfUf gcugUfcAfu agsusc	1118	1912-1932	GACUAUGACA 1174 GCAUCAAAUU U	
466 csusgaAfg AfAfUfgcu guucuuu	883	2047-2065	(vinu)sAfs 1119 agaAfcaGf cauuCfuUfc agsusu	1119	2047-2067	ACCUGAAGAA 1175 UGCUGUUUCUU U	
467 csusgaAfg AfAfUfgcu guucuuu	883	2047-2065	(vinu)sAfs 1120 agaAfcaGf cauuCfuUfc agsgsu	1120	2047-2067	ACCUGAAGAA 1176 UGCUGUUUCUU U	
468 cscsugAfa AfGfGfcca agaucaa	884	2095-2113	(vinu)sUfs 1121 gauCfuUfGf gccuUfuCfa ggsusu	1121	2095-2115	GCCCUGAAAG 1177 GCCAAGAUCA A	
469 cscsugAfa AfGfGfcca agaucaa	884	2095-2113	(vinu)sUfs 1122 gauCfuUfGf gccuUfuCfa ggsgsc	1122	2095-2115	GCCCUGAAAG 1178 GCCAAGAUCA A	
470 gsascuFfc UfGfCfauac aucuaaa	885	2144-2162	(vinu)sUfs 1123 uagAfuGfUf agcaGfcAfg ucsusu	1123	2144-2164	CUGACUGCUG 1179 CUACAUCAA U	
471 asgsguCfa GfUfAfucu aauauaa	886	1239-1257	(vinu)sUfs 1124 auaUfuAfGf auacUfgAfc cususu	1124	1239-1259	UCAGGUCAAG 1180 AUCUAAUAAA A	
472 gsgsaaUfu UfCfCfucc acccuua	887	1782-1800	(vinu)sAfs 1125 aggGfuGfGf aggaAfaUfu ccsusu	1125	1782-1802	UGGGAAUUUC 1181 CUCCACCCUU C	
473 gsasuuCfa CfCfUfuugg acgugua	888	1597-1615	(vinu)sAfs 1126 cacGfuCfAf aaggUfgAfa ucsusu	1126	1597-1617	CCGAUUCACC 1182 UUUGACGUGU A	
474 gsasggAfu GfAfCfagc ugccuga	889	1479-1497	(vinu)sCfs 1127 aggCfaCfGf ugucAfuCfc ucsusu	1127	1479-1499	UGGAGGAUGA 1183 CACGUGCCUG A	
475 csuscuAfu GfAfGfuuug ugacuuu	890	1679-1697	(vinu)sAfs 1128 aguCfaCfAf acucAfuAfg agsusa	1128	1679-1699	UACUCUAUGA 1184 GUUGUGACUU U	
476 asgsagGfa GfGfAfugg aacugca	891	1430-1448	(vinu)sGfs 1129 cagUfuCfCf auccUfcCfu cusasg	1129	1430-1450	CUAGAGGAGG 1185 AUGGAACUGC A	
477 gsasuuCfa CfCfUfuugg acgugua	888	1597-1615	(vinu)sAfs 1130 cacGfuCfAf aaggUfgAfa ucsgsg	1130	1597-1617	CCGAUUCACC 1186 UUUGACGUGU A	

TABLE 3 -continued

Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents.									
dsRNAsense AgentSequence ID 5' to 3'	SEQ ID NO	Range in NO	Sense Sequence NM_014430.4	Antisense Range in 5' to 3'	SEQ ID NO	Range in Target NO NM_014430.4	mRNA Sequence	Target ID	SEQ NO
478 uscsagGfu CfAfGfauu cuaauaa	892	1237-1255	(vinu)sUfs 1131	1237-1257	ACUCAGGUCA 1187				
			auuAfgAfUf		GUAUCUAAUA				
			acugAfcCfu		U				
			gasusu						
479 csasguauC fuAfAfUfa uaaggcucga	786	1245-1265	(vinu)sCfs 1188	1243-1265	GUCAGUAUCU 498				
			gagCfuuuaa		AAUUAAGCU				
			uuAfgAfuac		CGG				
			ugsasc						
480 usasauauA faGfCfUfc ggaguuuga	792	1252-1272	(vinu)sCfs 1189	1250-1272	UCUAAUUAUA 504				
			aaaCfuccga		GCUCGGAGUU				
			gcUfuAfauu		UGG				
			uasgsa						
481 csasguauC fuAfAfUfa uaaggcucga	786	1245-1265	(vinu)sCfs 1190	1243-1265	GUCAGUAUCU 498				
			gagCfuuuaa		AAUUAAGCU				
			uuAfgauacu		CGG				
			gsasc						
482 csasgaCfa guAfCfAfg gcuagauaa	1192	1942-1962	(vinu)sUfs 1191	1940-1962	UGCAGACAGU 538				
			aucUfagccu		ACAGGCCUAGA				
			guafcugucu		UAA				
			gscsa						

[0630] The nucleotide sequence presented in Table 3, utilize the following abbreviations set forth in Table 4.

TABLE 4

Abbreviations of Nucleotide Modifications.	
Abbreviation	Nucleotide/Linkage
(vin)	vinyl-phosphonate
(vinu)	5'-vinyl-phosphonate-2'-O-methyluridine
a	2'-O-methyladenosine
c	2'-O-methylcytidine
g	2'-O-methylguanosine
u	2'-O-methyluridine
Af	2'-fluoroadenosine
Cf	2'-fluorocytidine
Gf	2'-fluoroguanosine
Uf	2'-fluorouridine
S	Phosphorothioate linkage (between the two bases)

[0631] Various salts, mixed salts and free acid forms of the dsRNA agents are also provided herein. In some embodiments, the dsRNA agent is in a free acid form. In some embodiments, the dsRNA agent is in a salt form. In some embodiments, the dsRNA agent is in a sodium salt form. In some embodiments, wherein the dsRNA agent is in the sodium salt form, sodium ions are present in the composition comprising the dsRNA agent as counterions for substantially all of the phosphodiester or phosphorothioate groups present in the dsRNA agent. In some embodiments, wherein the dsRNA agent is in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester or phosphorothioate groups present in the dsRNA agent.

4.3 Modified RNAi Agents

[0632] In some embodiments, the agent (or any component thereof (e.g., any nucleic acid molecule thereof) (e.g.,

described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) comprises one or more modified nucleotide(s) (as defined herein). The modified agent may have one or more different (e.g., improved) properties relative to a corresponding unmodified agent. For example, the modified agent may exhibit decreased immunostimulatory activity (e.g., when administered to a subject), increased stability (e.g., in vivo, in a cell, when administered to a subject), and/or increased inhibition of expression of a target nucleic acid molecule (e.g., a target mRNA (e.g., a CIDEB mRNA)), or any combination thereof.

4.3.1 Nature of Nucleotide Modifications

[0633] Nucleotide modifications can include modification to any one of more of the nucleoside and/or the internucleoside linkage. Nucleoside modifications include modification to the sugar (e.g., ribose) moiety and/or the nucleobase. In some embodiments, the modified agent (or component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotides comprising a modified sugar moiety. In some embodiments, the modified agent (or component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotides comprising a modified internucleoside linkage. In some embodiments, the modified agent (or component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotides comprising one, two, or three of a modified sugar moiety, a modified nucleobase, and/or a modified internucleoside linkage.

[0634] Exemplary nucleotide modifications are described below and also known in the art, see, e.g., WO2021257782,

WO2013075035, WO2022246251, and WO2022271573, the entire contents of each of which is incorporated by reference herein for all purposes. Exemplary modifications are further provided in Hu, B., Zhong, L., Weng, Y. et al. Therapeutic siRNA: state of the art. *Sig Transduct Target Ther* 5, 101 (2020). <https://doi.org/10.1038/s41392-020-0207-x> (e.g., Table 2), the entire contents of each of which is incorporated by reference herein for all purposes.

4.3.1.1 Modified Nucleosides

[0635] In some embodiments, the modified agent (or any component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotide comprising a modified nucleoside. As discussed above, nucleoside modifications can include modification of the sugar (e.g., ribose) moiety and/or modification of the nucleobase.

(i) Sugar Modifications

[0636] In some embodiments, the modified agent (or any component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotides comprising a modified sugar (e.g., ribose) moiety.

[0637] The modified sugar (e.g., ribose) moiety can comprise, for example, a substituent at any one or more position of the sugar (e.g., ribose), including e.g., positions 2', 4', and/or 5'. In some embodiments, the modified sugar (e.g., ribose) comprises a substituent at 2' position of the sugar (e.g., ribose). In some embodiments, the modified sugar (e.g., ribose) comprises a substituent at 5' position of the sugar (e.g., ribose). In some embodiments, the modified sugar (e.g., ribose) comprises a substituent at 5' position of the sugar (e.g., ribose).

[0638] In some embodiments, the agent (or any component thereof) comprises any one or more of the following substituents (e.g., at any position of the sugar (e.g., ribose) (e.g., at position 2')): a group for improving the stability of the agent, a group for improving the pharmacokinetic properties of the agent, or a group for improving the pharmacodynamic properties of the agent, an RNA cleaving group, a reporter group, an intercalator, or other substituents having similar properties.

[0639] Exemplary substituents include, for example, but are not limited to, substitution (e.g., at any position of the sugar (e.g., ribose) (e.g., at position 2')) with any one of the following: OH; F; O—, S—, or N-alkyl; O—, S—, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Additional exemplary substitutions (e.g., at any position of the sugar (e.g., ribose) (e.g., at position 2')) include, for example, but are not limited to, substitution with any one of the following: O[(CH₂)_nO]m, CH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10.

[0640] In some embodiments, the modified sugar (e.g., ribose) comprises any one of the following modifications: 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-O-MOE), 2'-deoxy-2'-fluoro (2'-F), 2'-arabino-fluoro (2'-Ara-F), 2'-O-benzyl, 2'-O-methyl-4-pyridine (2-O-methyl-4-pyridine (2'-O—CH₂Py (4)), and 2'-O—N-alkyl acetamide (e.g., 2'-O—N-methyl acetamide (“NMA”), 2'-O—N-dimethyl acetamide, 2'-O—N-ethyl acetamide, and 2'-O—N-propyl acetamide). For example, see, e.g., U.S. Pat. No. 6,147,200, Prakash et al., 2003, Org. Lett., 5, 403-6, the entire contents of which is incorporated by reference herein for all purposes.

[0641] In some embodiments, the agent (or any component thereof) comprises any of the following substituents at the 2'-position of the sugar (e.g., ribose): C₁ to C₁₀ lower

alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, or a substituted silyl. In some embodiments, the agent (or any component thereof) comprises a 2'-methoxyethoxy (2'-O—CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (see, e.g., Martin et al., Helv. Chim. Acta, 1995, 78:486-504, the entire contents of which is incorporated by reference herein for all purposes) (i.e., an alkoxy-alkoxy group). In some embodiments, the agent (or any component thereof) comprises a 2'-dimethylaminooxyethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE; a 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O—CH₂—O—CH₂—N(CH₃)₂; a 5'-Me-2'-F nucleotide, a 5'-Me-2'-OMe nucleotide, a 5'-Me-2'-deoxynucleotide, (both R and S isomers in these three families); a 2'-alkoxy-alkyl; and 2'-NMA (N-methylacetamide).

[0642] Exemplary US patents that describe the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920; the entire contents of each of the foregoing are hereby incorporated herein by reference for all purposes. Exemplary sugar modifications are further provided in Hu, B., Zhong, L., Weng, Y. et al. Therapeutic siRNA: state of the art. *Sig Transduct Target Ther* 5, 101 (2020). <https://doi.org/10.1038/s41392-020-0207-x> (e.g., Table 2), the entire contents of each of which is incorporated by reference herein for all purposes.

(a) Non-Bicyclic Sugar Modifications

[0643] In some embodiments, the modified sugar (e.g., ribose) moiety comprises a non-bicyclic modified sugar (e.g., ribose) moiety. In some embodiments, the modified sugar (e.g., ribose) moiety comprises a furanosyl ring comprising one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. In some embodiments one or more non-bridging substituent of a non-bicyclic modified sugar moiety is branched. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 4', and/or 5' positions.

[0644] In some embodiments, non-bicyclic modified sugar moiety comprises a substituent group at the 2'-position of the sugar (e.g., ribose). Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-O-MOE), 2'-deoxy-2'-fluoro (2'-F), 2'-arabino-fluoro (2'-Ara-F), 2'-O-benzyl, 2'-O-methyl-4-pyridine (2-O-methyl-4-pyridine (2'-O—CH₂Py (4)), and 2'-O—N-alkyl acetamide (e.g., 2'-O—N-methyl acetamide (“NMA”), 2'-O—N-dimethyl acetamide, 2'-O—N-ethyl acetamide, and 2'-O—N-propyl acetamide). For example, see, e.g., U.S. Pat. No. 6,147,200, Prakash et al., 2003, Org. Lett., 5, 403-6, the entire contents of which is incorporated by reference herein for all purposes.

[0645] In some embodiments, the 2'-substituent group is a halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O—C₁-C₁₀ alkoxy, O—C₁-C₁₀ substituted alkoxy, O—C₁-C₁₀ alkyl, O—C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-

alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)—N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, or a 2'-substituent group described in any one of the following: Cook et al., U.S. Pat. No. 6,531,584; Cook et al., U.S. Pat. No. 5,859,221; and Cook et al., U.S. Pat. No. 6,005,087, the entire contents of which are incorporated herein by reference for all purposes. In some embodiments, these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkyne.

[0646] In some embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)—N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl. In some embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and OCH₂C(=O)—N(H)CH₃ ("NMA"). In some embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, OCH₂CH₂OCH₃, and OCH₂C(=O)—N(H)CH₃.

[0647] In some embodiments, non-bicyclic modified sugar moiety comprises a substituent group at the 3'-position of the sugar (e.g., ribose). Examples of substituent groups suitable for the 3'-position of modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl (e.g., methyl, ethyl).

[0648] In some embodiments, non-bicyclic modified sugar moiety comprises a substituent group at the 4'-position of the sugar (e.g., ribose). Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128.

[0649] In some embodiments, non-bicyclic modified sugar moiety comprises a substituent group at the 5'-position of the sugar (e.g., ribose). Examples of substituent groups suitable for the 5'-position of modified sugar moieties include, but are not limited to, vinyl (e.g., 5'-vinyl), alkoxy (e.g., methoxy (e.g., 5'-methoxy)), and alkyl (e.g., methyl (R or S) (e.g., 5'-methyl (R or S)), ethyl).

[0650] In some embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836, the entire contents of each of which is incorporated herein by reference for all purposes.

[0651] In some embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by isomeric configuration. For example, a 2'-deoxyfuranosyl sugar moiety

may be in seven isomeric configurations other than the naturally occurring β-D-deoxyribosyl configuration. Such modified sugar moieties are described in, e.g., WO 2019/157531, the entire contents of which are incorporated by reference herein for all purposes.

[0652] In some embodiments, the sugar (e.g., ribose) modification comprises an unlocked nucleotide (UNA). UNA is unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked sugar (e.g., ribose) residue. For example, in some embodiments, the bonds between C1'-C4' have been removed (i.e., the covalent carbon-oxygen-carbon bond between the C1' and C4' carbons). In some embodiments, the C2'-C3' bond (i.e., the covalent carbon-carbon bond between the C2' and C3' carbons) of the sugar (e.g., ribose) have been removed. See, e.g., Nuc. Acids Symp. Series, 52, 133-134 (2008) and Fluitter et al., Mol. Biosyst., 2009, 10, 1039, the entire contents of which are incorporated herein by reference. UNAs and methods of making are known in the art. See, e.g., U.S. Pat. No. 8,314,227; and US2013/0096289; US2013/0011922; and US2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

(b) Bicyclic Sugar Modifications

[0653] In some embodiments, the modified sugar (e.g., ribose) moiety comprises a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar (e.g., ribose) moiety. In some embodiments, the bicyclic sugar (e.g., ribose) moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-CH₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 7,399,845, Bhat et al., U.S. Pat. No. 7,569,686, Swayze et al., U.S. Pat. No. 7,741,457, and Swayze et al., U.S. Pat. No. 8,022,193), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (see, e.g., Prakash et al., U.S. Pat. No. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (see, e.g., Allerson et al., U.S. Pat. No. 7,696,345 and Allerson et al., U.S. Pat. No. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (see, e.g., Zhou, et al., J. Org. Chem., 2QQ9, 74, 118-134), 4'-CH₂-C(=CH₂)-2' and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 8,278,426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (see, e.g. Imanishi et al., U.S. Pat. No. 7,427,672). The entire contents of all of the foregoing references is incorporated by reference herein for all purposes.

[0654] In some embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: —[C(R_a)(R_b)]n-, —[C(R_a)(R_b)]n-O—, —C(R_a)=C(R_b)—, —C(R_a)=N—, —C(=NR_a)—, —C(=O)—, —C(=S)—, —O—, —Si(R_a)₂—, —S(=O)X—, and —N(R_a)—; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substi-

tuted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical, substituted C₅-C₇ alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(=O)—H), substituted acyl, CN, sulfonyl (S(=O)2—J1), or sulfoxyl (S(=O)—J1); and each J1 and J2 is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ aminoalkyl, or a protecting group.

[0655] Additional bicyclic sugar moieties are known in the art, see, for example: Freier et al., *Nucleic Acids Research*, 1997, 25 (22), 4429-4443; Alback et al., *J. Org. Chem.*, 2006, 71, 7731-7740; Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koskin et al., *Tetrahedron*, 1998, 54, 3607-3630; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 2007, 129, 8362-8379; Wengel et al., U.S. Pat. No. 7,053,207; Imanishi et al., U.S. Pat. No. 6,268,490; Imanishi et al., U.S. Pat. No. 6,770,748; Imanishi et al., U.S. RE44,779; Wengel et al., U.S. Pat. No. 6,794,499; Wengel et al., U.S. Pat. No. 6,670,461; Wengel et al., U.S. Pat. No. 7,034,133; Wengel et al., U.S. Pat. No. 8,080,644; Wengel et al., U.S. Pat. No. 8,034,909; Wengel et al., U.S. Pat. No. 8,153,365; Wengel et al., U.S. Pat. No. 7,572,582; Ramasamy et al., U.S. Pat. No. 6,525,191; Torsten et al., WO 2004/106356; Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. Pat. No. 7,547,684; Seth et al., U.S. Pat. No. 7,666,854; Seth et al., U.S. Pat. No. 8,088,746; Seth et al., U.S. Pat. No. 7,750,131; Seth et al., U.S. Pat. No. 8,030,467; Seth et al., U.S. Pat. No. 8,268,980; Seth et al., U.S. Pat. No. 8,546,556; Seth et al., U.S. Pat. No. 8,530,640; Migawa et al., U.S. Pat. No. 9,012,421; Seth et al., U.S. Pat. No. 8,501,805; and U.S. Patent Publication Nos. Allerson et al., US2008/0039618 and Migawa et al., US2015/0191727. The entire contents of all of the foregoing references is incorporated by reference herein for all purposes.

[0656] In some embodiments, the modified sugar (e.g., ribose) comprises a constrained ethyl nucleotide comprising a 4'-CH(CH₃)—O-2' bridge. In some embodiments, the constrained ethyl nucleotide is in the S conformation (S-cEt). In some embodiments, the modified sugar (e.g., ribose) comprises a conformationally restricted nucleotide (CRN). CRNs are nucleotide analogs with a linker connecting the C2' and C4' carbons of ribose or the C3 and —C5' carbons of ribose. Representative publications that teach the preparation of certain of the above include, but are not limited to, US2013/0190383; and WO2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

[0657] In some embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α-L configuration or in the β-D configuration. Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. Any of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and

β-D-ribofuranose (see, e.g., WO 99/14226, the entire contents of which are incorporated herein by reference for all purposes).

[0658] Additional representative U.S. patents and U.S. Patent Publications that teach the preparation of bicyclic nucleosides (e.g., locked nucleic acid) include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133; 7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

(ii) Nucleobase Modifications

[0659] In some embodiments, the modified agent (or any component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more nucleotides comprising a modified nucleobase.

[0660] As used herein, “unmodified” nucleobases refer to the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases include other synthetic and natural nucleobases.

[0661] Modified nucleobases include, but are not limited to, 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and 0-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 5-methylcytosine, 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, deoxythimidine (dT), 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (—C≡C—CH₃) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-Nbenzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. Pat. No. 3,687,808; *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J. I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, Crooke, S. T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S. T., Ed., CRC Press, 2008, 163-166 and 442-443; the entire contents of each of which is incorporated herein by reference for all purposes.

[0662] In some embodiments, the modified nucleobase comprises a pseudouridine, 2'thiouridine (s2U), N6'-methyladenosine, 5'methylcytidine (m⁵C), 5'fluoro-2'deoxyuridine, N-ethylpiperidine 7-EAA triazole modified adenine, N-ethylpiperidine 6'triazole modified adenine, 6-phenylpyrrolo-cytosine (PhpC), 2',4'-difluorotoloyl ribonucleoside (rF), or 5'nitroindole. In some embodiments, the modified nucleobase comprises a 5-substituted pyrimidine; 6-azapyrimidine; or N-2, N-6 and 0-6 substituted purines (including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine). 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

[0663] Representative U.S. patents an published applications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; 7,495,088; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,434,257; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; U.S. Pat. Nos. 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,681,941; 5,811,534; 5,750,692; 5,948,903; 5,587,470; 5,457,191; 5,763,588; 5,830,653; 5,808,027; 6,166,199; and 6,005,096, the entire contents of each of which is hereby incorporated herein by reference for all purposes. Exemplary nucleobase modifications are further provided in Hu, B., Zhong, L., Weng, Y. et al. Therapeutic siRNA: state of the art. *Sig Transduct Target Ther* 5, 101 (2020). <https://doi.org/10.1038/s41392-020-0207-x> (e.g., Table 2), the entire contents of each of which is incorporated by reference herein for all purposes.

4.3.1.2 Internucleoside Linkage Modifications

[0664] In some embodiments, the modified agent (or any component thereof) (e.g., antisense strand, sense strand, dsRNA agent, etc.) comprises one or more modified internucleoside linkage. Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of an agent (e.g., described herein).

[0665] The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. In some embodiments, the modified internucleoside linkage contains a normal 3'-5' linkage. In some embodiments, the modified internucleoside linkage contains a 2'-5' linkage. In some embodiments, the modified internucleoside linkage has an inverted polarity wherein the adjacent pairs of nucleoside units are linked e.g., 3'-5' to 5'-3' or 2'-5' to 5'-2'.

[0666] The two main classes of modified internucleoside linking can be defined by the presence or absence of a phosphorous atom.

[0667] Exemplary internucleoside linkage modifications are further provided in Hu, B., Zhong, L., Weng, Y. et al. Therapeutic siRNA: state of the art. *Sig Transduct Target Ther* 5, 101 (2020). <https://doi.org/10.1038/s41392-020-0207-x>

0207-x (e.g., Table 2), the entire contents of each of which is incorporated by reference herein for all purposes.

(i) Modified Phosphorous Containing Internucleoside Linkages

[0668] In some embodiments, the modified internucleoside linkage comprises a phosphorous atom. Representative modified phosphorus-containing internucleoside linkages include but are not limited to phosphorothioates (PS (Rp isomer or Sp isomer)) (e.g., 5'phosphorothioate), phosphotriesters, phosphoramidates (e.g., 3'-amino phosphoramidate and aminoalkylphosphoramidates), chiral phosphorothioates, phosphorodithioates (PS2), aminoalkylphosphotriesters, methyl and other alkyl phosphonates (e.g., methylphosphonate (MP), 3'-alkylene phosphonates), methoxypropyl-phosphonates (MOP), vinyl-phosphonate, 5'-(E)-vinylphosphonates, 5'methyl phosphonates, (S)-5'C-methyl with phosphates, phosphinates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, boranophosphates, and peptide nucleic acids (PNAs).

[0669] In some embodiments, the modified internucleotide linkage comprises a vinyl-phosphonate. In some embodiments, the modified internucleotide linkage comprises a vinyl-phosphonate-2'-O-methyl (e.g., a vinyl-phosphonate-2'-O-methyluridine).

[0670] Methods of preparing polynucleotides containing one or more modified phosphorus-containing internucleoside linkage are known in the art. See, e.g., U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat. RE39464, the entire contents of each of which are hereby incorporated herein by reference for all purposes. Exemplary modifications are further provided in Hu, B., Zhong, L., Weng, Y. et al. Therapeutic siRNA: state of the art. *Sig Transduct Target Ther* 5, 101 (2020). <https://doi.org/10.1038/s41392-020-0207-x> (e.g., Table 2), the entire contents of each of which is incorporated by reference herein for all purposes.

(ii) Modified Non-Phosphorous Containing Internucleoside Linkages

[0671] In some embodiments, the modified internucleoside linkage does not contain a phosphorous atom. Modified internucleoside linkages that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfona-

amide backbones; amide backbones; and others having mixed N, O, S, and CH₂ component parts.

[0672] Representative non-phosphorous containing internucleoside linking groups include but are not limited to methylenemethylimino ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{O}-\text{CH}_2-$), thiodiester, thionocarbamate ($-\text{O}-\text{C}(=\text{O}) (\text{NH})-\text{S}-$); siloxane ($-\text{O}-\text{SiH}_2-\text{O}-$); and N,N'-dimethylhydrazine ($-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-$).

[0673] Methods of preparing polynucleotides comprising modified internucleoside linkages do not contain a phosphorous atom are known in the art. See, e.g., U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

4.3.1.3 Additional Exemplary Nucleotide Modifications

[0674] In some embodiments, the modified agent comprises one or more RNA mimetic in which both the sugar and the internucleoside linkage of the nucleotide units are replaced with novel groups. The nucleobase units are maintained for hybridization with an appropriate nucleic acid target (e.g., a target mRNA). In some embodiments, the RNA mimetic is a peptide nucleic acid (PNA). In PNAs, the ribose moiety of the RNA nucleotide is replaced with an amide containing moiety (e.g., an aminoethylglycine). The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide. Representative US patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the agents described herein are described in, for example, in Nielsen et al., *Science*, 1991, 254, 1497-1500, the entire contents of which is incorporated by reference herein for all purposes.

[0675] Potentially stabilizing modifications to the terminal ends of the agents (e.g., described herein) can also be incorporated to agents described herein. For example, N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-O-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"-phosphate, inverted base dT (dT) and others. Such modifications are known in the art. See, e.g., WO2011/005861, the entire contents of which is incorporated herein by reference.

4.3.2 Extent of Modified Nucleotides

[0676] In some embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent) are modified. In some embodiments, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, substantially all of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In specific embodiments, all of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified.

[0677] In some embodiments, at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the sense and/or antisense strand are modified. For example, at least 50% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 55% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 60% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 65% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 70% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 75% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 80% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 85% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 90% of the nucleotides of the sense strand and/or antisense strand may be modified. For example, at least 95% of the nucleotides of the sense strand and/or antisense strand may be modified. In some embodiments, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified.

[0678] In some embodiments, substantially all (or all) of the nucleotides in the sense strand are modified. In some embodiments, substantially all (or all) of the nucleotides in the antisense strand are modified. In some embodiments, substantially all (or all) of the nucleotides in the sense strand and antisense strand are modified.

[0679] In some embodiments, at least one of the modified nucleotides comprises a modified sugar (e.g., ribose moiety). In some embodiments, at least one of the modified nucleotides comprises a modified nucleobase. In some embodiments, the sense strand comprises at least one modified internucleoside linkage and/or the antisense strand comprises at least one modified internucleoside linkage.

[0680] In some embodiments, not more than 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a dsRNA agent, RNAi agent, etc.) are unmodified.

fied. In some embodiments, not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified. In some embodiments, not more than 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified.

[0681] In some embodiments, at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent) are unmodified. In some embodiments, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified. In some embodiments, substantially all of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified. In some embodiments, all of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are unmodified. In some embodiments, the heterologous moiety enhances the distribution and/or uptake (e.g., into a cell, e.g., into a cell in a subject) of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) (e.g., as compared to an agent that lacks the heterologous moiety). In some embodiments, the heterologous moiety alters (e.g., extends) the lifetime (e.g., *in vivo*) of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) (e.g., as compared to an agent that lacks the heterologous moiety). In some embodiments, the heterologous moiety provides an enhanced affinity for a selected target, e.g., a selected molecule, cell type, compartment (e.g., cell type, tissue, organ or region of the body) (e.g., as compared to an agent that lacks the heterologous moiety).

[0682] In some embodiments, not more than 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, not more than 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the nucleotides of the agent (or any component (e.g., nucleic acid molecule) thereof) (e.g., described herein, e.g., an antisense strand, a sense strand, a dsRNA agent, RNAi agent, etc.) are modified. In some embodiments, the heterologous moiety imparts a new property on the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) to which it is conjugated. For example, fluorophores or reporter groups that enable detection of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0683] In some embodiments, the RNAi agent (e.g., antisense strand, sense strand, dsRNA agent (e.g., described herein)) comprises one or more non-naturally internucleoside linkage. In some embodiments, at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the internucleoside linkages of the RNAi agent (e.g., antisense strand, sense strand, dsRNA agent (e.g., described herein)) are non-naturally occurring. In some embodiments, at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of the or internucleoside linkages of the RNAi agent (e.g., antisense strand, sense strand, dsRNA agent (e.g., described herein)) are chemically modified.

100% of the or internucleoside linkages of the RNAi agent (e.g., antisense strand, sense strand, dsRNA agent (e.g., described herein)) are chemically modified.

4.4 Conjugates

[0684] In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) comprises a heterologous moiety (e.g., operably connected to the agent). Therefore, further provided herein are conjugates comprising an agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) and a heterologous moiety (e.g., operably connected to the agent). It is clear from the disclosure, but for the sake of clarity, the conjugate can comprise a modified agent (e.g., described herein, see, e.g., § 4.3).

[0685] In some embodiments, the heterologous moiety modifies one or more property of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) to which it is conjugated. Exemplary properties include, but are not limited to, pharmacodynamics, pharmacokinetics, stability, absorption, activity, tissue distribution, cellular distribution, cellular uptake, charge, half-life, clearance, and binding affinity to a target nucleic acid molecule (e.g., a target mRNA).

[0686] In some embodiments, the heterologous moiety enhances the distribution and/or uptake (e.g., into a cell, e.g., into a cell in a subject) of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) (e.g., as compared to an agent that lacks the heterologous moiety). In some embodiments, the heterologous moiety alters (e.g., extends) the lifetime (e.g., *in vivo*) of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) (e.g., as compared to an agent that lacks the heterologous moiety). In some embodiments, the heterologous moiety provides an enhanced affinity for a selected target, e.g., a selected molecule, cell type, compartment (e.g., cell type, tissue, organ or region of the body) (e.g., as compared to an agent that lacks the heterologous moiety).

[0687] In some embodiments, the heterologous moiety enhances the activity (e.g., in a cell, e.g., in a cell in a subject) of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) (e.g., as compared to an agent that lacks the heterologous moiety). Activity can include, e.g., degradation of a target mRNA (e.g., a CIDEB mRNA), inhibition of expression of a target gene (e.g., a CIDEB gene), and/or reduction in the expression of a target gene (e.g., a CIDEB gene).

[0688] In some embodiments, the heterologous moiety imparts a new property on the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) to which it is conjugated. For example, fluorophores or reporter groups that enable detection of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0689] It is to be understood the heterologous moieties can impart multiple (e.g., any combination of the foregoing) properties of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0690] In some embodiments, wherein the agent is a dsRNA agent comprising a double stranded region, the heterologous moiety does not take part in, does not alter, and/or does not interfere with, the creation of a double strand region.

4.4.1 Heterologous Moieties

[0691] Heterologous moieties, include for example, but are not limited to, carbohydrates, peptides, proteins (e.g., antibodies or functional fragments or variants thereof; ligands (e.g., of a target receptor)), lipids, polymers, small molecules, intercalators, reporter molecules, polyamines, polyamides, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterols, thiocolchoesters, cholic acid moieties, folate, lipophilic groups, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantanane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

[0692] In some embodiments, the heterologous moiety is a carbohydrate, peptide, protein (e.g., antibody or functional fragment or variant thereof, e.g., ligand (e.g., of a target receptor)), lipid, polymer, small molecule, or any combination thereof. In some embodiments, the heterologous moiety comprises an active drug substance. In some embodiments, the heterologous moiety does not contain an active drug substance.

[0693] Exemplary heterologous moieties (e.g., targeting moieties), further include but are not limited, to carbohydrate moieties (e.g., GalNAc and GalNAc derivatives (See, e.g., U.S. Pat. No. 8,106,022 and WO2019055633)); lipid moieties such as a cholesterol moiety (see, e.g., Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86:6553-6556); cholic acid (see, e.g., Manoharan et al., Biorg. Med. Chem. Lett., 1994, 4:1053-1060), a thioether, e.g., beryl-S-tritylthiol (see, e.g., Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Lett., 1993, 3:2765-2770); thiocolchoesters (see, e.g., Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538); aliphatic chains (e.g., dodecandiol or undecyl residues) (see, e.g., Saison-Behmoaras et al., EMBO J., 1991, 10:1111-1118; Kabanova et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54), phospholipids (e.g., dihexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate) (see, e.g., Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783); polyamine or polyethylene glycol chains (see, e.g., Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973); adamantanane acetic acids (see, e.g., Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654); palmityl moieties (see, e.g., Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237); and octadecylamine or hexylamino-carbonyloxycholesterol moiety (see, e.g., Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937). The entire contents of each of the foregoing references is incorporated herein by reference for all purposes. Additional carbohydrate heterologous moieties (and linkers) suitable for use in conjugates described herein include those described in PCT Publication Nos. WO 2014/179620 and WO 2014/179627, the entire contents of each of which are incorporated herein by reference for all purposes.

4.4.1.1 Targeting Moieties

[0694] In some embodiments, the heterologous moiety is a targeting moiety. In some embodiments, the targeting moiety enhances distribution of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand,

sense strand) to a target cell (or population of cells), tissue, and/or organ (e.g., as compared to an agent that lacks the targeting moiety). In some embodiments, the targeting moiety enhances the uptake of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) into a target cell (or population of cells) (e.g., as compared to an agent that lacks the targeting moiety). In some embodiments, the targeting moiety provides enhanced affinity for a selected target, e.g., molecule, cell, cell type, compartment, e.g., a cellular or organ compartment, tissue, organ or region of the body, (e.g., as compared to an agent that lacks the targeting moiety).

[0695] In some embodiments, the targeting moiety specifically binds to a target molecule (e.g., protein, carbohydrate, lipid, etc.) expressed on the surface of a target cell, tissue, and/or organ. In some embodiments, the target molecule is a protein, carbohydrate, or lipid. In some embodiments, the target molecule is a receptor.

(i) Hepatocyte Targeting Moieties

[0696] In some embodiments, the targeting moiety specifically binds to a target molecule (e.g., protein, carbohydrate, lipid, etc.) expressed by hepatocytes (e.g., on the surface of the surface of hepatocytes). In some embodiments, the targeting moiety specifically binds to a target molecule protein (e.g., receptor) expressed on the surface of hepatocytes.

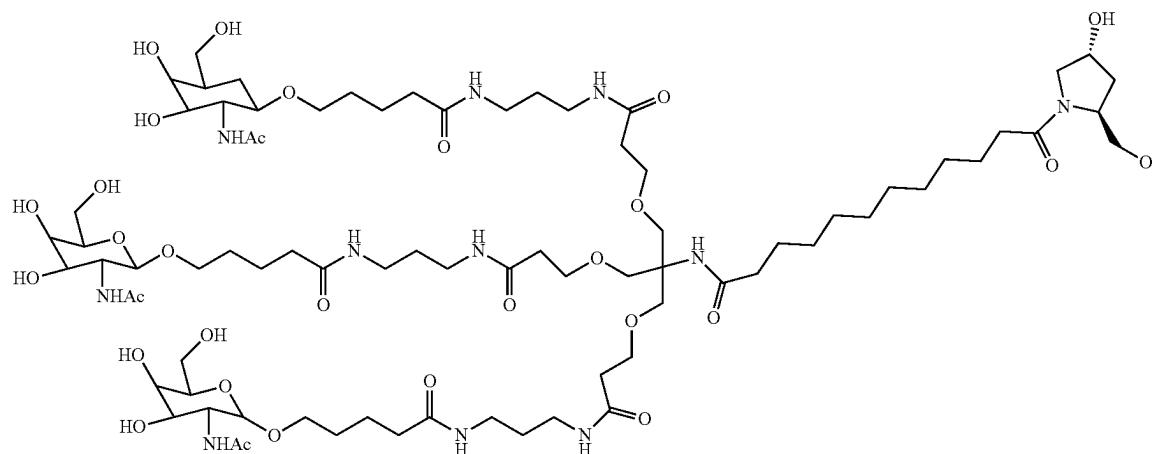
[0697] In some embodiments, the targeting moiety comprises a carbohydrate. Exemplary carbohydrate targeting moieties are described in WO2019055633, the entire contents of which is incorporated by reference herein for all purposes. In some embodiments, the carbohydrate is a monosaccharide. In some embodiments, the carbohydrate is a polysaccharide.

[0698] In some embodiments, the targeting moiety comprises at least one (e.g., at least 2, 3, 4, or more) N-acetylgalactosamine (GalNAc) or GalNAc derivative. In some embodiments, the targeting moiety comprise a plurality (e.g., 2, 3, 4, 5, or 6) of GalNAc moieties and/or GalNAc derivatives. In some embodiments, the targeting moiety comprise a plurality (e.g., 2, 3, 4, 5, or 6) of GalNAc moieties and/or GalNAc derivatives each independently attached to a plurality of nucleotides of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) through a plurality of linkers (e.g., monovalent linkers). In some embodiments, the GalNAc targeting moiety serves to target the agent to hepatocytes through specific binding to the asialoglycoprotein receptor.

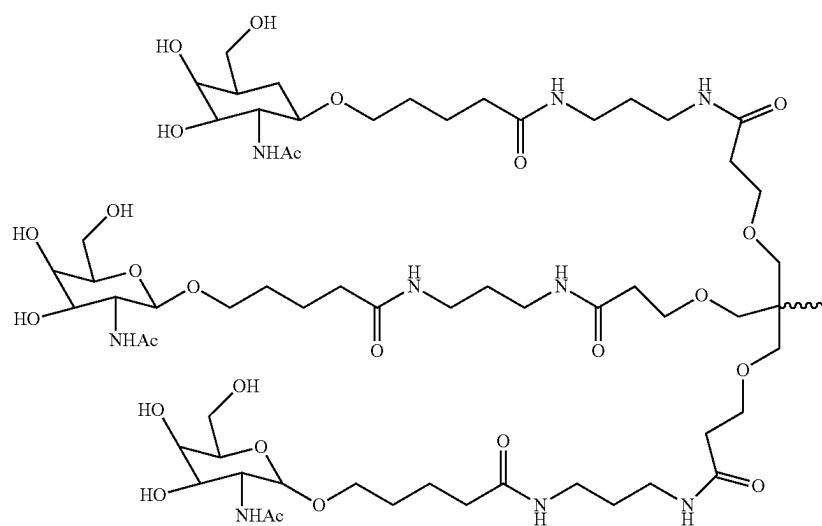
[0699] Exemplary GalNAc conjugates, which comprise one or more GalNAc and/or derivative thereof, are known the art. See, e.g., in U.S. Pat. No. 8,106,022, the entire contents of which is hereby incorporated herein by reference for all purposes. Additional exemplary GalNAc targeting moieties are described below.

[0700] In some embodiments, the targeting moiety (e.g., GalNAc targeting moiety) comprises any one of the following formulas:

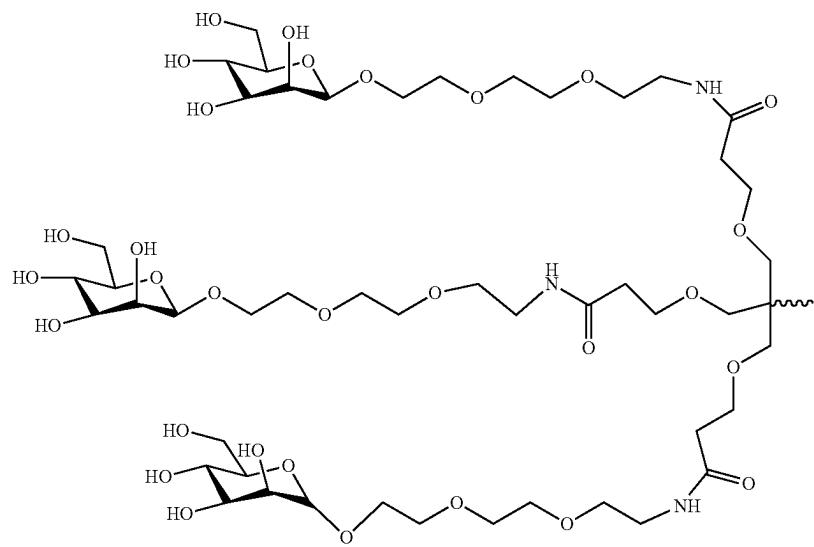
Formula I



Formula II

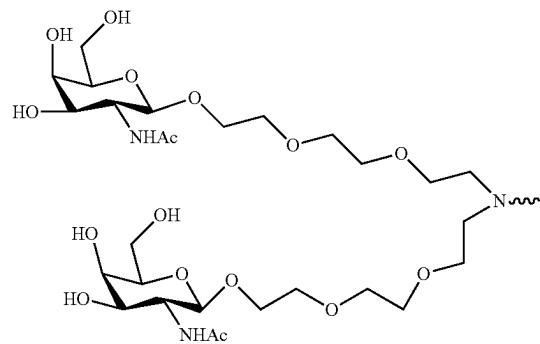


Formula III

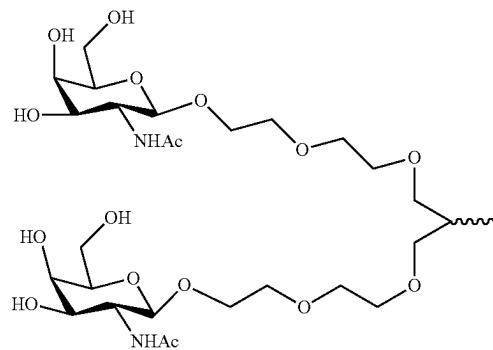


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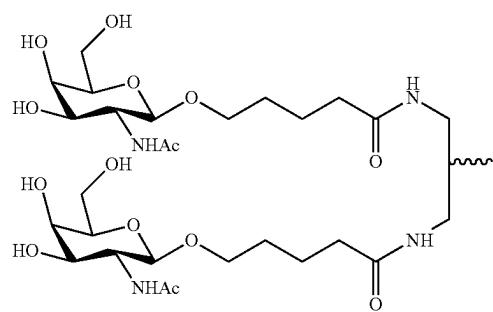
Formula IV



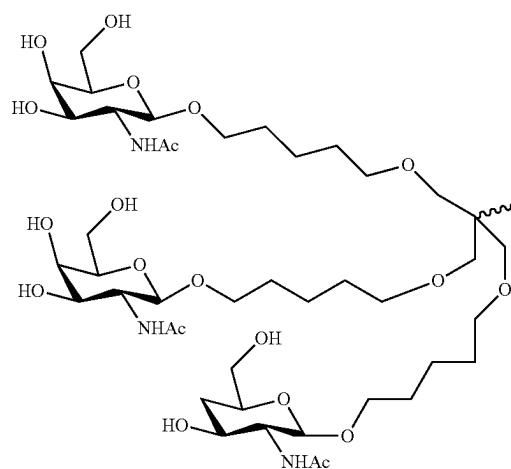
Formula V



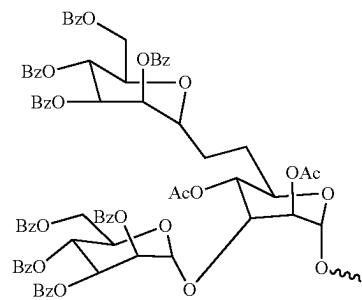
Formula VI



Formula VII

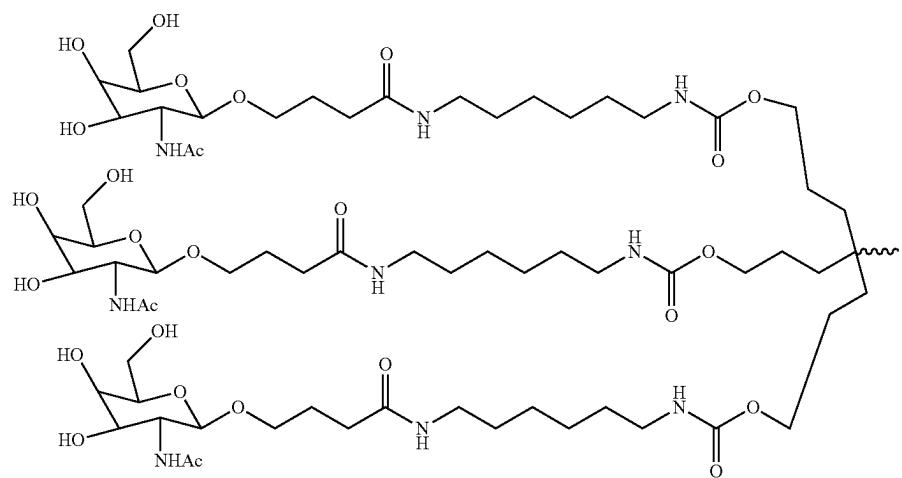


Formula VIII

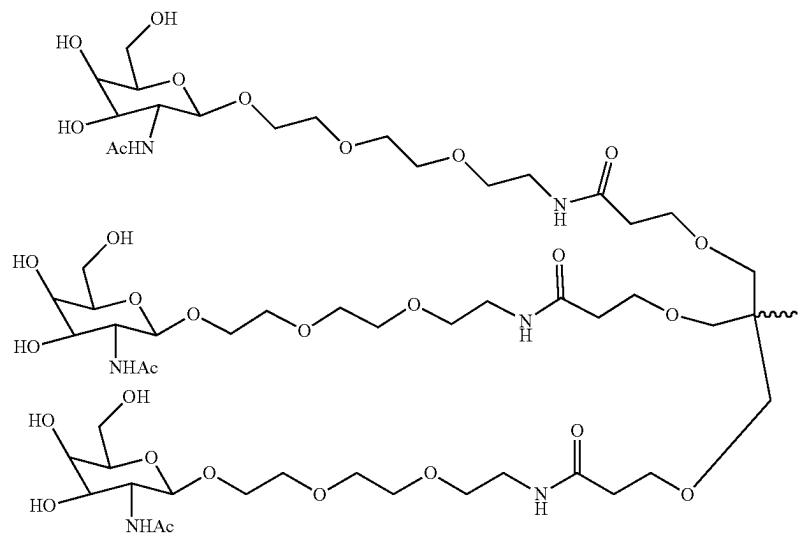


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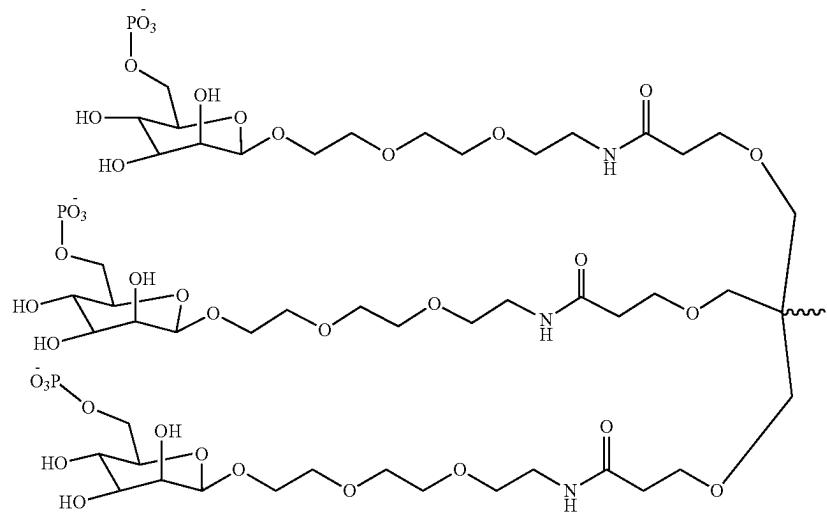
Formula IX



Formula X

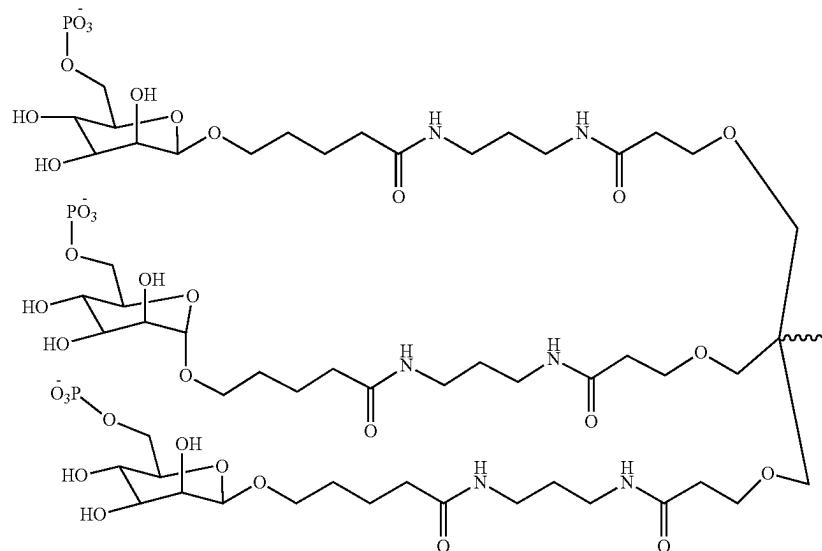


Formula XI

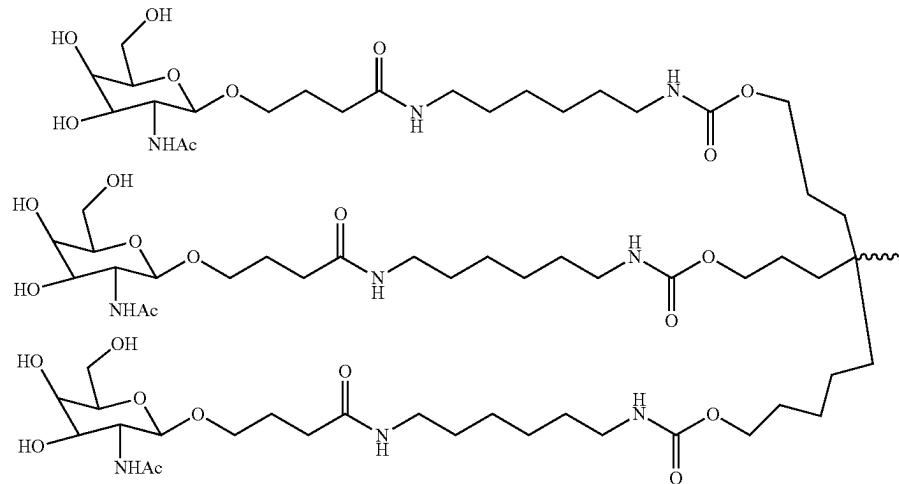


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Formula XII

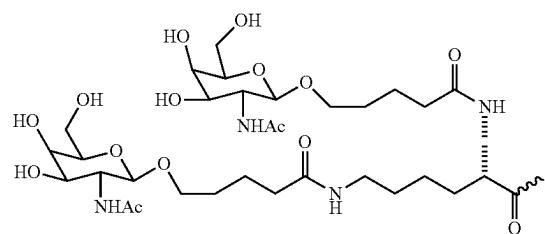


Formula XIII

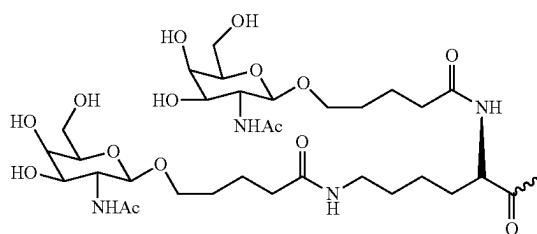


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Formula XIV

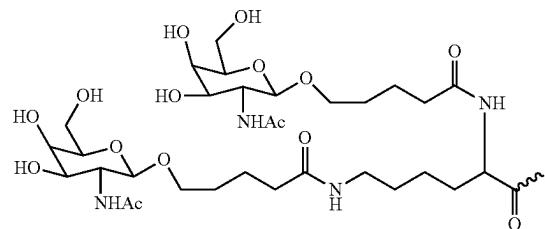


Formula XV



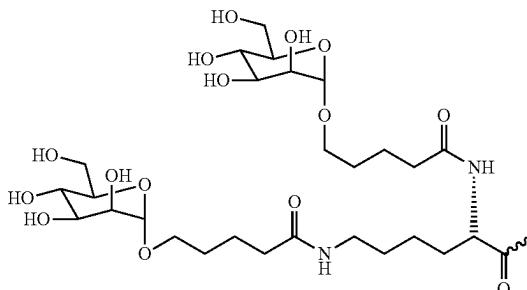
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Formula XVI

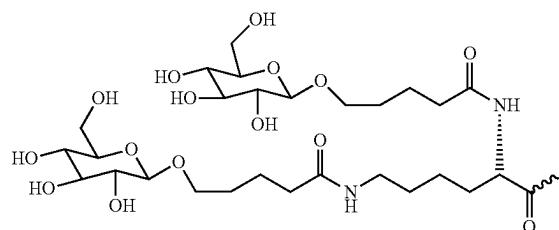


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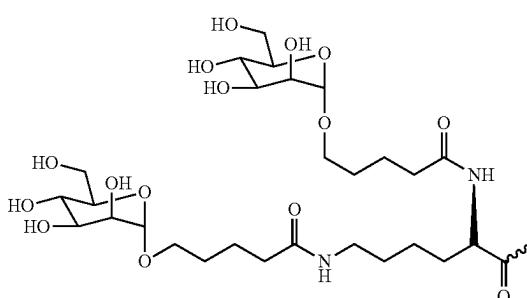
Formula XXI



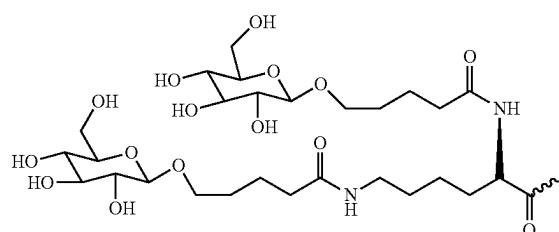
Formula XVII



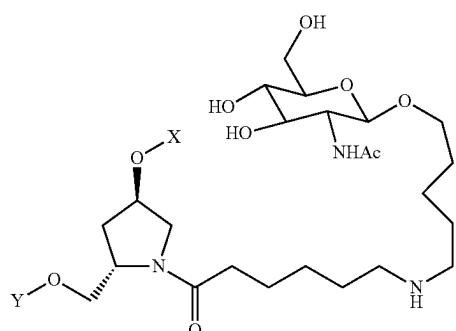
Formula XXII



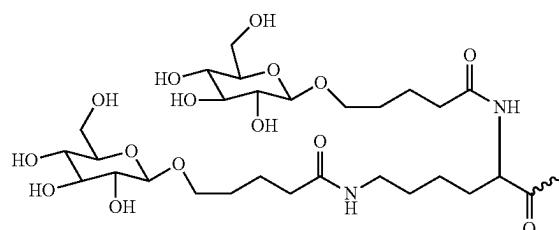
Formula XVIII



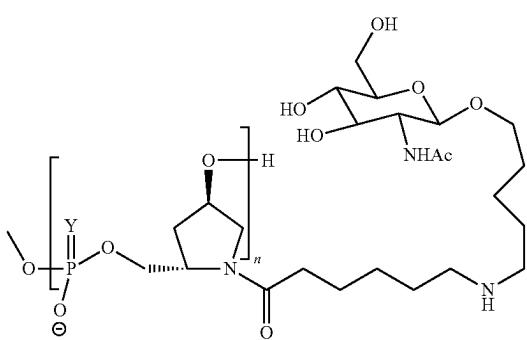
Formula XXIII



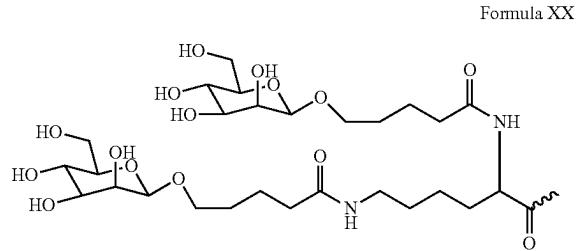
Formula XIX



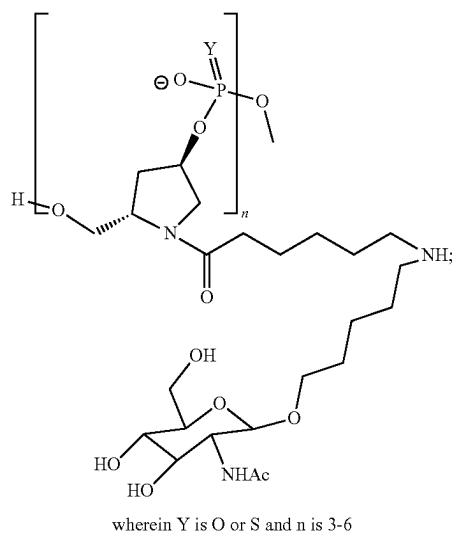
Formula XXIV



wherein Y is O or S and n is 3-6

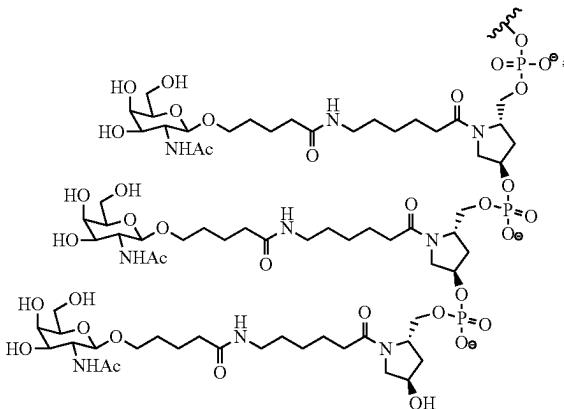


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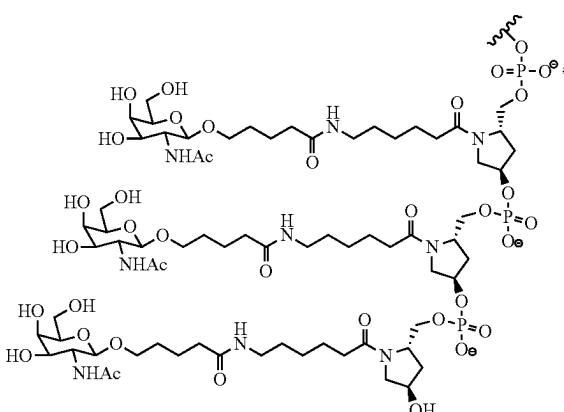


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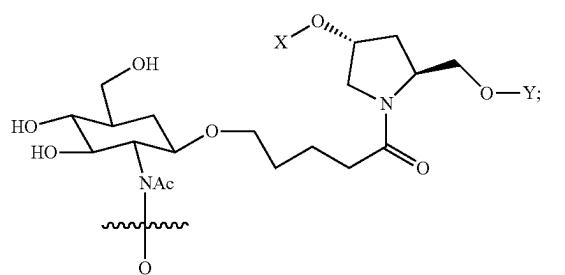
Formula XXVIII



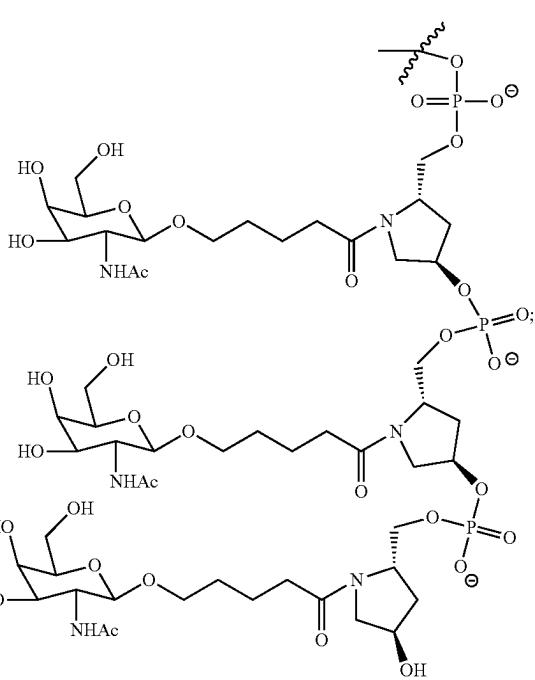
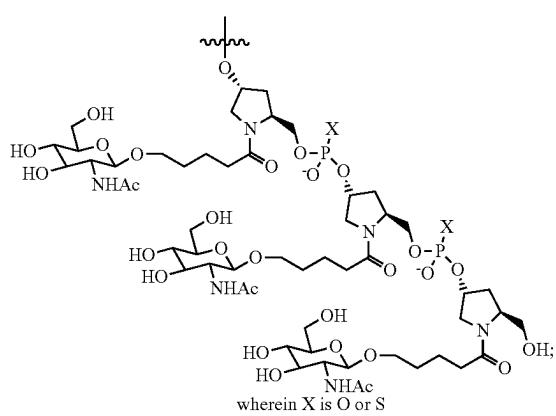
Formula XXIX



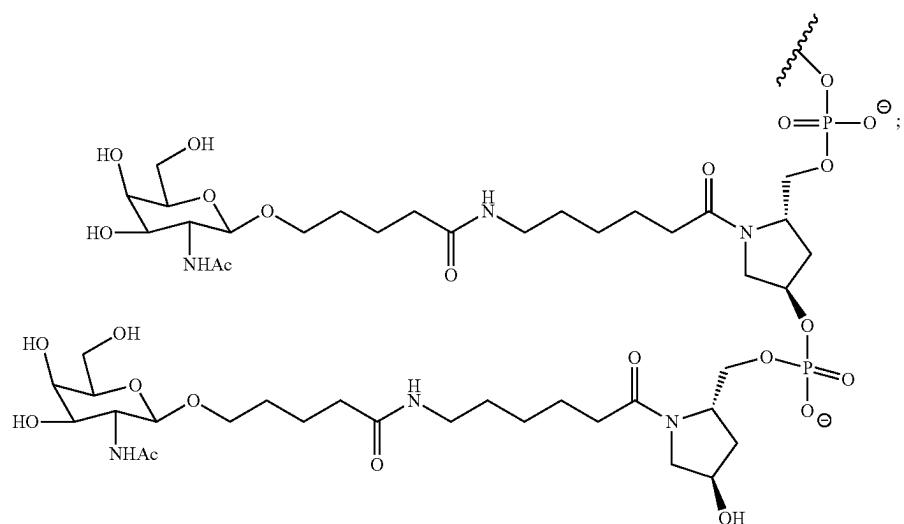
Formula XXX



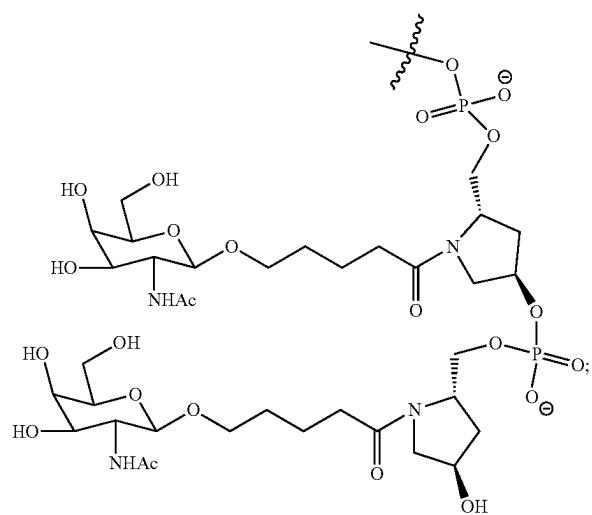
Formula XXVII



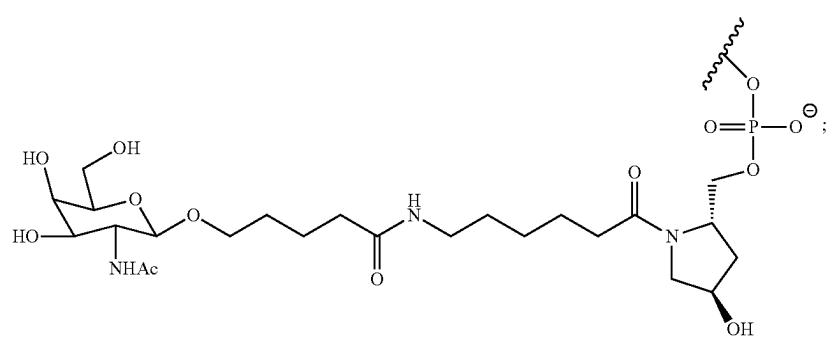
Formula XXXI



Formula XXXII

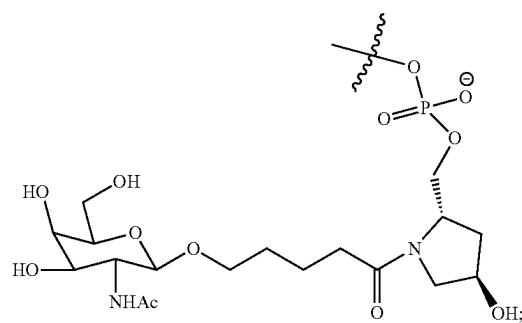


Formula XXXIII

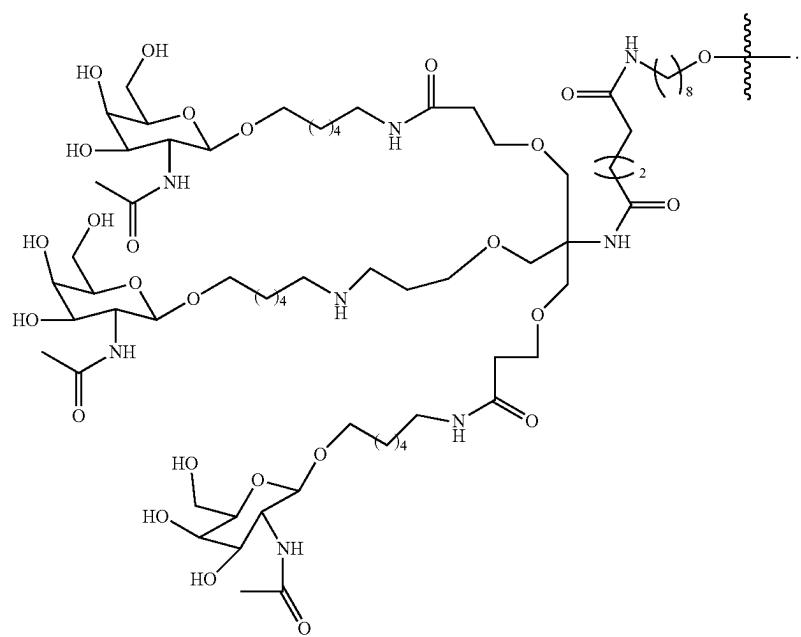


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Formula XXXIV

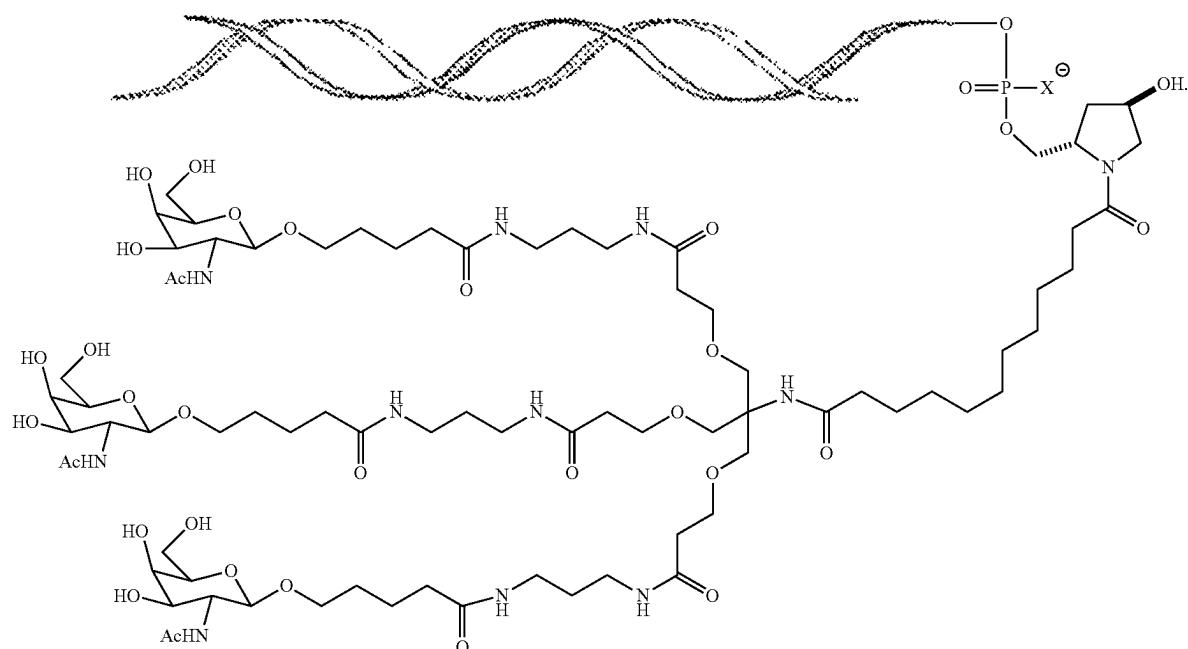


Formula XXXV



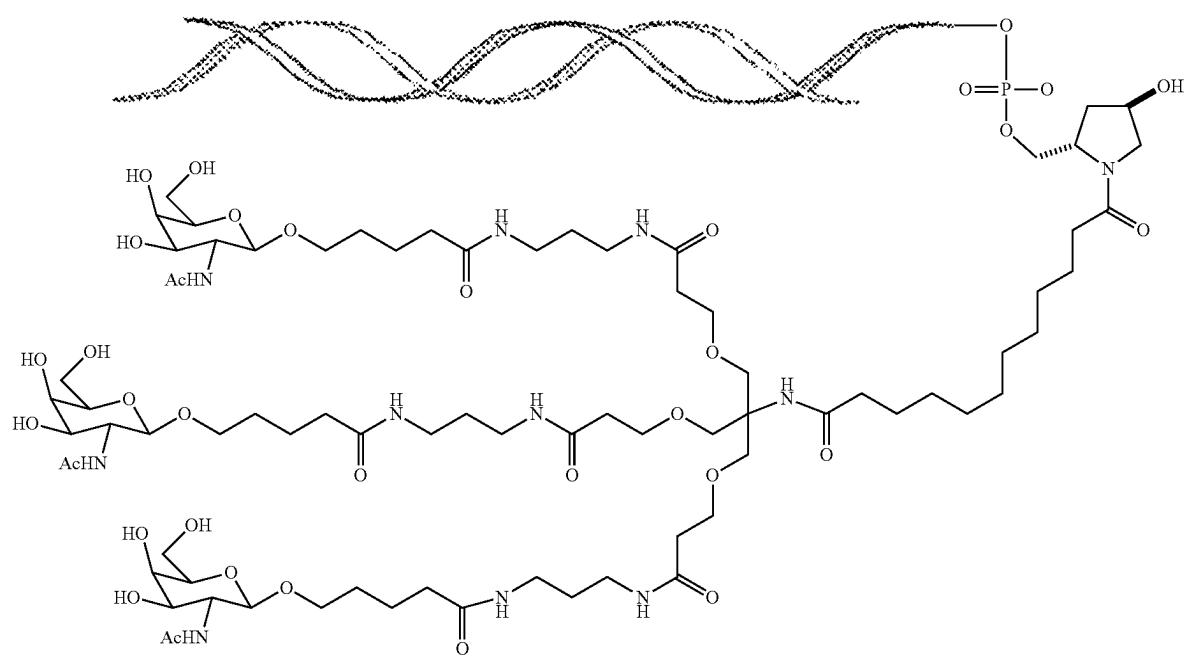
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Formula XXXVI



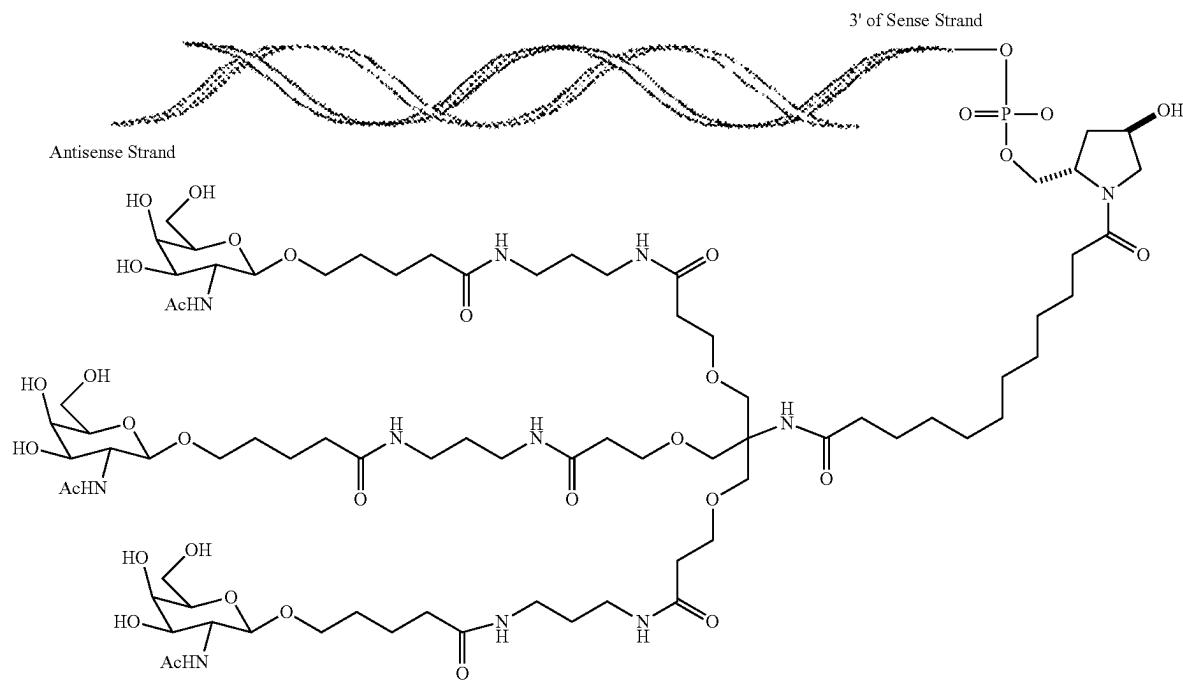
Wherein X is O or S

Formula XXXVII

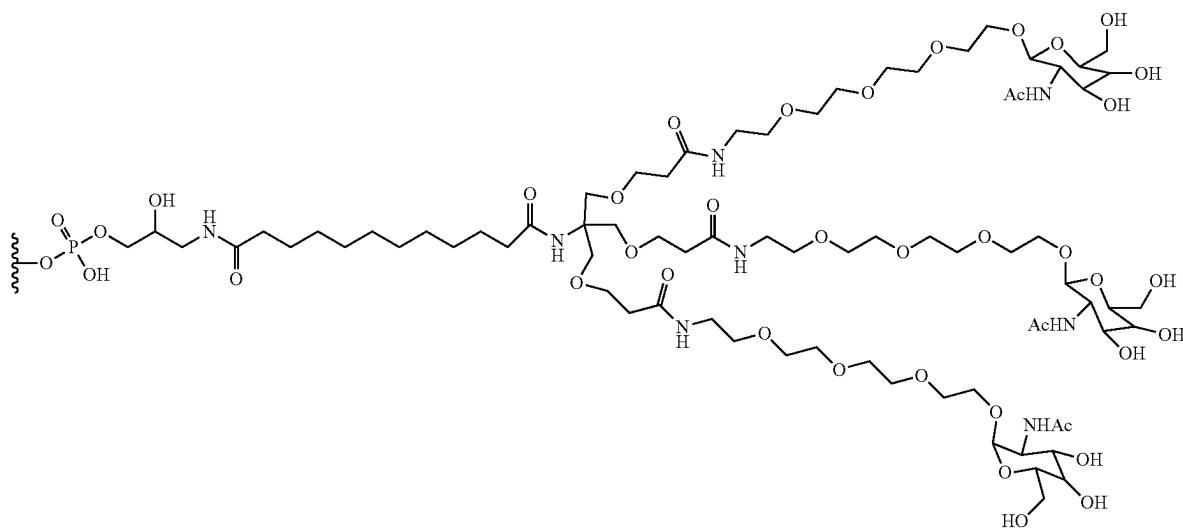


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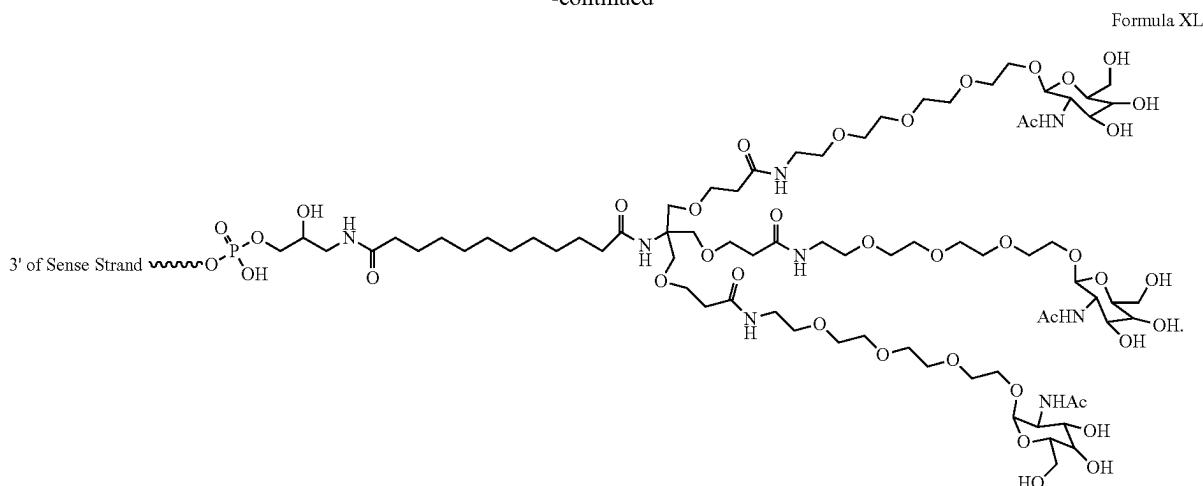
Formula XXXVIII



Formula XXXIX



-continued



[0701] In one embodiment, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in any one of Formulas I.

[0702] In one embodiment, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula I. In one embodiment, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula II.

[0703] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXVI. In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXVII. In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXVIII.

[0704] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXIX. In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XL.

[0705] In specific preferred embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 3' end of the sense strand. In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 5' end of the sense strand.

[0706] In some embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 3' end of the antisense strand. In some embodiments, the targeting moiety comprises the GalNAc targeting moiety set forth in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 5' end of the antisense strand.

[0707] In one embodiment, the targeting moiety comprises N-[tris(GalNAc)-amido-dodecanoyl]-4-hydroxyprolinol [Hyp-(GalNAc-alkyl)3]. In one embodiment, the targeting moiety comprises (2S,4R)-1-[29-[[2-(acetylamino)-2-deoxy- β -D-galactopyranosyl]oxy]-14,14-bis[[3-[3-[5-[[2-(acetylamino)-2-deoxy- β -D-galactopyranosyl]oxy]-1-oxopentyl]amino]propyl]amino]-3-oxopropoxy]methyl]-1,12,19,25-tetraoxo-16-oxa-13,20,24-triazanonacos-1-yl]-4-hydroxy-2-hydroxymethylpyrrolidine.

4.4.2 Linkers

[0708] In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) is directly attached to the heterologous moiety (e.g., targeting moiety) (e.g., directly attached through a single chemical bond). In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) is indirectly attached to the heterologous moiety (e.g., targeting moiety). In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) is indirectly attached to the heterologous moiety via a linker.

[0709] Suitable linkers for use in the conjugates described herein are known in the art and can be evaluated by a person of ordinary skill in the art using standard methods. Exemplary linkers and components thereof for use in the conjugates described herein are also described below.

atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18, 7-17, 8-17, 6-16, 7-17, or 8-16 atoms.

[0711] In some embodiments, the linker comprises ethylene glycol (e.g., triethylene glycol), nucleosides, or amino acid units. In some embodiments, the linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino. In some embodiments, the linker comprises groups selected from alkyl, amino, oxo, amide and ether groups. In some embodiments, the linker comprises groups selected from alkyl and amide groups. In some embodiments, the linker comprises groups selected from alkyl and other groups. In some embodiments, the linker comprises at least one phosphorus moiety. In some embodiments, the linker comprises at least one phosphate group. In some embodiments, the linker comprises at least one neutral linking group. Exemplary linkers include but are not limited to triethylene glycol (TEG), pyrrolidine, 8-amino-3,6-dioxaocanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), 6-aminohexanoic acid (AHEX or AHA). Additional exemplary linkers include but are not limited to substituted or unsubstituted C₁-C_w alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[0712] In some embodiments, the linker is bifunctional. In general, a bifunctional linker comprises at least two functional groups. One of the functional groups is selected to react with a particular site on an agent (e.g., described herein) and the other is selected to react with a heterologous moiety (e.g., described herein). Examples of functional groups used in a bifunctional linkers include but are not limited to electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In some embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

[0713] In some embodiments, the linker is a monovalent linker, a bivalent linker, a trivalent linker, or a tetravalent linker. In some embodiments, the linker comprises or consists of the linker set forth above in Formula I.

[0714] In specific embodiments, the linker comprises triethylene glycol (TEG). In specific embodiments, the linker consists of triethylene glycol (TEG). In specific embodiments, the linker is triethylene glycol (TEG).

4.4.2.1 Cleavable Linkers

[0715] In some embodiments, the linker is non-cleavable. In some embodiments, the linker is cleavable. Cleavable linkers contain at least one (or a plurality of) cleavable bonds that are susceptible to one or more cleavage agent. Exemplary classes of cleavable linkers include, but are not limited to, redox cleavable linkers, phosphate based cleavable linkers, acid cleavable linkers, ester-based cleavable linkers, and peptide-based cleavable linkers. In certain embodiments, a cleavable bond is selected from among: an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide.

[0716] Cleavable linkers may be advantageous when a stable conjugate is desired under a first set of conditions but under a second set of conditions it is advantageous to release the agent (e.g., described herein) from the heterologous moiety (e.g., described herein). For example, in some embodiments, it may be desirable to have a sufficiently stable conjugate outside of a cell (e.g., within a subject (e.g.,

within the blood or serum of a subject)), and upon entry into a cell (e.g., a target cell (e.g., a target cell within a subject)) have the linker cleaved to release the agent (e.g., described herein) from the heterologous moiety (e.g., described herein). In some embodiments, the linker is not cleaved (or is cleaved at a lower rate) under a first condition relative to under a second condition. In some embodiments, the first condition is within the blood (e.g., of a subject) (or in an in vitro system sufficient to mimic the conditions of the blood within a subject) and the second condition is with a cell (e.g., a cell within a subject) (or in an in vitro system sufficient to mimic the conditions of a cell within a subject).

[0717] The suitability of a cleavable linker can be assessed by standard methods known in the art. In general, the suitability of a cleavable linker can be evaluated by testing the ability of a cleavage agent (or condition) to cleave the candidate linker (e.g., the cleavage bond(s)). In some embodiments, it may be desirable to further test the ability of the linker to resist cleavage under a certain condition (e.g., within the blood or serum of subject, when in contact with a non-target cell, tissue, organ).

[0718] In some embodiments, the linker is a redox cleavable linker that is cleaved upon reduction or oxidation. An example of a reductively cleavable linker is a disulphide ($-\text{S}-\text{S}-$) containing linker. Redox cleavable linkers can be evaluated using methods analogous to those described above.

[0719] In some embodiments, the linker is a phosphate-based cleavable linker. A phosphate-based cleavable linker is cleaved by agents that degrade or hydrolyze the phosphate group. For example, in cells, enzymes such as phosphatases are capable of cleaving phosphate groups. Examples of phosphate-based linkers include those comprising any of the following $-\text{O}-\text{P}(\text{O})(\text{ORk})-\text{O}-$, $-\text{OP}(\text{S})(\text{ORk})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{SRk})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{ORk})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{ORk})-\text{S}-$, $-\text{S}-\text{P}(\text{O})(\text{ORk})-\text{S}-$, $-\text{OP}(\text{S})(\text{ORk})-\text{S}-$, $-\text{S}-\text{P}(\text{S})(\text{ORk})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{Rk})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{Rk})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{Rk})-\text{O}-$, $-\text{S}-\text{P}(\text{S})(\text{Rk})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{Rk})-\text{S}-$, $-\text{O}-\text{P}(\text{S})(\text{Rk})-\text{S}-$, wherein Rk at each occurrence can be, independently, C₁-C₂₀ alkyl, C₁-C₂₀ haloalkyl, C₆-C₁₀ aryl, or C₇-C₁₂ aralkyl. Exemplary embodiments include are $-\text{OP}(\text{O})(\text{OH})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{OH})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{SH})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{OH})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{OH})-\text{S}-$, $-\text{S}-\text{P}(\text{O})(\text{OH})-\text{S}-$, $-\text{O}-\text{P}(\text{S})(\text{OH})-\text{S}-$, $-\text{S}-\text{P}(\text{S})(\text{OH})-\text{O}-$, $-\text{O}-\text{P}(\text{O})(\text{H})-\text{O}-$, $-\text{O}-\text{P}(\text{S})(\text{H})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{H})-\text{O}-$, $-\text{S}-\text{P}(\text{S})(\text{H})-\text{O}-$, $-\text{S}-\text{P}(\text{O})(\text{H})-\text{S}-$, or $-\text{O}-\text{P}(\text{S})(\text{H})-\text{S}-$. Phosphate based cleavable linker can be evaluated using methods analogous to those described above.

[0720] In some embodiments, the linker is an acid cleavable linker. An acid cleavable linker is cleaved under acidic conditions. For example, in some embodiments the acid cleavable linker can be cleaved in an acidic environment with a pH of about 6.5 or less (e.g., about 6.0, 5.5, 5.0, or less). In some embodiments the acid cleavable linker can be cleaved by enzymes that can act as a general acid. In a cell (e.g., within a subject), specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linkers. Examples of acid cleavable linkers include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula $-\text{C}=\text{NN}-$, $\text{C}(\text{O})\text{O}$, or $-\text{OC}(\text{O})$. Acid cleavable linkers can be evaluated using methods analogous to those described above.

[0721] In some embodiments, the linker is an ester-based cleavable linker. An ester-based cleavable linker is cleaved by enzymes such as esterases and amidases in cells.

Examples of ester-based cleavable include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups. The cleavable bonds of ester cleavable linkers have the general formula —C(O)O— or —OC(O)—. Ester-based cleavable linkers can be evaluated using methods analogous to those described above.

[0722] In some embodiments, the linker is a peptide-based cleavable linker. A peptide-based cleavable linker is cleaved by enzymes such as peptidases and proteases (e.g., present in cells (e.g., cells within a subject)). Peptide-based cleavable linkers comprise peptide bonds formed between amino acids to yield polypeptides (e.g., dipeptides, tripeptides, etc.). As known in the art, peptide bonds. The peptide bonds (i.e., the amide bond) of the peptide linker is generally the site of cleavage. Peptide-based cleavable linkers can be evaluated using methods analogous to those described above.

4.4.3 Orientation

[0723] The heterologous moiety may be attached at any suitable position to the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0724] In some embodiments, the heterologous moiety is conjugated to the 5' end of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand). In some embodiments, the heterologous moiety is conjugated to the 3' end of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand). In some embodiments, a first heterologous moiety is conjugated to the 5' end of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) and a second heterologous moiety is conjugated to the 3' end of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand). The first and second heterologous moieties can be the same or different. In some embodiments, the heterologous moiety is conjugated to an internal site of the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0725] In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises an antisense strand. In some embodiments, the heterologous moiety is conjugated to the 5' end of the antisense strand. In some embodiments, the heterologous moiety is conjugated to the 3' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to the 5' end of the antisense strand and a second heterologous moiety is conjugated to the 3' end of the antisense strand. The first and second heterologous moieties can be the same or different. In some embodiments, the heterologous moiety is conjugated to an internal site of the antisense strand.

[0726] In some embodiments, the agent (e.g., RNAi agent, dsRNA agent) comprises a sense strand. In some embodiments, the heterologous moiety is conjugated to the 5' end of the sense strand. In some embodiments, the heterologous moiety is conjugated to the 3' end of the sense strand. In some embodiments, a first heterologous moiety is conjugated to the 5' end of the sense strand and a second heterologous moiety is conjugated to the 3' end of the sense strand. The first and second heterologous moieties can be the same or different. In some embodiments, the heterologous moiety is conjugated to an internal site of the sense strand.

[0727] The heterologous moiety may be attached to the 3' end of the sense and/or antisense strand. The heterologous moiety may be attached to the 5' end of the sense and/or antisense strand. The heterologous moiety may be attached to an internal site of the sense and/or antisense strand. The

heterologous moiety may be attached to the 3' end of the sense and antisense strand. The heterologous moiety may be attached to the 5' end of the sense and antisense strand. The heterologous moiety may be attached to an internal site of the sense and antisense strand.

[0728] In some embodiments, the agent (e.g., RNAi agent) comprises a dsRNA agent comprising a sense strand and an antisense strand. In some embodiments, the heterologous moiety is conjugated to the 5' end of the sense strand. In some embodiments, the heterologous moiety is conjugated to the 3' end of the sense strand. In some embodiments, a first heterologous moiety is conjugated to the 5' end of the sense strand and a second heterologous moiety is conjugated to the 3' end of the sense strand. The first and second heterologous moieties can be the same or different. In some embodiments, the heterologous moiety is conjugated to an internal site of the sense strand. In some embodiments, the heterologous moiety is conjugated to the 5' end of the sense strand. In some embodiments, the heterologous moiety is conjugated to the 3' end of the sense strand. In some embodiments, a first heterologous moiety is conjugated to the 5' end of the sense strand and a second heterologous moiety is conjugated to the 3' end of the sense strand. The first and second heterologous moieties can be the same or different. In some embodiments, the heterologous moiety is conjugated to an internal site of the sense strand.

[0729] In some embodiments, a first heterologous moiety is conjugated to the 5' end of the sense strand and a second heterologous moiety is conjugated to the 5' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to the 3' end of the sense strand and a second heterologous moiety is conjugated to the 3' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to the 5' end of the sense strand and a second heterologous moiety is conjugated to the 3' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to the 3' end of the sense strand and a second heterologous moiety is conjugated to the 5' end of the antisense strand. The first and second heterologous moieties can be the same or different.

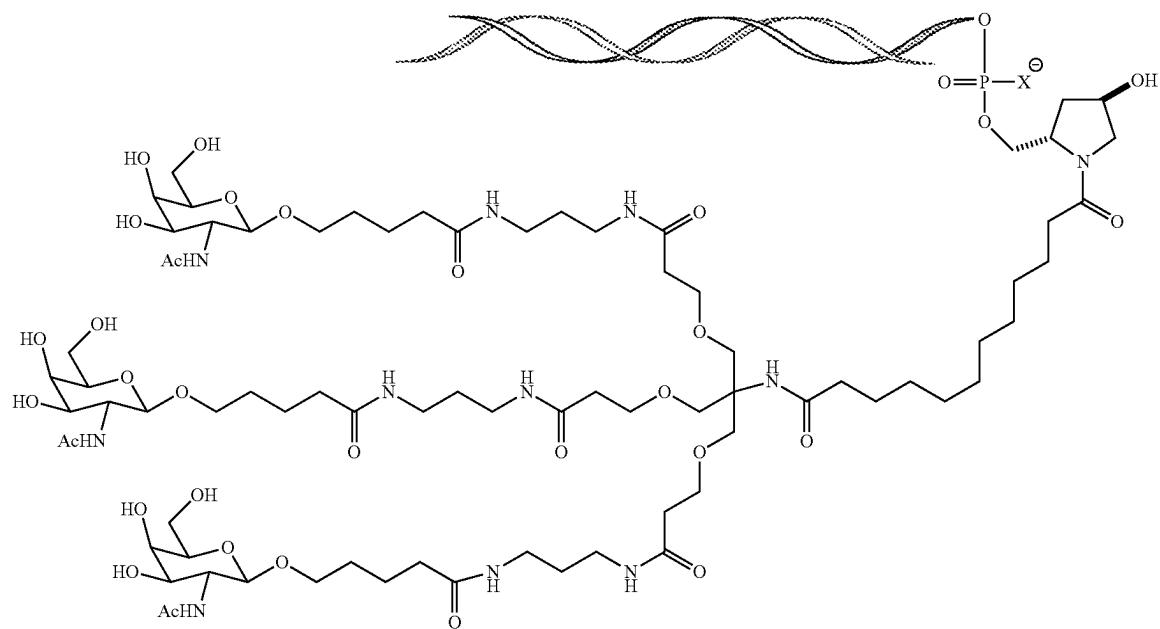
[0730] In some embodiments, a first heterologous moiety is conjugated to an internal site of the sense strand and a second heterologous moiety is conjugated to the 5' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to an internal site of the sense strand and a second heterologous moiety is conjugated to the 3' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to an internal site of the antisense strand and a second heterologous moiety is conjugated to the 3' end of the antisense strand. In some embodiments, a first heterologous moiety is conjugated to an internal site of the antisense strand and a second heterologous moiety is conjugated to the 5' end of the antisense strand. The first and second heterologous moieties can be the same or different.

4.4.4 Exemplary Conjugates

[0731] The structure of exemplary conjugates comprising a GalNAc targeting moiety and a linker via a linker for conjugation to an agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) described herein is provided below.

[0732] For example, in some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) is conjugated to a GalNAc targeting moiety through a linker e.g., as shown in the following schematic, wherein X is O or S (and further described in § 4.4.2).

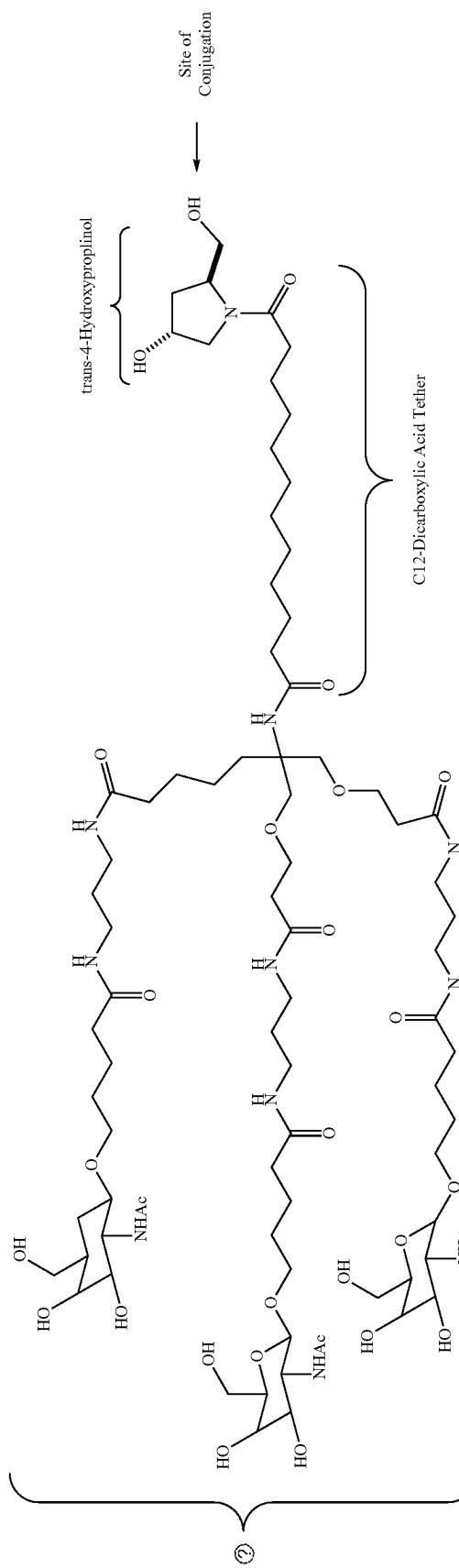
Formula XXXVI



Wherein X is O or S.

[0733] In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) is conjugated

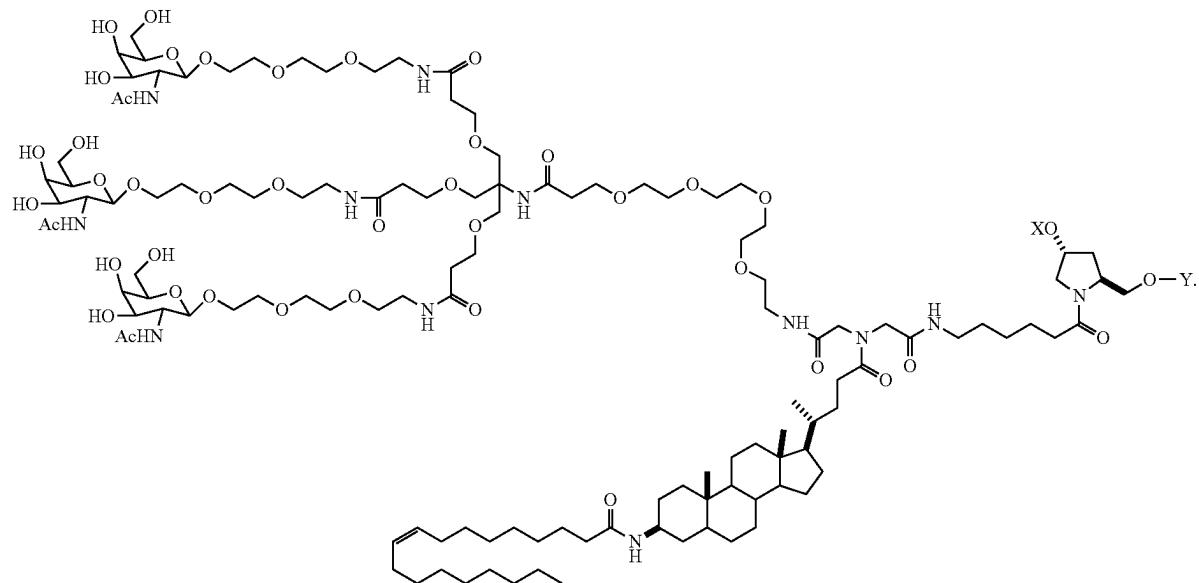
to the GalNAc targeting moiety as shown in the schematic below:



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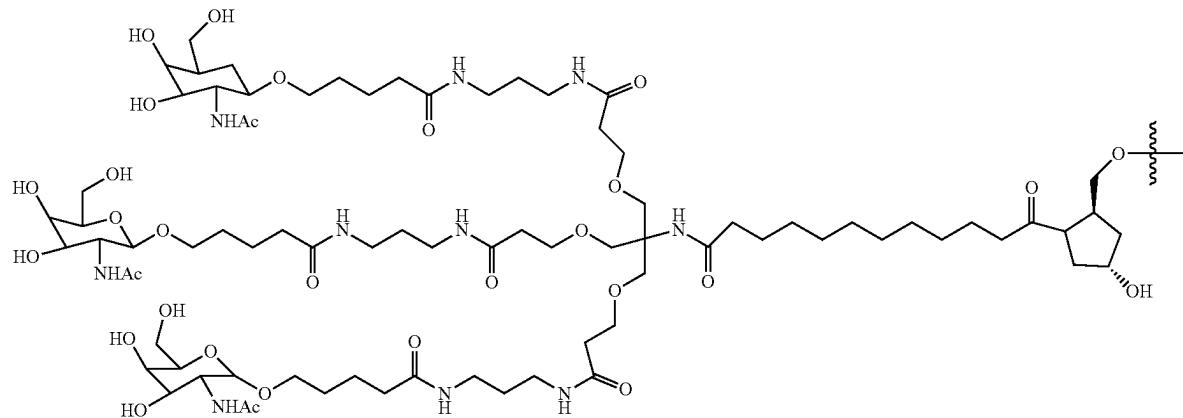
[0734] In some embodiments, the GalNAc targeting moiety and linker comprises that set forth below in Formula XXXVI wherein one of X or Y is a polynucleotide, the other is a hydrogen.

Formula XLI



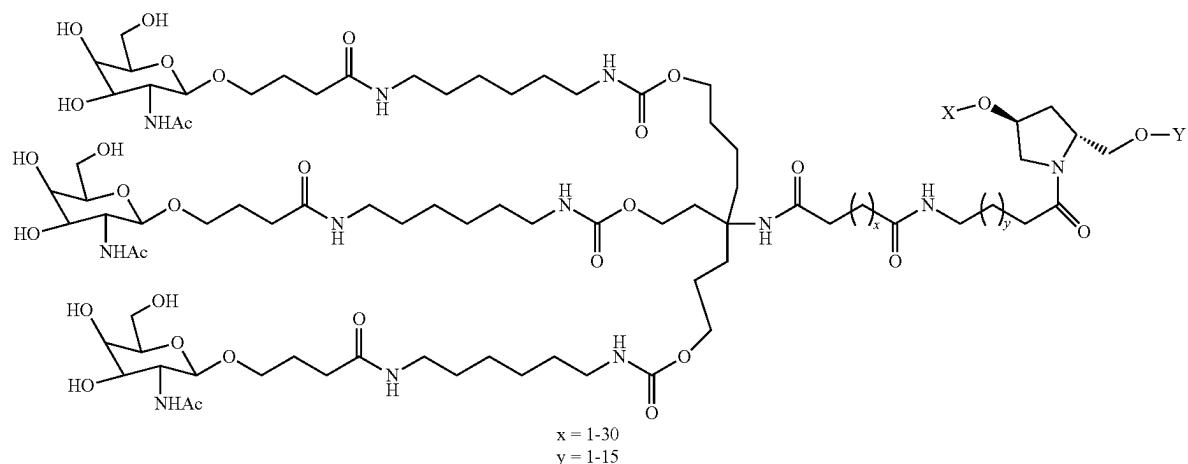
[0735] In some embodiments, the GalNAc targeting moiety and linker comprises that set forth in any one of the following formulas, wherein in any of the following formulas wherein one of X or Y is a polynucleotide, the other is a hydrogen:

XLII

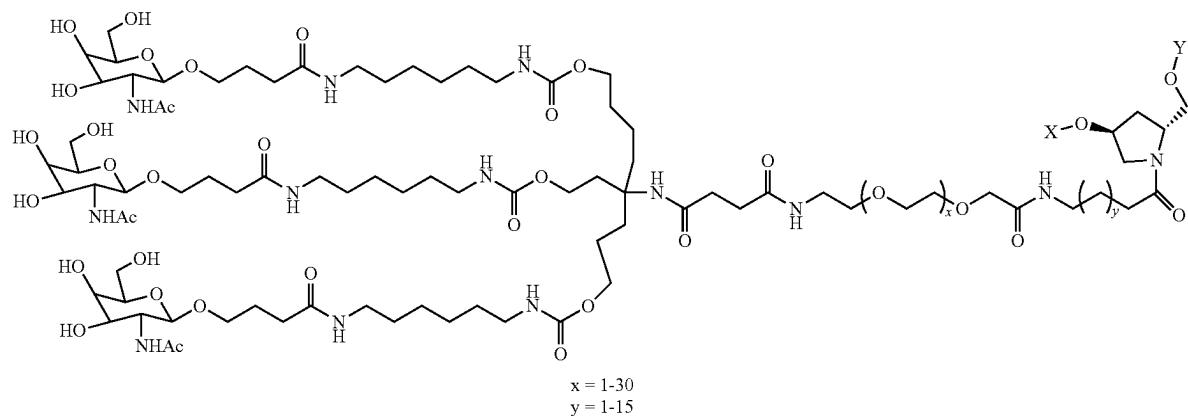


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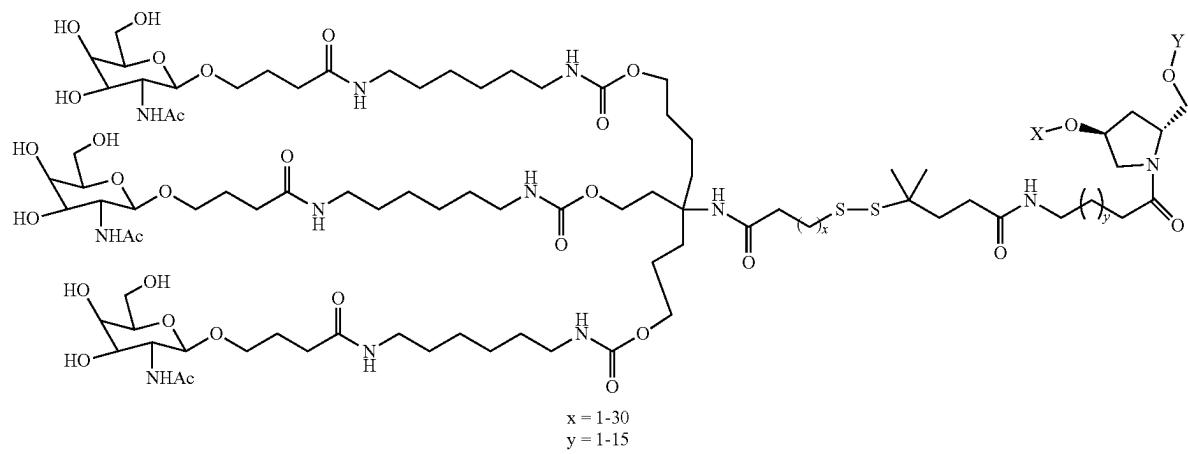
XLIII



Formula XLIV

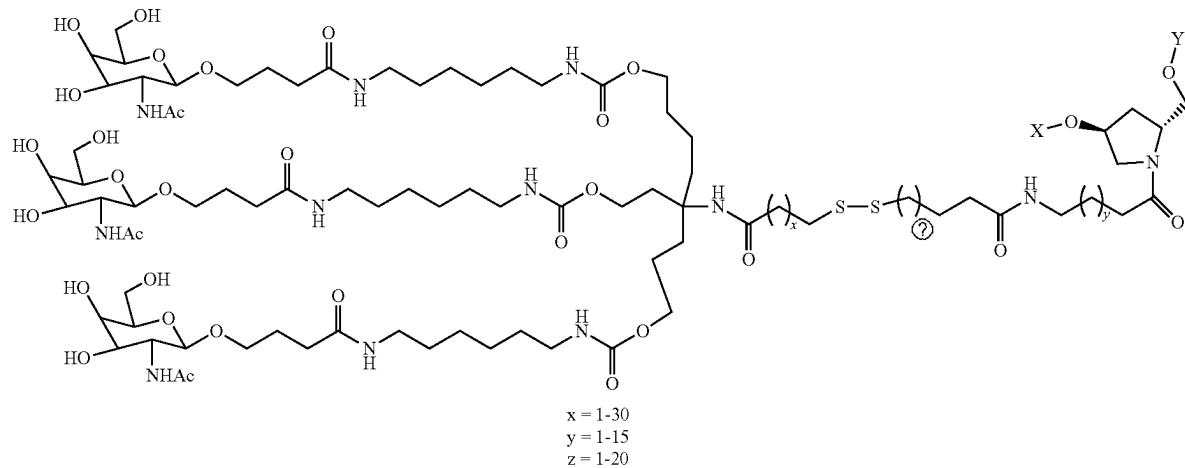


Formula XLV

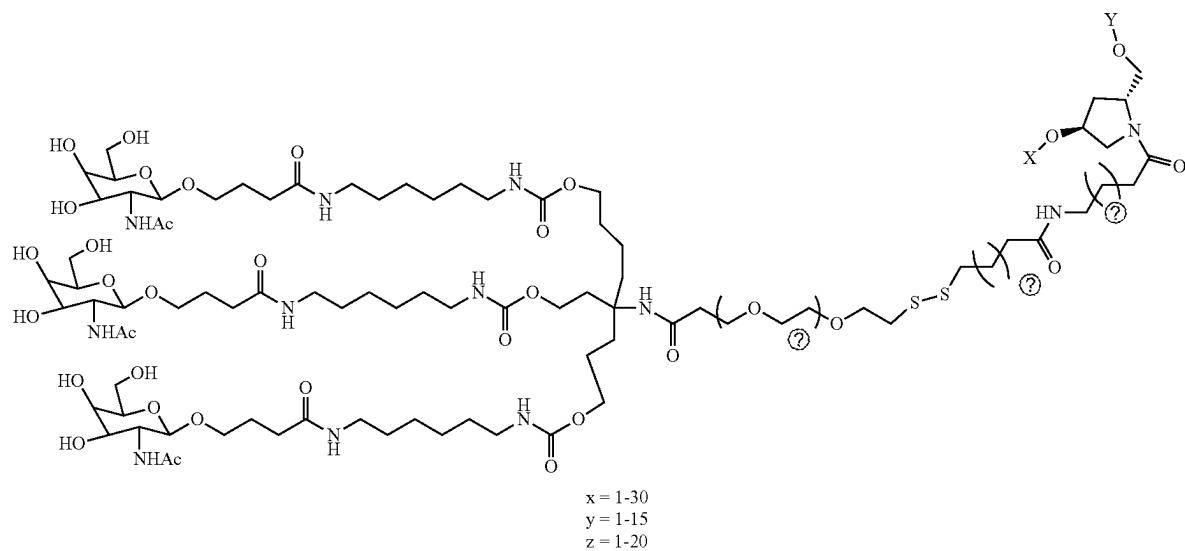


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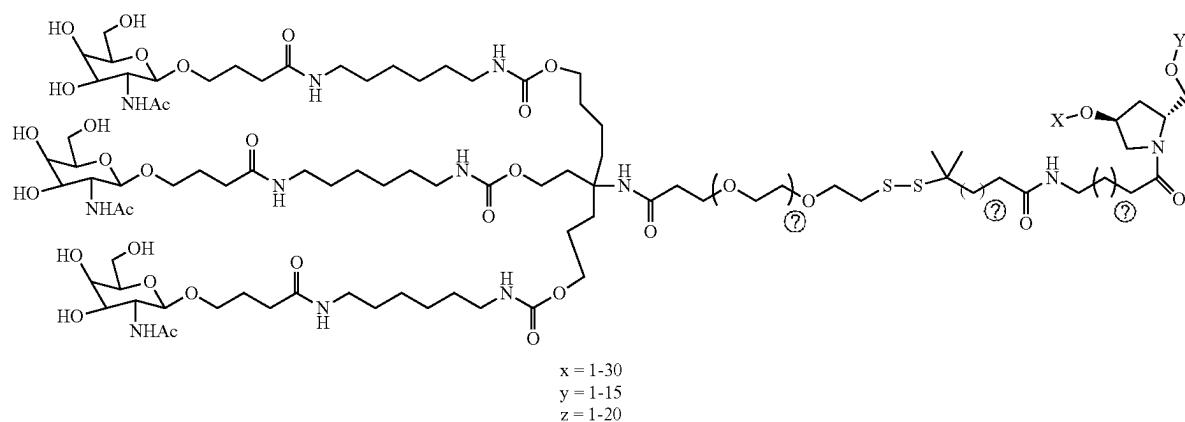
Formula XLVI



Formula XLVII

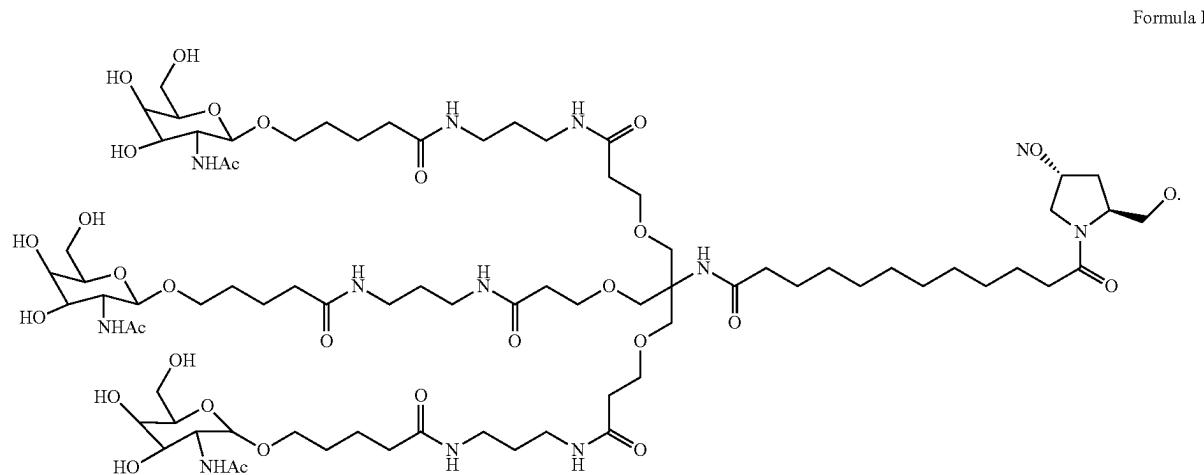


Formula XLVIII

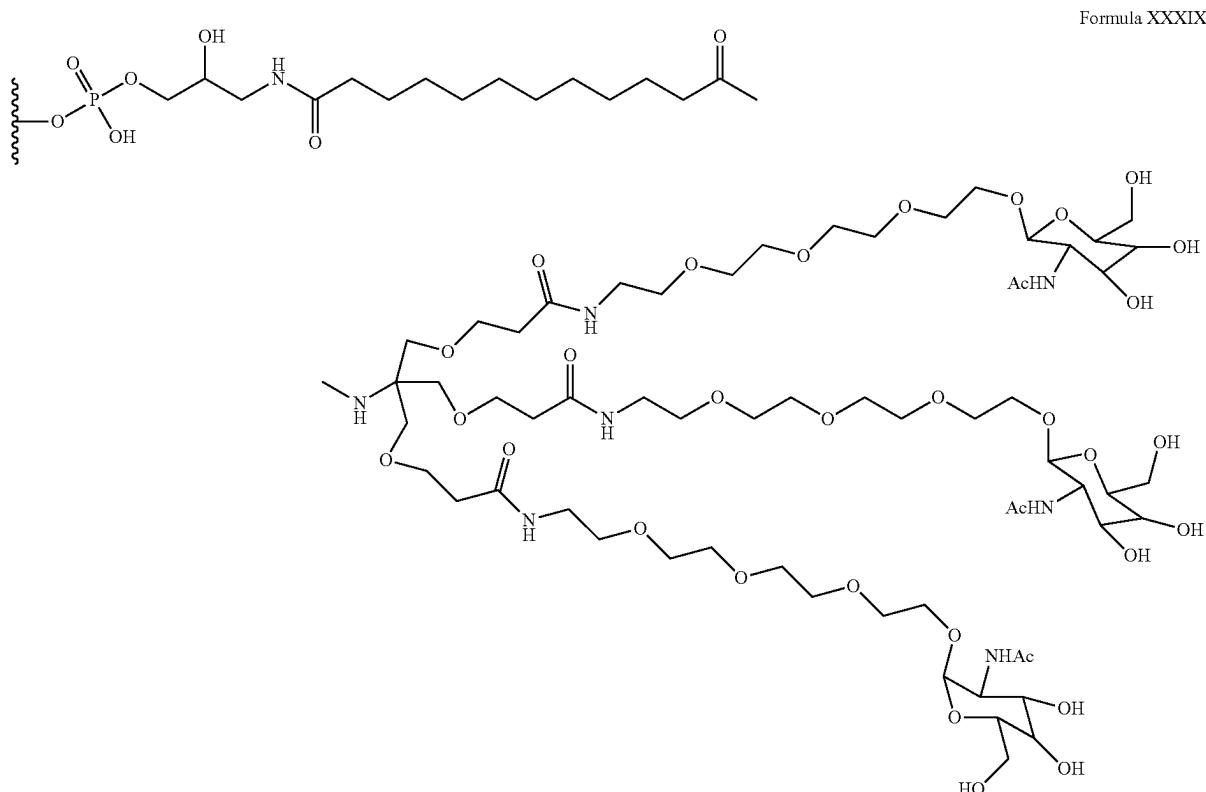


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[0736] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula I:



[0737] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XXXIX.



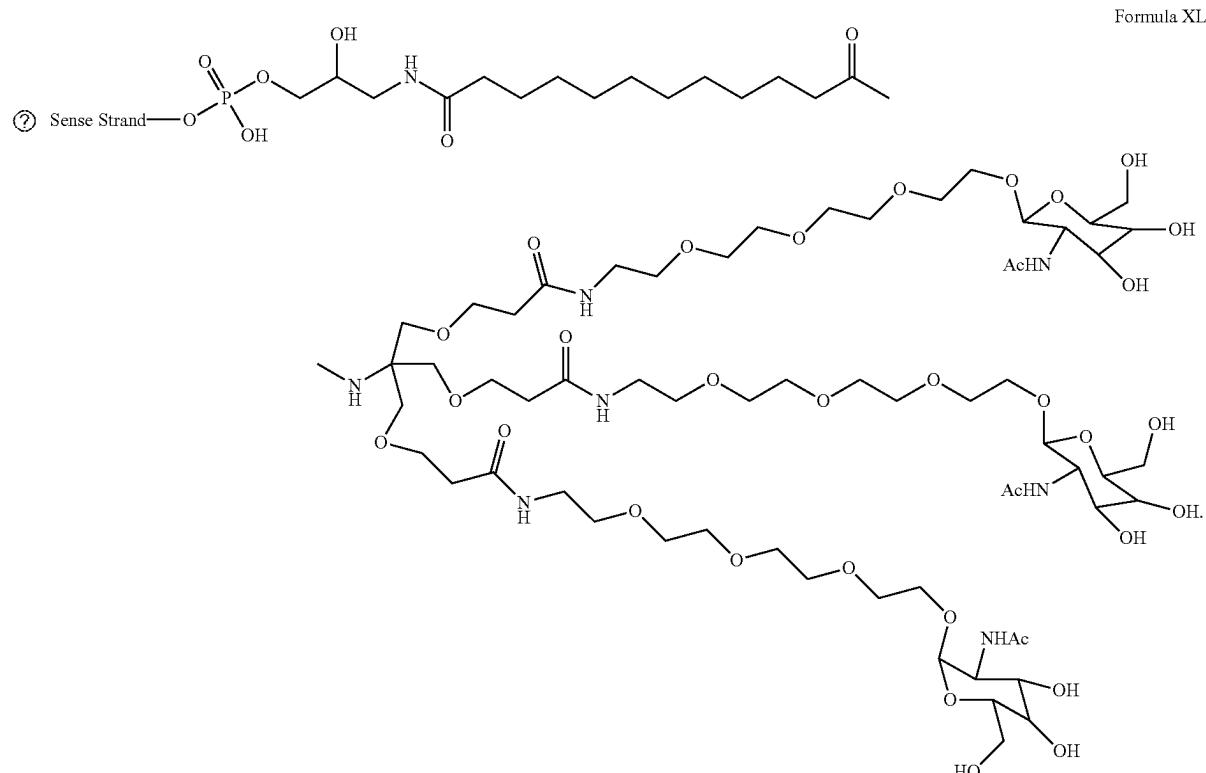
[0738] In specific preferred embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 3' end of the sense strand. In specific embodiments, the

targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 5' end of the sense strand.

[0739] In some embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 3' end of the antisense strand. In some embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker

set forth below in Formula XXXIX, wherein the dsRNA agent is operably connected to the targeting moiety via the 5' end of the antisense strand.

[0740] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XL.



[0741] In specific preferred embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XI, wherein the dsRNA agent is operably connected to the targeting moiety via the 3' end of the sense strand.

[0742] Further exemplary select conjugates are provided in Table 11 below.

TABLE 11

Exemplary dsRNA Agent Conjugates.

dsRNA Agent ID (Table 2)	dsRNA Agent ID (Table 2)	Corresponding Unconjugated dsRNA Agent ID (Table 3)	Corresponding Unconjugated dsRNA Agent ID (Table 3)	Sense Sequence	SEQ NO	Antisense Sequence	SEQ NO
				5' to 3'	5' to 3'	5' to 3'	5' to 3'
483	129	479		csasguauCfuAf AfUfauaaagcucg a (GalNAc-TEG)	1193	(vinu) sCfsgag CfuuaauuuAfgA fuacugsasc	1188
484	129	481		csasguauCfuAf AfUfauaaagcucg a (GalNAc-TEG)	1193	(vinu) sCfsgag CfuuaauuuAfgA uacugsasc	1190
485	172	482		csasgaCfaguAf CfAfggcuagaua a (GalNAc-TEG)	1194	(vinu) sUfsauc UfagccuguAfcu gucugscsa	1191

TABLE 11-continued

Exemplary dsRNA Agent Conjugates.

dsRNA Agent ID (Table 2)	dsRNA Agent ID (Table 3)	Corresponding Unconjugated Unmodified dsRNA Agent ID (Table 3)	Corresponding Unconjugated Modified dsRNA	Sense Sequence 5' to 3'	SEQ ID NO	Antisense Sequence 5' to 3'	SEQ ID NO
486	135		480	usasauauAfaGf CFUfcggaguuug a (GalNAc-TEG)	1195 (vinu)sCfsaaa CfuuccgagcUfuA fuauuasgsa		1189
487	173		409	asgsacagUfaCf AfGfgcuagauaa a (GalNAc-TEG)	1196 (vinu)sUfsuaau CfuAfGfccuguf aCfugucusgsc		1062

[0743] The nucleotide modifications set forth in Table 10, utilize the following abbreviations set forth in Table 4 above. As recited above, “(GalNAc-TEG)” recited in Table 10 indicates the conjugation of the GalNAc-TEG (see, e.g., Formula XXXIX above) to the 3' end of the sense strand of each dsRNA agent set forth in Table 10. The corresponding base modified dsRNA agent (set forth in Table 3) as well as the corresponding base unmodified dsRNA agent (set forth in Table 2) for each of the GalNAc-dsRNA agents 483-487 is also set forth in Table 11.

[0744] In specific embodiments, the conjugate comprises the sense strand and the antisense strand of a dsRNA agent conjugate set forth in Table 11. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of any one of dsRNA agent conjugates 483-487 set forth in Table 11. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of dsRNA agent conjugates 483. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of dsRNA agent conjugates 484. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of dsRNA agent conjugates 485. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of dsRNA agent conjugates 486. In specific embodiments, the conjugate comprises the sense strand and the antisense strand of dsRNA agent conjugates 487.

[0745] In specific embodiments, the conjugate is substantially similar to any one of dsRNA agent conjugates 483-487 set forth in Table 11. In specific embodiments, the conjugate is substantially similar to dsRNA agent conjugate 483. In specific embodiments, the conjugate is substantially similar to dsRNA agent conjugate 484. In specific embodiments, the conjugate is substantially similar to dsRNA agent conjugate 485. In specific embodiments, the conjugate is substantially similar to dsRNA agent conjugate 486. In specific embodiments, the conjugate is substantially similar to dsRNA agent conjugate 487.

[0746] In specific embodiments, the conjugate is any one of dsRNA agent conjugates 483-487 set forth in Table 11. In specific embodiments, the conjugate is dsRNA agent conjugate 483. In specific embodiments, the conjugate is dsRNA agent conjugate 484. In specific embodiments, the conjugate is dsRNA agent conjugate 485. In specific embodiments, the conjugate is dsRNA agent conjugate 486. In specific embodiments, the conjugate is dsRNA agent conjugate 487.

[0747] In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1193; and the antisense strand comprises the sequence set forth in SEQ ID NO: 1188. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1193; and the antisense strand comprises the sequence set forth in SEQ ID NO: 1190. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1194; and the antisense strand comprises the sequence set forth in SEQ ID NO: 1191. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1195; and the antisense strand comprises the sequence set forth in SEQ ID NO: 1189. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand comprises the sequence set forth in SEQ ID NO: 1196; and the antisense strand comprises the sequence set forth in SEQ ID NO: 1062.

[0748] In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand consists of the sequence set forth in SEQ ID NO: 1193; and the antisense strand consists of the sequence set forth in SEQ ID NO: 1188. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand consists of the sequence set forth in SEQ ID NO: 1193; and the antisense strand consists of the sequence set forth in SEQ ID NO: 1190. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand consists of the sequence set forth in SEQ ID NO: 1194; and the antisense strand consists of the sequence set forth in SEQ ID NO: 1191. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand consists of the sequence set forth in SEQ ID NO: 1195; and the antisense strand consists of the sequence set forth in SEQ ID NO: 1189. In specific embodiments, the dsRNA agent is a conjugate comprising a sense strand and an antisense stand, wherein the sense strand consists of the sequence set forth in SEQ ID NO: 1196; and the antisense strand consists of the sequence set forth in SEQ ID NO: 1062.

[0749] In specific embodiments, the dsRNA agent is a conjugate comprising the sense strand set forth in SEQ ID NO: 1193; and the antisense strand set forth in SEQ ID NO: 1188. In specific embodiments, the dsRNA agent is a conjugate comprising the sense strand set forth in SEQ ID NO: 1193; and the antisense strand set forth in SEQ ID NO: 1190. In specific embodiments, the dsRNA agent is a conjugate comprising the sense strand set forth in SEQ ID NO: 1194; and the antisense strand set forth in SEQ ID NO: 1191. In specific embodiments, the dsRNA agent is a conjugate comprising the sense strand set forth in SEQ ID NO: 1195; and the antisense strand set forth in SEQ ID NO: 1189. In specific embodiments, the dsRNA agent is a conjugate comprising the sense strand set forth in SEQ ID NO: 1196; and the antisense strand set forth in SEQ ID NO: 1062.

4.5 Activity of RNAi Agents & Conjugates Thereof

[0750] In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB). In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.). In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) mediates degradation of a target mRNA (e.g., a CIDEB (e.g., hCIDEB) mRNA). In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 50%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 75%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 80%. In some embodiments, the agent (e.g., RNAi

agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 90%. In some embodiments, the agent (e.g., RNAi agent, e.g., dsRNA agent) inhibits expression of a target gene (e.g., CIDEB) in a cell in a subject (e.g., a mammalian subject, e.g., a primate, human, non-human primate, mouse, rat, etc.) by at least about 95%.

[0751] Any one or more of the above activities can be evaluated in vitro, ex vivo, or in vivo. Any one or more of the above activities can be evaluated by standard methods known in the art. For example, by PCR (e.g., qPCR), branched DNA assays, or by a protein-based methods (such as immunofluorescence analysis (using, e.g., western blotting or flow cytometric techniques). In some embodiments, inhibition of gene (e.g., CIDEB (e.g., hCIDEB)) expression is determined by qPCR.

4.6 Methods of Making RNAi Agents & Conjugates Thereof

[0752] An agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand) can be synthesized by standard methods known in the art (e.g., chemical synthesis (e.g., solid phase synthesis)). See, e.g., "Current protocols in nucleic acid chemistry," Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, and See, e.g., Dong Y, Siegwart D J, Anderson D G. Strategies, design, and chemistry in siRNA delivery systems. *Adv Drug Deliv Rev.* 2019 April; 144:133-147. doi: 10.1016/j.addr.2019.05.004. Epub 2019 May 15. PMID: 31102606; PMCID: PMC6745264, the entire contents of each of which is incorporated by reference herein for all purposes. As such, further provided herein are methods of making an agent described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand).

[0753] For example, single stranded nucleic acid molecules (e.g., described herein) (e.g., antisense strands, sense strands) can be prepared using solution-phase or solid-phase organic synthesis or both. dsRNA agents (e.g., described herein) can be prepared using a two-step procedure, wherein the individual strands of the dsRNA agent are prepared separately and subsequently annealed. The individual strands of the dsRNA agent can be prepared using solution-phase or solid-phase organic synthesis or both. Regardless of the method of synthesis, the agents (e.g., described herein) (e.g., dsRNA agents described herein) can be prepared in a solution (e.g., an aqueous or organic solution) that is appropriate for formulation. For example, the dsRNA agent can be precipitated and redissolved in pure double-distilled water, and lyophilized. The lyophilized dsRNA agent can be resuspended in a solution appropriate for the intended formulation process.

[0754] Likewise, conjugates (e.g., described herein) can be synthesized utilizing standard methods known in the art. See, e.g., Dong Y, Siegwart D J, Anderson D G. Strategies, design, and chemistry in siRNA delivery systems. *Adv Drug Deliv Rev.* 2019 April; 144:133-147. doi: 10.1016/j.addr.2019.05.004. Epub 2019 May 15. PMID: 31102606; PMCID: PMC6745264, the entire contents of which is incorporated herein by reference for all purposes. A person of ordinary skill in the art can determine the appropriate conjugation method based on e.g., the heterologous moiety and the agent to be conjugated. For example, standard conjugation methods include, e.g., parallel synthesis methods and linear synthesis methods.

4.7 Vectors

[0755] In some embodiments, one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands) (see, e.g., §§ 4.2, 4.3) are contained in a vector (e.g., a non-viral vector (e.g., a plasmid), a viral vector). Thus, in one aspect, also provided herein are vectors (e.g., non-viral vectors (e.g., plasmids) viral vectors) comprising one or more agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand) (see, e.g., §§ 4.2, 4.3). Such vectors can be easily manipulated by methods well known to the ordinary person of skill in the art. The vector used can be any vector that is suitable for cloning nucleic acid molecules that can be used for transcription of the nucleic acid molecule of interest (e.g., an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand) (see, e.g., §§ 4.2, 4.3).

[0756] In some embodiments, the vector is a viral vector. Viral vectors include both RNA and DNA based vectors. The vectors can be designed to meet a variety of specifications. For example, viral vectors can be engineered to be capable or incapable of replication in prokaryotic and/or eukaryotic cells. In some embodiments, the vector is replication deficient. In some embodiments, the vector is replication competent. Vectors can be engineered or selected that either will (or will not) integrate in whole or in part into the genome of host cells, resulting (or not (e.g., episomal expression)) in stable host cells comprising the desired nucleic acid in their genome.

[0757] Exemplary viral vectors include, but are not limited to, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, retrovirus vectors, poxvirus vectors, parapoxvirus vectors, vaccinia virus vectors, fowlpox virus vectors, herpes virus vectors, adeno-associated virus vectors, alphavirus vectors, lentivirus vectors, rhabdovirus vectors, measles virus, Newcastle disease virus vectors, picornaviruses vectors, anellovectors, or lymphocytic choriomeningitis virus vectors. In some embodiments, the viral vector is an adenovirus vector, adeno-associated virus vector, lentivirus vector, anellovector (as described, for example, in U.S. Pat. No. 11,446,344, the entire contents of which is incorporated by reference herein for all purposes).

[0758] In some embodiments, the vector is an adenoviral vector (e.g., human adenoviral vector, e.g., HAdV or AdHu). In some embodiments, the adenovirus vector has the E1 region deleted, rendering it replication-deficient in human cells. Other regions of the adenovirus such as E3 and E4 may also be deleted. Exemplary adenovirus vectors include, but are not limited to, those described in e.g., WO2005071093 or WQ2006048215, the entire contents of each of which is incorporated by reference herein for all purposes. In some embodiments, the adenovirus-based vector used is a simian adenovirus, thereby avoiding dampening of the immune response after vaccination by pre-existing antibodies to common human entities such as AdHu5. Exemplary, simian adenovirus vectors include AdCh63 (see, e.g., WO2005071093, the entire contents of which is incorporated by reference herein for all purposes) or AdCh68.

[0759] Viral vectors can be generated through the use of a packaging/producer cell line (e.g., a mammalian cell line) using standard methods known to the person of ordinary skill in the art. Generally, a nucleic acid construct (e.g., a plasmid) encoding the transgene (e.g., an agent described herein) (along with additional elements e.g., a promoter, inverted terminal repeats (ITRs) flanking the transgene, a plasmid encoding e.g., viral replication and structural proteins, along with one or more helper plasmids a host cell

(e.g., a host cell line) are transfected into a host cell line (i.e., the packing/producer cell line). In some instances, depending on the viral vector, a helper plasmid may also be needed that include helper genes from another virus (e.g., in the instance of adeno-associated viral vectors). Eukaryotic expression plasmids are commercially available from a variety of suppliers, for example the plasmid series: pcDNATM, pCR3.1TM, pCMVTM, pFRTTM, pVAX1TM, pCITM, NanoplasmidTM, and Pcgags. The person of ordinary skill in the art is aware of numerous transfection methods and any suitable method of transfection may be employed (e.g., using a biochemical substance as carrier (e.g., lipofectamine), by mechanical means, or by electroporation.). The cells are cultured under conditions suitable and for a sufficient time for plasmid expression. The viral particles may be purified from the cell culture medium using standard methods known to the person of ordinary skill in the art. For example, by centrifugation followed by e.g., chromatography or ultrafiltration.

[0760] In some embodiments, the vector is a plasmid. A person of ordinary skill in the art is aware of suitable plasmids for expression of the DNA of interest. For example, Suitable plasmid DNA may be generated to allow efficient production of the encoded RNA in cell lines, e.g., in insect cell lines, for example using vectors as described in WO2009150222A2 and as defined in PCT claims 1 to 33, the disclosure relating to claims 1 to 33 of WO2009150222A2 the entire contents of which is incorporated by reference herein for all purposes.

4.8 Carriers

[0761] In some embodiments, one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) or a vector comprising any of the foregoing is formulated within one or more carrier.

[0762] Therefore, further provided herein are carriers comprising any one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) or a vector comprising any of the foregoing.

[0763] Any of the foregoing (e.g., one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) or a vector comprising any of the foregoing) can be encapsulated within a carrier, chemically conjugated to a carrier, associated with the carrier. In this context, the term “associated” refers to the essentially stable combination of an agent described herein (or a conjugate comprising the same) (or a vector comprising the same) with one or more molecules of a carrier (e.g., one or more lipids of a lipid-based carrier, e.g., an LNP, liposome, lipoplex, and/or nanoliposome) into larger complexes or assemblies without covalent binding. In this context, the term “encapsulation” refers to the incorporation of an agent described herein (or a conjugate comprising the same) (or a vector comprising the same) into a carrier (e.g., a lipid-based carrier, e.g., an LNP, liposome, lipoplex, and/or nanoliposome) wherein the agent described herein (or the conjugate comprising the same) (or the vector comprising the same) is entirely contained within the interior space of the carrier (e.g., the lipid-based carrier, e.g., the LNP, liposome, lipoplex, and/or nanoliposome).

[0764] Exemplary carriers includes, but are not limited to, lipid-based carriers (e.g., lipid nanoparticles (LNPs), liposomes, lipoplexes, and nanoliposomes). In some embodiments, the carrier is a lipid-based carrier. In some embodi-

ments, the carrier is an LNP. In some embodiments, the LNP comprises a cationic lipid, a neutral lipid, a cholesterol, and/or a PEG lipid. Lipid based carriers are further described below in § 4.8.1.

4.8.1 Lipid Based Carriers/Lipid Nanoformulations

[0765] In some embodiments, an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) is encapsulated or associated with one or more lipids (e.g., cationic lipids and/or neutral lipids), thereby forming lipid-based carriers such as lipid nanoparticles (LNPs), liposomes, lipoplexes, or nanoliposomes.

[0766] In some embodiments, an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) is encapsulated in one or more lipids (e.g., cationic lipids and/or neutral lipids), thereby forming lipid-based carriers such as lipid nanoparticles (LNPs), liposomes, lipoplexes, or nanoliposomes. In some embodiments, an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) is associated with one or more lipids (e.g., cationic lipids and/or neutral lipids), thereby forming lipid-based carriers such as lipid nanoparticles (LNPs), liposomes, lipoplexes, or nanoliposomes. In some embodiments, an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) is encapsulated in LNPs (e.g., as described herein).

[0767] The agents (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) described herein may be completely or partially located in the interior space of the LNPs, liposomes, lipoplexes, and/or nanoliposomes, within the lipid layer/membrane, or associated with the exterior surface of the lipid layer/membrane. One purpose of incorporating an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) into LNPs, liposomes, lipoplexes, and/or nanoliposomes is to protect the agent from an environment which may contain enzymes or chemicals or conditions that degrade the agent from molecules or conditions that cause the rapid excretion of the agent. Moreover, incorporating an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) into LNPs, liposomes, lipoplexes, and/or nanoliposomes may promote the uptake of the agent, and hence, may enhance the therapeutic effect of the agent (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing). Accordingly, incorporating an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing), into LNPs, liposomes, lipoplexes, and/or nanoliposomes may be

particularly suitable for a pharmaceutical composition described herein, e.g., for intramuscular and/or intradermal administration.

[0768] In some embodiments, an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) is formulated into a lipid-based carrier (or lipid nanoformulation). In some embodiments, the lipid-based carrier (or lipid nanoformulation) is a liposome or a lipid nanoparticle (LNP). In one embodiment, the lipid-based carrier is an LNP.

[0769] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises a cationic lipid (e.g., an ionizable lipid), a non-cationic lipid (e.g., phospholipid), a structural lipid (e.g., cholesterol), and a PEG-modified lipid. In some embodiments, the lipid-based carrier (or lipid nanoformulation) contains one or more agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing), or a pharmaceutically acceptable salt thereof.

[0770] As described herein, suitable compounds to be used in the lipid-based carrier (or lipid nanoformulation) include all the isomers and isotopes of the compounds described above, as well as all the pharmaceutically acceptable salts, solvates, or hydrates thereof, and all crystal forms, crystal form mixtures, and anhydrides or hydrates.

[0771] In addition to one or more agent described herein, the lipid-based carrier (or lipid nanoformulation) may further include a second lipid. In some embodiments, the second lipid is a cationic lipid, a non-cationic (e.g., neutral, anionic, or zwitterionic) lipid, or an ionizable lipid.

[0772] One or more naturally occurring and/or synthetic lipid compounds may be used in the preparation of the lipid-based carrier (or lipid nanoformulation).

[0773] The lipid-based carrier (or lipid nanoformulation) may contain positively charged (cationic) lipids, neutral lipids, negatively charged (anionic) lipids, or a combination thereof.

4.8.1.1 Cationic Lipids (Positively Charged) and Ionizable Lipids

[0774] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises one or more cationic lipids, e.g., a cationic lipid that can exist in a positively charged or neutral form depending on pH, or an amine-containing lipid that can be readily protonated. In some embodiments, the cationic lipid is a lipid capable of being positively charged, e.g., under physiological conditions.

[0775] Exemplary cationic lipids include one or more amine group(s) which bear the positive charge. Examples of positively charged (cationic) lipids include, but are not limited to, N,N'-dimethyl-N,N'-dioctacyl ammonium bromide (DDAB) and chloride DDAC), N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), 3 β -[N-(N',N'-dimethylaminoethyl)carbamoyl] cholesterol (DC-chol), 1,2-dioleoyloxy-3-[trimethylammonio]-propane (DOTAP), 1,2-diacytadecyloxy-3-[trimethylammonio]-propane (DSTAP), and 1,2-dioleoyloxypropyl-3-dimethyl-hydroxy ethyl ammonium chloride (DORI), N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-dimethyl-2,3-dioleyloxypropylamine (DODMA), 1,2-Diolcoyl-3-Dimethylammonium-propane (DODAP), 1,2-

Diolcoylcarbamyl-3-Dimethylammonium-propane (DOCDAP), 1,2-Dilincoyl-3-Dimethylammonium-propane (DLINDAP), 3-Dimethylamino-2-(Cholest-5-en-3-beta-oxybutan-4-oxy)-1-(cis,cis-9,12-octadecadienoxy) propane (CLinDMA), 2-[5'-(cholest-5-en-3-beta-oxy)-3'-oxapentoxy]-3-dimethyl-1-(cis, cis-9',12'-octadecadienoxy) propane (CpLin DMA), N,N-Dimethyl-3,4-dioleyloxybenzylamine (DMOBA), and the cationic lipids described in e.g. Martin et al., *Current Pharmaceutical Design*, pages 1-394, the entire contents of which are incorporated by reference herein for all purposes. In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises more than one cationic lipid.

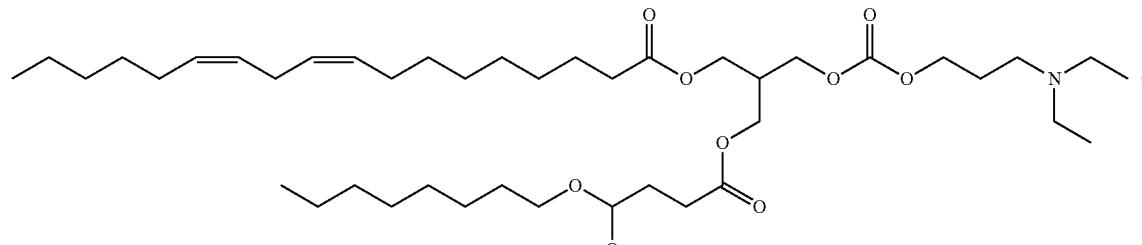
[0776] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises a cationic lipid having an effective pKa over 6.0. In some embodiments, the lipid-

based carrier (or lipid nanoformulation) further comprises a second cationic lipid having a different effective pKa (e.g., greater than the first effective pKa) than the first cationic lipid.

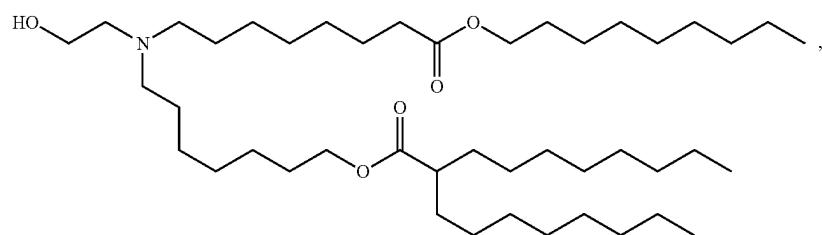
[0777] In some embodiments, cationic lipids that can be used in the lipid-based carrier (or lipid nanoformulation) include, for example those described in Table 4 of WO 2019/217941, the entire contents of which are incorporated by reference herein for all purposes.

[0778] In some embodiments, the cationic lipid is an ionizable lipid (e.g., a lipid that is protonated at low pH, but that remains neutral at physiological pH). In some embodiments, the lipid-based carrier (or lipid nanoformulation) may comprise one or more additional ionizable lipids, different than the ionizable lipids described herein. Exemplary ionizable lipids include, but are not limited to,

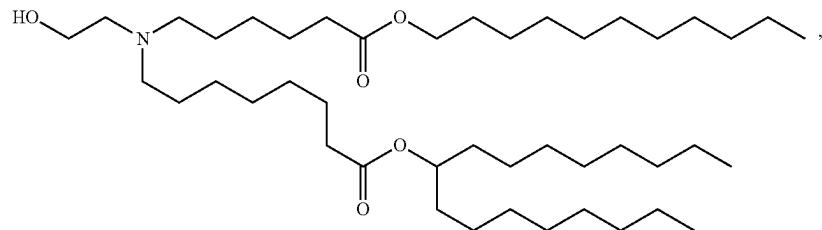
(LP01)



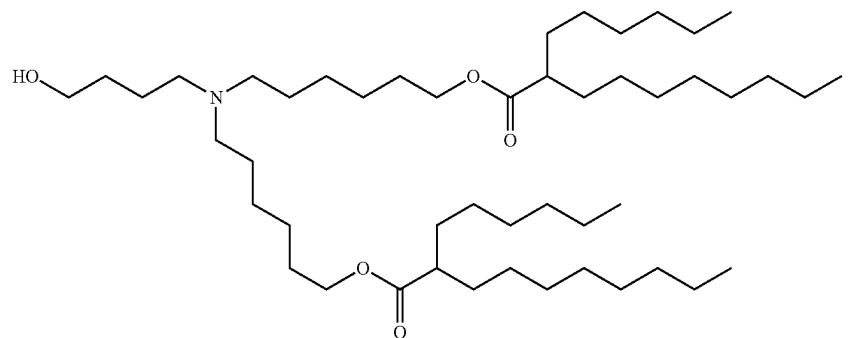
(SM-086)



(SM-102)

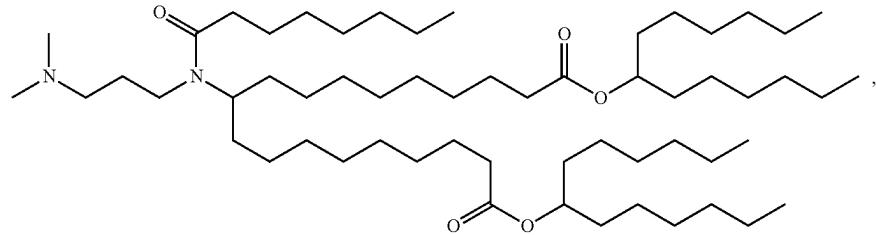


(ALC-0315)

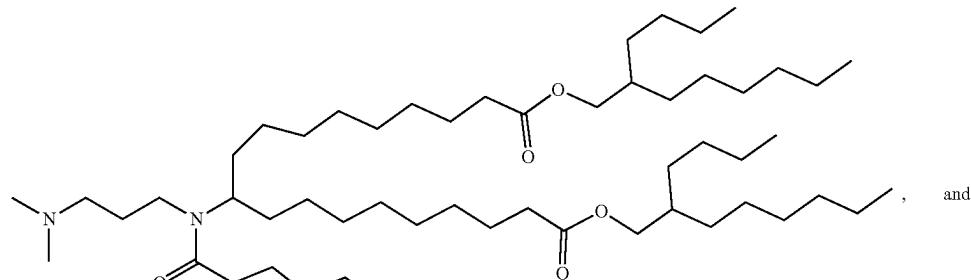


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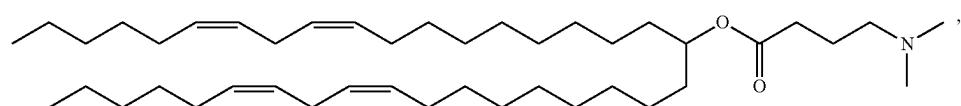
(Lipid 10)



(Lipid A9)



(DLin-MC3-DMA)



[0779] (see WO2017004143A1, the entire contents of which is incorporated herein by reference for all purposes).

[0780] In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises one or more compounds described by WO 2021/113777 (e.g., a lipid of Formula (3) such as a lipid of Table 3 of WO 2021/113777), the entire contents of which are incorporated by reference herein for all purposes.

[0781] In one embodiment, the ionizable lipid is a lipid disclosed in Hou, X., et al. Nat Rev Mater 6, 1078-1094 (2021). <https://doi.org/10.1038/s41578-021-00358-0> (e.g., L319, C12-200, and DLin-MC3-DMA), (the entire contents of which are incorporated by reference herein for all purposes).

[0782] Examples of other ionizable lipids that can be used in lipid-based carrier (or lipid nanoformulation) include, without limitation, one or more of the following formulas: X of US 2016/0311759; I of US20150376115 or in US 2016/0376224; Compound 5 or Compound 6 in US 2016/0376224; I, IA, or II of U.S. Pat. No. 9,867,888; I, II or III of US 2016/0151284; I, IA, II, or IIA of US 2017/0210967; 1-c of US 2015/0140070; A of US 2013/0178541; I of US 2013/0303587 or US 2013/0123338; I of US 2015/0141678; II, III, IV, or V of US 2015/0239926; I of US 2017/0119904; I or II of WO 2017/117528; A of US 2012/0149894; A of US 2015/0057373; A of WO 2013/116126; A of US 2013/0090372; A of US 2013/0274523; A of US 2013/0274504; A of US 2013/0053572; A of WO 2013/016058; A of WO 2012/162210; I of US 2008/042973; I, II, III, or IV of US 2012/01287670; I or II of US 2014/0200257; I, II, or III of US 2015/0203446; I or III of US 2015/0005363; I, IA, IB, IC, ID, II, IIA, IIB, IIC, IID, or III-XXIV of US 2014/0308304; of US 2013/0338210; I, II, III, or IV of WO

2009/132131; A of US 2012/01011478; I or XXXV of US 2012/0027796; XIV or XVII of US 2012/0058144; of US 2013/0323269; I of US 2011/0117125; I, II, or III of US 2011/0256175; I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII of US 2012/0202871; I, II, III, IV, V, VI, VII, VIII, X, XII, XIII, XIV, XV, or XVI of US 2011/0076335; I or II of US 2006/008378; I of WO2015/074085 (e.g., ATX-002); I of US 2013/0123338; I or X-A-Y-Z of US 2015/0064242; XVI, XVII, or XVIII of US 2013/0022649; I, II, or III of US 2013/0116307; I, II, or III of US 2013/0116307; I or II of US 2010/0062967; I-X of US 2013/0189351; I of US 2014/0039032; V of US 2018/0028664; I of US 2016/0317458; I of US 2013/0195920; 5, 6, or 10 of U.S. Pat. No. 10,221,127; III-3 of WO 2018/081480; I-5 or 1-8 of WO 2020/081938; I of WO 2015/199952 (e.g., compound 6 or 22) and Table 1 therein; 18 or 25 of U.S. Pat. No. 9,867,888; A of US 2019/0136231; II of WO 2020/219876; 1 of US 2012/0027803; OF-02 of US 2019/0240349; 23 of U.S. Pat. No. 10,086,013; cKK-E12/A6 of Miao et al (2020); C12-200 of WO 2010/053572; 7C1 of Dahlman et al (2017); 304-O13 or 503-O13 of Whitehead et al; TS-P4C2 of U.S. Pat. No. 9,708,628; I of WO 2020/106946; I of WO 2020/106946; (1), (2), (3), or (4) of WO 2021/113777; and any one of Tables 1-16 of WO 2021/113777, the entire contents of each of which are incorporated by reference herein for all purposes.

[0783] In some embodiments, the lipid-based carrier (or lipid nanoformulation) further includes biodegradable ionizable lipids, for instance, (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyloxy)-2-(((3-(diethylamino)propoxy)carbonyloxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyloxy)-2-(((3-(diethylamino)propoxy)carbonyloxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate). See, e.g., lipids of WO 2019/067992, WO

2017/173054, WO 2015/095340, and WO 2014/136086, the entire contents of each of which are incorporated by reference herein for all purposes.

4.8.1.2 Non-Cationic Lipids (e.g., Phospholipids)

[0784] In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises one or more non-cationic lipids. In some embodiments, the non-cationic lipid is a phospholipid. In some embodiments, the non-cationic lipid is a phospholipid substitute or replacement. In some embodiments, the non-cationic lipid is a negatively charged (anionic) lipid.

[0785] Exemplary non-cationic lipids include, but are not limited to, distearoyl-sn-glycero-phosphoethanolamine, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), monomethyl-phosphatidylethanolamine (such as 16-O-monomethyl PE), dimethyl-phosphatidylethanolamine (such as 16-O-dimethyl PE), 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidylethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucylphosphatidylcholine (DEPC), palmitoyloleoylphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), Sodium 1,2-ditetradecanoyl-sn-glycero-3-phosphate (DMPA), phosphatidylcholine (lecithin), phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), phosphatidylethanolamine (cephalin), cardiolipin, phosphatidic acid, cerebrosides, dicytrophosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, or mixtures thereof. It is understood that other diacylphosphatidylcholine and diacylphosphatidylethanolamine phospholipids can also be used. The acyl groups in these lipids are preferably acyl groups derived from fatty acids having C₁₀-C₂₄ carbon chains, e.g., lauroyl, myristoyl, palmitoyl, stearoyl, or olcoyl. Additional exemplary lipids, in certain embodiments, include, without limitation, those described in Kim et al. (2020) dx.doi.org/10.1021/acs.nanolett.0c01386, the entire contents of which are incorporated by reference herein for all purposes. Such lipids include, in some embodiments, plant lipids found to improve liver transfection with mRNA (e.g., DGTS).

[0786] In some embodiments, the lipid-based carrier (or lipid nanoformulation) may comprise a combination of distearoylphosphatidylcholine/cholesterol, dipalmitoylphosphatidylcholine/cholesterol, dimyristoylphosphatidylcholine/cholesterol, 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC)/cholesterol, or egg sphingomyelin/cholesterol.

[0787] Other examples of suitable non-cationic lipids include, without limitation, nonphosphorous lipids such as, e.g., stearylamine, dodecylamine, hexadecylamine, acetyl

palmitate, glycerol ricinoleate, hexadecyl stearate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethoxylated fatty acid amides, dioctadecyl dimethyl ammonium bromide, ceramide, sphingomyelin, and the like. Other non-cationic lipids are described in WO 2017/099823 or US 2018/0028664, the entire contents of each of which are incorporated by reference herein for all purposes.

[0788] In one embodiment, the lipid-based carrier (or lipid nanoformulation) further comprises one or more non-cationic lipid that is oleic acid or a compound of Formula I, II, or IV of US 2018/0028664, the entire contents of which are incorporated by reference herein for all purposes.

[0789] The non-cationic lipid content can be, for example, 0-30% (mol) of the total lipid components present. In some embodiments, the non-cationic lipid content is 5-20% (mol) or 10-15% (mol) of the total lipid components present.

[0790] In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises a neutral lipid, and the molar ratio of an ionizable lipid to a neutral lipid ranges from about 2:1 to about 8:1 (e.g., about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, or 8:1).

[0791] In some embodiments, the lipid-based carrier (or lipid nanoformulation) does not include any phospholipids.

[0792] In some embodiments, the lipid-based carrier (or lipid nanoformulation) can further include one or more phospholipids, and optionally one or more additional molecules of similar molecular shape and dimensions having both a hydrophobic moiety and a hydrophilic moiety (e.g., cholesterol).

4.8.1.3 Structural Lipids

[0793] The lipid-based carrier (or lipid nanoformulation) described herein may further comprise one or more structural lipids. As used herein, the term "structural lipid" refers to sterols (e.g., cholesterol) and also to lipids containing sterol moieties.

[0794] Incorporation of structural lipids in the lipid nanoparticle may help mitigate aggregation of other lipid in the particle. Structural lipids can be selected from the group including but not limited to, cholesterol or cholesterol derivative, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, tomatine, ursolic acid, alpha-tocopherol, hopanoids, phytosterols, steroids, and mixtures thereof. In some embodiments, the structural lipid is a sterol. In certain embodiments, the structural lipid is a steroid. In certain embodiments, the structural lipid is cholesterol. In certain embodiments, the structural lipid is an analog of cholesterol. In certain embodiments, the structural lipid is alpha-tocopherol.

[0795] In some embodiments, structural lipids may be incorporated into the lipid-based carrier at molar ratios ranging from about 0.1 to 1.0 (cholesterol phospholipid).

[0796] In some embodiments, sterols, when present, can include one or more of cholesterol or cholesterol derivatives, such as those described in WO 2009/127060 or US 2010/0130588, the entire contents of each of which are incorporated by reference herein for all purposes. Additional exemplary sterols include phytosterols, including those described in Eygeris et al. (2020), Nano Lett. 2020; 20(6): 4543-4549, the entire contents of which are incorporated by reference herein for all purposes.

[0797] In some embodiments, the structural lipid is a cholesterol derivative. Non-limiting examples of cholesterol

derivatives include polar analogues such as 5a-cholestanol, 53-coprostanol, cholesteryl-(2'-hydroxy)-ethyl ether, cholesteryl-(4'-hydroxy)-butyl ether, and 6-ketocholestanol; non-polar analogues such as 5a-cholestane, cholestenone, 5a-cholestanone, 5p-cholestanone, and cholesteryl decanoate; and mixtures thereof. In some embodiments, the cholesterol derivative is a polar analogue, e.g., cholesteryl-(4'-hydroxy)-butyl ether. Exemplary cholesterol derivatives are described in WO 2009/127060 and US 2010/0130588, the entire contents of each of which are incorporated by reference herein for all purposes.

[0798] In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises sterol in an amount of 0-50 mol % (e.g., 0-10 mol %, 10-20 mol %, 20-50 mol %, 20-30 mol %, 30-40 mol %, or 40-50 mol %) of the total lipid components.

4.8.1.4 Polymers and Polyethylene Glycol (PEG)-Lipids

[0799] In some embodiments, the lipid-based carrier (or lipid nanoformulation) may include one or more polymers or co-polymers, e.g., poly(lactic-co-glycolic acid) (PFLG) nanoparticles.

[0800] In some embodiments, the lipid-based carrier (or lipid nanoformulation) may include one or more polyethylene glycol (PEG) lipid. Examples of useful PEG-lipids include, but are not limited to, 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-(mPEG 350 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-550] (mPEG 550 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-750] (mPEG 750 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-1000] (mPEG 1000 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-2000] (mPEG 2000 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-3000] (mPEG 3000 PE); 1,2-Diacyl-sn-Glycero-3-Phosphoethanolamine-N-[Methoxy (Polyethylene glycol)-(mPEG 5000 PE); N-Acyl-Sphingosine-1-[Succinyl](Methoxy Polyethylene Glycol) 750] (mPEG 750 Ceramide); N-Acyl-Sphingosine-1-[Succinyl](Methoxy Polyethylene Glycol) 2000] (mPEG 2000 Ceramide); and N-Acyl-Sphingosine-1-[Succinyl](Methoxy Polyethylene Glycol) 5000] (mPEG 5000 Ceramide). In some embodiments, the PEG lipid is a polyethyleneglycol-diacylglycerol (i.e., polyethyleneglycol diacylglycerol (PEG-DAG), PEG-cholesterol, or PEG-DMB) conjugate.

[0801] In some embodiments, the lipid-based carrier (or nanoformulation) includes one or more conjugated lipids

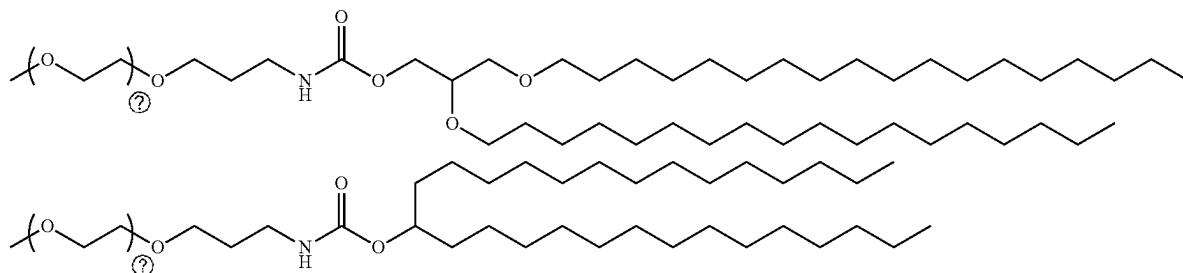
(such as PEG-conjugated lipids or lipids conjugated to polymers described in Table 5 of WO 2019/217941, the entire contents of which are incorporated by reference herein for all purposes). In some embodiments, the one or more conjugated lipids is formulated with one or more ionic lipids (e.g., non-cationic lipid such as a neutral or anionic, or zwitterionic lipid); and one or more sterols (e.g., cholesterol).

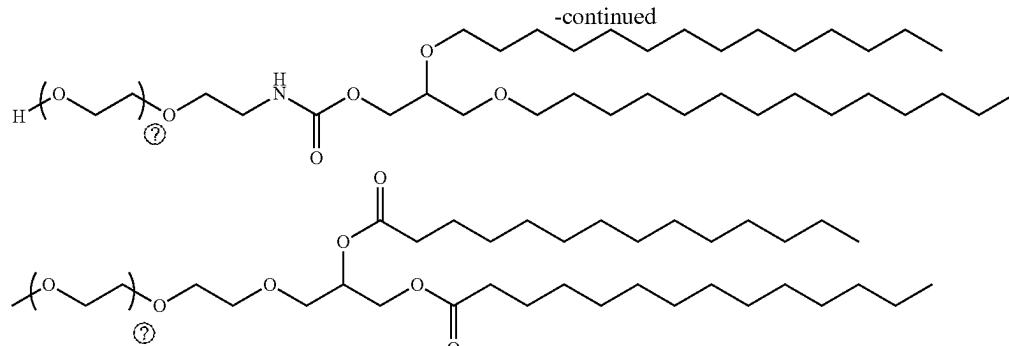
[0802] The PEG conjugate can comprise a PEG-dilaurylglycerol (C12), a PEG-dimyristylglycerol (C14), a PEG-dipalmitoylglycerol (C16), a PEG-disterylglycerol (C18), PEG-dilaurylglycamide (C12), PEG-dimyristylglycamide (C14), PEG-dipalmitoylglycamide (C16), and PEG-disterylglycamide (C18).

[0803] In some embodiments, conjugated lipids, when present, can include one or more of PEG-diacylglycerol (DAG) (such as 1-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (PEG-DMG)), PEG-dialkoxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanolamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-O-(2',3'-di(tetradecanoyloxy)propyl-1-O-(w-methoxy (polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypropylcarbam, N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-disearoyl-sn-glycero-3-phosphoethanolamine sodium salt, and those described in Table 2 of WO 2019/051289 (the entire contents of which are incorporated by reference herein for all purposes), and combinations of the foregoing.

[0804] Additional exemplary PEG-lipid conjugates are described, for example, in U.S. Pat. Nos. 5,885,613, 6,287,591, US 2003/0077829, US 2003/0077829, US 2005/0175682, US 2008/0020058, US 2011/0117125, US 2010/0130588, US 2016/0376224, US 2017/0119904, US 2018/0028664, and WO 2017/099823, the entire contents of each of which are incorporated by reference herein for all purposes.

[0805] In some embodiments, the PEG-lipid is a compound of Formula III, III-a-1, III-a-2, III-b-1, III-b-2, or V of US 2018/0028664, which is incorporated herein by reference in its entirety. In some embodiments, the PEG-lipid is of Formula II of US 2015/0376115 or US 2016/0376224, the entire contents of each of which are incorporated by reference herein for all purposes. In some embodiments, the PEG-DAA conjugate can be, for example, PEG-dilauryloxypropyl, PEG-dimyristyloxypropyl, PEG-dipalmityloxypropyl, or PEG-distearyoxypropyl. In some embodiments, the PEG-lipid includes one of the following:





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[0806] In some embodiments, lipids conjugated with a molecule other than a PEG can also be used in place of PEG-lipid. For example, polyoxazoline (POZ)-lipid conjugates, polyamide-lipid conjugates (such as ATTA-lipid conjugates), and cationic-polymer lipid (GPL) conjugates can be used in place of or in addition to the PEG-lipid.

[0807] Exemplary conjugated lipids, e.g., PEG-lipids, (POZ)-lipid conjugates, ATTA-lipid conjugates and cationic polymer-lipids, include those described in Table 2 of WO 2019/051289A9, the entire contents of which are incorporated by reference herein for all purposes.

[0808] In some embodiments, the conjugated lipid (e.g., the PEGylated lipid) can be present in an amount of 0-20 mol % of the total lipid components present in the lipid-based carrier (or lipid nanoformulation). In some embodiments, the conjugated lipid (e.g., the PEGylated lipid) content is 0.5-10 mol % or 2-5 mol % of the total lipid components.

[0809] When needed, the lipid-based carrier (or lipid nanoformulation) described herein may be coated with a polymer layer to enhance stability in vivo (e.g., sterically stabilized LNPs).

[0810] Examples of suitable polymers include, but are not limited to, poly(ethylene glycol), which may form a hydrophilic surface layer that improves the circulation half-life of liposomes and enhances the amount of lipid nanoformulations (e.g., liposomes or LNPs) that reach therapeutic targets. See, e.g., Working et al., *J Pharmacol Exp Ther.* 289: 1128-1133 (1999); Gabizon et al., *J Controlled Release* 53: 275-279 (1998); Adlakha Hutcheon et al., *Nat Biotechnol* 17: 775-779 (1999); and Koning et al., *Biochim Biophys Acta* 1420: 153-167 (1999), the entire contents of each of which are incorporated by reference herein for all purposes.

4.8.1.5 Percentages of Lipid Nanoformulation Components

[0811] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) (or a vector comprising any of the foregoing), optionally a non-cationic lipid (e.g., a phospholipid), a sterol, a neutral lipid, and optionally conjugated lipid (e.g., a PEGylated lipid) that inhibits aggregation of particles. In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises an agent (e.g., an agent described herein (e.g., RNAi agent, double

stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing)). The amounts of these components can be varied independently and to achieve desired properties. For example, in some embodiments, the ionizable lipid including the lipid compounds described herein is present in an amount from about 20 mol % to about 100 mol % (e.g., 20-90 mol %, 20-80 mol %, 20-70 mol %, 25-100 mol %, 30-70 mol %, 30-60 mol %, 30-40 mol %, 40-50 mol %, or 50-90 mol %) of the total lipid components; a non-cationic lipid (e.g., phospholipid) is present in an amount from about 0 mol % to about 50 mol % (e.g., 0-40 mol %, 0-30 mol %, 5-50 mol %, 5-40 mol %, 5-30 mol %, or 5-10 mol %) of the total lipid components, a conjugated lipid (e.g., a PEGylated lipid) in an amount from about 0.5 mol % to about 20 mol % (e.g., 1-10 mol % or 5-10%) of the total lipid components, and a sterol in an amount from about 0 mol % to about 60 mol % (e.g., 0-50 mol %, 10-60 mol %, 10-50 mol %, 15-60 mol %, 15-50 mol %, 20-50 mol %, 20-40 mol %) of the total lipid components, provided that the total mol % of the lipid component does not exceed 100%.

[0812] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises about 25-100 mol % of the ionizable lipid including the lipid compounds described herein, about 0-50 mol % phospholipid, about 0-50 mol % sterol, and about 0-10 mol % PEGylated lipid.

[0813] In some embodiments, the lipid-based carrier comprises an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) that is formulated in a lipid nanoparticle, wherein the lipid nanoparticle comprises about 25-100 mol % of the ionizable lipid including the lipid compounds described herein, about 0-50 mol % phospholipid, about 0-50 mol % sterol, and about 0-10 mol % PEGylated lipid. In some embodiments, the encapsulation efficiency of the agent may be at least 70%.

[0814] In one embodiment, the lipid-based carrier (or lipid nanoformulation) comprises about 25-100 mol % of the ionizable lipid including the lipid compounds described herein; about 0-40 mol % phospholipid (e.g., DSPC), about 0-50 mol % sterol (e.g., cholesterol), and about 0-10 mol % PEGylated lipid.

[0815] In some embodiments, the lipid-based carrier comprises an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand

(or a conjugate comprising the same)) (or a vector comprising any of the foregoing) that is formulated in a lipid nanoparticle, wherein the lipid nanoparticle comprises about 25-100 mol % of the ionizable lipid including the lipid compounds described herein; about 0-40 mol % phospholipid (e.g., DSPC), about 0-50 mol % sterol (e.g., cholesterol), and about 0-10 mol % PEGylated lipid. In some embodiments, the encapsulation efficiency of the agent may be at least 70%.

[0816] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises about 30-60 mol % (e.g., about 35-55 mol %, or about 40-50 mol %) of the ionizable lipid including the lipid compounds described herein, about 0-30 mol % (e.g., 5-25 mol %, or 10-20 mol %) phospholipid, about 15-50 mol % (e.g., 18.5-48.5 mol %, or 30-40 mol %) sterol, and about 0-10 mol % (e.g., 1-5 mol %, or 1.5-2.5 mol %) PEGylated lipid.

[0817] In some embodiments, the lipid-based carrier comprises an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) that is formulated in a lipid nanoparticle, wherein the lipid nanoparticle comprises about 30-60 mol % (e.g., about 35-55 mol %, or about 40-50 mol %) of the ionizable lipid including the lipid compounds described herein, about 0-30 mol % (e.g., 5-25 mol %, or 10-20 mol %) phospholipid, about 15-50 mol % (e.g., 18.5-48.5 mol %, or 30-40 mol %) sterol, and about 0-10 mol % (e.g., 1-5 mol %, or 1.5-2.5 mol %) PEGylated lipid. In some embodiments, the encapsulation efficiency of the agent may be at least 70%.

[0818] In some embodiments, molar ratios of ionizable lipid/sterol/phospholipid (or another structural lipid)/PEG-lipid/additional components is varied in the following ranges: ionizable lipid (25-100%); phospholipid (DSPC) (0-40%); sterol (0-50%); and PEG lipid (0-5%).

[0819] In some embodiments, the lipid-based carrier comprises an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) that is formulated in a lipid nanoparticle, wherein the lipid nanoparticle comprises molar ratios of ionizable lipid/sterol/phospholipid (or another structural lipid)/PEG-lipid/additional components in the following ranges: ionizable lipid (25-100%); phospholipid (DSPC) (0-40%); sterol (0-50%); and PEG lipid (0-5%). In some embodiments, the encapsulation efficiency of the agent may be at least 70%.

[0820] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises, by mol % or wt % of the total lipid components, 50-75% ionizable lipid (including the lipid compound as described herein), 20-40% sterol (e.g., cholesterol or derivative), 0 to 10% non-cationic-lipid, and 1-10% conjugated lipid (e.g., the PEGylated lipid).

[0821] In some embodiments, the lipid-based carrier comprises an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) that is formulated in a lipid nanoparticle, wherein the lipid nanoparticle comprises, by mol % or wt % of the total lipid components, 50-75% ionizable lipid (including the lipid compound as described herein), 20-40% sterol (e.g., cholesterol or derivative), 0 to 10% non-cationic-lipid, and 1-10% conjugated lipid (e.g.,

the PEGylated lipid). In some embodiments, the encapsulation efficiency of the agent may be at least 70%.

[0822] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises (i) an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing); (ii) a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the lipid-based carrier; (iii) a non-cationic lipid comprising a mixture of a phospholipid and a cholesterol derivative thereof, wherein the phospholipid comprises from 3 mol % to 15 mol % of the total lipid present in the lipid-based carrier and the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the lipid-based carrier; and (iv) a conjugated lipid comprising 0.5 mol % to 2 mol % of the total lipid present in the particle.

[0823] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises (i) an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing); (ii) a cationic lipid comprising from 50 mol % to 85 mol % of the total lipid present in the lipid-based carrier; (iii) a non-cationic lipid comprising from 13 mol % to 49.5 mol % of the total lipid present in the lipid-based carrier; and (d) a conjugated lipid comprising from 0.5 mol % to 2 mol % of the total lipid present in the lipid-based carrier.

[0824] In some embodiments, the phospholipid component in the mixture may be present from 2 mol % to 20 mol %, from 2 mol % to 15 mol %, from 2 mol % to 12 mol %, from 4 mol % to 15 mol %, from 4 mol % to 10 mol %, from 5 mol % to 10 mol %, (or any fraction of these ranges) of the total lipid components. In some embodiments, the lipid-based carrier (or lipid nanoformulation) is phospholipid-free.

[0825] In some embodiments, the sterol component (e.g. cholesterol or derivative) in the mixture may comprise from 25 mol % to 45 mol %, from 25 mol % to 40 mol %, from 25 mol % to 35 mol %, from 25 mol % to 30 mol %, from 30 mol % to 45 mol %, from 30 mol % to 40 mol %, from 30 mol % to 35 mol %, from 35 mol % to 40 mol %, from 27 mol % to 37 mol %, or from 27 mol % to 35 mol % (or any fraction of these ranges) of the total lipid components.

[0826] In some embodiments, the non-ionizable lipid components in the lipid-based carrier (or lipid nanoformulation) may be present from 5 mol % to 90 mol %, from 10 mol % to 85 mol %, or from 20 mol % to 80 mol % (or any fraction of these ranges) of the total lipid components.

[0827] The ratio of total lipid components to the agent (e.g., an encapsulated agent such as an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing) can be varied as desired. For example, the total lipid components to the agent (mass or weight) ratio can be from about 10:1 to about 30:1. In some embodiments, the total lipid components to the agent ratio (mass/mass ratio; w/w ratio) can be in the range of from about 1:1 to about 25:1, from about 10:1 to about 14:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. The amounts of total lipid components and the agent can be adjusted to provide a desired N/P ratio, for example, N/P ratio of 3, 4, 5, 6, 7, 8,

9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or higher. Generally, the lipid-based carrier (or lipid nanoformulation's) overall lipid content can range from about 5 mg/ml to about 30 mg/mL. Nitrogen: phosphate ratios (N:P ratio) is evaluated at values between 0.1 and 100.

[0828] The efficiency of encapsulation of an agent (e.g., an agent described herein), describes the amount of agent that is encapsulated or otherwise associated with a lipid nanoformulation (e.g., liposome or LNP) after preparation, relative to the initial amount provided. The encapsulation efficiency is desirably high (e.g., at least 70%, 80%, 90%, 95%, close to 100%). The encapsulation efficiency may be measured, for example, by comparing the amount of agent in a solution containing the liposome or LNP before and after breaking up the liposome or LNP with one or more organic solvents or detergents. An anion exchange resin may be used to measure the amount of free agent in a solution. Fluorescence may be used to measure the amount of free agent in a solution. For the lipid-based carrier (or lipid nanoformulation) described herein, the encapsulation efficiency of a protein and/or nucleic acid may be at least 50%, for example 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the encapsulation efficiency may be at least 70%. In some embodiments, the encapsulation efficiency may be at least 80%. In some embodiments, the encapsulation efficiency may be at least 90%. In some embodiments, the encapsulation efficiency may be at least 95%.

4.9 Host Cells

[0829] In one aspect, provided herein are host cells comprising any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 0); a vector described herein (see, e.g., § 4.6); a conjugate described herein (see, e.g., § 4.4); a carrier described herein (see, e.g., § 4.8); or any combination thereof. In some embodiments, the host cell comprises an RNAi agent described herein, a dsRNA agent described herein, an antisense strand described herein, and/or a sense strand described herein. In some embodiments, the host cell is *in vitro*, *ex vivo*, or *in vivo*.

4.10 Pharmaceutical Compositions

[0830] In one aspect, provided herein are pharmaceutical compositions comprising any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3); a vector described herein (see, e.g., § 4.6); a conjugate described herein (see, e.g., § 4.4); a carrier described herein (see, e.g., § 4.8); and/or a host cell described herein (see, e.g., § 4.9); or any combination thereof; and a pharmaceutically acceptable excipient (see, e.g., Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA, the entire contents of which is incorporated by reference herein for all purposes).

[0831] In one aspect, also provided herein are methods of making pharmaceutical compositions described herein comprising providing any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3); a vector described herein (see, e.g., § 4.6); a conjugate described herein (see, e.g., § 4.4); a

carrier described herein (see, e.g., § 4.8); and/or a host cell described herein (see, e.g., § 4.9); and formulating it into a pharmaceutically acceptable composition by the addition of one or more pharmaceutically acceptable excipient.

[0832] Also provided herein are pharmaceutical compositions comprising any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); vector described herein; conjugate described herein; carrier described herein; and/or cell described herein, wherein the pharmaceutical composition lacks a predetermined threshold amount or a detectable amount of a process impurity or contaminant, e.g., lacks a predetermined threshold amount or a detectable amount of a process-related impurity such as host cell proteins, host cell DNA, or a cell culture component (e.g., inducers, antibiotics, or media components); a product-related impurity (e.g., precursors, fragments, aggregates, degradation products); or a contaminant, e.g., endotoxin, bacteria, viral contaminant.

[0833] Acceptable excipients (e.g., carriers and stabilizers) are preferably nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, or other organic acids; antioxidants including ascorbic acid or methionine; preservatives (such as octadecyltrimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; or m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, or other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG).

[0834] A pharmaceutical composition may be formulated for any route of administration to a subject. Non-limiting embodiments include parenteral administration, such as intramuscular, intradermal, subcutaneous, transcutaneous, or mucosal.

[0835] In one embodiment, the pharmaceutical composition is formulated for administration by intramuscular, intradermal, or subcutaneous injection. In one embodiment, the pharmaceutical composition is formulated for administration by intramuscular injection. In one embodiment, the pharmaceutical composition is formulated for administration by intradermal injection. In one embodiment, the pharmaceutical composition is formulated for administration by subcutaneous injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions. The injectables can contain one or more excipients. Exemplary excipients include, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, or other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethylanolamine oleate or cyclodextrins. In some embodiments, the

pharmaceutical composition is formulated in a single dose. In some embodiments, the pharmaceutical compositions if formulated as a multi-dose.

[0836] Pharmaceutically acceptable excipients used in the parenteral preparations described herein include for example, aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents or other pharmaceutically acceptable substances. Examples of aqueous vehicles, which can be incorporated in one or more of the formulations described herein, include sodium chloride injection, Ringer's injection, isotonic dextrose injection, sterile water injection, dextrose or lactated Ringer's injection. Nonaqueous parenteral vehicles, which can be incorporated in one or more of the formulations described herein, include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil or peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to the parenteral preparations described herein and packaged in multiple-dose containers, which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride or benzethonium chloride. Isotonic agents, which can be incorporated in one or more of the formulations described herein, include sodium chloride or dextrose. Buffers, which can be incorporated in one or more of the formulations described herein, include phosphate or citrate. Antioxidants, which can be incorporated in one or more of the formulations described herein, include sodium bisulfate. Local anesthetics, which can be incorporated in one or more of the formulations described herein, include procaine hydrochloride. Suspending and dispersing agents, which can be incorporated in one or more of the formulations described herein, include sodium carboxymethylcellulose, hydroxypropyl methylcellulose or polyvinylpyrrolidone. Emulsifying agents, which can be incorporated in one or more of the formulations described herein, include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions, which can be incorporated in one or more of the formulations described herein, is EDTA. Pharmaceutical carriers, which can be incorporated in one or more of the formulations described herein, also include ethyl alcohol, polyethylene glycol or propylene glycol for water miscible vehicles; or sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0837] The precise dose to be employed in a pharmaceutical composition will also depend on the route of administration, and the seriousness of the condition caused by it, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the subject (including age, body weight, and health), other medications administered, or whether therapy is prophylactic or therapeutic. Therapeutic dosages are preferably titrated to optimize safety and efficacy.

4.11 Methods of Use

[0838] Provided herein are various methods of utilizing any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3); a vector described herein (see, e.g., § 4.6); a conjugate described herein (see, e.g., § 4.4); a carrier

described herein (see, e.g., § 4.8); a host cell described herein (see, e.g., § 4.9); and/or a pharmaceutical composition described herein (see, e.g., § 4.10); or any combination thereof.

[0839] In some aspects, the methods described herein comprise administering one or more of the foregoing to a subject. Exemplary subjects include mammals, e.g., humans, non-human mammals, e.g., non-human primates. In some embodiments, the subject is a human.

[0840] The dosage of any of the foregoing, to be administered to a subject in accordance with any of the methods described herein can be determined in accordance with standard techniques known to those of ordinary skill in the art, including the route of administration, the age and weight of the subject.

[0841] In some embodiments, the agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3) or a conjugate thereof (see, e.g., § 4.4) is administered to a subject at a dose of from about 1-10 mg/kg, 2-10 mg/kg, 3-10 mg/kg, 4-10 mg/kg, 5-10 mg/kg, 6-10 mg/kg, 7-10 mg/kg, 8-10 mg/kg 9-10 mg/kg, 1-5 mg/kg, 1-4 mg/kg, 1-3 mg/kg, 1-2 mg/kg, 1-2.5 mg/kg, 2-5 mg/kg, 2-4 mg/kg, 2-3 mg/kg, or 2-2.5 mg/kg. In some embodiments, the agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3) or a conjugate thereof (see, e.g., § 4.4) is administered to a subject at a dose of about 1 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, or 10 mg/kg. In some embodiments, the agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3) or a conjugate thereof (see, e.g., § 4.4) is administered to a subject at least once per month, once per month, at least twice per month, twice per month, at least once a week, or once per week.

4.11.1 Methods of Delivery

[0842] Provided herein are, inter alia, various methods of delivering any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein; or any combination thereof to e.g., a cell, subject, a cell within a subject.

[0843] In one aspect, provided herein are methods of delivering any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein; or any combination thereof to a cell, the method comprising introducing into a cell any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein into the cell, to thereby deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition into the cell. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is introduced in an amount and for a time sufficient

to deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition into the cell. In some embodiments, the cell is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the cell is *in vitro* or *ex vivo*. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is *ex vivo*. In some embodiments, the cell is *in vivo*.

[0844] In one aspect, provided herein are methods of delivering any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein; or any combination thereof to a subject, the method comprising administering to a subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein into the cell, to thereby deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition to the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered in an amount and for a time sufficient to deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition to the subject.

[0845] In one aspect, provided herein are methods of delivering any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein; or any combination thereof to a cell within a subject, the method comprising administering to a cell within a subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein into the cell, to thereby deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition to the cell within the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered in an amount and for a time sufficient to deliver the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition to the cell within the subject.

4.11.2 Methods of Reducing or Inhibiting CIDEB Expression

[0846] In one aspect, provided herein are methods of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell, the method comprising introducing into the cell any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the

cell. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is introduced in an amount and for a time sufficient to reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell. In some embodiments, the cell is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the cell is *in vitro* or *ex vivo*. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is *ex vivo*. In some embodiments, the cell is *in vivo*.

[0847] In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR). In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 50% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR). In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 75% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR). In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 80% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR). In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 90% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR). In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 95% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

[0848] In one aspect, provided herein are methods of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell in a subject, the method comprising administering to a subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

[0849] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell in a subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to reduce or inhibit

expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

[0850] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

[0851] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for the reduction or inhibition of CIDEB (e.g., hCIDEB) expression in a cell in a subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g., as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

[0852] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for use in a method of reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in a cell in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to reduce or inhibit expression of CIDEB (e.g., hCIDEB) in the cell in the subject. In some embodiments, the level of CIDEB (e.g., hCIDEB) expression in the cell is reduced by at least about 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% (e.g.,

as compared to suitable control) (e.g., as measured by an assay known in the art or described herein, e.g., qPCR).

4.11.3 Methods of Treating, Ameliorating, or Preventing a CIDEB Associated Disease

[0853] In one aspect, provided herein are methods of treating, ameliorating, or preventing a disease in a subject, the method comprising administering to the subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent a disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the disease in the subject.

[0854] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0855] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0856] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for the treatment, amelioration, or prevention of a CIDEB (e.g., hCIDEB) associated disease in a subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0857] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for use in a method of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharma-

ceutical composition described herein, to thereby treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0858] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in treating a disease in a subject, preferably a CIDEB (e.g., hCIDEB) associated disease, more preferably a liver disease.

[0859] In one aspect, provided herein are methods of treating, ameliorating, or preventing a CIDEB (e.g., hCIDEB) associated disease in a subject, the method comprising administering to the subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the CIDEB (e.g., hCIDEB) associated disease in the subject.

[0860] The following applicable to any of the foregoing methods, in specific embodiments, the treating, ameliorating, or preventing of the CIDEB associated disease is mediated (at least in part) by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0861] The following applicable to any of the foregoing methods, in some embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0862] In specific embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the CIDEB associated disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the CIDEB associated disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78(6):p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the CIDEB associated disease is the liver fibrosis, liver inflammation, cir-

rhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the CIDEB associated disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the CIDEB associated disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the CIDEB associated disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0863] In specific embodiments, the CIDEB associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

4.11.4 Methods of Treating, Ameliorating, or Preventing a Liver Disease

[0864] In one aspect, provided herein are methods of treating, ameliorate, or preventing a liver disease in a subject, the method comprising administering to the subject any one more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand); a vector described herein; a conjugate described herein; a carrier described herein; a host cell described herein; and/or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the liver disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the liver disease in the subject.

[0865] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of treating, ameliorating, or preventing a liver disease in a subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the liver disease in the subject.

[0866] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use in a method of treating, ameliorating, or preventing a liver disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the liver disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the liver disease in the subject.

[0867] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for the treatment, amelioration, or prevention of a liver disease in a subject. In some embodiments, the agent (e.g., RNAi agent,

dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the liver disease in the subject.

[0868] In one aspect, provided herein are uses of dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions in the manufacture of a medicament for use in a method of treating, ameliorating, or preventing a liver disease in a subject, the method comprising administering to the subject a dsRNA agent described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the liver disease in the subject. In some embodiments, the agent (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), conjugate, vector, carrier, or pharmaceutical composition is administered to the subject in an amount and for a time sufficient to treat, ameliorate, or prevent the liver disease in the subject.

[0869] The following applicable to any of the foregoing methods, in specific embodiments, the treating, ameliorating, or preventing of the liver disease is mediated (at least in part) by reducing or inhibiting expression of CIDEB (e.g., hCIDEB) in the subject (e.g., a population of cells within the subject).

[0870] The following applicable to any of the foregoing aspects, in some embodiments, the liver disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatoic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatoic liver disease (MetALD), steatoic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0871] In specific embodiments, the liver disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the liver disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the liver disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78(6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the liver disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the liver disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the liver disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial

infarction, or heart failure. In specific embodiments, the liver disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0872] In specific embodiments, the liver disease is fatty liver disease, steatoic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

4.11.5 Methods of Diagnosing and/or Prognosticating a Liver Disease

[0873] In one aspect, provided herein are methods of diagnosing a liver disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the somatic mutation indicates that the subject has a liver disease.

[0874] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0875] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an anti-sense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0876] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB

mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0877] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0878] In one aspect, provided herein are methods of diagnosing and/or prognosticating a liver disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the somatic mutation indicates that the subject has a liver disease, is at risk of developing a liver disease, is at risk of developing a more severe form of a liver disease, and/or is at risk of developing a disease associated with a liver disease.

[0879] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0880] In some embodiments, the method further comprises (c) administering to the subject an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0881] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not

detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0882] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0883] In one aspect, provided herein are methods of prognosticating a liver disease in a subject, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the somatic mutation indicates that the subject is at risk of developing a liver disease, is at risk of developing a more severe form of a liver disease, and/or is at risk of developing a disease associated with a liver disease.

[0884] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0885] In some embodiments, the method further comprises (c) administering to the subject an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some preferred embodiments, the agent is an inhibitory nucleic acid molecule. In some preferred embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition described herein).

tical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0886] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0887] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0888] The following applicable to any of the foregoing aspects, in some embodiments, the liver disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0889] In specific embodiments, the liver disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the liver disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the liver disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78 (6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the liver disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the liver disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the liver disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the liver disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0890] In specific embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

[0891] In specific embodiments, the liver disease is a CIDEB associated disease.

[0892] In some embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0893] In specific embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the CIDEB associated disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the CIDEB associated disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78(6):p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the CIDEB associated disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the CIDEB associated disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the CIDEB associated disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the CIDEB associated disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0894] In specific embodiments, the CIDEB associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

4.11.6 Methods of Screening, Identifying, and Selecting a Subject for Treatment with a CIDEB Inhibitory Agent

[0895] In one aspect, provided herein are methods of screening a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA,

or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the subject is selected for administration of an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if the somatic mutation is present.

[0896] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0897] In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0898] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0899] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0900] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0901] In one aspect, provided herein are methods of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the subject is selected for administration of an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if the somatic mutation is present.

[0902] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0903] In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein (or a vector, conjugate, or carrier comprising the same)).

same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0904] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0905] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0906] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0907] In one aspect, provided herein are methods of identifying a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the presence of the somatic mutation indicates that the subject is identified for administration of an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB.

[0908] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or

having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0909] In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some preferred embodiments, the agent is an inhibitory nucleic acid molecule. In some preferred embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0910] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0911] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0912] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule

that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0913] In one aspect, provided herein are methods of identifying a subject having a disease who is likely to respond to treatment with an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, wherein the subject is identified as a subject likely to respond to treatment with an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if the somatic mutation is present.

[0914] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0915] In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0916] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described

herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0917] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (c) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0918] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0919] In one aspect, provided herein are methods of selecting a therapy for a subject having a disease who is likely to respond to treatment with an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject; (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, and (c) selecting a therapy for a subject comprising an agent (e.g., inhibitory nucleic acid molecule (e.g., an RNA agent (e.g., a dsRNA agent described herein)) that inhibits expression of CIDEB if the somatic mutation is present.

[0920] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0921] In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some embodiments, the inhibitory nucleic acid

molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0922] In some embodiments, the method further comprises (d) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0923] In some embodiments, the method further comprises (d) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if one or more somatic CIDEB mutation is not detected in the DNA, RNA, or protein. In some embodiments, the method further comprises (d) administering an alternative therapeutic agent for treatment of the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB to the subject if a somatic CIDEB mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[0924] In some embodiments, the subject is undergoing or has undergone treatment with a different therapeutic agent for the disease that is not an inhibitory nucleic acid molecule that inhibits expression of CIDEB and/or function of CIDEB. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic CIDEB mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of CIDEB is administered to the subject.

[0925] The following applicable to any of the foregoing aspects, in some embodiments, the disease is a liver disease. In some embodiments, the liver disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease

(MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0926] In specific embodiments, the liver disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the liver disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the liver disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78 (6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the liver disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the liver disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the liver disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the liver disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0927] In specific embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

[0928] In specific embodiments, the disease is a CIDEB associated disease.

[0929] In some embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0930] In specific embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the CIDEB associated disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the CIDEB associated disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomencla-

ture, Hepatology 78 (6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the CIDEB associated disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the CIDEB associated disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the CIDEB associated disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0931] In specific embodiments, the CIDEB associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

4.11.7 In Vitro Methods of Screening Samples for Somatic CIDEB Mutations

[0932] In one aspect, provided herein are methods of screening a sample from a subject for the presence or absence of one or more somatic CIDEB mutation, the method comprising (a) isolating and purifying DNA, RNA, or protein from a sample obtained from the subject; (b) detecting the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein.

[0933] In some embodiments, (a) comprises isolating and purifying DNA, or having DNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA. In some embodiments, (a) comprises isolating and purifying RNA, or having RNA isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the RNA. In some embodiments, (a) comprises isolating and purifying protein, or having protein isolated and purified, from a sample obtained from the subject; and (b) comprises detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the protein.

[0934] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of CIDEB if one or more somatic CIDEB mutation is detected in the DNA, RNA, or protein. In some embodiments, the agent comprises a nucleic acid molecule, small molecule, protein, peptide. In some preferred embodiments, the agent is a nucleic acid molecule. In some embodiments, the inhibitory nucleic acid molecule comprises one or more RNA agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand, an siRNA agent, an antisense oligonucleotide) (or a vector comprising or encoding the RNA agent described herein, e.g., a vector described herein; a conjugate comprising the RNA agent described herein, e.g., a conjugate described herein; a carrier comprising the RNA agent described herein (or a vector or conjugate comprising

the same), e.g., a carrier described herein; and/or a pharmaceutical composition comprising the RNA agent described herein (or a vector, conjugate, or carrier comprising the same), e.g., a pharmaceutical composition described herein). In some embodiments, the RNA agent is a dsRNA agent described herein comprising a sense strand and an antisense strand.

[0935] In one aspect, provided herein are methods of characterizing a DNA molecule in a sample from a subject having a disease, the method comprising (a) isolating and purifying DNA (or having DNA isolated and purified) in a sample from the subject; (b) analyzing the DNA (e.g., sequencing at least a portion of the CIDEB gene in the DNA); and (c) determining the presence or absence of a somatic CIDEB mutation in the DNA molecule.

[0936] In one aspect, provided herein are methods of characterizing a disease in a subject, the method comprising (a) isolating and purifying DNA (or having DNA isolated and purified) in a sample from the subject; (b) detecting the presence or absence of a somatic CIDEB mutation in the DNA; and (c) characterizing the liver disease as somatic CIDEB mutation positive or somatic CIDEB mutation negative based on the detection.

[0937] The following applicable to any of the foregoing aspects, in some embodiments, the subject is suspected of having, has been diagnosed with, or has a liver disease. In some embodiments, the liver disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0938] In specific embodiments, the liver disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the liver disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the liver disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, Hepatology 78 (6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the liver disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the liver disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the liver disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the liver

disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0939] In specific embodiments, the liver disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

[0940] In specific embodiments, the liver disease is a CIDEB associated disease.

[0941] In some embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), cirrhosis, metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction associated fatty liver disease (MAFLD), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), cryptogenic SLD, liver fibrosis, liver failure, jaundice, a liver infection (e.g., hepatitis C infection, hepatitis B infection), or a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure).

[0942] In specific embodiments, the CIDEB associated disease is fatty liver disease, liver inflammation, NASH or NAFLD. In specific embodiments, the CIDEB associated disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In specific embodiments, the CIDEB associated disease is MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD. See, e.g., Rinella M. et al., A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78 (6): p 1966-1986 December 2023, the entire contents of which is incorporated herein by reference for all purposes. In specific embodiments, the CIDEB associated disease is the liver fibrosis, liver inflammation, cirrhosis, liver failure, or jaundice. In specific embodiments, the disease is obesity or type-2 diabetes. In specific embodiments, the CIDEB associated disease is a liver infection (e.g., hepatitis C infection, hepatitis B infection). In specific embodiments, the liver infection is a hepatitis infection. In specific embodiments, the hepatitis infection is a hepatitis C infection or hepatitis B infection. In specific embodiments, the CIDEB associated disease is a cardiovascular disease (e.g., atherosclerosis, coronary artery disease, myocardial infarction, or heart failure). In specific embodiments, the cardiovascular disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure. In specific embodiments, the CIDEB associated disease is atherosclerosis, coronary artery disease, myocardial infarction, or heart failure.

[0943] In specific embodiments, the CIDEB associated disease is fatty liver disease, steatotic liver disease, liver inflammation, NASH, NAFLD, MASLD, MASH, MAFLD, MetALD, SLD, or cryptogenic SLD.

4.12 Kits

[0944] In one aspect, provided herein are kits comprising any one or more agent described herein (e.g., an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (see, e.g., §§ 4.2, 4.3); a vector described herein (see, e.g., § 4.6); a conjugate described herein (see, e.g., § 4.4); a carrier described herein (see, e.g., § 4.8); a host cell described herein (see, e.g., § 4.9); and/or a pharmaceutical

composition described herein (see, e.g., § 4.10); or any combination thereof. In addition, the kit may comprise a liquid vehicle for solubilizing or diluting, and/or technical instructions. The technical instructions of the kit may contain information about administration and dosage and subject groups.

[0945] In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), vector (e.g., described herein), conjugate (e.g., described herein), carrier (e.g., described herein), host cell (e.g., described herein), and/or pharmaceutical composition (e.g., described herein) is provided in a separate part of the kit. In some embodiments, the agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), vector (e.g., described herein), conjugate (e.g., described herein), carrier (e.g., described herein), host cell (e.g., described herein), and/or pharmaceutical composition (e.g., described herein) is optionally lyophilized, spray-dried, or spray-freeze dried. The kit may further contain as a part a vehicle (e.g., buffer solution) for solubilizing the dried or lyophilized any agent (e.g., described herein) (e.g., RNAi agent, dsRNA agent, antisense strand, sense strand), vector (e.g., described herein), conjugate (e.g., described herein), carrier (e.g., described herein), host cell (e.g., described herein), and/or pharmaceutical composition (e.g., described herein).

[0946] In some embodiments, the kit comprises a single dose container. In some embodiments, the kit comprises a multi-dose container. In some embodiments, the kit comprises an administration device (e.g., an injector for intradermal injection or a syringe for intramuscular injection).

[0947] Any of the kits described herein may be used in any of the methods described herein (see, e.g., § 4.11).

5. EXAMPLES

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5.1	Example 1. CIDEB selection in Nonalcoholic Steatohepatitis.

[0948] The selection of CIDEB in the context of nonalcoholic steatohepatitis (NASH) was evaluated. Briefly, liver samples from 46 subjects with NASH and 20 subjects without liver disease were sequenced using Nanoseq at a mean sequencing depth of 549 Dx per sample in NASH and 1218 Dx per sample in normal liver. Results of interest in the primary sample (defined as a global q-value<0.1) were restricted hypothesis tested in the control analysis. In the primary sample, CIDEB had an enrichment ratio of 11.6 and a global q-value=0.077; there was no indication of selection in the normal liver samples. Taken together, these findings

indicate that CIDEB is positively selected for in NASH, meaning that cell clones with mutations in the CIDEB gene proliferate under NASH disease conditions.

5.2 Example 2. Design of CIDEB Targeting RNAi Agents

[0949] dsRNA agents targeting hCIDEB (NCBI Ref.: NM_014430.4) were designed. The nucleotide sequence of the unmodified CIDEB sense and antisense strands of each of the dsRNA agents are set forth in Table 2; and the nucleotide sequence of the exemplary modified CIDEB sense and antisense strands of each of the dsRNA agents are set forth in Table 3.

5.3 Example 3. Synthesis of CIDEB Targeting RNAi Agents

[0950] The dsRNA agents set forth in Table 2 and Table 3 were synthesized using standard methods known in the art and described herein. Briefly, the dsRNA agents were synthesized using a Mermade 192 synthesizer (BioAutomation) on controlled pore glass (500-1000 Å) solid supports loaded with a first nucleotide of interest. Upon completion of the solid phase synthesis, solid-supported polynucleotides were treated with Methylamine (40% aqueous) at room temperature in 96 well plates for approximately 2 hours to afford cleavage from the solid support and subsequent removal of relevant protecting groups. Polynucleotides were precipitated by the addition of 1 mL of 9:1 acetonitrile:ethanol or 1:1 ethanol:isopropanol. The plates were then centrifuged at 4° C. for 45 minutes and the supernatant removed. The polynucleotide pellet was resuspended in 20 mM NaOAc and subsequently desalted using a HiTrap size exclusion column (5 mL, GE Healthcare) on an Agilent LC system equipped with an autosampler, UV detector, conductivity meter, and fraction collector. Desalted samples were collected in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

[0951] Duplexing of single strands was performed on a Tecan liquid handling robot. Sense and antisense single strands were combined in an equimolar ratio to a final concentration of 10 µM in 1×PBS in 96 well plates, the plate was sealed, incubated at 100° C. for 10 minutes, and was subsequently allowed to return slowly to room temperature over a period of 2-3 hours. The concentration and identity of each duplex was confirmed and is then subsequently utilized for screening assays.

5.4 Example 4. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Hep3B Cells

[0952] Each of dsRNA Agents 240-478 set forth in Table 3 above were evaluated for their ability to knockdown hCIDEB expression in vitro in Hep3B Cells.

[0953] Briefly, Hep3B cells (ATCC) were seeded at 15,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated hCIDEB targeting dsRNA agent (either 0.3 nM or 20 nM) using Lipofectamine RNAiMax (0.3 µL/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of hCIDEB was assessed utilizing a standard branched DNA (bDNA) assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to the manufacturer's instructions. The expression of hCIDEB was normalized to

the expression of human GAPDH. Each treatment group was run in quadruplicate, the mean and standard deviation calculated.

[0954] Table 5 shows the percent of hCIDEB mRNA remaining after treatment with the indicated dsRNA agent (normalized to GAPDH and relative to control treated cells set to 100%).

TABLE 5

dsRNA	Range % hCIDEB mRNA Remaining (Normalized to GAPDH)	
	Agent	CIDEB/GAPDH
	20 nM	0.3 nM
240	80-95	75-85
241	70-90	65-85
242	60-80	55-80
243	70-100	70-90
244	85-115	70-95
245	95-120	90-105
246	65-100	70-90
247	65-95	70-95
248	70-95	65-80
249	75-90	75-90
250	75-95	70-85
251	80-95	60-95
252	70-95	60-85
253	70-105	50-95
254	75-110	60-95
255	95-145	70-100
256	60-95	55-85
257	70-105	60-100
258	30-45	35-45
259	85-130	75-105
260	65-100	70-80
261	85-100	60-85
262	70-110	55-80
263	85-110	70-90
264	30-40	35-45
265	80-95	50-65
266	70-95	50-65
267	55-85	50-135
268	60-95	55-65
269	70-110	70-90
270	70-105	60-90
271	60-110	55-85
272	65-105	60-95
273	70-105	60-95
274	60-90	55-90
275	65-90	45-95
276	60-90	55-95
277	65-105	70-105
278	65-110	65-110
279	70-115	70-100
280	80-110	70-90
281	70-100	60-75
282	60-95	55-70
283	65-105	50-65
284	65-105	55-70
285	65-110	60-70
286	55-75	55-65
287	30-55	40-50
288	70-115	65-75
289	65-115	70-85
290	90-110	70-95
291	70-120	60-90
292	70-120	65-90
293	70-105	55-95
294	90-130	60-105
295	70-110	60-100
296	80-125	65-95
297	55-80	65-90
298	45-75	60-85
299	75-130	70-110
300	65-85	60-75

TABLE 5-continued

Range % hCIDEB mRNA Remaining (Normalized to GAPDH).		
dsRNA	CIDEB/GAPDH	
Agent	20 nM	0.3 nM
301	45-85	60-80
302	35-80	55-75
303	30-55	40-55
304	50-85	55-80
305	45-80	50-75
306	50-90	60-75
307	50-85	60-85
308	50-80	50-70
309	55-75	65-80
310	60-90	70-85
311	55-80	70-110
312	50-75	70-95
313	45-75	75-105
314	45-65	75-100
315	40-75	80-100
316	45-75	70-115
317	45-70	65-100
318	45-70	65-95
319	60-90	65-90
320	60-75	70-85
321	60-80	75-90
322	50-80	80-100
323	55-90	85-115
324	55-85	85-115
325	50-90	80-105
326	80-95	85-105
327	75-115	85-95
328	125-140	105-115
329	70-100	75-100
330	65-90	85-100
331	105-130	100-115
332	105-150	100-110
333	60-75	70-90
334	70-80	85-95
335	60-90	75-95
336	85-135	80-95
337	55-75	65-80
338	55-80	70-90
339	60-85	80-95
340	65-90	75-90
341	60-95	75-85
342	85-105	80-110
343	50-80	55-95
344	55-100	60-80
345	55-100	65-75
346	50-95	60-75
347	50-100	65-80
348	55-90	65-80
349	80-105	80-100
350	65-115	70-90
351	55-105	65-95
352	70-105	75-85
353	70-105	90-105
354	55-90	70-95
355	70-120	90-105
356	50-80	65-75
357	50-90	70-80
358	5-15	10-15
359	10-20	10-15
360	15-30	25-35
361	10-20	15-20
362	35-60	40-55
363	5-15	10-20
364	5-15	10-20
365	5-15	10-15
366	5-10	5-15
367	0-10	5-10
368	0-15	5-10
369	5-10	5-15
370	15-30	20-30
371	20-25	20-30

TABLE 5-continued

Range % hCIDEB mRNA Remaining (Normalized to GAPDH).		
dsRNA	CIDEB/GAPDH	
Agent	20 nM	0.3 nM
372	10-20	10-20
373	10-15	5-15
374	5-10	5-10
375	5-20	10-15
376	5-10	5-15
377	15-35	25-35
378	30-40	45-60
379	55-70	50-75
380	5-20	15-25
381	10-20	10-20
382	45-60	35-50
383	35-50	50-60
384	25-35	25-35
385	35-50	35-45
386	30-45	20-25
387	5-10	10-15
388	5-10	10-15
389	15-20	10-20
390	10-15	10-20
391	5-15	10-15
392	60-65	65-80
393	30-60	25-85
394	15-20	20-30
395	45-70	55-75
396	30-45	50-70
397	10-15	15-20
398	10-20	15-25
399	10-20	15-30
400	10-20	15-25
401	10-20	10-20
402	45-60	40-60
403	5-15	15-20
404	5-10	5-15
405	10-20	10-20
406	10-20	10-15
407	10-20	10-20
408	10-15	10-15
409	10-15	5-15
410	10-25	25-35
411	5-15	10-20
412	5-15	10-15
413	10-20	15-25
414	5-15	10-15
415	10-20	15-25
416	10-15	20-30
417	10-20	20-35
418	10-15	15-25
419	10-15	15-30
420	45-65	40-70
421	10-20	15-20
422	5-15	10-25
423	40-55	65-70
424	55-80	85-105
425	65-95	100-115
426	50-80	85-105
427	55-85	90-115
428	55-80	85-100
429	60-90	85-100
430	65-90	80-95
431	70-90	80-90
432	60-90	65-85
433	45-70	60-70
434	30-60	50-55
435	35-65	50-65
436	60-105	80-90
437	55-85	75-90
438	55-90	75-80
439	80-125	85-100
440	15-25	20-25
441	10-15	15-20
442	5-15	5-15

TABLE 5-continued

Range % hCIDEB mRNA Remaining (Normalized to GAPDH).		
dsRNA	CIDEB/GAPDH	
Agent	20 nM	0.3 nM
443	5-10	5-10
444	10-20	15-20
445	40-70	65-80
446	5-10	5-10
447	5-10	5-10
448	15-30	15-25
449	15-25	15-20
450	15-25	10-15
451	10-15	5-15
452	10-20	10-15
453	15-35	10-20
454	5-15	10-20
455	15-25	15-20
456	5-20	10-20
457	10-20	15-20
458	10-20	10-20
459	10-25	15-20
460	10-20	10-15
461	5-20	10-20
462	5-10	5-15
463	0-10	5-10
464	0-10	5-10
465	0-10	5-10
466	10-15	15-20
467	5-15	10-15
468	35-55	50-60
469	35-50	30-40
470	5-10	5-15
471	5-10	5-15
472	5-15	10-20
473	5-15	20-25
474	5-10	10-20
475	5-10	10-20
476	0-10	10-15
477	10-20	15-25
478	5-10	10-15

5.5 Example 5. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes

[0955] Each of dsRNA Agents 366, 367, 388, 404, 411, 442, 443, 446, 447, 462, 463, 464, 465, 467, 470, 471, 474, 475, 476, and 478 set forth in Table 3 above were evaluated for their ability to knockdown hCIDEB expression in vitro in primary human hepatocytes.

[0956] Briefly, primary human hepatocytes were seeded at 15,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated hCIDEB targeting dsRNA agent (20 nM, 0.3 nM) using Lipofectamine RNAiMax (0.3 µl/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of hCIDEB was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of hCIDEB was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate.

[0957] Table 6 shows the calculated IC50 (nM), IC80 (nM), and the remaining hCIDEB mRNA percent (normalized to GAPDH) (mean of quadruplicates).

TABLE 6

IC50, IC80, and Max % Inhibition of hCIDEB mRNA (Normalized to GAPDH).			
dsRNA Agent	IC50 [nM]	IC80 [nM]	% Maximum Inhibition
366	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
367	>0.0001 ≤ 0.001	>0.001 ≤ 0.01	>90 ≤ 100
388	>0.01 ≤ 0.1	>0.01 ≤ 0.1	>90 ≤ 100
404	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
411	>0.01 ≤ 0.1	>0.1 ≤ 1	>90 ≤ 100
442	>0.01 ≤ 0.1	>0.01 ≤ 0.1	>90 ≤ 100
443	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
446	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
447	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
462	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
463	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
464	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
465	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
467	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
470	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
471	>0.0001 ≤ 0.001	>0.001 ≤ 0.01	>90 ≤ 100
474	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
475	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100
476	>0.001 ≤ 0.01	>0.001 ≤ 0.01	>90 ≤ 100
478	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>90 ≤ 100

5.6 Example 6. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes

[0958] Each of dsRNA Agents 368, 369, 373, 374, 375, 376, 380, 443, 387, 389, 390, 391, 474, 473, 477, 457, 397, 472, 403, 405, 406, 408, 409, 411, 414, 415, or 417 set forth in Table 3 above were evaluated for their ability to knockdown hCIDEB expression in vitro in primary human hepatocytes.

[0959] Briefly, primary human hepatocytes were seeded at 80,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated hCIDEB targeting dsRNA agent (20 nM, 4 nM, 0.8 nM, 0.16 nM, 0.032 nM, 0.0064 nM, 0.00128 nM, 0.000256 nM, 0.0000512 nM, or 0.00001024 nM) using Lipofectamine RNAiMax (0.3 µl/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of hCIDEB was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of hCIDEB was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate.

[0960] Table 7 shows the calculated IC50 (nM), IC80 (nM), and the remaining hCIDEB mRNA percent (normalized to GAPDH) (mean of quadruplicates).

TABLE 7

IC50, IC80, and Max % Inhibition of hCIDEB mRNA (Normalized to GAPDH).			
DsRNA Agent	IC50 [nM]	IC80 [nM]	% Maximum Inhibition
368	>0.001 ≤ 0.01	>0.01 ≤ 0.1	>80 ≤ 90
369	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
373	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
374	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
375	>0.01 ≤ 0.1	N/A	>70 ≤ 80
376	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90

TABLE 7-continued

IC50, IC80, and Max % Inhibition of hCIDE� mRNA (Normalized to GAPDH).			
DsRNA Agent	IC50 [nM]	IC80 [nM]	% Maximum Inhibition
380	>0.1 ≤ 1	N/A	>60 ≤ 70
443	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
387	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
388	>0.01 ≤ 0.1	>1 ≤ 5	>80 ≤ 90
390	>0.01 ≤ 0.1	N/A	>70 ≤ 80
391	>0.01 ≤ 0.1	N/A	>80 ≤ 90
474	>0.1 ≤ 1	N/A	>70 ≤ 80
473	>0.01 ≤ 0.1	N/A	>70 ≤ 80
477	>0.01 ≤ 0.1	N/A	>70 ≤ 80
457	>0.01 ≤ 0.1	>1 ≤ 5	>80 ≤ 90
397	>0.1 ≤ 1	N/A	>70 ≤ 80
472	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
403	>0.1 ≤ 1	N/A	>70 ≤ 80
405	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
406	>0.01 ≤ 0.1	N/A	>70 ≤ 80
408	>0.001 ≤ 0.01	>0.1 ≤ 1	>80 ≤ 90
409	>0.001 ≤ 0.01	>0.1 ≤ 1	>80 ≤ 90
411	>0.01 ≤ 0.1	N/A	>70 ≤ 80
414	>0.01 ≤ 0.1	>0.1 ≤ 1	>80 ≤ 90
415	>0.1 ≤ 1	N/A	>70 ≤ 80
417	>0.1 ≤ 1	N/A	>70 ≤ 80

5.7 Example 7. In Vitro dsRNA Agent Mediated Knockdown of hCIDE� in Primary Cyno Hepatocytes

[0961] Each of dsRNA Agents 368, 369, 373, 374, 375, 376, 387, 388, 390, 391, 405, 406, 408, 409, 411, 414, 443, 457, 472 or 477 set forth in Table 3 above were evaluated for their ability to knockdown hCIDE� expression in vitro in primary cynomolgus macaque (cyno) hepatocytes.

[0962] Briefly, primary cyno hepatocytes were seeded at 60,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated hCIDE� targeting dsRNA agent (20 nM, 0.1 nM) using Lipofectamine RNAiMax (0.3 µl/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of cyno CIDE� was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of cyno CIDE� was normalized to the expression of cyno GAPDH. Each treatment group was run in quadruplicate.

[0963] Table 8 shows the percent of cyno CIDE� mRNA remaining after treatment with the indicated dsRNA agent (normalized to GAPDH and relative to control treated cells set to 100%).

TABLE 8

Range % cyno CIDE� mRNA Remaining (Normalized to GAPDH).		
dsRNA	CIDE�/GAPDH	
Agent	20 nM	0.1 nM
368	10-15	15-20
369	10-15	35-40
373	10-15	20-25
374	10-15	20-25
375	20-25	60-70
376	10-15	30-40
387	10-15	30-40

TABLE 8-continued

Range % cyno CIDE� mRNA Remaining (Normalized to GAPDH).		
dsRNA	CIDE�/GAPDH	
Agent	20 nM	0.1 nM
388	15-20	50-60
390	20-25	60-70
391	15-20	30-40
405	20-25	40-50
406	20-25	30-40
408	10-15	15-20
409	15-20	20-25
411	20-25	70-80
414	50-60	80-90
443	10-15	25-30
457	15-20	30-40
472	10-15	40-50
477	50-60	70-80

5.8 Example 8. In Vitro GalNAc-dsRNA Agent Mediated Knockdown of hCIDE� in Hep3B Cells

[0964] Each of GalNAc-dsRNA Agents 483, 484, 485, 486, and 487 set forth in Table 11 above were evaluated for their ability to knockdown hCIDE� expression in vitro in Hep3B cells. Each base modified siRNA was synthesized as a GalNAc conjugate, introduced as the triantennary GalNAc-TEG cluster at the 3'-end of each of the sense strand.

[0965] The corresponding base modified dsRNA agent (set forth in Table 3) as well as the corresponding base unmodified dsRNA agent (set forth in Table 2) for each of the GalNAc-dsRNA agents 483-487 is also set forth in Table 11.

[0966] Briefly, Hep3B cells (ATCC) were seeded at 15,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated hCIDE� targeting dsRNA agent (either 0.3 nM or 20 nM) using Lipofectamine RNAiMax (0.3 µl/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of hCIDE� was assessed utilizing a standard branched DNA (bDNA) assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to the manufacturer's instructions. The expression of hCIDE� was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate, the mean and standard deviation calculated.

[0967] Table 9 shows the percent of hCIDE� mRNA remaining after treatment with the indicated GalNAc-dsRNA Agent (normalized to GAPDH and relative to control treated cells set to 100%).

TABLE 9

Range % hCIDE� mRNA Remaining (Normalized to GAPDH).		
dsRNA Agent	CIDE�/GAPDH	
	20 nM	0.3 nM
487	10-15	5-10
483	5-10	5-10
486	5-10	5-10
484	5-10	5-10
485	5-10	10-15

5.9 Example 9. In Vitro GalNAc-dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes

[0968] Each of GalNAc-dsRNA Agents 483, 484, 485, 486, and 487 set forth in Table 11 above were evaluated for their ability to knockdown hCIDEB expression in vitro. Each base modified siRNA was synthesized as GalNAc conjugates, introduced as the triantennary GalNAc-TEG cluster at the 3'-end of each of the sense strands.

[0969] The corresponding base modified dsRNA agent (set forth in Table 3) as well as the corresponding base unmodified dsRNA agent (set forth in Table 2) for each of the GalNAc-dsRNA agents 483-487 is set forth in Table 11.

[0970] Briefly, primary human hepatocytes were seeded at 90,000 cells per well in a standard 96 well plate. The cells were treated with the indicated hCIDEB targeting GalNAc-dsRNA agent by uptake (5000 nM, 1250 nM, 313 nM, 78.1 nM, 19.5 nM, 4.88 nM, 1.22 nM, 0.305 nM, 0.0763 nM, or 0.0191 nM) and incubated for 48 hours. The level of hCIDEB was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of hCIDEB was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate.

[0971] Table 10 shows the calculated IC₅₀ (nM), IC₈₀ (nM), and the remaining hCIDEB mRNA percent (normalized to GAPDH) (mean of quadruplicates).

TABLE 10

DsRNA Agent	IC ₅₀ [nM]	IC ₈₀ [nM]	% Maximum Inhibition
487	>1 ≤ 5	>20 ≤ 30	>80 ≤ 90
483	>1 ≤ 5	>10 ≤ 20	>80 ≤ 90
486	>1 ≤ 5	>40 ≤ 50	>80 ≤ 90
484	>1 ≤ 5	>50 ≤ 60	>80 ≤ 90
485	>1 ≤ 5	>30 ≤ 40	>80 ≤ 90

[0972] The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying FIGURES. Such modifications are intended to fall within the scope of the appended claims.

[0973] All references (e.g., publications or patents or patent applications) cited herein are incorporated herein by reference in their entireties and for all purposes to the same extent as if each individual reference (e.g., publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[0974] Other embodiments are within the following claims.

SEQUENCE LISTING

The patent application contains a lengthy sequence listing. A copy of the sequence listing is available in electronic form from the USPTO web site (<https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20250263702A1>). An electronic copy of the sequence listing will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of cell death inducing DNA fragmentation factor alpha like effector (CIDEB),

wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

2. The dsRNA agent of claim 1, wherein the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

3.-4. (canceled)

5. The dsRNA agent of claim 1, wherein

(a) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleo-

tide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 172;

(b) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 132;

(c) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 173; or

(d) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence set forth in SEQ ID NO: 138.

6.-10. (canceled)

11. A dsRNA agent for inhibiting expression of CIDEB, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of any one of the antisense strands of any one of dsRNA agents 1-482 set forth in Table 2 or Table 3; and

the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of the sense strand of the corresponding dsRNA agent set forth in Table 2 or Table 3.

12. (canceled)

13. The dsRNA agent of claim **11**, wherein

(a) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of the antisense strand of dsRNA agent 129; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of dsRNA agent 129;

(b) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of the antisense strand of dsRNA agent 135; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of dsRNA agent 135;

(c) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of the antisense strand of dsRNA agent 169; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of dsRNA agent 169; or

(d) the nucleotide sequence of the antisense strand differs by no more than 5 nucleotides from the nucleotide sequence of the antisense strand of dsRNA agent 170; and the nucleotide sequence of the sense strand differs by no more than 5 nucleotides from the nucleotide sequence of dsRNA agent 170.

14.-18. (canceled)

19. A dsRNA agent for inhibiting expression of CIDEB, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein the sense strand comprises at least 15 (e.g., 16, 17, 18, 19, 20, 21) contiguous nucleotides of and differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5 (e.g., 3 (e.g., 0, 1, 2, or 3))) nucleotides from nucleotides 50-90, 60-90, 68-106, 81-103, 138-190, 169-206, 232-254, 230-300, 280-312, 298-327, 444-498, 510-538, 521-558, 560-617, 692-778, 720-750, 740-780, 750-790, 760-780, 880-920, 890-940, 890-950, 920-970, 930-980, 961-1037, 1035-1060, 1105-1133, 1171-1213, 1216-1287, 1220-1270, 1230-1280, 1240-1290, 1250-1300, 1240-1270, 1240-1280, 1235-1270, 1245-1265, 1247-1267, 1252-1272, 1294-1346, 1366-1400, 1370-1410, 1360-1400, 1470-1510, 1410-1460, 1520-1560, 1580-1620, 1640-1680, 1640-1690, 1670-1710, 1700-1740, 1700-1745, 1724-1753, 1750-1790, 1757-1812, 1770-1810, 1833-1864, 1880-1920, 1900-1940, 1900-1927, 1915-1966, 1920-1970, 1930-1970, 1930-1965, 1940-1970, 1940-1965, 1937-1957, 1942-1962, 1938-1958, 1943-1963, 2010-2060, 2020-2060, 2030-2070, 2082-2110, 2080-2120, 2090-2130, 2130-2170,

2143-2198, 2197-2225, 2210-2250, 2215-2260, 2240-2280, 2250-2280, 2250-2290, or 2260-2290 of SEQ ID NO: 1;

wherein the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of and differing by no more than 5 nucleotides from the nucleotide sequence of the corresponding complementary nucleotide sequence of SEQ ID NO: 2.

20.-24. (canceled)

25. A dsRNA agent for inhibiting expression of CIDEB, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the antisense strand comprises at least 15 contiguous nucleotides of and differing by no more than 5 nucleotides from the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191.

26.-70. (canceled)

71. A conjugate comprising the dsRNA agent of claim **1** and a heterologous moiety.

72.-95. (canceled)

96. A vector encoding the antisense strand, the sense strand, or both the antisense and sense strand of claim **1**.

97. A carrier comprising the dsRNA agent of claim **1**.

98.-99. (canceled)

100. A cell (or population of cells) comprising the dsRNA agent of claim **1**.

101. A pharmaceutical composition comprising the dsRNA agent of claim **1**, and a pharmaceutically acceptable excipient.

102. A kit comprising the dsRNA agent of claim **1**.

103. A method of delivering a dsRNA agent to a cell, the method comprising introducing into a cell the dsRNA agent of claim **1**, to thereby deliver the dsRNA agent into the cell.

104.-106. (canceled)

107. A method of reducing or inhibiting expression of CIDEB in a cell, the method comprising delivering into the cell the dsRNA agent of claim **1**, to thereby reduce or inhibit expression of CIDEB in the cell.

108. (canceled)

109. A method of treating, ameliorating, or preventing a CIDEB associated disease in a subject, the method comprising administering to the subject the dsRNA agent of claim **1**, to thereby treat, ameliorate, or prevent the CIDEB associated disease in the subject.

110.-116. (canceled)

117. A method of diagnosing a CIDEB associated disease in a subject, the method comprising

(a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject;

(b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein,

wherein the presence of the one or more somatic mutation indicates that the subject has a CIDEB associated disease.

118.-126. (canceled)

127. A method of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of CIDEB, the method comprising

- (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject;
- (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein,
wherein the subject is selected for administration of the inhibitory nucleic acid molecule if the one or more somatic mutation is present.

128.-130. (canceled)

131. A method of treating, ameliorating, or preventing a CIDEB associated disease in a subject, the method comprising

- (a) isolating and purifying DNA, RNA, or protein, or having DNA, RNA, or protein isolated and purified, from a sample obtained from the subject;

- (b) detecting, or having detected, the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein, and
- (c) administering to the subject an inhibitory nucleic acid that inhibits expression of CIDEB if the one or more CIDEB somatic mutation is detected in the DNA, RNA, or protein.

132.-141. (canceled)

142. An in vitro method of screening a sample from a subject for one or more somatic CIDEB mutation, the method comprising

- (a) isolating and purifying DNA, RNA, or protein from a sample obtained from the subject; and
- (b) detecting the presence or absence of one or more somatic CIDEB mutation in the DNA, RNA, or protein.

143.-152. (canceled)

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