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RNAI AGENTS TARGETING CIDEB AND RELATED METHODS

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).

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Background/Summary

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 (CIDEB). The disclosure further relates to pharmaceutical compositions comprising the same; and methods of utilizing the same, including, e.g., methods of treating CIDEB 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, CIDEB, and CIDEC. 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 CIDEC are primarily expressed in adipose tissue, while CIDEB 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 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., 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 (CIDEB) (e.g., human CIDEB (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 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 ID NO: 315; 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: 132; (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: 356; 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: 173; or (d) 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; 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: 138.

[0012] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173; or (d) the nucleotide sequence of the antisense strand

comprises the nucleotide sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138.

[0013] 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: 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: 1192; (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: 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; (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: 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: 786; (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: 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: 827; 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: 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: 792.

[0014] 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: 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: 1192; (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: 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; (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: 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: 786; (d) 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; 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: 827; 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 set forth in SEQ ID NO: 1189; 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: 792.

[0015] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192; (b) the nucleotide sequence of the antisense strand comprises 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; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786; (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827; or (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID

NO: 1189; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792.

[0016] 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 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 set forth in Table 2 or Table 3; 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 of the sense strand of the corresponding dsRNA agent set forth in Table 2 or Table 3.

[0017] 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 set forth in Table 2 or Table 3; 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 sense strand of the corresponding dsRNA agent set forth in Table 2 or Table 3.

[0018] 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 of the antisense strand of dsRNA agent 129; 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 of dsRNA agent 129; (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 of the antisense strand of dsRNA agent 135; 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 of dsRNA agent 135; (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 of the antisense strand of dsRNA agent 169; 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 of dsRNA agent 169; 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 of the antisense strand of dsRNA agent 170; 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 of dsRNA agent 170.

[0019] 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 of the antisense strand of dsRNA agent 129; 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 129; (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 of the antisense strand of dsRNA agent 135; 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 135; (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 169; 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 169; or (d) 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 170; 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 170.

[0020] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 129; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 129; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 135;

and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 135; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 169; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 169; or (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 170; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 170.

[0021] 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 of the antisense strand of dsRNA agent 479; 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 of dsRNA agent 479; (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 of the antisense strand of dsRNA agent 481; 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 of dsRNA agent 481; (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 of the antisense strand of dsRNA agent 482; 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 of dsRNA agent 482; (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 of the antisense strand of dsRNA agent 480; 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 of dsRNA agent 480; or (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 of the antisense strand of dsRNA agent 409; 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 of dsRNA agent 409.

[0022] 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 of the antisense strand of dsRNA agent 479; 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 479; (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 of the antisense strand of dsRNA agent 481; 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 481; (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 482; 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 482; (d) 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 480; 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 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 (c) 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.

[0033] In some embodiments, the nucleotide sequence of the antisense strand comprises at least 21 (e.g., 21, 22, or 23) contiguous nucleotides of 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 18 (e.g., 18, 19, 20, 21) contiguous nucleotides of 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.

[0034] In some embodiments, (a) 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 set forth in SEQ ID NO: 355; and 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 set forth in SEQ ID NO: 172; (b) 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 set forth in SEQ ID NO: 315; and 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 set forth in SEQ ID NO: 132; (c) 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 set forth in SEQ ID NO: 356; and 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 set forth in SEQ ID NO: 173; or (d) 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 set forth in SEQ ID NO: 321; and 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 set forth in SEQ ID NO: 138.

[0035] In some embodiments, (a) 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 set forth in SEQ ID NO: 1191; and 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 set forth in SEQ ID NO: 1192; (b) 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 set forth in SEQ ID NO: 1188; and 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 set forth in SEQ ID NO: 786; (c) 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 set forth in SEQ ID NO: 1190; and 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 set forth in SEQ ID NO: 786; (d) 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 set forth in SEQ ID NO: 1062; and 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 set forth in SEQ ID NO: 827; or (e) 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 set forth in SEQ ID NO: 1189; and 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 set forth in SEQ ID NO: 792.

[0036] 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 strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482.

[0037] 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 of the dsRNA agent.

[0038] 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 strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 of the dsRNA agent.

[0039] In some embodiments, the nucleotide sequence of the antisense strand comprises at least 21 (e.g., 21, 22, or 23) contiguous nucleotides 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; and wherein the nucleotide sequence of the sense strand comprises at least 18 (e.g., 18, 19, 20, 21) contiguous nucleotides of the nucleotide sequence of the corresponding sense strand of the dsRNA agent.

[0040] In some embodiments, (a) 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 the antisense strand of dsRNA agent 129; and 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 sense strand of dsRNA agent 129; (b) 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 the antisense strand of dsRNA agent 135; and 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 sense strand of dsRNA agent 135; (c) 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 the antisense strand of dsRNA agent 169; and 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 sense strand of dsRNA agent 169; or (d) 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 the antisense strand of dsRNA agent 170; and 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 sense strand of dsRNA agent 170.

[0041] In some embodiments, (a) 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 the antisense strand of dsRNA agent 409; and 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 sense strand of dsRNA agent 409; (b) 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 the antisense strand of dsRNA agent 479; and 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 sense strand of dsRNA agent 479; (c) 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 the antisense strand of dsRNA agent 480; and 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 sense strand of dsRNA agent 480; (d) 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 the antisense strand of dsRNA agent 481; and 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 sense strand of dsRNA agent 481; or (c) 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 the antisense strand of dsRNA agent 482; and 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 sense strand of dsRNA agent 482.

[0042] 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 (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1192; (b) the nucleotide sequence of the antisense strand comprises 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; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 786; (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 827; or (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 792.

[0043] 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 (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: 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: 1192; (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: 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; (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: 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: 786; (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: 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: 827; 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: 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: 792.

[0044] 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 (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: 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: 1192; (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: 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; (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: 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: 786; (d) 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; 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: 827; or (e) 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; 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: 792.

[0045] 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 (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.

[0046] 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 (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 ID NO: 315; 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: 132; (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: 356; 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: 173; or (d) 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; 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: 138.

[0047] 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 (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 172; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 132; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 173; or (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 138.

[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:
##STR00001##
[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 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; 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: 1195; 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 set forth in SEQ ID NO: 1062; 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: 1196.

[0075] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises 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: 1193; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1193; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1194; (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1195; or (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1196.

[0076] In some embodiments, the conjugate comprises any one of dsRNA agents 483-487.

[0077] 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 of the antisense strand of dsRNA agent 483; 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 of dsRNA agent 483; (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 of the antisense strand of dsRNA agent 484; 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 of dsRNA agent 484; (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 of the antisense strand of dsRNA agent 485; 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

of dsRNA agent 485; (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 of the antisense strand of dsRNA agent 486; 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 of dsRNA agent 486; 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 of the antisense strand of dsRNA agent 487; 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 of dsRNA agent 487.

[0078] 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 of the antisense strand of dsRNA agent 483; 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 483; (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 of the antisense strand of dsRNA agent 484; 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 484; (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 485; 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 485; (d) 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 486; 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 486; or (e) 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 487; 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 487.

[0079] In some embodiments, (a) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 483; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 483; (b) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 484; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 484; (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 485; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 485; (d) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 486; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 486; or (c) the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand of dsRNA agent 487; and the nucleotide sequence of the sense strand comprises of the sense strand of dsRNA agent 487.

[0080] In one aspect, provided herein are vectors (e.g., a viral vector, a non-viral vector) encoding an antisense strand described herein, a sense strand described herein, or both an antisense described herein and a sense strand described herein.

[0081] In one aspect, provided herein are carriers comprising a dsRNA agent described herein, a conjugate described herein, or a vector described herein.

[0082] In some embodiments, the carrier comprises a nanoparticle, a polymer, a lipid-based delivery system, as 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.

Description

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.

[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 unilocular 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 is 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 unilocular 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-US-00002 TABLE 1 The mRNA and Amino Acid Sequence of a Reference hCIDEB Protein. SEQ ID Description Amino Acid Sequence NO hCIDEB mRNA CCCUUCCGGUGGAGCCAGCGCUGCGACCGCCUGCAGAAGGUUGACUGC 1
NCBI Ref.: GUGGUAGGGGGCCCAGAGCAAGCCGAAGGCAAGCACGAUGGCGCUCAC
NM_014430.4 CAGCCGGCCCACCCGCGCCCCGUGCCGCCCGGAGCCCCAGCGGGCGCC
CCGCAGCCGUGCCAGCGUCACGCUGUAGCAGCCGAGCAUCAGCCCGAA
AGGAAGCACGAAAGCGGUCAGAGUCUCCAGGCUCAGGUGGGCGGCGGC
GUGGACCGGCGACGGGUGGCACAGCUGGCAUACGCGGUCCCUCCACAG
GUGGCGGUAGACGGCGGCCGGGACGGCGAGCAACAGGGCGGCCAGCCA
GACCGCCAGCAGCAGGCGGCGGGCCAGGGCCGGGCUGCGCAGCCGAGG
CGCCAGGAAGGGGCGGGUGACUGCGAGGCAGCGCUGCAGGCUGAGCAG
GCCGGUGAGCAGCACGCUGGCGUACAUGCUGAGCGCGCACACGUAGUA
CACCGCCUUGCAGCCCGCCUGGCCCAGCGGCCAGGCCUGCCGGGUCAG
GAAGGCCACAAAGAGCGGCGUGAGCAGCAGCACCGCGCCGUCGGCCAG
CGCCAGGUGCAGCACAAGCGUGGCCGCCAGCGGUCGCCCCCGUGCAGG
CCGCCAGCCCGCCAAGCUCCACACCACGAAGCCGUUGCCAGGCAGCCC
CAGCAGCGCCGCCAGCAGCAGGAAGGCUGUGCCUGUGGCCCGCGAAGU
CUUCCAGCUCAGCAGUGUCUCGUUCCCUGGGGGACGGUAGCAGACCGA
CAUCCUUCUGGGCCUACAGGACACAGAAAAAAAGUGGGGAAGCUGGGG
GACCCUACAAGGAUCCUUGGCAGGAAAGCAGGGAUUGUGUUCAUUUGA
GGGUUUCACUGUCAGUGAGAGUCUCAGCUUCCAUGCAACUGUCCAUCA
CGGCUGCAACUGAAAUCAGAGCUGGGACACAGCGCACCAGAAGCUAAA
GUCUUGAUGCCAUCAAAGGACAUCCCUGCCCCAUUCACAUCUCUGUCA

CGUCCACUAAUCGGCAAAAGGAGAAAAGUGAGAGAAGAUGACCUAAGU
GUGACUGCAGCAGGCAGCUCUGGAAAAUGAAGCCAGAGCAGUGAGCCA
GCCCCUCCUCCGACCAAGGAGGAAGGAAAGAGCAGCCCCAGCACAGGA
GAGAACCACCCAGCCCAGAAGUUCCAGGGAAGGAACUCUCCGGUCCAC
CAUGGAGUACCUCUCAGCUCUGAACCCCAGUGACUUACUCAGGUCAGU
AUCUAAUAUAAGCUCGGAGUUUGGACGGAGGGUCUGGACCUCAGCUCC
ACCACCCCAGCGACCUUUCCGUGUCUGUGAUCACAAGCGGACCAUCCG
GAAAGGCCUGACAGCUGCCACCCGCCAGGAGCUGCUAGCCAAAGCAUU
GGAGACCCUACUGCUGAAUGGAGUGCUAACCCUGGUGCUAGAGGAGGA
UGGAACUGCAGUGGACAGUGAGGACUUCUUCCAGCUGCUGGAGGAUGA
CACGUGCCUGAUGGUGUUGCAGUCUGGUCAGAGCUGGAGCCCUACAAG
GAGUGGAGUGCUGUCAUAUGGCCUGGGACGGGAGAGGCCCAAGCACAG
CAAGGACAUCGCCCGAUUCACCUUUGACGUGUACAAGCAAAACCCUCG
AGACCUCUUUGGCAGCCUGAAUGUCAAAGCCACAUUCUACGGGCUCUA
CUCUAUGAGUUGUGACUUUCAAGGACUUGGCCCAAAGAAAGUACUCAG
GGAGCUCCUUCGUUGGACCUCCACACUGCUGCAAGGCCUGGGCCAUAU
GUUGCUGGGAAUUUCCUCCACCCUUCGUCAUGCAGUGGAGGGGGCUGA
GCAGUGGCAGCAGAAGGGCCGCCUCCAUUCCUACUAAGGGGCUCUGAG
CUUCUGCCCCCAGAAUCAUUCCAACCGACCCACUGCAAAGACUAUGAC
AGCAUCAAAUUUCAGGACCUGCAGACAGUACAGGCUAGAUAACCCACC
CAAUUUCCCCACUGUCCUCUGAUCCCCUCGUGACAGAACCUUUCAGCA
UAACGCCUCACAUCCCAAGUCUAUACCCUUACCUGAAGAAUGCUGUUC
UUUCCUAGCCACCUUUCUGGCCUCCCACUUGCCCUGAAAGGCCAAGAU
CAAGAUGUCCCCCAGGCAUCUUGAUCCCAGCCUGACUGCUGCUACAUC
UAAUCCCCUACCAAUGCCUCCUGUCCCUAAACUCCCCAGCAUACUGAU
GACAGCCCUCUCUGACUUUACCUUGAGAUCUGUCUUCAUACCCUUCCC
CUCAAACUAACAAAAACAUUUCCAAUAAAAAUAUCAAAUAUUUACCAC UAA Reverse
UUAGUGGUAAAUAUUUGAUAUUUUUAUUGGAAAUGUUUUUGUUAGUUU 2
Complement GAGGGGAAGGGUAUGAAGACAGAUCUCAAGGUAAAGUCAGAGAGGGCU
of hCIDEB GUCAUCAGUAUGCUGGGGAGUUUAGGGACAGGAGGCAUUGGUAGGGGA
mRNA UUAGAUGUAGCAGCAGUCAGGCUGGGAUCAAGAUGCCUGGGGGACAUC
UUGAUCUUGGCCUUUCAGGGCAAGUGGGAGGCCAGAAAGGUGGCUAGG
AAAGAACAGCAUUCUUCAGGUAAGGGUAUAGACUUGGGAUGUGAGGCG
UUAUGCUGAAAGGUUCUGUCACGAGGGGAUCAGAGGACAGUGGGGAAA
UUGGGUGGGUUAUCUAGCCUGUACUGUCUGCAGGUCCUGAAAUUUGAU
GCUGUCAUAGUCUUUGCAGUGGGUCGGUUGGAAUGAUUCUGGGGGCAG
AAGCUCAGAGCCCCUUAGUAGGAAUGGAGGCGGCCCUUCUGCUGCCAC
UGCUCAGCCCCCUCCACUGCAUGACGAAGGGUGGAGGAAAUUCCCAGC
AACAUAUGGCCCAGGCCUUGCAGCAGUGUGGAGGUCCAACGAAGGAGC
UCCCUGAGUACUUUCUUUGGGCCAAGUCCUUGAAAGUCACAACUCAUA
GAGUAGAGCCCGUAGAAUGUGGCUUUGACAUUCAGGCUGCCAAAGAGG
UCUCGAGGGUUUUGCUUGUACACGUCAAAGGUGAAUCGGGCGAUGUCC
UUGCUGUGCUUGGGCCUCUCCCGUCCCAGGCCAUAUGACAGCACUCCA
CUCCUUGUAGGGCUCCAGCUCUGACCAGACUGCAACACCAUCAGGCAC
GUGUCAUCCUCCAGCAGCUGGAAGAAGUCCUCACUGUCCACUGCAGUU
CCAUCCUCCUCUAGCACCAGGGUUAGCACUCCAUUCAGCAGUAGGGUC
UCCAAUGCUUUGGCUAGCAGCUCCUGGCGGGUGGCAGCUGUCAGGCCU
UUCCGGAUGGUCCGCUUGUGAUCACAGACACGGAAAGGUCGCUGGGGU
GGUGGAGCUGAGGUCCAGACCCUCCGUCCAAACUCCGAGCUUAUAUUA
GAUACUGACCUGAGUAAGUCACUGGGGUUCAGAGCUGAGAGGUACUCC

AUGGUGGACCGGAGAGUUCCUUCCCUGGAACUUCUGGGCUGGGUGGUU
CUCUCCUGUGCUGGGGCUGCUCUUUCCUUCCUCCUUGGUCGGAGGAGG
GGCUGGCUCACUGCUCUGGCUUCAUUUUCCAGAGCUGCCUGCUGCAGU
CACACUUAGGUCAUCUUCUCUCACUUUUCUCCUUUUGCCGAUUAGUGG
ACGUGACAGAGAUGUGAAUGGGGCAGGGAUGUCCUUUGAUGGCAUCAA
GACUUUAGCUUCUGGUGCGCUGUGUCCCAGCUCUGAUUUCAGUUGCAG
CCGUGAUGGACAGUUGCAUGGAAGCUGAGACUCUCACUGACAGUGAAA
CCCUCAAAUGAACACAAUCCCUGCUUUCCUGCCAAGGAUCCUUGUAGG
GUCCCCCAGCUUCCCCACUUUUUUUCUGUGUCCUGUAGGCCCAGAAGG
AUGUCGGUCUGCUACCGUCCCCCAGGGAACGAGACACUGCUGAGCUGG
AAGACUUCGCGGGCCACAGGCACAGCCUUCCUGCUGCUGGCGGCGCUG
CUGGGGCUGCCUGGCAACGGCUUCGUGGUGUGGAGCUUGGCGGGCUGG
CGGCCUGCACGGGGGCGACCGCUGGCGGCCACGCUUGUGCUGCACCUG
GCGCUGGCCGACGGCGCGGUGCUGCUGCUCACGCCGCUCUUUGUGGCC
UUCCUGACCCGGCAGGCCUGGCCGCUGGGCCAGGCGGGCUGCAAGGCG
GUGUACUACGUGUGCGCGCUCAGCAUGUACGCCAGCGUGCUGCUCACC
GGCCUGCUCAGCCUGCAGCGCUGCCUCGCAGUCACCCGCCCCUUCCUG
GCGCCUCGGCUGCGCAGCCCGGCCCUGGCCCGCCGCCUGCUGCUGGCG
GUCUGGCUGGCCGCCCUGUUGCUCGCCGUCCCGGCCGCCGUCUACCGC
CACCUGUGGAGGGACCGCGUAUGCCAGCUGUGCCACCCGUCGCCGGUC
CACGCCGCCGCCCACCUGAGCCUGGAGACUCUGACCGCUUUCGUGCUU
CCUUUCGGGCUGAUGCUCGGCUGCUACAGCGUGACGCUGGCACGGCUG
CGGGGCGCCCGCUGGGGCUCCGGGCGGCACGGGGCGCGGGUGGGCCGG
CUGGUGAGCGCCAUCGUGCUUGCCUUCGGCUUGCUCUGGGCCCCCUAC
CACGCAGUCAACCUUCUGCAGGCGGUCGCAGCGCUGGCUCCACCGGAA GGG hCIDEB
MEYLSALNPSDLLRSVSNISSEFGRRVWTSAPPPQRPFRVCDHKRTIR 3 Protein
KGLTAATRQELLAKALETLLLNGVLTLVLEEDGTAVDSEDFFQLLEDD NCBI Ref.:
TCLMVLQSGQSWSPTRSGVLSYGLGRERPKHSKDIARFTFDVYKQNPR NP_055245
DLFGSLNVKATFYGLYSMSCDFQGLGPKKVLRELLRWTSTLLQGLGHM
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, 23-27, 23-26, 23-25, or 23-24 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of from about 19-25 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of from about 19-23 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of from about 21-25 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of from about 21-23 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of about 19, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of about 19 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of about 20 nucleotides. In some embodiments, the target nucleic acid molecule comprises or consists of about 21 nucleotides. In some embodiments, the target nucleic acid molecule 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.
4.2.1.2 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, 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 antisense 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 antisense 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 antisense 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.
[0183] In some embodiments, the antisense 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

antisense 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 antisense strand comprises or consists of about 21 nucleotides. In some embodiments, the antisense 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.

4.2.1.3 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 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 antisense 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 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 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 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: 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 CIDEB 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 of any one of the antisense strands 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 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: 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 CIDEB 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

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: 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, 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.

[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 98% 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. 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 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 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 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 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 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 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 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, 792, 827, or 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 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 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.

[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, 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 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, 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 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 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: 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 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.

[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 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: 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 CIDEB 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., 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.

[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 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: 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 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 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 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 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.

[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, 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 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, 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 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, 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 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 comprises 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 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 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; and 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 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; and 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 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; and 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.

[0467] 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; and 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 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; and 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 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; and 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 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; and 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.

[0468] 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 sense strand is 100% identical to 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 is 100% identical to the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0469] 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; and 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 sense strand consists of 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 consists of the nucleotide sequence of any one of the antisense strands set forth in Table 2 or Table 3.

[0470] 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 any one of the sense 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; 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 any one of the sense 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; 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 any one of the sense 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; 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 any one of the sense 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 (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 any one of the sense strands set forth in Table 2 or Table 3.

[0471] 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, 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 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; 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 Table 2 or Table 3. In some embodiments, the antisense strand comprises from about 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; 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 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; 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 Table 2 or Table 3.

[0472] 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 any one of the sense strands set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 any one of the sense strands set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 any one of the sense strands set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 any one of the sense strands set forth in Table 2 or Table 3. 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 Table 2 or Table 3; 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 Table 2 or Table 3. 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 Table 2 or Table 3; 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 Table 2 or Table 3. 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 Table 2 or Table 3; 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 Table 2 or Table 3.

[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, 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 the corresponding sense strand 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; 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 the corresponding sense strand set forth in Table 2 or Table 3. In some embodiments, the antisense strand comprises from about 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; 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 the corresponding sense strand 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; 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 the corresponding sense strand set forth in Table 2 or Table 3.

[0477] 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 any one of the antisense strands set forth in Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3. 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 Table 2 or Table 3; 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 corresponding sense strand set forth in Table 2 or Table 3.

[0478] 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 the corresponding sense strand set forth in Table 2 or Table 3 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the corresponding sense strand set forth in Table 2 or Table 3.

[0479] 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 the corresponding sense strand set forth in Table 2 or Table 3.

[0480] 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; and 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 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; and 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 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: 4-186, 553-601, 658-892, or 1192; and 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 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; and 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.

[0481] 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; and 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 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; and 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 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; and 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 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; and 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.

[0482] 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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 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; and 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.

[0483] 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; and 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 sense strand consists of the nucleotide sequence set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192; and 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.

[0484] 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 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 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.

[0485] 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 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 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 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; 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 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 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 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 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 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 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 any one of the sense strands set forth in any one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192.

[0486] 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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, 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 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 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 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 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.

[0487] 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 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 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 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 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 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 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, 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 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, 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 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, 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 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, 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 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, 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 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 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 (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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; 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 (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 (e.g., as set forth in one

of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192).

[0491] 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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, 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 the corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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 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 the corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). In some embodiments, the antisense strand comprises from about 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 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 the corresponding sense strand (e.g., as set forth in 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 the corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192).

[0492] 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 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 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 corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192). 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 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 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 (e.g., as set forth in 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, 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 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, 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 (e.g., as set forth in 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, 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 any one of SEQ ID NOS: 187-369, 602-657, 893-1131, or 1188-1191; 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 corresponding sense strand (e.g., as set forth in 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 the corresponding sense strand (e.g., as set forth in 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 the corresponding sense strand (e.g., as set forth in 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 the corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192).

[0493] 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 the corresponding sense strand (e.g., as set forth in 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.

[0494] 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 the corresponding sense strand (e.g., as set forth in one of SEQ ID NOS: 4-186, 553-601, 658-892, or 1192).

[0495] 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; 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. 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; 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. 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; 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: 172. 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; 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: 172.

[0496] 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; and the nucleotide sequence of the sense 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: 172. 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; and 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 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; and 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 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; and 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.

[0497] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 172.

[0498] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 355; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 172.

[0499] 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 the antisense strand set forth in SEQ ID NO: 355; 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 sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 sense strand set forth in SEQ ID NO: 172.

[0500] 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 the antisense strand set forth in SEQ ID NO: 355; 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, 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 the sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 the sense strand set forth in SEQ ID NO: 172. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 355; 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 the sense strand set forth in SEQ ID NO: 172. 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 the antisense strand set forth in SEQ ID NO: 355; 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 the sense strand set forth in SEQ ID NO: 172.

[0501] In some embodiments, the antisense strand comprises 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: 355; and the sense strand comprises 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: 172. In some embodiments, the antisense strand comprises 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: 355; and the sense strand comprises 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: 172. In some embodiments, the antisense strand comprises 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: 355; and the sense strand 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: 172. In some embodiments, the antisense strand comprises 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: 355; and the sense strand comprises 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: 172. In some embodiments, the antisense strand comprises 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: 355; and the sense strand comprises 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: 172. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 355; and the sense strand comprises 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 set forth in SEQ ID NO: 172. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 355; and the sense strand comprises 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 set forth in SEQ ID NO: 172.

[0502] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 172 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 172.

[0503] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 172.

[0504] 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: 355; 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: 172. 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: 355; 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: 172. 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: 355; 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: 172. 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: 355; 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: 172. 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: 355; 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: 172. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 355; and the sense strand 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 set forth in SEQ ID NO: 172. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 355; and the sense strand 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 set forth in SEQ ID NO: 172.

[0505] 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: 355 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: 355; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 172 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 172.

[0506] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 355; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 172.

[0507] 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; 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. 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; 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: 132. 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; 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: 132. 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; 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: 132.
[0508] 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; and the nucleotide sequence of the sense 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: 132. 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; and 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 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; and 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 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; and 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.
[0509] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 132.

[0510] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 315; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 132.

[0511] 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 the antisense strand set forth in SEQ ID NO: 315; 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 sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 sense strand set forth in SEQ ID NO: 132.

[0512] 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 the antisense strand set forth in SEQ ID NO: 315; 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, 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 the sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 the sense strand set forth in SEQ ID NO: 132. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 315; 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 the sense strand set forth in SEQ ID NO: 132. 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 the antisense strand set forth in SEQ ID NO: 315; 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 the sense strand set forth in SEQ ID NO: 132.

[0513] In some embodiments, the antisense strand comprises 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: 315; and the sense strand comprises 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: 132. In some embodiments, the antisense strand comprises 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: 315; and the sense strand comprises 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: 132. In some embodiments, the antisense strand comprises 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: 315; and the sense strand 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: 132. In some embodiments, the antisense strand comprises 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: 315; and the sense strand comprises 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: 132. In some embodiments, the antisense strand comprises 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: 315; and the sense strand comprises 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: 132. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 315; and the sense strand comprises 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 set forth in SEQ ID NO: 132. In some embodiments, the antisense strand comprises 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

set forth in SEQ ID NO: 315; and the sense strand comprises 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 set forth in SEQ ID NO: 132.

[0514] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 132 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 132.

[0515] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 132.

[0516] 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: 315; 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: 132. 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: 315; 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: 132. 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: 315; 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: 132. 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: 315; 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: 132. 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: 315; 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: 132. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 315; and the sense strand 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 set forth in SEQ ID NO: 132. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 315; and the sense strand 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 set forth in SEQ ID NO: 132.

[0517] 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: 315 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: 315; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 132 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 132.

[0518] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 315; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 132.

[0519] 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; 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. 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; 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: 173. 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; 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: 173. 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; 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: 173.

[0520] 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; and the nucleotide sequence of the sense 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: 173. 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; and 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 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; and 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 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; and 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.

[0521] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 173.

[0522] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 356; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 173.

[0523] 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 the antisense strand set forth in SEQ ID NO: 356; 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 sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 sense strand set forth in SEQ ID NO: 173.

[0524] 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 the antisense strand set forth in SEQ ID NO: 356; 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, 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 the sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 the sense strand set forth in SEQ ID NO: 173. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 356; 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 the sense strand set forth in SEQ ID NO: 173. 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 the antisense strand set forth in SEQ ID NO: 356; 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 the sense strand set forth in SEQ ID NO: 173.

[0525] In some embodiments, the antisense strand comprises 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 comprises 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 comprises 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 comprises 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 comprises 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 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 comprises 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 comprises 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 comprises 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 comprises 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 comprises 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 set forth in SEQ ID NO: 356; and the sense strand comprises 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 set forth in SEQ ID NO: 173. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 356; and the sense strand comprises 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 set forth in SEQ ID NO: 173.

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

[0529] 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: 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 consists of 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.

[0530] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 356; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 173.

[0531] 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; 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. 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; 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: 138. 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; 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: 138. 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; 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: 138.

[0532] 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; and the nucleotide sequence of the sense 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: 138. 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; and 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 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; and 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 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 nucleotide sequence set forth in SEQ ID NO: 321; and 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.

[0533] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand is 100% identical to the nucleotide

sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 138.

[0534] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 321; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 138.

[0535] 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 the antisense strand set forth in SEQ ID NO: 321; 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 sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 sense strand set forth in SEQ ID NO: 138.

[0536] 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 the antisense strand set forth in SEQ ID NO: 321; 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, 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 the sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 the sense strand set forth in SEQ ID NO: 138. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 321; 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 the sense strand set forth in SEQ ID NO: 138. 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 the antisense strand set forth in SEQ ID NO: 321; 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 the sense strand set forth in SEQ ID NO: 138.

[0537] In some embodiments, the antisense strand comprises 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: 321; and the sense strand comprises 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: 138. In some embodiments, the antisense strand comprises 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: 321; and the sense strand comprises 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: 138. In some embodiments, the antisense strand comprises 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: 321; and the sense strand 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: 138. In some embodiments, the antisense strand comprises 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: 321; and the sense strand comprises 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: 138. In some embodiments, the antisense strand comprises 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: 321; and the sense strand comprises 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: 138. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 321; and the sense strand comprises 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 set forth in SEQ ID NO: 138.

In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 321; and the sense strand comprises 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 set forth in SEQ ID NO: 138.

[0538] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 138 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 138.

[0539] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 138.

[0540] 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: 321; 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: 138. 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: 321; 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: 138. 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: 321; 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: 138. 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: 321; 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: 138. 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: 321; 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: 138. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 321; and the sense strand 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 set forth in SEQ ID NO: 138. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 321; and the sense strand 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 set forth in SEQ ID NO: 138.

[0541] 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: 321 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: 321; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 138 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 138.

[0542] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 321; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 138.

[0543] 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; 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: 827. 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; 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: 827. 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; 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: 827. 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; 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: 827.

[0544] 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; and the nucleotide sequence of the sense 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: 827. 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; and 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 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; and 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 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; and 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.

[0545] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 827.

[0546] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1062; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 827.

[0547] 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 the antisense strand set forth in SEQ ID NO: 1062; 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 sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 sense strand set forth in SEQ ID NO: 827.

[0548] 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 the antisense strand set forth in SEQ ID NO: 1062; 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, 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 the sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 the sense strand set forth in SEQ ID NO: 827. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 1062; 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 the sense strand set forth in SEQ ID NO: 827. 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 the antisense strand set forth in SEQ ID NO: 1062; 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 the sense strand set forth in SEQ ID NO: 827.

[0549] In some embodiments, the antisense strand comprises 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: 1062; and the sense strand comprises 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: 827. In some embodiments, the antisense strand comprises 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: 1062; and the sense strand comprises 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: 827. In some embodiments, the antisense strand comprises 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: 1062; and the sense strand 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: 827. In some embodiments, the antisense strand comprises 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: 1062; and the sense strand comprises 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: 827. In some embodiments, the antisense strand comprises 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: 1062; and the sense strand comprises 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: 827. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1062; and the sense strand comprises 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 set forth in SEQ ID NO: 827. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1062; and the sense strand comprises 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 set forth in SEQ ID NO: 827.

[0550] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 827 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 827.

[0551] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 827.

[0552] 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: 1062; 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: 827. 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: 1062; 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: 827. 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: 1062; 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: 827. 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: 1062; 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: 827. 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: 1062; 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: 827. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1062; and the sense strand 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 set forth in SEQ ID NO: 827. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 1062; and the sense strand 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 set forth in SEQ ID NO: 827.

[0553] 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: 1062 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: 1062; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 827 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 827.

[0554] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1062; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 827.

[0555] 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; 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: 792. 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; 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: 792. 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; 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: 792. 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; 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: 792.

[0556] 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; and the nucleotide sequence of the sense 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: 792. 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; and 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 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; and 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 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; and 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.

[0557] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 792.

[0558] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1189; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 792.

[0559] 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 the antisense strand set forth in SEQ ID NO: 1189; 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 sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 sense strand set forth in SEQ ID NO: 792.

[0560] 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 the antisense strand set forth in SEQ ID NO: 1189; 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, 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 the sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 the sense strand set forth in SEQ ID NO: 792. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 1189; 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 the sense strand set forth in SEQ ID NO: 792. 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 the antisense strand set forth in SEQ ID NO: 1189; 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 the sense strand set forth in SEQ ID NO: 792.

[0561] In some embodiments, the antisense strand comprises 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: 1189; and the sense strand comprises 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: 792. In some embodiments, the antisense strand comprises 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: 1189; and the sense strand comprises 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: 792. In some embodiments, the antisense strand comprises 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: 1189; and the sense strand 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: 792. In some embodiments, the antisense strand comprises 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: 1189; and the sense strand comprises 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: 792. In some embodiments, the antisense strand comprises 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: 1189; and the sense strand comprises 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: 792. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1189; and

the sense strand comprises 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 set forth in SEQ ID NO: 792. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1189; and the sense strand comprises 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 set forth in SEQ ID NO: 792.

[0562] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 792 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 792.

[0563] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 792.

[0564] 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: 1189; 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: 792. 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: 1189; 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: 792. 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: 1189; 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: 792. 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: 1189; 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: 792. 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: 1189; 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: 792. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1189; and the sense strand 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 set forth in SEQ ID NO: 792. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 1189; and the sense strand 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 set forth in SEQ ID NO: 792.

[0565] 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: 1189 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: 1189; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 792 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 792.

[0566] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1189; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 792.

[0567] 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; 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: 1192. 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; 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: 1192. 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; 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: 1192. 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; 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: 1192.

[0568] 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; and the nucleotide sequence of the sense 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: 1192. 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; and 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 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; and 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 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; and 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.

[0569] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1192.

[0570] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1191; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1192.

[0571] 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 the antisense strand set forth in SEQ ID NO: 1191; 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 sense strand set forth in SEQ ID NO: 1192. 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 the antisense strand set forth in SEQ ID NO: 1191; 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 sense strand set forth in SEQ ID NO: 1192. 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 the antisense strand set forth in SEQ ID NO: 1191; 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 sense strand set forth in SEQ ID NO: 1192. 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 the antisense strand set forth in SEQ ID NO: 1191; 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 sense strand set forth in SEQ ID NO: 1192. 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 the antisense strand set forth in SEQ ID NO: 1191; 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 sense strand set forth in SEQ ID NO: 1192.

[0572] 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 the antisense strand set forth in SEQ ID NO: 1191; 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, 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 the sense strand set forth in SEQ ID NO: 1192. 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 the antisense strand set forth in SEQ ID NO: 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 the sense strand set forth in SEQ ID NO: 1192. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 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 the sense strand set forth in SEQ ID NO: 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 the antisense strand set forth in SEQ ID NO: 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 the sense strand set forth in SEQ ID NO: 1192.

[0573] In some embodiments, the antisense strand comprises 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: 1191; and the sense strand comprises 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: 1192. In some embodiments, the antisense strand comprises 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: 1191; and the sense strand comprises 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: 1192. In some embodiments, the antisense strand comprises 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: 1191; and the sense strand 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: 1192. In some embodiments, the antisense strand comprises 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: 1191; and the sense strand comprises 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: 1192. In some embodiments, the antisense strand comprises 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: 1191; and the sense strand comprises 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: 1192. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1191; and the sense strand comprises 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 set forth in SEQ ID NO: 1192. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1191; and the sense strand comprises 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 set forth in SEQ ID NO: 1192.

[0574] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 1192.

[0575] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 1192.

[0576] 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: 1191; 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: 1192. 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: 1191; 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: 1192. 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: 1191; 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: 1192. 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: 1191; 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: 1192. 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: 1191; 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: 1192. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1191; and the sense strand 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 set forth in SEQ ID NO: 1192. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 1191; and the sense strand 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 set forth in SEQ ID NO: 1192.

[0577] 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: 1191 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: 1191; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 1192 differing by no more than 3 (e.g., 0, 1, 2, or 3) nucleotides from the sense strand set forth in SEQ ID NO: 1192.

[0578] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1191; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 1192.

[0579] 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; 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: 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: 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: 1190; 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 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; 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.

[0580] 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; and the nucleotide sequence of the sense 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: 786. 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; 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: 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; 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 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; and 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.

[0581] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786.

[0582] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in SEQ ID NO: 1190; and 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 antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 786.

[0583] 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 the antisense strand set forth in SEQ ID NO: 1190; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 sense strand set forth in SEQ ID NO: 786.

[0584] 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 the antisense strand set forth in SEQ ID NO: 1190; 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, 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 the sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 the sense strand set forth in SEQ ID NO: 786. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 1190; 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 the sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1190; 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 the sense strand set forth in SEQ ID NO: 786.

[0585] In some embodiments, the antisense strand comprises 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: 1190; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1190; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1190; and the sense strand 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: 786. In some embodiments, the antisense strand comprises 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: 1190; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1190; and the sense strand comprises 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: 786. In some embodiments, the antisense

strand comprises 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 set forth in SEQ ID NO: 1190; and the sense strand comprises 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 set forth in SEQ ID NO: 786. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1190; and the sense strand comprises 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 set forth in SEQ ID NO: 786.

[0586] In some embodiments, the nucleotide sequence of the antisense strand comprises 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 comprises 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.

[0587] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1190; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 786.

[0588] 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: 1190; 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: 786. 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: 1190; 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: 786. 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: 1190; 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: 786. 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: 1190; 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: 786. 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: 1190; 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: 786. 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)

nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1190; and the sense strand 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 set forth in SEQ ID NO: 786. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 1190; and the sense strand 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 set forth in SEQ ID NO: 786.

[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 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; 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 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; and 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.

[0593] 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; and 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 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; and 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 antisense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and 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 antisense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and 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 antisense strand is at least 97%, identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and 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 antisense strand is at least 98% identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and 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 antisense strand is at least 99% identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and 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 antisense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence set forth in SEQ ID NO: 786.

[0594] In some embodiments, the nucleotide sequence of the antisense strand comprises 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. In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand consists of the nucleotide sequence set forth in SEQ ID NO: 786.

[0595] 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 the antisense strand set forth in SEQ ID NO: 1188; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 sense strand set forth in SEQ ID NO: 786.

[0596] 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 the antisense strand set forth in SEQ ID NO: 1188; 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, 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 the sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 the sense strand set forth in SEQ ID NO: 786. In some embodiments, the antisense strand comprises from about 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 the antisense strand set forth in SEQ ID NO: 1188; 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 the sense strand set forth in SEQ ID NO: 786. 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 the antisense strand set forth in SEQ ID NO: 1188; 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 the sense strand set forth in SEQ ID NO: 786.

[0597] In some embodiments, the antisense strand comprises 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: 1188; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1188; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1188; and the sense strand 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: 786. In some embodiments, the antisense strand comprises 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: 1188; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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: 1188; and the sense strand comprises 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: 786. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1188; and the sense strand comprises 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 set forth in SEQ ID NO: 786. In some embodiments, the antisense strand comprises 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 set forth in SEQ ID NO: 1188; and the sense strand comprises 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 set forth in SEQ ID NO: 786.

[0598] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of the antisense strand 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 of the antisense strand set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand comprises 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.

[0599] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand set forth in SEQ ID NO: 786.

[0600] 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: 1188; 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: 786. 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: 1188; 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: 786. 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: 1188; 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: 786. 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: 1188; 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: 786. 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: 1188; 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: 786. 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) nucleotides from the nucleotide sequence of the antisense strand set forth in SEQ ID NO: 1188; and the sense strand 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 set forth in SEQ ID NO: 786. In some embodiments, the antisense strand 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 set forth in SEQ ID NO: 1188; and the sense strand 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 set forth in SEQ ID NO: 786.

[0601] 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: 1188 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: 1188; 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.

[0602] In some embodiments, the nucleotide sequence of the antisense strand consists of the nucleotide sequence of antisense strand set forth in SEQ ID NO: 1188; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand set forth in SEQ ID NO: 786.

[0603] 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; 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 of the sense strand of the corresponding (the same) dsRNA agent. 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; 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 sense strand of the corresponding (the same) dsRNA agent. 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; 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 the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0604] 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the corresponding (the same) dsRNA agent differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one 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 of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of the corresponding (the same) dsRNA agent differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strand of the corresponding (the same) dsRNA agent differing by no more than 1 (e.g., 0 or 1) nucleotide from the sense strand of the corresponding (the same) dsRNA agent.

[0605] 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; and 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 the sense strand of the corresponding (the same) dsRNA agent. 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; and 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 the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to

the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0606] 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0607] 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 the antisense strand of any one of dsRNA agents 1-482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 sense strand of the corresponding (the same) dsRNA agent.

[0608] 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 the antisense strand of any one of dsRNA agents 1-482; 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, 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 the sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises from about 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 the antisense strand of any one of dsRNA agents 1-482; 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 the sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 1-482; 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 the sense strand of the corresponding (the same) dsRNA agent.

[0609] 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 1-482; 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 1-482; 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 1-482; 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 antisense strand of any one of dsRNA agents 1-482; 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 1-482; 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 1-482; 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 1-482; 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.

[0610] 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 1-482 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 1-482; 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 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.

[0611] In some embodiments, the nucleotide sequence of the antisense strand comprises or consists of the nucleotide sequence the antisense strand of any one of dsRNA agents 1-482; 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.

[0612] 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; 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 of the sense strand of the corresponding (the same) dsRNA agent. 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; 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 sense strand of the corresponding (the same) dsRNA agent. 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; 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 the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand differs by no more than 1 (e.g., 0 or 1) nucleotide from the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0613] 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the corresponding (the same) dsRNA agent differing by no more than 5 (e.g., 0, 1, 2, 3, 4, or 5) nucleotides from the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one 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 of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strands of the corresponding (the same) dsRNA agent differing by no more than 2 (e.g., 0, 1, or 2) nucleotides from the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of any one of the sense strand of the corresponding (the same) dsRNA agent differing by no more than 1 (e.g., 0 or 1) nucleotide from the sense strand of the corresponding (the same) dsRNA agent.

[0614] 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; and 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 the sense strand of the corresponding (the same) dsRNA agent. 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; and 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 the sense strand of the

corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 97%, identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 98% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is at least 99% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand is 100% identical to the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0615] 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; and the nucleotide sequence of the sense strand comprises the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent. 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; and the nucleotide sequence of the sense strand consists of the nucleotide sequence of the sense strand of the corresponding (the same) dsRNA agent.

[0616] 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 sense strand of the corresponding (the same) dsRNA agent.

[0617] 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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, 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 the sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 the sense strand of the corresponding (the same) dsRNA agent. In some embodiments, the antisense strand comprises from about 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 the sense strand of the corresponding (the same) dsRNA agent. 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 the antisense strand of any one of dsRNA agents 129, 135, 169, 170, 409, 479, 480, 481, or 482; 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 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 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 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 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 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 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 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 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 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 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 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 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 at least 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.

[0623] 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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. 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; and 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises from about 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; and 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. 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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2.

[0624] 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 (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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, 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., 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 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 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, 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 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 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 1225-1285, 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 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.

[0626] 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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. 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, 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, the sense strand comprises from about 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; and 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

corresponding complementary nucleotide sequence of SEQ ID NO: 2. 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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2.

[0627] 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 (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 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 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2. In some embodiments, 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., 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 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 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 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 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 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, 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 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 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.

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-US-00003 TABLE 2 Unmodified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents. dsRNA 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 NO 1 AGAGCAAGC 4 63-83 UGCUUGCCUU 187 61-83 CCAGAGCAAG 370 CGAAGGCAA CGGCUUGCUC CCGAAGGCAA GCA UGG GCA 2 AAGCCGAAG 5 68-88 UAUCGUGCUU 188 66-88 GCAAGCCGAA 371 GCAAGCACG GCCUUCGGCU GGCAAGCACG AUA UGC AUG 3 AGCCGAAGG 6 69-89 UCAUCGUGCU 189 67-89 CAAGCCGAAG 372 CAAGCACGA UGCCUUCGGC GCAAGCACGA UGA UUG UGG 4 CCGAAGGCA 7 71-91 UGCCAUCGUG 190 69-91 AGCCGAAGGC 373

AGCACGAUG CUUGCCUUCG AAGCACGAUG GCA GCU GCG 5 CGAAGGCAA 8 72-92 UCGCCAUCGU 191 70-92 GCCGAAGGCA 374 GCACGAUGG GCUUGCCUUC AGCACGAUGG CGA GGC CGC 6 GGCAAGCAC 9 76-96 UUGAGCGCCA 192 74-96 AAGGCAAGCA 375 GAUGGCGCU UCGUGCUUGC CGAUGGCGCU CAA CUU CAC 7 GCAAGCACG 10 77-97 UGUGAGCGCC 193 75-97 AGGCAAGCAC 376 AUGGCGCUC AUCGUGCUUG GAUGGCGCUC ACA CCU ACC 8 CAAGCACGA 11 78-98 UGGUGAGCGC 194 76-98 GGCAAGCACG 377 UGGCGCUCA CAUCGUGCUU AUGGCGCUCA CCA GCC CCA 9 AAGCACGAU 12 79-99 UUGGUGAGCG 195 77-99 GCAAGCACGA 378 GGCGCUCAC CCAUCGUGCU UGGCGCUCAC CAA UGC CAG 10 ACGAUGGCG 13 83-103 UCGGCUGGUG 196 81-103 GCACGAUGGC 379 CUCACCAGC AGCGCCAUCG GCUCACCAGC CGA UGC CGG 11 CCCCGCAGC 14 143-163 UACGCUGGCA 197 141-163 CGCCCCGCAG 380 CGUGCCAGC CGGCUGCGGG CCGUGCCAGC GUA GCG GUC 12 GCAGCCGUG 15 147-167 UCGUGACGCU 198 145-167 CCGCAGCCGU 381 CCAGCGUCA GGCACGGCUG GCCAGCGUCA CGA CGG CGC 13 CAGCCGUGC 16 148-168 UGCGUGACGC 199 146-168 CGCAGCCGUG 382 CAGCGUCAC UGGCACGGCU CCAGCGUCAC GCA GCG GCU 14 AGCCGUGCC 17 149-169 UAGCGUGACG 200 147-169 GCAGCCGUGC 383 AGCGUCACG CUGGCACGGC CAGCGUCACG CUA UGC CUG 15 GCCGUGCCA 18 150-170 UCAGCGUGAC 201 148-170 CAGCCGUGCC 384 GCGUCACGC GCUGGCACGG AGCGUCACGC UGA CUG UGU 16 CGUGCCAGC 19 152-172 UUACAGCGUG 202 150-172 GCCGUGCCAG 385 GUCACGCUG ACGCUGGCAC CGUCACGCUG UAA GGC UAG 17 GCCAGCGUC 20 155-175 UUGCUACAGC 203 153-175 GUGCCAGCGU 386 ACGCUGUAG GUGACGCUGG CACGCUGUAG CAA CAC CAG 18 CCAGCGUCA 21 156-176 UCUGCUACAG 204 154-176 UGCCAGCGUC 387 CGCUGUAGC CGUGACGCUG ACGCUGUAGC AGA GCA AGC 19 CAGCGUCAC 22 157-177 UGCUGCUACA 205 155-177 GCCAGCGUCA 388 GCUGUAGCA GCGUGACGCU CGCUGUAGCA GCA GGC GCC 20 GCGUCACGC 23 159-179 UCGGCUGCUA 206 157-179 CAGCGUCACG 389 UGUAGCAGC CAGCGUGACG CUGUAGCAGC CGA CUG CGA 21 CGUCACGCU 24 160-180 UUCGGCUGCU 207 158-180 AGCGUCACGC 390 GUAGCAGCC ACAGCGUGAC UGUAGCAGCC GAA GCU GAG 22 GUCACGCUG 25 161-181 UCUCGGCUGC 208 159-181 GCGUCACGCU 391 UAGCAGCCG UACAGCGUGA GUAGCAGCCG AGA CGC AGC 23 CACGCUGUA 26 163-183 UUGCUCGGCU 209 161-183 GUCACGCUGU 392 GCAGCCGAG GCUACAGCGU AGCAGCCGAG CAA GAC CAU 24 ACGCUGUAG 27 164-184 UAUGCUCGGC 210 162-184 UCACGCUGUA 393 CAGCCGAGC UGCUACAGCG GCAGCCGAGC AUA UGA AUC 25 GCUGUAGCA 28 166-186 UUGAUGCUCG 211 164-186 ACGCUGUAGC 394 GCCGAGCAU GCUGCUACAG AGCCGAGCAU CAA CGU CAG 26 AGCCGAGCA 29 174-194 UUUUCGGGCU 212 172-194 GCAGCCGAGC 395 UCAGCCCGA GAUGCUCGGC AUCAGCCCGA AAA UGC AAG 27 CGAGCAUCA 30 177-197 UUCCUUUCGG 213 175-197 GCCGAGCAUC 396 GCCCGAAAG GCUGAUGCUC AGCCCGAAAG GAA GGC GAA 28 CAGCCCGAA 31 184-204 UUCGUGCUUC 214 182-204 AUCAGCCCGA 397 AGGAAGCAC CUUUCGGGCU AAGGAAGCAC GAA GAU GAA 29 AGCCCGAAA 32 185-205 UUUCGUGCUU 215 183-205 UCAGCCCGAA 398 GGAAGCACG CCUUUCGGGC AGGAAGCACG AAA UGA AAA 30 GCCCGAAAG 33 186-206 UUUUCGUGCU 216 184-206 CAGCCCGAAA 399 GAAGCACGA UCCUUUCGGG GGAAGCACGA AAA CUG AAG 31 CGGCGGCGU 34 234-254 UGUCGCCGGU 217 232-254 GGCGGCGGCG 400 GGACCGGCG CCACGCCGCC UGGACCGGCG ACA GCC ACG 32 GGCGGCGUG 35 235-255 UCGUCGCCGG 218 233-255 GCGGCGGCGU 401 GACCGGCGA UCCACGCCGC GGACCGGCGA CGA CGC CGG 33 GCGGCGUGG 36 236-256 UCCGUCGCCG 219 234-256 CGGCGGCGUG 402 ACCGGCGAC GUCCACGCCG GACCGGCGAC GGA CCG GGG 34 GUGGACCGG 37 241-261 UGCCACCCGU 220 239-261 GCGUGGACCG 403 CGACGGGUG CGCCGGUCCA

GCGACGGGUG GCA CGC GCA 35 UGGACCGGC 38 242-262 UUGCCACCCG 221 240-262
CGUGGACCGG 404 GACGGGUGG UCGCCGGUCC CGACGGGUGG CAA ACG CAC 36
GGACCGGCG 39 243-263 UGUGCCACCC 222 241-263 GUGGACCGGC 405 ACGGGUGGC
GUCGCCGGUC GACGGGUGGC ACA CAC ACA 37 GACCGGCGA 40 244-264
UUGUGCCACC 223 242-264 UGGACCGGCG 406 CGGGUGGCA CGUCGCCGGU
ACGGGUGGCA CAA CCA CAG 38 CGGCGACGG 41 247-267 UAGCUGUGCC 224 245-267
ACCGGCGACG 407 GUGGCACAG ACCCGUCGCC GGUGGCACAG CUA GGU CUG 39
GCGACGGGU 42 249-269 UCCAGCUGUG 225 247-269 CGGCGACGGG 408 GGCACAGCU
CCACCCGUCG UGGCACAGCU GGA CCG GGC 40 GGUGGCACA 43 255-275
UCGUAUGCCA 226 253-275 CGGGUGGCAC 409 GCUGGCAUA GCUGUGCCAC
AGCUGGCAUA CGA CCG CGC 41 GUGGCACAG 44 256-276 UGCGUAUGCC 227 254-276
GGGUGGCACA 410 CUGGCAUAC AGCUGUGCCA GCUGGCAUAC GCA CCC GCG 42
UGGCACAGC 45 257-277 UCGCGUAUGC 228 255-277 GGUGGCACAG 411 UGGCAUACG
CAGCUGUGCC CUGGCAUACG CGA ACC CGG 43 CCUCCACAG 46 280-300
UUCUACCGCC 229 278-300 UCCCUCCACA 412 GUGGCGGUA ACCUGUGGAG
GGUGGCGGUA GAA GGA GAC 44 UCCACAGGU 47 282-302 UCGUCUACCG 230 280-302
CCUCCACAGG 413 GGCGGUAGA CCACCUGUGG UGGCGGUAGA CGA AGG CGG 45
CACAGGUGG 48 284-304 UGCCGUCUAC 231 282-304 UCCACAGGUG 414 CGGUAGACG
CGCCACCUGU GCGGUAGACG GCA GGA GCG 46 GUGGCGGUA 49 289-309
UCGGCCGCCG 232 287-309 AGGUGGCGGU 415 GACGGCGGC UCUACCGCCA
AGACGGCGGC CGA CCU CGG 47 CGGCCGGGA 50 303-323 UGUUGCUCGC 233 301-323
GGCGGCCGGG 416 CGGCGAGCA CGUCCCGGCC ACGGCGAGCA ACA GCC ACA 48
GGCCGGGAC 51 304-324 UUGUUGCUCG 234 302-324 GCGGCCGGGA 417 GGCGAGCAA
CCGUCCCGGC CGGCGAGCAA CAA CGC CAG 49 CUGGCGUAC 52 449-469
UGCGCUCAGC 235 447-469 CGCUGGCGUA 418 AUGCUGAGC AUGUACGCCA
CAUGCUGAGC GCA GCG GCG 50 UGGCGUACA 53 450-470 UCGCGCUCAG 236 448-470
GCUGGCGUAC 419 UGCUGAGCG CAUGUACGCC AUGCUGAGCG CGA AGC CGC 51
GGCGUACAU 54 451-471 UGCGCGCUCA 237 449-471 CUGGCGUACA 420 GCUGAGCGC
GCAUGUACGC UGCUGAGCGC GCA CAG GCA 52 GCGUACAUG 55 452-472
UUGCGCGCUC 238 450-472 UGGCGUACAU 421 CUGAGCGCG AGCAUGUACG
GCUGAGCGCG CAA CCA CAC 53 GCUGAGCGC 56 460-480 UACUACGUGU 239 458-480
AUGCUGAGCG 422 GCACACGUA GCGCGCUCAG CGCACACGUA GUA CAU GUA 54
CUGAGCGCG 57 461-481 UUACUACGUG 240 459-481 UGCUGAGCGC 423 CACACGUAG
UGCGCGCUCA GCACACGUAG UAA GCA UAC 55 GAGCGCGCA 58 463-483
UUGUACUACG 241 461-483 CUGAGCGCGC 424 CACGUAGUA UGUGCGCGCU
ACACGUAGUA CAA CAG CAC 56 CGCGCACAC 59 466-486 UCGGUGUACU 242 464-486
AGCGCGCACA 425 GUAGUACAC ACGUGUGCGC CGUAGUACAC CGA GCU CGC 57
GCGCACACG 60 467-487 UGCGGUGUAC 243 465-487 GCGCGCACAC 426 UAGUACACC
UACGUGUGCG GUAGUACACC GCA CGC GCC 58 CGCACACGU 61 468-488
UGGCGGUGUA 244 466-488 CGCGCACACG 427 AGUACACCG CUACGUGUGC
UAGUACACCG CCA GCG CCU 59 GCACACGUA 62 469-489 UAGGCGGUGU 245 467-489
GCGCACACGU 428 GUACACCGC ACUACGUGUG AGUACACCGC CUA CGC CUU 60
CACACGUAG 63 470-490 UAAGGCGGUG 246 468-490 CGCACACGUA 429 UACACCGCC
UACUACGUGU GUACACCGCC UUA GCG UUG 61 ACACGUAGU 64 471-491
UCAAGGCGGU 247 469-491 GCACACGUAG 430 ACACCGCCU GUACUACGUG
UACACCGCCU UGA UGC UGC 62 ACGUAGUAC 65 473-493 UUGCAAGGCG 248 471-493
ACACGUAGUA 431 ACCGCCUUG GUGUACUACG CACCGCCUUG CAA UGU CAG 63
CGUAGUACA 66 474-494 UCUGCAAGGC 249 472-494 CACGUAGUAC 432 CCGCCUUGC
GGUGUACUAC ACCGCCUUGC AGA GUG AGC 64 GUAGUACAC 67 475-495
UGCUGCAAGG 250 473-495 ACGUAGUACA 433 CGCCUUGCA CGGUGUACUA

CCGCCUUGCA GCA CGU GCC 65 GCCUGCCGG 68 515-535 UGCCUUCCUG 251 513-535 AGGCCUGCCG 434 GUCAGGAAG ACCCGGCAGG GGUCAGGAAG GCA CCU GCC 66 CAGGAAGGC 69 526-546 UCGCUCUUUG 252 524-546 GUCAGGAAGG 435 CACAAAGAG UGGCCUUCCU CCACAAAGAG CGA GAC CGG 67 GGAAGGCCA 70 528-548 UGCCGCUCUU 253 526-548 CAGGAAGGCC 436 CAAAGAGCG UGUGGCCUUC ACAAAGAGCG GCA CUG GCG 68 GAAGGCCAC 71 529-549 UCGCCGCUCU 254 527-549 AGGAAGGCCA 437 AAAGAGCGG UUGUGGCCUU CAAAGAGCGG CGA CCU CGU 69 AAGGCCACA 72 530-550 UACGCCGCUC 255 528-550 GGAAGGCCAC 438 AAGAGCGGC UUUGUGGCCU AAAGAGCGGC GUA UCC GUG 70 AGGCCACAA 73 531-551 UCACGCCGCU 256 529-551 GAAGGCCACA 439 AGAGCGGCG CUUUGUGGCC AAGAGCGGCG UGA UUC UGA 71 GGCCACAAA 74 532-552 UUCACGCCGC 257 530-552 AAGGCCACAA 440 GAGCGGCGU UCUUUGUGGC AGAGCGGCGU GAA CUU GAG 72 CCACAAAGA 75 534-554 UGCUCACGCC 258 532-554 GGCCACAAAG 441 GCGGCGUGA GCUCUUUGUG AGCGGCGUGA GCA GCC GCA 73 CACAAAGAG 76 535-555 UUGCUCACGC 259 533-555 GCCACAAAGA 442 CGGCGUGAG CGCUCUUUGU GCGGCGUGAG CAA GGC CAG 74 AGCACCGCG 77 557-577 UCUGGCCGAC 260 555-577 GCAGCACCGC 443 CCGUCGGCC GGCGCGGUGC GCCGUCGGCC AGA UGC AGC 75 CGCGCCGUC 78 562-582 UUGGCGCUGG 261 560-582 ACCGCGCCGU 444 GGCCAGCGC CCGACGGCGC CGGCCAGCGC CAA GGU CAG 76 GCGCCGUCG 79 563-583 UCUGGCGCUG 262 561-583 CCGCGCCGUC 445 GCCAGCGCC GCCGACGGCG GGCCAGCGCC AGA CGG AGG 77 CAGCACAAG 80 586-606 UUGGCGGCCA 263 584-606 UGCAGCACAA 446 CGUGGCCGC CGCUUGUGCU GCGUGGCCGC CAA GCA CAG 78 AGCACAAGC 81 587-607 UCUGGCGGCC 264 585-607 GCAGCACAAG 447 GUGGCCGCC ACGCUUGUGC CGUGGCCGCC AGA UGC AGC 79 GCACAAGCG 82 588-608 UGCUGGCGGC 265 586-608 CAGCACAAGC 448 UGGCCGCCA CACGCUUGUG GUGGCCGCCA GCA CUG GCG 80 CAAGCGUGG 83 591-611 UACCGCUGGC 266 589-611 CACAAGCGUG 449 CCGCCAGCG GGCCACGCUU GCCGCCAGCG GUA GUG GUC 81 AAGCGUGGC 84 592-612 UGACCGCUGG 267 590-612 ACAAGCGUGG 450 CGCCAGCGG CGGCCACGCU CCGCCAGCGG UCA UGU UCG 82 AGCGUGGCC 85 593-613 UCGACCGCUG 268 591-613 CAAGCGUGGC 451 GCCAGCGGU GCGGCCACGC CGCCAGCGGU CGA UUG CGC 83 GCGUGGCCG 86 594-614 UGCGACCGCU 269 592-614 AAGCGUGGCC 452 CCAGCGGUC GGCGGCCACG GCCAGCGGUC GCA CUU GCC 84 GGCUGUGCC 87 697-717 UCGCGGGCCA 270 695-717 AAGGCUGUGC 453 UGUGGCCCG CAGGCACAGC CUGUGGCCCG CGA CUU CGA 85 GCCUGUGGC 88 703-723 UAGACUUCGC 271 701-723 GUGCCUGUGG 454 CCGCGAAGU GGGCCACAGG CCCGCGAAGU CUA CAC CUU 86 CUGUGGCCC 89 705-725 UGAAGACUUC 272 703-725 GCCUGUGGCC 455 GCGAAGUCU GCGGGCCACA CGCGAAGUCU UCA GGC UCC 87 GCCCGCGAA 90 710-730 UAGCUGGAAG 273 708-730 UGGCCCGCGA 456 GUCUUCCAG ACUUCGCGGG AGUCUUCCAG CUA CCA CUC 88 CCCGCGAAG 91 711-731 UGAGCUGGAA 274 709-731 GGCCCGCGAA 457 UCUUCCAGC GACUUCGCGG GUCUUCCAGC UCA GCC UCA 89 CCGCGAAGU 92 712-732 UUGAGCUGGA 275 710-732 GCCCGCGAAG 458 CUUCCAGCU AGACUUCGCG UCUUCCAGCU CAA GGC CAG 90 UCCAGCUCA 93 723-743 UCGAGACACU 276 721-743 CUUCCAGCUC 459 GCAGUGUCU GCUGAGCUGG AGCAGUGUCU CGA AAG CGU 91 CAGCUCAGC 94 725-745 UAACGAGACA 277 723-745 UCCAGCUCAG 460 AGUGUCUCG CUGCUGAGCU CAGUGUCUCG UUA GGA UUC 92 GCGCACCAG 95 944-964 UGACUUUAGC 278 942-964 CAGCGCACCA 461 AAGCUAAAG UUCUGGUGCG GAAGCUAAAG UCA CUG UCU 93 CAGAAGCUA 96 950-970 UCAUCAAGAC 279 948-970 ACCAGAAGCU 462 AAGUCUUGA UUUAGCUUCU AAAGUCUUGA UGA GGU UGC 94 AGAAGCUAA 97 951-971 UGCAUCAAGA 280 949-971 CCAGAAGCUA 463 AGUCUUGAU CUUUAGCUUC

AAGUCUUGAU GCA UGG GCC 95 GAAGCUAAA 98 952-972 UGGCAUCAAG 281 950-972 CAGAAGCUAA 464 GUCUUGAUG ACUUUAGCUU AGUCUUGAUG CCA CUG CCA 96 AAGCUAAAG 99 953-973 UUGGCAUCAA 282 951-973 AGAAGCUAAA 465 UCUUGAUGC GACUUUAGCU GUCUUGAUGC CAA UCU CAU 97 GCUAAAGUC 100 955-975 UGAUGGCAUC 283 953-975 AAGCUAAAGU 466 UUGAUGCCA AAGACUUUAG CUUGAUGCCA UCA CUU UCA 98 GAUGCCAUC 101 966-986 UGGAUGUCCU 284 964-986 UUGAUGCCAU 467 AAAGGACAU UUGAUGGCAU CAAAGGACAU CCA CAA CCC 99 AUGCCAUCA 102 967-987 UGGGAUGUCC 285 965-987 UGAUGCCAUC 468 AAGGACAUC UUUGAUGGCA AAAGGACAUC CCA UCA CCU 100 GCCAUCAAA 103 969-989 UCAGGGAUGU 286 967-989 AUGCCAUCAA 469 GGACAUCCC CCUUUGAUGG AGGACAUCCC UGA CAU UGC 101 CAUCUCUGU 104 998-1018 UUAGUGGACG 287 996-1018 CACAUCUCUG 470 CACGUCCAC UGACAGAGAU UCACGUCCAC UAA GUG UAA 102 AUCUCUGUC 105 999-1019 UUUAGUGGAC 288 997-1019 ACAUCUCUGU 471 ACGUCCACU GUGACAGAGA CACGUCCACU AAA UGU AAU 103 UCUCUGUCA 106 1000-1020 UAUUAGUGGA 289 998-1020 CAUCUCUGUC 472 CGUCCACUA CGUGACAGAG ACGUCCACUA AUA AUG AUC 104 CUCUGUCAC 107 1001-1021 UGAUUAGUGG 290 999-1021 AUCUCUGUCA 473 GUCCACUAA ACGUGACAGA CGUCCACUAA UCA GAU UCG 105 UCUGUCACG 108 1002-1022 UCGAUUAGUG 291 1000-1022 UCUCUGUCAC 474 UCCACUAAU GACGUGACAG GUCCACUAAU CGA AGA CGG 106 CUGUCACGU 109 1003-1023 UCCGAUUAGU 292 1001-1023 CUCUGUCACG 475 CCACUAAUC GGACGUGACA UCCACUAAUC GGA GAG GGC 107 UGUCACGUC 110 1004-1024 UGCCGAUUAG 293 1002-1024 UCUGUCACGU 476 CACUAAUCG UGGACGUGAC CCACUAAUCG GCA AGA GCA 108 GUCACGUCC 111 1005-1025 UUGCCGAUUA 294 1003-1025 CUGUCACGUC 477 ACUAAUCGG 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 UCCUUUUGCC 298 1008-1030 ACGUCCACUA 481 UCGGCAAAA GAUUAGUGGA AUCGGCAAAA GGA CGU GGA 113 UCCACUAAU 116 1011-1031 UUCCUUUUGC 299 1009-1031 CGUCCACUAA 482 CGGCAAAAG CGAUUAGUGG UCGGCAAAAG GAA ACG GAG 114 CCACUAAUC 117 1012-1032 UCUCCUUUUG 300 1010-1032 GUCCACUAAU 483 GGCAAAAGG CCGAUUAGUG CGGCAAAAGG AGA GAC AGA 115 CACUAAUCG 118 1013-1033 UUCUCCUUUU 301 1011-1033 UCCACUAAUC 484 GCAAAAGGA GCCGAUUAGU GGCAAAAGGA GAA GGA GAA 116 ACUAAUCGG 119 1014-1034 UUUCUCCUUU 302 1012-1034 CCACUAAUCG 485 CAAAAGGAG UGCCGAUUAG GCAAAAGGAG AAA UGG AAA 117 GAGAAGAUG 120 1040-1060 UCACACUUAG 303 1038-1060 GAGAGAAGAU 486 ACCUAAGUG GUCAUCUUCU GACCUAAGUG UGA CUC UGA 118 UCCUCCGAC 121 1110-1130 UCUUCCUCCU 304 1108-1130 CCUCCUCCGA 487 CAAGGAGGA UGGUCGGAGG CCAAGGAGGA AGA AGG AGG 119 CCAGGGAAG 122 1176-1196 UCCGGAGAGU 305 1174-1196 UUCCAGGGAA 488 GAACUCUCC UCCUUCCCUG GGAACUCUCC GGA GAA GGU 120 CAGGGAAGG 123 1177-1197 UACCGGAGAG 306 1175-1197 UCCAGGGAAG 489 AACUCUCCG UUCCUUCCCU GAACUCUCCG GUA GGA GUC 121 AGGAACUCU 124 1183-1203 UUGGUGGACC 307 1181-1203 GAAGGAACUC 490 CCGGUCCAC GGAGAGUUCC UCCGGUCCAC CAA UUC CAU 122 GGAACUCUC 125 1184-1204 UAUGGUGGAC 308 1182-1204 AAGGAACUCU 491 CGGUCCACC CGGAGAGUUC CCGGUCCACC AUA CUU AUG 123 ACUCUCCGG 126 1187-1207 UUCCAUGGUG 309 1185-1207 GAACUCUCCG 492 UCCACCAUG

GACCGGAGAG GUCCACCAUG GAA UUC GAG 124 CUCCGGUCC 127 1190-1210 UUACUCCAUG 310 1188-1210 CUCUCCGGUC 493 ACCAUGGAG GUGGACCGGA CACCAUGGAG UAA GAG UAC 125 UGAACCCCA 128 1221-1241 UGAGUAAGUC 311 1219-1241 UCUGAACCCC 494 GUGACUUAC ACUGGGGUUC AGUGACUUAC UCA AGA UCA 126 GUGACUUAC 129 1230-1250 UUACUGACCU 312 1228-1250 CAGUGACUUA 495 UCAGGUCAG GAGUAAGUCA CUCAGGUCAG UAA CUG UAU 127 GACUUACUC 130 1232-1252 UGAUACUGAC 313 1230-1252 GUGACUUACU 496 AGGUCAGUA CUGAGUAAGU CAGGUCAGUA UCA CAC UCU 128 CUUACUCAG 131 1234-1254 UUAGAUACUG 314 1232-1254 GACUUACUCA 497 GUCAGUAUC ACCUGAGUAA GGUCAGUAUC UAA GUC UAA 129 CAGUAUCUA 132 1245-1265 UCGAGCUUAU 315 1243-1265 GUCAGUAUCU 498 AUAUAAGCU AUUAGAUACU AAUAUAAGCU CGA GAC CGG 130 GUAUCUAAU 133 1247-1267 UUCCGAGCUU 316 1245-1267 CAGUAUCUAA 499 AUAAGCUCG AUAUUAGAUA UAUAAGCUCG GAA CUG GAG 131 UAUCUAAUA 134 1248-1268 UCUCCGAGCU 317 1246-1268 AGUAUCUAAU 500 UAAGCUCGG UAUAUUAGAU AUAAGCUCGG AGA ACU AGU 132 AUCUAAUAU 135 1249-1269 UACUCCGAGC 318 1247-1269 GUAUCUAAUA 501 AAGCUCGGA UUAUAUUAGA UAAGCUCGGA GUA UAC GUU 133 UCUAAUAUA 136 1250-1270 UAACUCCGAG 319 1248-1270 UAUCUAAUAU 502 AGCUCGGAG CUUAUAUUAG AAGCUCGGAG UUA AUA UUU 134 CUAAUAUAA 137 1251-1271 UAAACUCCGA 320 1249-1271 AUCUAAUAUA 503 GCUCGGAGU GCUUAUAUUA AGCUCGGAGU UUA GAU UUG 135 UAAUAUAAG 138 1252-1272 UCAAACUCCG 321 1250-1272 UCUAAUAUAA 504 CUCGGAGUU AGCUUAUAUU GCUCGGAGUU UGA AGA UGG 136 AUAUAAGCU 139 1254-1274 UUCCAAACUC 322 1252-1274 UAAUAUAAGC 505 CGGAGUUUG CGAGCUUAUA UCGGAGUUUG GAA UUA GAC 137 UAUAAGCUC 140 1255-1275 UGUCCAAACU 323 1253-1275 AAUAUAAGCU 506 GGAGUUUGG CCGAGCUUAU CGGAGUUUGG ACA AUU ACG 138 AUAAGCUCG 141 1256-1276 UCGUCCAAAC 324 1254-1276 AUAUAAGCUC 507 GAGUUUGGA UCCGAGCUUA GGAGUUUGGA CGA UAU CGG 139 GCUCGGAGU 142 1260-1280 UCCUCCGUCC 325 1258-1280 AAGCUCGGAG 508 UUGGACGGA AAACUCCGAG UUUGGACGGA GGA CUU GGG 140 GGAGUUUGG 143 1264-1284 UAGACCCUCC 326 1262-1284 UCGGAGUUUG 509 ACGGAGGGU GUCCAAACUC GACGGAGGGU CUA CGA CUG 141 CACCCCAGC 144 1299-1319 UACGGAAAGG 327 1297-1319 ACCACCCCAG 510 GACCUUUCC UCGCUGGGGU CGACCUUUCC GUA GGU GUG 142 GUCUGUGAU 145 1319-1339 UGUCCGCUUG 328 1317-1339 GUGUCUGUGA 511 CACAAGCGG UGAUCACAGA UCACAAGCGG ACA CAC ACC 143 UCUGUGAUC 146 1320-1340 UGGUCCGCUU 329 1318-1340 UGUCUGUGAU 512 ACAAGCGGA GUGAUCACAG CACAAGCGGA CCA ACA CCA 144 CUGUGAUCA 147 1321-1341 UUGGUCCGCU 330 1319-1341 GUCUGUGAUC 513 CAAGCGGAC UGUGAUCACA ACAAGCGGAC CAA GAC CAU 145 UGUGAUCAC 148 1322-1342 UAUGGUCCGC 331 1320-1342 UCUGUGAUCA 514 AAGCGGACC UUGUGAUCAC CAAGCGGACC AUA AGA AUC 146 GUGAUCACA 149 1323-1343 UGAUGGUCCG 332 1321-1343 CUGUGAUCAC 515 AGCGGACCA CUUGUGAUCA AAGCGGACCA UCA CAG UCC 147 AGGAGCUGC 150 1371-1391 UUGCUUUGGC 333 1369-1391 CCAGGAGCUG 516 UAGCCAAAG UAGCAGCUCC CUAGCCAAAG CAA UGG CAU 148 AGCUGCUAG 151 1374-1394 UCAAUGCUUU 334 1372-1394 GGAGCUGCUA 517 CCAAAGCAU GGCUAGCAGC GCCAAAGCAU UGA UCC UGG 149 CUGCUAGCC 152 1376-1396 UUCCAAUGCU 335 1374-1396 AGCUGCUAGC 518 AAAGCAUUG UUGGCUAGCA CAAAGCAUUG GAA GCU GAG 150 UGCUAGCCA 153 1377-1397 UCUCCAAUGC 336 1375-1397 GCUGCUAGCC 519 AAGCAUUGG UUUGGCUAGC AAAGCAUUGG AGA AGC AGA 151 CUAGCCAAA 154 1379-1399 UGUCUCCAAU 337 1377-1399 UGCUAGCCAA 520 GCAUUGGAG GCUUUGGCUA AGCAUUGGAG ACA GCA ACC 152 UAGCCAAAG 155 1380-1400

UGGUCUCCAA 338 1378-1400 GCUAGCCAAA 521 CAUUGGAGA UGCUUUGGCU GCAUUGGAGA CCA AGC CCC 153 GGAGCUCCU 156 1729-1749 UAGGUCCAAC 339 1727-1749 AGGGAGCUCC 522 UCGUUGGAC GAAGGAGCUC UUCGUUGGAC CUA CCU CUC 154 GAGCUCCUU 157 1730-1750 UGAGGUCCAA 340 1728-1750 GGGAGCUCCU 523 CGUUGGACC CGAAGGAGCU UCGUUGGACC UCA CCC UCC 155 AGCUCCUUC 158 1731-1751 UGGAGGUCCA 341 1729-1751 GGAGCUCCUU 524 GUUGGACCU ACGAAGGAGC CGUUGGACCU CCA UCC CCA 156 AGGCCUGGG 159 1762-1782 UGCAACAUAU 342 1760-1782 CAAGGCCUGG 525 CCAUAUGUU GGCCCAGGCC GCCAUAUGUU GCA UUG GCU 157 GCCUGGGCC 160 1764-1784 UCAGCAACAU 343 1762-1784 AGGCCUGGGC 526 AUAUGUUGC AUGGCCCAGG CAUAUGUUGC UGA CCU UGG 158 CUGGGCCAU 161 1766-1786 UCCCAGCAAC 344 1764-1786 GCCUGGGCCA 527 AUGUUGCUG AUAUGGCCCA UAUGUUGCUG GGA GGC GGA 159 UGGGCCAUA 162 1767-1787 UUCCCAGCAA 345 1765-1787 CCUGGGCCAU 528 UGUUGCUGG CAUAUGGCCC AUGUUGCUGG GAA AGG GAA 160 AUGUUGCUG 163 1775-1795 UGAGGAAAUU 346 1773-1795 AUAUGUUGCU 529 GGAAUUUCC CCCAGCAACA GGGAAUUUCC UCA UAU UCC 161 CUGGGAAUU 164 1781-1801 UAGGGUGGAG 347 1779-1801 UGCUGGGAAU 530 UCCUCCACC GAAAUUCCCA UUCCUCCACC CUA GCA CUU 162 UUCCUCCAC 165 1789-1809 UCAUGACGAA 348 1787-1809 AUUUCCUCCA 531 CCUUCGUCA GGGUGGAGGA CCCUUCGUCA UGA AAU UGC 163 AAGGGCCGC 166 1838-1858 UUAGGAAUGG 349 1836-1858 AGAAGGGCCG 532 CUCCAUUCC AGGCGGCCCU CCUCCAUUCC UAA UCU UAC 164 GGCCGCCUC 167 1841-1861 UUAGUAGGAA 350 1839-1861 AGGGCCGCCU 533 CAUUCCUAC UGGAGGCGGC CCAUUCCUAC UAA CCU UAA 165 ACUGCAAAG 168 1904-1924 UGCUGUCAUA 351 1902-1924 CCACUGCAAA 534 ACUAUGACA GUCUUUGCAG GACUAUGACA GCA UGG GCA 166 CAGCAUCAA 169 1920-1940 UGGUCCUGAA 352 1918-1940 GACAGCAUCA 535 AUUUCAGGA AUUUGAUGCU AAUUUCAGGA CCA GUC CCU 167 UCAGGACCU 170 1932-1952 UGUACUGUCU 353 1930-1952 UUUCAGGACC 536 GCAGACAGU GCAGGUCCUG UGCAGACAGU ACA AAA ACA 168 GCAGACAGU 171 1941-1961 UAUCUAGCCU 354 1939-1961 CUGCAGACAG 537 ACAGGCUAG GUACUGUCUG UACAGGCUAG AUA CAG AUA 169 CAGACAGUA 172 1942-1962 UUAUCUAGCC 355 1940-1962 UGCAGACAGU 538 CAGGCUAGA UGUACUGUCU ACAGGCUAGA UAA GCA UAA 170 AGACAGUAC 173 1943-1963 UUUAUCUAGC 356 1941-1963 GCAGACAGUA 539 AGGCUAGAU CUGUACUGUC CAGGCUAGAU AAA UGC AAC 171 UCCCACUUG 174 2087-2107 UGCCUUUCAG 357 2085-2107 CCUCCCACUU 540 CCCUGAAAG GGCAAGUGGG GCCCUGAAAG GCA AGG GCC 172 CUGCUGCUA 175 2148-2168 UGGGAUUAGA 358 2146-2168 GACUGCUGCU 541 CAUCUAAUC UGUAGCAGCA ACAUCUAAUC CCA GUC CCC 173 UGCUGCUAC 176 2149-2169 UGGGGAUUAG 359 2147-2169 ACUGCUGCUA 542 AUCUAAUCC AUGUAGCAGC CAUCUAAUCC CCA AGU CCU 174 GCUGCUACA 177 2150-2170 UAGGGGAUUA 360 2148-2170 CUGCUGCUAC 543 UCUAAUCCC GAUGUAGCAG AUCUAAUCCC CUA CAG CUA 175 ACAUCUAAU 178 2156-2176 UAUUGGUAGG 361 2154-2176 CUACAUCUAA 544 CCCCUACCA GGAUUAGAUG UCCCCUACCA AUA UAG AUG 176 AUCUAAUCC 179 2158-2178 UGCAUUGGUA 362 2156-2178 ACAUCUAAUC 545 CCUACCAAU GGGGAUUAGA CCCUACCAAU GCA UGU GCC 177 CCCCUACCA 180 2165-2185 UACAGGAGGC 363 2163-2185 AUCCCCUACC 546 AUGCCUCCU AUUGGUAGGG AAUGCCUCCU GUA GAU GUC 178 CCCUACCAA 181 2166-2186 UGACAGGAGG 364 2164-2186 UCCCCUACCA 547 UGCCUCCUG CAUUGGUAGG AUGCCUCCUG UCA GGA UCC 179 ACCAAUGCC 182 2170-2190 UUAGGGACAG 365 2168-2190 CUACCAAUGC 548 UCCUGUCCC GAGGCAUUGG CUCCUGUCCC UAA UAG UAA 180 CCAAUGCCU 183 2171-2191 UUUAGGGACA 366 2169-2191 UACCAAUGCC 549 CCUGUCCCU GGAGGCAUUG

UCCUGUCCCU AAA GUA AAA 181 AUGCCUCCU 184 2174-2194 UAGUUUAGGG 367 2172-2194 CAAUGCCUCC 550 GUCCCUAAA ACAGGAGGCA UGUCCCUAAA CUA UUG CUC 182 UGCCUCCUG 185 2175-2195 UGAGUUUAGG 368 2173-2195 AAUGCCUCCU 551 UCCCUAAAC GACAGGAGGC GUCCCUAAAC UCA AUU UCC 183 UACUGAUGA 186 2202-2222 UAGAGAGGGC 369 2200-2222 CAUACUGAUG 552 CAGCCCUCU UGUCAUCAGU ACAGCCCUCU CUA AUG CUG 184 AGCUCAGCA 553 726-746 UGAACGAGAC 602 724-746 CCAGCUCAGC 1132 GUGUCUCGU ACUGCUGAGC AGUGUCUCGU UCA UGG UCC 185 GCUCAGCAG 554 727-747 UGGAACGAGA 603 725-747 CAGCUCAGCA 1133 UGUCUCGUU CACUGCUGAG GUGUCUCGUU CCA CUG CCC 186 GGACGGUAG 555 752-772 UAUGUCGGUC 604 750-772 GGGGACGGUA 1134 CAGACCGAC UGCUACCGUC GCAGACCGAC AUA CCC AUC 187 ACGGUAGCA 556 754-774 UGGAUGUCGG 605 752-774 GGACGGUAGC 1135 GACCGACAU UCUGCUACCG AGACCGACAU CCA UCC CCU 188 CGGUAGCAG 557 755-775 UAGGAUGUCG 606 753-775 GACGGUAGCA 1136 ACCGACAUC GUCUGCUACC GACCGACAUC CUA GUC CUU 189 AGCAGACCG 558 759-779 UCAGAAGGAU 607 757-779 GUAGCAGACC 1137 ACAUCCUUC GUCGGUCUGC GACAUCCUUC UGA UAC UGG 190 GCAGACCGA 559 760-780 UCCAGAAGGA 608 758-780 UAGCAGACCG 1138 CAUCCUUCU UGUCGGUCUG ACAUCCUUCU GGA CUA GGG 191 UCCAUGCAA 560 894-914 UGUGAUGGAC 609 892-914 CUUCCAUGCA 1139 CUGUCCAUC AGUUGCAUGG ACUGUCCAUC ACA AAG ACG 192 CCAUGCAAC 561 895-915 UCGUGAUGGA 610 893-915 UUCCAUGCAA 1140 UGUCCAUCA CAGUUGCAUG CUGUCCAUCA CGA GAA CGG 193 CAUGCAACU 562 896-916 UCCGUGAUGG 611 894-916 UCCAUGCAAC 1141 GUCCAUCAC ACAGUUGCAU UGUCCAUCAC GGA GGA GGC 194 AACUGUCCA 563 901-921 UUGCAGCCGU 612 989-921 GCAACUGUCC 1142 UCACGGCUG GAUGGACAGU AUCACGGCUG CAA UGC CAA 195 ACUGUCCAU 564 902-922 UUUGCAGCCG 613 900-922 CAACUGUCCA 1143 CACGGCUGC UGAUGGACAG UCACGGCUGC AAA UUG AAC 196 GUCCAUCAC 565 905-925 UCAGUUGCAG 614 903-925 CUGUCCAUCA 1144 GGCUGCAAC CCGUGAUGGA CGGCUGCAAC UGA CAG UGA 197 AUCACGGCU 566 909-929 UAUUUCAGUU 615 907-929 CCAUCACGGC 1145 GCAACUGAA GCAGCCGUGA UGCAACUGAA AUA UGG AUC 198 UGGGACACA 567 935-955 UUUCUGGUGC 616 933-955 GCUGGGACAC 1146 GCGCACCAG GCUGUGUCCC AGCGCACCAG AAA AGC AAG 199 GACACAGCG 568 938-958 UAGCUUCUGG 617 936-958 GGGACACAGC 1147 CACCAGAAG UGCGCUGUGU GCACCAGAAG CUA CCC CUA 200 ACAGCGCAC 569 941-961 UUUUAGCUUC 618 939-961 ACACAGCGCA 1148 CAGAAGCUA UGGUGCGCUG CCAGAAGCUA AAA UGU AAG 201 GCCACAUUC 570 1659-1677 UGAGCCCGUA 619 1659-1679 AAGCCACAUU 1149 UACGGGCUC GAAUGUGGCU CUACGGGCUC A U U 202 GAAAGUACU 571 1715-1733 UAGCUCCCUG 620 1715-1735 AAGAAAGUAC 1150 CAGGGAGCU AGUACUUUCU UCAGGGAGCU A U C 203 GUCUAUACC 572 2033-2051 UUCAGGUAAG 621 2033-2053 AAGUCUAUAC 1151 CUUACCUGA GGUAUAGACU CCUUACCUGA A U A 204 GCUGCUAGC 573 1373-1391 UAAUGCUUUG 622 1373-1393 GAGCUGCUAG 1152 CAAAGCAUU GCUAGCAGCU CCAAAGCAUU A C G 205 GGAGUGGAG 574 1534-1552 UAUGACAGCA 623 1534-1554 AAGGAGUGGA 1153 UGCUGUCAU CUCCACUCCU GUGCUGUCAU A U A 206 GGCCAAGAU 575 2102-2120 UGACAUCUUG 624 2102-2122 AAGGCCAAGA 1154 CAAGAUGUC AUCUUGGCCU UCAAGAUGUC A U C 207 CUUGAGAUC 576 2228-2246 UAUGAAGACA 625 2228-2248 ACCUUGAGAU 1155 UGUCUUCAU GAUCUCAAGU CUGUCUUCAU A U ACC 208 CUUGAGAUC 576 2228-2246 UAUGAAGACA 626 2228-2248 UUACCUUGAG 1156 UGUCUUCAU GAUCUCAAGG AUCUGUCUUC A U AUA 209 CCUCAAACU 577 2254-2272 UGUUUUUGUU 627 2254-2274 CCCCUCAAAC 1157 AACAAAAAC AGUUUGAGGG UAACAAAAAC A G A 210 CUCAAACUA 578 2255-2273 UUGUUUUUGU 628 2255-2275 CCCUCAAACU 1158

ACAAAAACA UAGUUUGAGG AACAAAAACA A G U 211 CAAACUAAC 579 2257-2275 UAAUGUUUUU 629 2257-2277 CUCAAACUAA 1159 AAAAACAUU GUUAGUUUGA CAAAAACAUU A G U 212 CUAACAAAA 580 2261-2279 UUGGAAAUGU 630 2261-2281 AACUAACAAA 1160 ACAUUUCCA UUUUGUUAGU AACAUUUCCA A U A 213 CAAAAACAU 581 2265-2283 UUUAUUGGAA 631 2265-2285 AACAAAAACA 1161 UUCCAAUAA AUGUUUUUGU UUUCCAAUAA A U A 214 CCAAUAAAA 582 2276-2294 UAUUUGAUAU 632 2276-2296 UUCCAAUAAA 1162 AUAUCAAAU UUUUAUUGGA AAUAUCAAAU A A A 215 CAAUAAAAA 583 2277-2295 UUAUUUGAUA 633 2277-2297 UCCAAUAAAA 1163 UAUCAAAUA UUUUUAUUGG AUAUCAAAUA A A U 216 CCAAAGCAU 584 1381-1399 UGGGUCUCCA 634 1381-1401 AGCCAAAGCA 1164 UGGAGACCC AUGCUUUGGU UUGGAGACCC A U U 217 CAGGUCAGU 585 1238-1256 UAUAUUAGAU 635 1238-1258 CUCAGGUCAG 1165 AUCUAAUAU ACUGACCUGU UAUCUAAUAU A U A 218 AUGUCAAAG 586 1651-1669 UAGAAUGUGG 636 1651-1671 GAAUGUCAAA 1166 CCACAUUCU CUUUGACAUU GCCACAUUCU A C A 219 GCUCUACUC 587 1673-1691 UCAACUCAUA 637 1673-1693 GGGCUCUACU 1167 UAUGAGUUG GAGUAGAGCU CUAUGAGUUG A U U 220 CUAUGAGUU 588 1681-1699 UGAAAGUCAC 638 1681-1701 CUCUAUGAGU 1168 GUGACUUUC AACUCAUAGA UGUGACUUUC A G A 221 UAUGAGUUG 589 1682-1700 UUGAAAGUCA 639 1682-1702 UCUAUGAGUU 1169 UGACUUUCA CAACUCAUAG GUGACUUUCA A A A 222 GGCCCAAAG 590 1707-1725 UGAGUACUUU 640 1707-1727 UUGGCCCAAA 1170 AAAGUACUC CUUUGGGCCU GAAAGUACUC A U A 223 GCCAUAUGU 591 1768-1786 UUUCCCAGCA 641 1768-1788 GGGCCAUAUG 1171 UGCUGGGAA ACAUAUGGCU UUGCUGGGAA A U U 224 CCCACUGCA 592 1899-1979 UCAUAGUCUU 642 1899-1981 GACCCACUGC 1172 AAGACUAUG UGCAGUGGGU AAAGACUAUG A U A 225 GACUAUGAC 593 1910-1928 UUUUGAUGCU 643 1910-1930 AAGACUAUGA 1173 AGCAUCAAA GUCAUAGUCU CAGCAUCAAA A U U 226 CUAUGACAG 594 1912-1930 UAAUUUGAUG 644 1912-1932 GACUAUGACA 1174 CAUCAAAUU CUGUCAUAGU GCAUCAAAUU A C U 227 CUGAAGAAU 595 2047-2065 UAAGAACAGC 645 2047-2067 ACCUGAAGAA 1175 GCUGUUCUU AUUCUUCAGU UGCUGUUCUU A U U 228 CUGAAGAAU 595 2047-2065 UAAGAACAGC 646 2047-2067 ACCUGAAGAA 1176 GCUGUUCUU AUUCUUCAGG UGCUGUUCUU A U U 229 CCUGAAAGG 596 2095-2113 UUGAUCUUGG 647 2095-2115 GCCCUGAAAG 1177 CCAAGAUCA CCUUUCAGGU GCCAAGAUCA A U A 230 CCUGAAAGG 596 2095-2113 UUGAUCUUGG 648 2095-2115 GCCCUGAAAG 1178 CCAAGAUCA CCUUUCAGGG GCCAAGAUCA A C A 231 GACUGCUGC 597 2144-2162 UUUAGAUGUA 649 2144-2164 CUGACUGCUG 1179 UACAUCUAA GCAGCAGUCU CUACAUCUAA A U U 232 AGGUCAGUA 598 1239-1257 UUAUAUUAGA 650 1239-1259 UCAGGUCAGU 1180 UCUAAUAUA UACUGACCUU AUCUAAUAUA A U A 233 GGAAUUUCC 599 1782-1800 UAAGGGUGGA 651 1782-1802 UGGGAAUUUC 1181 UCCACCCUU GGAAAUUCCU CUCCACCCUU A U C 234 GAUUCACCU 600 1597-1615 UACACGUCAA 652 1597-1617 CCGAUUCACC 1182 UUGACGUGU AGGUGAAUCU UUUGACGUGU A U A 235 GAGGAUGAC 601 1479-1497 UCAGGCACGU 653 1479-1499 UGGAGGAUGA 1183 ACGUGCCUG GUCAUCCUCU CACGUGCCUG A U A 236 CUCUAUGAG 602 1679-1697 UAAGUCACAA 654 1679-1699 UACUCUAUGA 1184 UUGUGACUU CUCAUAGAGU GUUGUGACUU A A U 237 AGAGGAGGA 603 1430-1448 UGCAGUUCCA 655 1430-1450 CUAGAGGAGG 1185 UGGAACUGC UCCUCCUCUA AUGGAACUGC A G A 238 GAUUCACCU 600 1597-1615 UACACGUCAA 656 1597-1617 CCGAUUCACC 1186 UUGACGUGU AGGUGAAUCG UUUGACGUGU A G A 239 UCAGGUCAG 601 1237-1255 UUAUUAGAUA 657 1237-1257 ACUCAGGUCA 1187 UAUCUAAUA CUGACCUGAU GUAUCUAAUA A U 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-US-00004 TABLE 3 Modified Sense and Antisense Strand Sequences of CIDEB dsRNA Agents. dsRNA 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 NO 240 asgsagcaA 658 63-83 (vinu)sGfs 893 61-83 CCAGAGCAAG 370 fgCfCfGfa cuuGfcCfUf CCGAAGGCAA aggcaagca ucggCfuUfg GCA cucusgsg 241 asasgccgA 659 68-88 (vinu)sAfs 894 66-88 GCAAGCCGAA 371 faGfGfCfa ucgUfgCfUf GGCAAGCACG agcacgaua ugccUfuCfg AUG gcuusgsc 242 asgsccgaA 660 69-89 (vinu)sCfs 895 67-89 CAAGCCGAAG 372 fgGfCfAfa aucGfuGfCf GCAAGCACGA gcacgauga uugcCfuUfc UGG ggcususg 243 cscsgaagG 661 71-91 (vinu)sGfs 896 69-91 AGCCGAAGGC 373 fcAfAfGfc ccaUfcGfUf AAGCACGAUG acgauggca gcuuGfcCfu GCG ucggscsu 244 csgsaaggC 662 72-92 (vinu)sCfs 897 70-92 GCCGAAGGCA 374 faAfGfCfa gccAfuCfGf AGCACGAUGG cgauggcga ugcuUfgCfc CGC uucgsgsc 245 gsgscaagC 663 76-96 (vinu)sUfs 898 74-96 AAGGCAAGCA 375 faCfGfAfu gagCfgCfCf CGAUGGCGCU ggcgcucaa aucgUfgCfu CAC ugccsusu 246 gscsaagcA 664 77-97 (vinu)sGfs 899 75-97 AGGCAAGCAC 376 fcGfAfUfg ugaGfcGfCf GAUGGCGCUC gcgcucaca caucGfuGfc ACC uugcscsu 247 csasagcaC 665 78-98 (vinu)sGfs 900 76-98 GGCAAGCACG 377 fgAfUfGfg gugAfgCfGf AUGGCGCUCA cgcucacca ccauCfgUfg CCA cuugscsc 248 asasgcacG 666 79-99 (vinu)sUfs 901 77-99 GCAAGCACGA 378 faUfGfGfc gguGfaGfCf UGGCGCUCAC gcucaccaa gccaUfcGfu CAG gcuusgsc 249 ascsgaugG 667 83-103 (vinu)sCfs 902 81-103 GCACGAUGGC 379 fcGfCfUfc ggcUfgGfUf GCUCACCAGC accagccga gagcGfcCfa CGG ucgusgsc 250 cscsccgcA 668 143-163 (vinu)sAfs 903 141-163 CGCCCCGCAG 380 fgCfCfGfu cgcUfgGfCf CCGUGCCAGC gccagcgua acggCfuGfc GUC ggggscsg 251 gscsagccG 669 147-167 (vinu)sCfs 904 145-167 CCGCAGCCGU 381 fuGfCfCfa gugAfcGfCf GCCAGCGUCA gcgucacga uggcAfcGfg CGC cugcsgsg 252 csasgccgU 670 148-168 (vinu)sGfs 905 146-168 CGCAGCCGUG 382 fgCfCfAfg cguGfaCfGf CCAGCGUCAC cgucacgca cuggCfaCfg GCU gcugscsg 253 asgsccguG 671 149-169 (vinu)sAfs 906 147-169 GCAGCCGUGC 383 fcCfAfGfc gcgUfgAfCf CAGCGUCACG gucacgcua gcugGfcAfc CUG ggcusgsc 254 gscscgugC 672 150-170 (vinu)sCfs 907 148-170 CAGCCGUGCC 384 fcAfGfCfg agcGfuGfAf AGCGUCACGC ucacgcuga cgcuGfgCfa UGU cggcsusg 255 csgsugccA 673 152-172 (vinu)sUfs 908 150-172 GCCGUGCCAG 385 fgCfGfUfc acaGfcGfUf CGUCACGCUG acgcuguaa gacgCfuGfg UAG cacgsgsc 256 gscscagcG 674 155-175 (vinu)sUfs 909 153-175 GUGCCAGCGU 386 fuCfAfCfg gcuAfcAfGf CACGCUGUAG cuguagcaa cgugAfcGfc CAG uggcsasc 257 cscsagcgU 675 156-176 (vinu)sCfs 910 154-176 UGCCAGCGUC 387 fcAfCfGfc ugcUfaCfAf ACGCUGUAGC uguagcaga gcguGfaCfg AGC cuggscsa 258 csasgcguC 676 157-177 (vinu)sGfs 911 155-177 GCCAGCGUCA 388 faCfGfCfu cugCfuAfCf CGCUGUAGCA guagcagca agcgUfgAfc GCC gcugsgsc 259 gscsgucaC 677 159-179 (vinu)sCfs 912 157-179 CAGCGUCACG 389 fgCfUfGfu ggcUfgCfUf CUGUAGCAGC agcagccga acagCfgUfg CGA acgcsusg 260 csgsucacG 678 160-180 (vinu)sUfs 913 158-180 AGCGUCACGC 390 fcUfGfUfa cggCfuGfCf UGUAGCAGCC gcagccgaa uacaGfcGfu GAG gacgscsu 261 gsuscacgC 679 161-181 (vinu)sCfs 914 159-181 GCGUCACGCU 391 fuGfUfAfg ucgGfcUfGf GUAGCAGCCG cagccgaga cuacAfgCfg AGC ugacsgsc 262 csascgcuG 680 163-183 (vinu)sUfs 915 161-183 GUCACGCUGU 392 fuAfGfCfa gcuCfgGfCf AGCAGCCGAG gccgagcaa ugcuAfcAfg CAU

cgugsasc 263 ascsgcugU 681 164-184 (vinu)sAfs 916 162-184 UCACGCUGUA 393 faGfCfAfg ugcUfcGfGf GCAGCCGAGC ccgagcaua cugcUfaCfa AUC gcgusgsa 264 gscsuguaG 682 166-186 (vinu)sUfs 917 164-186 ACGCUGUAGC 394 fcAfGfCfc gauGfcUfCf AGCCGAGCAU gagcaucaa ggcuGfcUfa CAG cagcsgsu 265 asgsccgaG 683 174-194 (vinu)sUfs 918 172-194 GCAGCCGAGC 395 fcAfUfCfa uucGfgGfCf AUCAGCCCGA gcccgaaaa ugauGfcUfc AAG ggcusgsc 266 csgsagcaU 684 177-197 (vinu)sUfs 919 175-197 GCCGAGCAUC 396 fcAfGfCfc ccuUfuCfGf AGCCCGAAAG cgaaaggaa ggcuGfaUfg GAA cucgsgsc 267 csasgcccG 685 184-204 (vinu)sUfs 920 182-204 AUCAGCCCGA 397 faAfAfGfg cguGfcUfUf AAGGAAGCAC aagcacgaa ccuuUfcGfg GAA gcugsasu 268 asgscccgA 686 185-205 (vinu)sUfs 921 183-205 UCAGCCCGAA 398 faAfGfGfa ucgUfgCfUf AGGAAGCACG agcacgaaa uccuUfuCfg AAA ggcusgsa 269 gscsccgaA 687 186-206 (vinu)sUfs 922 184-206 CAGCCCGAAA 399 faGfGfAfa uucGfuGfCf GGAAGCACGA gcacgaaaa uuccUfuUfc AAG gggcsusg 270 csgsgcggC 688 234-254 (vinu)sGfs 923 232-254 GGCGGCGGCG 400 fgUfGfGfa ucgCfcGfGf UGGACCGGCG ccggcgaca uccaCfgCfc ACG gccgscsc 271 gsgscggcG 689 235-255 (vinu)sCfs 924 233-255 GCGGCGGCGU 401 fuGfGfAfc gucGfcCfGf GGACCGGCGA cggcgacga guccAfcGfc CGG cgccsgsc 272 gscsggcgU 690 236-256 (vinu)sCfs 925 234-256 CGGCGGCGUG 402 fgGfAfCfc cguCfgCfCf GACCGGCGAC ggcgacgga ggucCfaCfg GGG ccgcscsg 273 gsusggacc 691 241-261 (vinu)sGfs 926 239-261 GCGUGGACCG 403 fgGfCfGfa ccaCfcCfGf GCGACGGGUG cggguggca ucgcCfgGfu GCA ccacsgsc 274 usgsgaccG 692 242-262 (vinu)sUfs 927 240-262 CGUGGACCGG 404 fgCfGfAfc gccAfcCfCf CGACGGGUGG ggguggcaa gucgCfcGfg CAC uccascsg 275 gsgsaccgG 693 243-263 (vinu)sGfs 928 241-263 GUGGACCGGC 405 fcGfAfCfg ugcCfaCfCf GACGGGUGGC gguggcaca cgucGfcCfg ACA guccsasc 276 gsasccggC 694 244-264 (vinu)sUfs 929 242-264 UGGACCGGCG 406 fgAfCfGfg gugCfcAfCf ACGGGUGGCA guggcacaa ccguCfgCfc CAG ggucscsa 277 csgsgcgaC 695 247-267 (vinu)sAfs 930 245-267 ACCGGCGACG 407 fgGfGfUfg gcuGfuGfCf GGUGGCACAG gcacagcua caccCfgUfc CUG gccgsgsu 278 gscsgacgG 696 249-269 (vinu)sCfs 931 247-269 CGGCGACGGG 408 fgUfGfGfc cagCfuGfUf UGGCACAGCU acagcugga gccaCfcCfg GGC ucgcscsg 279 gsgsuggcA 697 255-275 (vinu)sCfs 932 253-275 CGGGUGGCAC 409 fcAfGfCfu guaUfgCfCf AGCUGGCAUA ggcauacga agcuGfuGfc CGC caccscsg 280 gsusggcaC 698 256-276 (vinu)sGfs 933 254-276 GGGUGGCACA 410 faGfCfUfg cguAfuGfCf GCUGGCAUAC gcauacgca cagcUfgUfg GCG ccacscsc 281 usgsgcacA 699 257-277 (vinu)sCfs 934 255-277 GGUGGCACAG 411 fgCfUfGfg gcgUfaUfGf CUGGCAUACG cauacgcga ccagCfuGfu CGG gccascsc 282 cscsuccaC 700 280-300 (vinu)sUfs 935 278-300 UCCCUCCACA 412 faGfGfUfg cuaCfcGfCf GGUGGCGGUA gcgguagaa caccUfgUfg GAC gaggsgsa 283 uscscacaG 701 282-302 (vinu)sCfs 936 280-302 CCUCCACAGG 413 fgUfGfGfc gucUfaCfCf UGGCGGUAGA gguagacga gccaCfcUfg CGG uggasgsg 284 csascaggU 702 284-304 (vinu)sGfs 937 282-304 UCCACAGGUG 414 fgGfCfGfg ccgUfcUfAf GCGGUAGACG uagacggca ccgcCfaCfc GCG ugugsgsa 285 gsusggcgG 703 289-309 (vinu)sCfs 938 287-309 AGGUGGCGGU 415 fuAfGfAfc ggcCfgCfCf AGACGGCGGC ggcggccga gucuAfcCfg CGG ccacscsu 286 csgsgccgG 704 303-323 (vinu)sGfs 939 301-323 GGCGGCCGGG 416 fgAfCfGfg uugCfuCfGf ACGGCGAGCA cgagcaaca ccguCfcCfg ACA gccgscsc 287 gsgsccggG 705 304-324 (vinu)sUfs 940 302-324 GCGGCCGGGA 417 faCfGfGfc guuGfcUfCf CGGCGAGCAA gagcaacaa gccgUfcCfc CAG ggccsgsc 288 csusggcgU 706 449-469 (vinu)sGfs 941 447-469 CGCUGGCGUA 418 faCfAfUfg cgcUfcAfGf CAUGCUGAGC cugagcgca caugUfaCfg GCG ccagscsg 289 usgsgcguA 707 450-470 (vinu)sCfs 942 448-470 GCUGGCGUAC 419 fcAfUfGfc gcgCfuCfAf AUGCUGAGCG ugagcgcga gcauGfuAfc CGC gccasgsc 290 gsgscguaC 708 451-471 (vinu)sGfs 943 449-471 CUGGCGUACA 420 faUfGfCfu cgcGfcUfCf UGCUGAGCGC gagcgcgca agcaUfgUfa GCA cgccsasg 291 gscsguacA 709 452-472 (vinu)sUfs 944 450-472 UGGCGUACAU 421 fuGfCfUfg gcgCfgCfUf GCUGAGCGCG agcgcgcaa cagcAfuGfu CAC acgcscsa 292 gscsugagC 710 460-480 (vinu)sAfs 945 458-480 AUGCUGAGCG 422 fgCfGfCfa cuaCfgUfGf CGCACACGUA cacguagua ugcgCfgCfu GUA

cagcsasu 293 csusgagcG 711 461-481 (vinu)sUfs 946 459-481 UGCUGAGCGC 423 fcGfCfAfc acuAfcGfUf GCACACGUAG acguaguaa gugcGfcGfc UAC ucagscsa 294 gsasgcgcG 712 463-483 (vinu)sUfs 947 461-483 CUGAGCGCGC 424 fcAfCfAfc guaCfuAfCf ACACGUAGUA guaguacaa guguGfcGfc CAC gcucsasg 295 csgscgcaC 713 466-486 (vinu)sCfs 948 464-486 AGCGCGCACA 425 faCfGfUfa gguGfuAfCf CGUAGUACAC guacaccga uacgUfgUfg CGC cgcgscsu 296 gscsgcacA 714 467-487 (vinu)sGfs 949 465-487 GCGCGCACAC 426 fcGfUfAfg cggUfgUfAf GUAGUACACC uacaccgca cuacGfuGfu GCC gcgcsgsc 297 csgscacaC 715 468-488 (vinu)sGfs 950 466-488 CGCGCACACG 427 fgUfAfGfu gcgGfuGfUf UAGUACACCG acaccgcca acuaCfgUfg CCU ugcgscsg 298 gscsacacG 716 469-489 (vinu)sAfs 951 467-489 GCGCACACGU 428 fuAfGfUfa ggcGfgUfGf AGUACACCGC caccgccua uacuAfcGfu CUU gugcsgsc 299 csascacgU 717 470-490 (vinu)sAfs 952 468-490 CGCACACGUA 429 faGfUfAfc aggCfgGfUf GUACACCGCC accgccuua guacUfaCfg UUG ugugscsg 300 ascsacguA 718 471-491 (vinu)sCfs 953 469-491 GCACACGUAG 430 fgUfAfCfa aagGfcGfGf UACACCGCCU ccgccuuga uguaCfuAfc UGC gugusgsc 301 ascsguagU 719 473-493 (vinu)sUfs 954 471-493 ACACGUAGUA 431 faCfAfCfc gcaAfgGfCf CACCGCCUUG gccuugcaa ggugUfaCfu CAG acgusgsu 302 csgsuaguA 720 474-494 (vinu)sCfs 955 472-494 CACGUAGUAC 432 fcAfCfCfg ugcAfaGfGf ACCGCCUUGC ccuugcaga cgguGfuAfc AGC uacgsusg 303 gsusaguaC 721 475-495 (vinu)sGfs 956 473-495 ACGUAGUACA 433 faCfCfGfc cugCfaAfGf CCGCCUUGCA cuugcagca gcggUfgUfa GCC cuacsgsu 304 gscscugcC 722 515-535 (vinu)sGfs 957 513-535 AGGCCUGCCG 434 fgGfGfUfc ccuUfcCfUf GGUCAGGAAG aggaaggca gaccCfgGfc GCC aggcscsu 305 csasggaaG 723 526-546 (vinu)sCfs 958 524-546 GUCAGGAAGG 435 fgCfCfAfc gcuCfuUfUf CCACAAAGAG aaagagcga guggCfcUfu CGG ccugsasc 306 gsgsaaggC 724 528-548 (vinu)sGfs 959 526-548 CAGGAAGGCC 436 fcAfCfAfa ccgCfuCfUf ACAAAGAGCG agagcggca uuguGfgCfc GCG uuccsusg 307 gsasaggcC 725 529-549 (vinu)sCfs 960 527-549 AGGAAGGCCA 437 faCfAfAfa gccGfcUfCf CAAAGAGCGG gagcggcga uuugUfgGfc CGU cuucscsu 308 asasggccA 726 530-550 (vinu)sAfs 961 528-550 GGAAGGCCAC 438 fcAfAfAfg cgcCfgCfUf AAAGAGCGGC agcggcgua cuuuGfuGfg GUG ccuuscsc 309 asgsgccaC 727 531-551 (vinu)sCfs 962 529-551 GAAGGCCACA 439 faAfAfGfa acgCfcGfCf AAGAGCGGCG gcggcguga ucuuUfgUfg UGA gccususc 310 gsgsccacA 728 532-552 (vinu)sUfs 963 530-552 AAGGCCACAA 440 faAfGfAfg cacGfcCfGf AGAGCGGCGU cggcgugaa cucuUfuGfu GAG ggccsusu 311 cscsacaaA 729 534-554 (vinu)sGfs 964 532-554 GGCCACAAAG 441 fgAfGfCfg cucAfcGfCf AGCGGCGUGA gcgugagca cgcuCfuUfu GCA guggscsc 312 csascaaaG 730 535-555 (vinu)sUfs 965 533-555 GCCACAAAGA 442 faGfCfGfg gcuCfaCfGf GCGGCGUGAG cgugagcaa ccgcUfcUfu CAG ugugsgsc 313 asgscaccG 731 557-577 (vinu)sCfs 966 555-577 GCAGCACCGC 443 fcGfCfCfg uggCfcGfAf GCCGUCGGCC ucggccaga cggcGfcGfg AGC ugcusgsc 314 csgscgccG 732 562-582 (vinu)sUfs 967 560-582 ACCGCGCCGU 444 fuCfGfGfc ggcGfcUfGf CGGCCAGCGC cagcgccaa gccgAfcGfg CAG cgcgsgsu 315 gscsgccgU 733 563-583 (vinu)sCfs 968 561-583 CCGCGCCGUC 445 fcGfGfCfc uggCfgCfUf GGCCAGCGCC agcgccaga ggccGfaCfg AGG gcgcsgsg 316 csasgcacA 734 586-606 (vinu)sUfs 969 584-606 UGCAGCACAA 446 faGfCfGfu ggcGfgCfCf GCGUGGCCGC ggccgccaa acgcUfuGfu CAG gcugscsa 317 asgscacaA 735 587-607 (vinu)sCfs 970 585-607 GCAGCACAAG 447 fgCfGfUfg uggCfgGfCf CGUGGCCGCC gccgccaga cacgCfuUfg AGC ugcusgsc 318 gscsacaaG 736 588-608 (vinu)sGfs 971 586-608 CAGCACAAGC 448 fcGfUfGfg cugGfcGfGf GUGGCCGCCA ccgccagca ccacGfcUfu GCG gugcsusg 319 csasagcgU 737 591-611 (vinu)sAfs 972 589-611 CACAAGCGUG 449 fgGfCfCfg ccgCfuGfGf GCCGCCAGCG ccagcggua cggcCfaCfg GUC cuugsusg 320 asasgcguG 738 592-612 (vinu)sGfs 973 590-612 ACAAGCGUGG 450 fgCfCfGfc accGfcUfGf CCGCCAGCGG cagcgguca gcggCfcAfc UCG gcuusgsu 321 asgscgugG 739 593-613 (vinu)sCfs 974 591-613 CAAGCGUGGC 451 fcCfGfCfc gacCfgCfUf CGCCAGCGGU agcggucga ggcgGfcCfa CGC cgcususg 322 gscsguggC 740 594-614 (vinu)sGfs 975 592-614 AAGCGUGGCC 452 fcGfCfCfa cgaCfcGfCf GCCAGCGGUC gcggucgca uggcGfgCfc GCC

acgcsusu 323 gsgscuguG 741 697-717 (vinu)sCfs 976 695-717 AAGGCUGUGC 453 fcCfUfGfu gcgGfgCfCf CUGUGGCCCG ggcccgcga acagGfcAfc CGA agccsusu 324 gscscuguG 742 703-723 (vinu)sAfs 977 701-723 GUGCCUGUGG 454 fgCfCfCfg gacUfuCfGf CCCGCGAAGU cgaagucua cgggCfcAfc CUU aggcsasc 325 csusguggC 743 705-725 (vinu)sGfs 978 703-725 GCCUGUGGCC 455 fcCfGfCfg aagAfcUfUf CGCGAAGUCU aagucuuca cgcgGfgCfc UCC acagsgsc 326 gscsccgcG 744 710-730 (vinu)sAfs 979 708-730 UGGCCCGCGA 456 faAfGfUfc gcuGfgAfAf AGUCUUCCAG uuccagcua gacuUfcGfc CUC gggcscsa 327 cscscgcgA 745 711-731 (vinu)sGfs 980 709-731 GGCCCGCGAA 457 faGfUfCfu agcUfgGfAf GUCUUCCAGC uccagcuca agacUfuCfg UCA cgggscsc 328 cscsgcgaA 746 712-732 (vinu)sUfs 981 710-732 GCCCGCGAAG 458 fgUfCfUfu gagCfuGfGf UCUUCCAGCU ccagcucaa aagaCfuUfc CAG gcggsgsc 329 uscscagcU 747 723-743 (vinu)sCfs 982 721-743 CUUCCAGCUC 459 fcAfGfCfa gagAfcAfCf AGCAGUGUCU gugucucga ugcuGfaGfc CGU uggasasg 330 csasgcucA 748 725-745 (vinu)sAfs 983 723-745 UCCAGCUCAG 460 fgCfAfGfu acgAfgAfCf CAGUGUCUCG gucucguua acugCfuGfa UUC gcugsgsa 331 gscsgcacC 749 944-964 (vinu)sGfs 984 942-964 CAGCGCACCA 461 faGfAfAfg acuUfuAfGf GAAGCUAAAG cuaaaguca cuucUfgGfu UCU gcgcsusg 332 csasgaagC 750 950-970 (vinu)sCfs 985 948-970 ACCAGAAGCU 462 fuAfAfAfg aucAfaGfAf AAAGUCUUGA ucuugauga cuuuAfgCfu UGC ucugsgsu 333 asgsaagcU 751 951-971 (vinu)sGfs 986 949-971 CCAGAAGCUA 463 faAfAfGfu cauCfaAfGf AAGUCUUGAU cuugaugca acuuUfaGfc GCC uucusgsg 334 gsasagcuA 752 952-972 (vinu)sGfs 987 950-972 CAGAAGCUAA 464 faAfGfUfc gcaUfcAfAf AGUCUUGAUG uugaugcca gacuUfuAfg CCA cuucsusg 335 asasgcuaA 753 953-973 (vinu)sUfs 988 951-973 AGAAGCUAAA 465 faGfUfCfu ggcAfuCfAf GUCUUGAUGC ugaugccaa agacUfuUfa CAU gcuuscsu 336 gscsuaaaG 754 955-975 (vinu)sGfs 989 953-975 AAGCUAAAGU 466 fuCfUfUfg augGfcAfUf CUUGAUGCCA augccauca caagAfcUfu UCA uagcsusu 337 gsasugccA 755 966-986 (vinu)sGfs 990 964-986 UUGAUGCCAU 467 fuCfAfAfa gauGfuCfCf CAAAGGACAU ggacaucca uuugAfuGfg CCC caucsasa 338 asusgccaU 756 967-987 (vinu)sGfs 991 965-987 UGAUGCCAUC 468 fcAfAfAfg ggaUfgUfCf AAAGGACAUC gacauccca cuuuGfaUfg CCU gcauscsa 339 gscscaucA 757 969-989 (vinu)sCfs 992 967-989 AUGCCAUCAA 469 faAfGfGfa aggGfaUfGf AGGACAUCCC caucccuga uccuUfuGfa UGC uggcsasu 340 csasucucU 758 998-1018 (vinu)sUfs 993 996-1018 CACAUCUCUG 470 fgUfCfAfc aguGfgAfCf UCACGUCCAC guccacuaa gugaCfaGfa UAA gaugsusg 341 asuscucuG 759 999-1019 (vinu)sUfs 994 997-1019 ACAUCUCUGU 471 fuCfAfCfg uagUfgGfAf CACGUCCACU uccacuaaa cgugAfcAfg AAU agausgsu 342 uscsucugU 760 1000- (vinu)sAfs 995 998-1020 CAUCUCUGUC 472 fcAfCfGfu 1020 uuaGfuGfGf ACGUCCACUA ccacuaaua acguGfaCfa AUC gagasusg 343 csuscuguC 761 1001-1021 (vinu)sGfs 996 999-1021 AUCUCUGUCA 473 faCfGfUfc auuAfgUfGf CGUCCACUAA cacuaauca gacgUfgAfc UCG agagsasu 344 uscsugucA 762 1002-1022 (vinu)sCfs 997 1000-1022 UCUCUGUCAC 474 fcGfUfCfc gauUfaGfUf GUCCACUAAU acuaaucga ggacGfuGfa CGG cagasgsa 345 csusgucaC 763 1003-1023 (vinu)sCfs 998 1001-1023 CUCUGUCACG 475 fgUfCfCfa cgaUfuAfGf UCCACUAAUC cuaaucgga uggaCfgUfg GGC acagsasg 346 usgsucacG 764 1004-1024 (vinu)sGfs 999 1002-1024 UCUGUCACGU 476 fuCfCfAfc ccgAfuUfAf CCACUAAUCG uaaucggca guggAfcGfu GCA gacasgsa 347 gsuscacgU 765 1005-1025 (vinu)sUfs 1000 1003-1025 CUGUCACGUC 477 fcCfAfCfu gccGfaUfUf CACUAAUCGG aaucggcaa agugGfaCfg CAA ugacsasg 348 uscsacguC 766 1006-1026 (vinu)sUfs 1001 1004-1026 UGUCACGUCC 478 fcAfCfUfa ugcCfgAfUf ACUAAUCGGC aucggcaaa uaguGfgAfc AAA gugascsa 349 csascgucc 767 1007-1027 (vinu)sUfs 1002 1005-1027 GUCACGUCCA 479 faCfUfAfa uugCfcGfAf CUAAUCGGCA ucggcaaaa uuagUfgGfa AAA cgugsasc 350 csgsuccaC 768 1009-1029 (vinu)sCfs 1003 1007-1029 CACGUCCACU 480 fuAfAfUfc uuuUfgCfCf AAUCGGCAAA ggcaaaaga gauuAfgUfg AGG gacgsusg 351 gsusccacU 769 1010-1030 (vinu)sCfs 1004 1008-1030 ACGUCCACUA 481 faAfUfCfg cuuUfuGfCf AUCGGCAAAA gcaaaagga cgauUfaGfu GGA ggacsgsu 352 uscscacuA 770 1011-1031 (vinu)sUfs 1005 1009-1031

CGUCCACUAA 482 faUfCfGfg ccuUfuUfGf UCGGCAAAAG caaaaggaa ccgaUfuAfg GAG uggascsg 353 cscsacuaA 771 1012-1032 (vinu)sCfs 1006 1010-1032 GUCCACUAAU 483 fuCfGfGfc uccUfuUfUf CGGCAAAAGG aaaaggaga gccgAfuUfa AGA guggsasc 354 csascuaaU 772 1013-1033 (vinu)sUfs 1007 1011-1033 UCCACUAAUC 484 fcGfGfCfa cucCfuUfUf GGCAAAAGGA aaaggagaa ugccGfaUfu GAA agugsgsa 355 ascsuaauC 773 1014-1034 (vinu)sUfs 1008 1012-1034 CCACUAAUCG 485 fgGfCfAfa ucuCfcUfUf GCAAAAGGAG aaggagaaa uugcCfgAfu AAA uagusgsg 356 gsasgaagA 774 1040-1060 (vinu)sCfs 1009 1038-1060 GAGAGAAGAU 486 fuGfAfCfc acaCfuUfAf GACCUAAGUG uaaguguga ggucAfuCfu UGA ucucsusc 357 uscscuccG 775 1110-1130 (vinu)sCfs 1010 1108-1130 CCUCCUCCGA 487 faCfCfAfa uucCfuCfCf CCAAGGAGGA ggaggaaga uuggUfcGfg AGG aggasgsg 358 cscsagggA 776 1176-1196 (vinu)sCfs 1011 1174-1196 UUCCAGGGAA 488 faGfGfAfa cggAfgAfGf GGAACUCUCC cucuccgga uuccUfuCfc GGU cuggsasa 359 csasgggaA 777 1177-1197 (vinu)sAfs 1012 1175-1197 UCCAGGGAAG 489 fgGfAfAfc ccgGfaGfAf GAACUCUCCG ucuccggua guucCfuUfc GUC ccugsgsa 360 asgsgaacU 778 1183-1203 (vinu)sUfs 1013 1181-1203 GAAGGAACUC 490 fcUfCfCfg gguGfgAfCf UCCGGUCCAC guccaccaa cggaGfaGfu CAU uccususc 361 gsgsaacuC 779 1184-1204 (vinu)sAfs 1014 1182-1204 AAGGAACUCU 491 fuCfCfGfg uggUfgGfAf CCGGUCCACC uccaccaua ccggAfgAfg AUG uuccsusu 362 ascsucucC 780 1187-1207 (vinu)sUfs 1015 1185-1207 GAACUCUCCG 492 fgGfUfCfc ccaUfgGfUf GUCCACCAUG accauggaa ggacCfgGfa GAG gagususc 363 csusccggU 781 1190-1210 (vinu)sUfs 1016 1188-1210 CUCUCCGGUC 493 fcCfAfCfc acuCfcAfUf CACCAUGGAG auggaguaa ggugGfaCfc UAC ggagsasg 364 usgsaaccC 782 1221-1241 (vinu)sGfs 1017 1219-1241 UCUGAACCCC 494 fcAfGfUfg aguAfaGfUf AGUGACUUAC acuuacuca cacuGfgGfg UCA uucasgsa 365 gsusgacuU 783 1230-1250 (vinu)sUfs 1018 1228-1250 CAGUGACUUA 495 faCfUfCfa acuGfaCfCf CUCAGGUCAG ggucaguaa ugagUfaAfg UAU ucacsusg 366 gsascuuaC 784 1232-1252 (vinu)sGfs 1019 1230-1252 GUGACUUACU 496 fuCfAfGfg auaCfuGfAf CAGGUCAGUA ucaguauca ccugAfgUfa UCU agucsasc 367 csusuacuC 785 1234-1254 (vinu)sUfs 1020 1232-1254 GACUUACUCA 497 faGfGfUfc agaUfaCfUf GGUCAGUAUC aguaucuaa gaccUfgAfg UAA uaagsusc 368 csasguauC 786 1245-1265 (vinu)sCfs 1021 1243-1265 GUCAGUAUCU 498 fuAfAfUfa gagCfuUfAf AAUAUAAGCU uaagcucga uauuAfgAfu CGG acugsasc 369 gsusaucuA 787 1247-1267 (vinu)sUfs 1022 1245-1267 CAGUAUCUAA 499 faUfAfUfa ccgAfgCfUf UAUAAGCUCG agcucggaa uauaUfuAfg GAG auacsusg 370 usasucuaA 788 1248-1268 (vinu)sCfs 1023 1246-1268 AGUAUCUAAU 500 fuAfUfAfa uccGfaGfCf AUAAGCUCGG gcucggaga uuauAfuUfa AGU gauascsu 371 asuscuaaU 789 1249-1269 (vinu)sAfs 1024 1247-1269 GUAUCUAAUA 501 faUfAfAfg cucCfgAfGf UAAGCUCGGA cucggagua cuuaUfaUfu GUU agausasc 372 uscsuaauA 790 1250-1270 (vinu)sAfs 1025 1248-1270 UAUCUAAUAU 502 fuAfAfGfc acuCfcGfAf AAGCUCGGAG ucggaguua gcuuAfuAfu UUU uagasusa 373 csusaauaU 791 1251-1271 (vinu)sAfs 1026 1249-1271 AUCUAAUAUA 503 faAfGfCfu aacUfcCfGf AGCUCGGAGU cggaguuua agcuUfaUfa UUG uuagsasu 374 usasauauA 792 1252-1272 (vinu)sCfs 1027 1250-1272 UCUAAUAUAA 504 faGfCfUfc aaaCfuCfCf GCUCGGAGUU ggaguuuga gagcUfuAfu UGG auuasgsa 375 asusauaaG 793 1254-1274 (vinu)sUfs 1028 1252-1274 UAAUAUAAGC 505 fcUfCfGfg ccaAfaCfUf UCGGAGUUUG aguuuggaa ccgaGfcUfu GAC auaususa 376 usasuaagC 794 1255-1275 (vinu)sGfs 1029 1253-1275 AAUAUAAGCU 506 fuCfGfGfa uccAfaAfCf CGGAGUUUGG guuuggaca uccgAfgCfu ACG uauasusu 377 asusaagcU 795 1256-1276 (vinu)sCfs 1030 1254-1276 AUAUAAGCUC 507 fcGfGfAfg gucCfaAfAf GGAGUUUGGA uuuggacga cuccGfaGfc CGG uuausasu 378 gscsucggA 796 1260-1280 (vinu)sCfs 1031 1258-1280 AAGCUCGGAG 508 fgUfUfUfg cucCfgUfCf UUUGGACGGA gacggagga caaaCfuCfc GGG gagcsusu 379 gsgsaguuU 797 1264-1284 (vinu)sAfs 1032 1262-1284 UCGGAGUUUG 509 fgGfAfCfg gacCfcUfCf GACGGAGGGU gagggucua cgucCfaAfa CUG cuccsgsa 380 csascccA 798 1299-1319 (vinu)sAfs 1033 1297-1319 ACCACCCCAG 510 fgCfGfAfc cggAfaAfGf CGACCUUUCC cuuuccgua gucgCfuGfg GUG

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faCfAfGfg uauCfuAfGf CAGGCUAGAU cuagauaaa ccugUfaCfu AAC gucusgsc 410 uscsccacU 828 2087-2107 (vinu)sGfs 1063 2085-2107 CCUCCCACUU 540 fuGfCfCfc ccuUfuCfAf GCCCUGAAAG ugaaaggca gggcAfaGfu GCC gggasgsg 411 csusgcugC 829 2148-2168 (vinu)sGfs 1064 2146-2168 GACUGCUGCU 541 fuAfCfAfu ggaUfuAfGf ACAUCUAAUC cuaauccca auguAfgCfa CCC gcagsusc 412 usgscugcU 830 2149-2169 (vinu)sGfs 1065 2147-2169 ACUGCUGCUA 542 faCfAfUfc gggAfuUfAf CAUCUAAUCC uaaucccca gaugUfaGfc CCU agcasgsu 413 gscsugcuA 831 2150-2170 (vinu)sAfs 1066 2148-2170 CUGCUGCUAC 543 fcAfUfCfu gggGfaUfUf AUCUAAUCCC aaucccca agauGfuAfg CUA cagcsasg 414 ascsaucuA 832 2156-2176 (vinu)sAfs 1067 2154-2176 CUACAUCUAA 544 faUfCfCfc uugGfuAfGf UCCCCUACCA cuaccaaua gggaUfuAfg AUG augusasg 415 asuscuaaU 833 2158-2178 (vinu)sGfs 1068 2156-2178 ACAUCUAAUC 545 fcCfCfCfu cauUfgGfUf CCCUACCAAU accaaugca agggGfaUfu GCC agausgsu 416 cscsccuaC 834 2165-2185 (vinu)sAfs 1069 2163-2185 AUCCCCUACC 546 fcAfAfUfg cagGfaGfGf AAUGCCUCCU ccuccugua cauuGfgUfa GUC ggggsasu 417 cscscuacC 835 2166-2186 (vinu)sGfs 1070 2164-2186 UCCCCUACCA 547 faAfUfGfc acaGfgAfGf AUGCCUCCUG cuccuguca gcauUfgGfu UCC agggsgsa 418 ascscaauG 836 2170-2190 (vinu)sUfs 1071 2168-2190 CUACCAAUGC 548 fcCfUfCfc aggGfaCfAf CUCCUGUCCC uguccccuaa ggagGfcAfu UAA uggusasg 419 cscsaaugC 837 2171-2191 (vinu)sUfs 1072 2169-2191 UACCAAUGCC 549 fcUfCfCfu uagGfgAfCf UCCUGUCCCU gucccuaaa aggaGfgCfa AAA uuggsusa 420 asusgccuC 838 2174-2194 (vinu)sAfs 1073 2172-2194 CAAUGCCUCC 550 fcUfGfUfc guuUfaGfGf UGUCCCUAAA ccuaaacua gacaGfgAfg CUC gcaususg 421 usgsccucC 839 2175-2195 (vinu)sGfs 1074 2173-2195 AAUGCCUCCU 551 fuGfUfCfc aguUfuAfGf GUCCCUAAAC cuaaacuca ggacAfgGfa UCC ggcasusu 422 usascugaU 840 2202-2222 (vinu)sAfs 1075 2200-2222 CAUACUGAUG 552 fgAfCfAfg gagAfgGfGf ACAGCCCUCU cccucucua cuguCfaUfc CUG aguasusg 423 asgscucaG 841 726-746 (vinu)sGfs 1076 724-746 CCAGCUCAGC 1132 fcAfGfUfg aacGfaGfAf AGUGUCUCGU ucucguuca cacuGfcUfg UCC agcusgsg 424 gscsucagC 842 727-747 (vinu)sGfs 1077 725-747 CAGCUCAGCA 1133 faGfUfGfu gaaCfgAfGf GUGUCUCGUU cucguucca acacUfgCfu CCC gagcsusg 425 gsgsacggU 843 752-772 (vinu)sAfs 1078 750-772 GGGGACGGUA 1134 faGfCfAfg uguCfgGfUf GCAGACCGAC accgacaua cugcUfaCfc AUC guccscsc 426 ascsgguaG 844 754-774 (vinu)sGfs 1079 752-774 GGACGGUAGC 1135 fcAfGfAfc gauGfuCfGf AGACCGACAU cgacaucca gucuGfcUfa CCU ccguscsc 427 csgsguagC 845 755-775 (vinu)sAfs 1080 753-775 GACGGUAGCA 1136 faGfAfCfc ggaUfgUfCf GACCGACAUC gacauccua ggucUfgCfu CUU accgsusc 428 asgscagaC 846 759-779 (vinu)sCfs 1081 757-779 GUAGCAGACC 1137 fcGfAfCfa agaAfgGfAf GACAUCCUUC uccuucuga ugucGfgUfc UGG ugcusasc 429 gscsagacC 847 760-780 (vinu)sCfs 1082 758-780 UAGCAGACCG 1138 fgAfCfAfu cagAfaGfGf ACAUCCUUCU ccuucugga auguCfgGfu GGG cugcsusa 430 uscscaugC 848 894-914 (vinu)sGfs 1083 892-914 CUUCCAUGCA 1139 faAfCfUfg ugaUfgGfAf ACUGUCCAUC uccaucaca caguUfgCfa ACG uggasasg 431 cscsaugcA 849 895-915 (vinu)sCfs 1084 893-915 UUCCAUGCAA 1140 faCfUfGfu gugAfuGfGf CUGUCCAUCA ccaucacga acagUfuGfc CGG auggsasa 432 csasugcaA 850 896-916 (vinu)sCfs 1085 894-916 UCCAUGCAAC 1141 fcUfGfUfc cguGfaUfGf UGUCCAUCAC caucacgga gacaGfuUfg GGC caugsgsa 433 asascuguC 851 901-921 (vinu)sUfs 1086 989-921 GCAACUGUCC 1142 fcAfUfCfa gcaGfcCfGf AUCACGGCUG cggcugcaa ugauGfgAfc CAA aguusgsc 434 ascsugucC 852 902-922 (vinu)sUfs 1087 900-922 CAACUGUCCA 1143 faUfCfAfc ugcAfgCfCf UCACGGCUGC ggcugcaaa gugaUfgGfa AAC cagususg 435 gsusccauC 853 905-925 (vinu)sCfs 1088 903-925 CUGUCCAUCA 1144 faCfGfGfc aguUfgCfAf CGGCUGCAAC ugcaacuga gccgUfgAfu UGA ggacsasg 436 asuscacgG 854 909-929 (vinu)sAfs 1089 907-929 CCAUCACGGC 1145 fcUfGfCfa uuuCfaGfUf UGCAACUGAA acugaaaua ugcaGfcCfg AUC ugausgsg 437 usgsggacA 855 935-955 (vinu)sUfs 1090 933-955 GCUGGGACAC 1146 fcAfGfCfg ucuGfgUfGf AGCGCACCAG caccagaaa cgcuGfuGfu AAG cccasgsc 438 gsascacaG 856 938-958 (vinu)sAfs 1091 936-958 GGGACACAGC 1147 fcGfCfAfc

gcuUfcUfGf GCACCAGAAG cagaagcua gugcGfcUfg CUA ugucscsc 439 ascsagcgC 857 941-961 (vinu)sUfs 1092 939-961 ACACAGCGCA 1148 faCfCfAfg uuaGfcUfUf CCAGAAGCUA aagcuaaaa cuggUfgCfg AAG cugusgsu 440 gscscaCfa 858 1659-1677 (vinu)sGfs 1093 1659-1679 AAGCCACAUU 1149 UfUfCfuac agcCfcGfUf CUACGGGCUC gggcuca agaaUfgUfg U gcsusu 441 gsasaaGfu 859 1715-1733 (vinu)sAfs 1094 1715-1735 AAGAAAGUAC 1150 AfCfUfcag gcuCfcCfUf UCAGGGAGCU ggagcua gaguAfcUfu C ucsusu 442 gsuscuAfu 860 2033-2051 (vinu)sUfs 1095 2033-2053 AAGUCUAUAC 1151 AfCfCfcuu cagGfuAfAf CCUUACCUGA accugaa ggguAfuAfg A acsusu 443 gscsugCfu 861 1373-1391 (vinu)sAfs 1096 1373-1393 GAGCUGCUAG 1152 AfGfCfcaa augCfuUfUf CCAAAGCAUU agcauua ggcuAfgCfa G gcsusc 444 gsgsagUfg 862 1534-1552 (vinu)sAfs 1097 1534-1554 AAGGAGUGGA 1153 GfAfGfugc ugaCfaGfCf GUGCUGUCAU ugucaua acucCfaCfu A ccsusu 445 gsgsccAfa 863 2102-2120 (vinu)sGfs 1098 2102-2122 AAGGCCAAGA 1154 GfAfUfcaa acaUfcUfUf UCAAGAUGUC gauguca gaucUfuGfg C ccsusu 446 csusugAfg 864 2228-2246 (vinu)sAfs 1099 2228-2248 ACCUUGAGAU 1155 AfUfCfugu ugaAfgAfCf CUGUCUUCAU cuucaua agauCfuCfa ACC agsusu 447 csusugAfg 864 2228-2246 (vinu)sAfs 1100 2228-2248 UUACCUUGAG 1156 AfUfCfugu ugaAfgAfCf AUCUGUCUUC cuucaua agauCfuCfa AUA agsgsu 448 cscsucAfa 865 2254-2272 (vinu)sGfs 1101 2254-2274 CCCCUCAAAC 1157 AfCfUfaac uuuUfuGfUf UAACAAAAAC aaaaaca uaguUfuGfa A ggsgsg 449 csuscaAfa 866 2255-2273 (vinu)sUfs 1102 2255-2275 CCCUCAAACU 1158 CfUfAfaca guuUfuUfGf AACAAAAACA aaaacaa uuagUfuUfg U agsgsg 450 csasaaCfu 867 2257-2275 (vinu)sAfs 1103 2257-2277 CUCAAACUAA 1159 AfAfCfaaa augUfuUfUf CAAAAACAUU aacauua uguuAfgUfu U ugsasg 451 csusaaCfa 868 2261-2279 (vinu)sUfs 1104 2261-2281 AACUAACAAA 1160 AfAfAfaca ggaAfaUfGf AACAUUUCCA uuuccaa uuuuUfgUfu A agsusu 452 csasaaAfa 869 2265-2283 (vinu)sUfs 1105 2265-2285 AACAAAAACA 1161 CfAfUfuuc uauUfgGfAf UUUCCAAUAA caauaaa aaugUfuUfu A ugsusu 453 cscsaaUfa 870 2276-2294 (vinu)sAfs 1106 2276-2296 UUCCAAUAAA 1162 AfAfAfaua uuuGfaUfAf AAUAUCAAAU ucaaaua uuuuUfaUfu A ggsasa 454 csasauAfa 871 2277-2295 (vinu)sUfs 1107 2277-2297 UCCAAUAAAA 1163 AfAfAfuau auuUfgAfUf AUAUCAAAUA caaauaa auuuUfuAfu U ugsgsa 455 cscsaaAfg 872 1381-1399 (vinu)sGfs 1108 1381-1401 AGCCAAAGCA 1164 CfAfUfugg gguCfuCfCf UUGGAGACCC agaccca aaugCfuUfu U ggsusu 456 csasggUfc 873 1238-1256 (vinu)sAfs 1109 1238-1258 CUCAGGUCAG 1165 AfGfUfauc uauUfaGfAf UAUCUAAUAU uaauaua uacuGfaCfc A ugsusu 457 asusguCfa 874 1651-1669 (vinu)sAfs 1110 1651-1671 GAAUGUCAAA 1166 AfAfGfcca gaaUfgUfGf GCCACAUUCU cauucua gcuuUfgAfc A aususc 458 gscsucUfa 875 1673-1691 (vinu)sCfs 1111 1673-1693 GGGCUCUACU 1167 CfUfCfuau aacUfcAfUf CUAUGAGUUG gaguuga agagUfaGfa U gcsusu 459 csusauGfa 876 1681-1699 (vinu)sGfs 1112 1681-1701 CUCUAUGAGU 1168 GfUfUfgug aaaGfuCfAf UGUGACUUUC acuuuca caacUfcAfu A agsasg 460 usasugAfg 877 1682-1700 (vinu)sUfs 1113 1682-1702 UCUAUGAGUU 1169 UfUfGfuga gaaAfgUfCf GUGACUUUCA cuuucaa acaaCfuCfa A uasgsa 461 gsgsccCfa 878 1707-1725 (vinu)sGfs 1114 1707-1727 UUGGCCCAAA 1170 AfAfGfaaa aguAfcUfUf GAAAGUACUC guacuca ucuuUfgGfg A ccsusu 462 gscscaUfa 879 1768-1786 (vinu)sUfs 1115 1768-1788 GGGCCAUAUG 1171 UfGfUfugc uccCfaGfCf UUGCUGGGAA ugggaaa aacaUfaUfg U gcsusu 463 cscscaCfu 880 1899-1979 (vinu)sCfs 1116 1899-1981 GACCCACUGC 1172 GfCfAfaag auaGfuCfUf AAAGACUAUG acuauga uugcAfgUfg A ggsusu 464 gsascuAfu 881 1910-1928 (vinu)sUfs 1117 1910-1930 AAGACUAUGA 1173 GfAfCfagc uugAfuGfCf CAGCAUCAAA aucaaaa ugucAfuAfg U ucsusu 465 csusauGfa 882 1912-1930 (vinu)sAfs 1118 1912-1932 GACUAUGACA 1174 CfAfGfcau auuUfgAfUf GCAUCAAAUU caaauua gcugUfcAfu U agsusc 466 csusgaAfg 883 2047-2065 (vinu)sAfs 1119 2047-2067 ACCUGAAGAA 1175 AfAfUfgcu agaAfcAfGf UGCUGUUCUU guucuua cauuCfuUfc U agsusu 467 csusgaAfg 883 2047-2065 (vinu)sAfs 1120 2047-2067 ACCUGAAGAA 1176 AfAfUfgcu agaAfcAfGf UGCUGUUCUU guucuua cauuCfuUfc U agsgsu 468 cscsugAfa 884 2095-2113 (vinu)sUfs 1121 2095-2115

GCCCUGAAAG 1177 AfGfGfcca gauCfuUfGf GCCAAGAUCA agaucaa gccuUfuCfa A ggsusu 469 cscsugAfa 884 2095-2113 (vinu)sUfs 1122 2095-2115 GCCCUGAAAG 1178 AfGfGfcca gauCfuUfGf GCCAAGAUCA agaucaa gccuUfuCfa A ggsgsc 470 gsascuGfc 885 2144-2162 (vinu)sUfs 1123 2144-2164 CUGACUGCUG 1179 UfGfCfuac uagAfuGfUf CUACAUCUAA aucuaaa agcaGfcAfg U ucsusu 471 asgsguCfa 886 1239-1257 (vinu)sUfs 1124 1239-1259 UCAGGUCAGU 1180 GfUfAfucu auaUfuAfGf AUCUAAUAUA aauauaa auacUfgAfc A cususu 472 gsgsaaUfu 887 1782-1800 (vinu)sAfs 1125 1782-1802 UGGGAAUUUC 1181 UfCfCfucc aggGfuGfGf CUCCACCCUU acccuua aggaAfaUfu C ccsusu 473 gsasuuCfa 888 1597-1615 (vinu)sAfs 1126 1597-1617 CCGAUUCACC 1182 CfCfUfuug cacGfuCfAf UUUGACGUGU acgugua aaggUfgAfa A ucsusu 474 gsasggAfu 889 1479-1497 (vinu)sCfs 1127 1479-1499 UGGAGGAUGA 1183 GfAfCfacg aggCfaCfGf CACGUGCCUG ugccuga ugucAfuCfc A ucsusu 475 csuscuAfu 890 1679-1697 (vinu)sAfs 1128 1679-1699 UACUCUAUGA 1184 GfAfGfuug aguCfaCfAf GUUGUGACUU ugacuua acucAfuAfg U agsusa 476 asgsagGfa 891 1430-1448 (vinu)sGfs 1129 1430-1450 CUAGAGGAGG 1185 GfGfAfugg cagUfuCfCf AUGGAACUGC aacugca auccUfcCfu A cusasg 477 gsasuuCfa 888 1597-1615 (vinu)sAfs 1130 1597-1617 CCGAUUCACC 1186 CfCfUfuug cacGfuCfAf UUUGACGUGU acgugua aaggUfgAfa A ucsgsg 478 uscsagGfu 892 1237-1255 (vinu)sUfs 1131 1237-1257 ACUCAGGUCA 1187 CfAfGfuau auuAfgAfUf GUAUCUAAUA cuaauaa acugAfcCfu U gasusu 479 csasguauC 786 1245-1265 (vinu)sCfs 1188 1243-1265 GUCAGUAUCU 498 fuAfAfUfa gagCfuuaua AAUAUAAGCU uaagcucga uuAfgAfuac CGG ugsasc 480 usasauauA 792 1252-1272 (vinu)sCfs 1189 1250-1272 UCUAAUAUAA 504 faGfCfUfc aaaCfuccga GCUCGGAGUU ggaguuuga gcUfuAfuau UGG uasgsa 481 csasguauC 786 1245-1265 (vinu)sCfs 1190 1243-1265 GUCAGUAUCU 498 fuAfAfUfa gagCfuuaua AAUAUAAGCU uaagcucga uuAfgauacu CGG gsasc 482 csasgaCfa 1192 1942-1962 (vinu)sUfs 1191 1940-1962 UGCAGACAGU 538 guAfCfAfg aucUfagccu ACAGGCUAGA gcuagauaa guAfcugucu UAA gscsa

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

TABLE-US-00005 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 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 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 C.sub.1 to C.sub.10 alkyl or C.sub.2 to C.sub.10 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[(CH.sub.2).sub.nO]m, CH.sub.3, O(CH.sub.2).sub.nOCH.sub.3, O(CH.sub.2).sub.nNH.sub.2, O(CH.sub.2).sub.nCH.sub.3, O(CH.sub.2).sub.nONH.sub.2, and O(CH.sub.2).sub.nON [(CH.sub.2).sub.nCH.sub.3)].sub.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)).

[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): C.sub.1 to C.sub.10 lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH.sub.3, OCN, Cl, Br, CN, CF.sub.3, OCF.sub.3, SOCH.sub.3, SO.sub.2CH.sub.3, ONO.sub.2, NO.sub.2, N.sub.3, NH.sub.2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, or a substituted silyl. In some embodiments, the agent (or any component thereof) comprises a 2′-methoxyethoxy (2′-O—CH.sub.2CH.sub.2OCH.sub.3, 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(CH.sub.2).sub.2ON(CH.sub.3).sub.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—CH.sub.2—O—CH.sub.2—N(CH.sub.3) 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′-alkoxyalkyl; 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—CH.sub.2Py (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, CF.sub.3, OCF.sub.3, O—C.sub.1-C.sub.10 alkoxy, O—C.sub.1-C.sub.10 substituted alkoxy, O—C.sub.1-C.sub.10 alkyl, O—C.sub.1-C.sub.10 substituted alkyl, S-alkyl, N(R.sub.m)-alkyl, O-alkenyl, S-alkenyl, N(R.sub.m)-alkenyl, O-alkynyl, S-alkynyl, N(R.sub.m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH2)2SCH3,0(CH2)2ON(Rm)(Rn) or OCH2C(═O)—N(Rm)(Rn), where each R.sub.m and R.sub.n is, independently, H, an amino protecting group, or substituted or unsubstituted C.sub.1-C.sub.10 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 (NO.sub.2), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl.

[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, NH.sub.2, N.sub.3, OCF.sub.3, OCH.sub.3, O(CH.sub.2).sub.3NH.sub.2, CH.sub.2CH═CH.sub.2, OCH.sub.2CH═CH.sub.2, OCH.sub.2CH.sub.2OCH.sub.3, O(CH.sub.2).sub.2SCH.sub.3, O(CH.sub.2).sub.2ON(R.sub.m)(R.sub.n), O(CH.sub.2).sub.2O(CH.sub.2).sub.2N(CH.sub.3).sub.2, and N-substituted acetamide (OCH.sub.2C(═O)—N(R.sub.m)(R.sub.n)), where each R.sub.m and R.sub.n is, independently, H, an amino protecting group, or substituted or unsubstituted C.sub.1-C.sub.10 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, OCH.sub.3, OCH.sub.2CH.sub.2OCH.sub.3, O(CH.sub.2).sub.2SCH.sub.3, O(CH.sub.2).sub.2ON(CH.sub.3).sub.2, O(CH.sub.2).sub.2O(CH.sub.2).sub.2N(CH.sub.3).sub.2, and OCH.sub.2C(═O)—N(H)CH.sub.3 (“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, OCH.sub.3, OCH.sub.2CH.sub.2OCH.sub.3, and OCH.sub.2C(═O)—N(H)CH.sub.3.

[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 Fluiter 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′-CH.sub.2-2′, 4′-(CH.sub.2).sub.2-2′, 4′-(CH.sub.2).sub.3-2′, 4′-CH.sub.2—O-.sub.2′ (“LNA”), 4′-CH.sub.2—S-2′, 4′-(CH.sub.2).sub.2—O-2′ (“ENA”), 4′-CH(CH.sub.3)—O-2′ (referred to as “constrained ethyl” or “cEt”), 4′-CH.sub.2—O—CH.sub.2-2′, 4′-CH.sub.2—N(R)-2′, 4′-CH(CH.sub.2OCH.sub.3)—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(CH.sub.3)(CH.sub.3)—O-2′ and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 8,278,283), 4′-CH.sub.2—N(OCH.sub.3)-2′ and analogs thereof (see, e.g., Prakash et al., U.S. Pat. No. 8,278,425), 4′-CH.sub.2—O—N(CH.sub.3)-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′-CH.sub.2—C(H)(CH.sub.3)-2′ (see, e.g., Zhou, et al., J. Org. Chem., 2QQ9, 74, 118-134), 4′-CH.sub.2—C(═CH.sub.2)-2′ and analogs thereof (see, e.g., Seth et al., U.S. Pat. No. 8,278,426), 4′-C(R.sub.aR.sub.b)—N(R)—O-2′, 4′-C(R.sub.aR.sub.b)—O—N(R)-2′, 4′-CH.sub.2—O—N(R)-2′, and 4′-CH.sub.2—N(R)—O-2′, wherein each R, R.sub.a, and R.sub.b is, independently, H, a protecting group, or C.sub.1-C.sub.12 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.sub.a)(R.sub.b)]n-, —[C(R.sub.a)(R.sub.b)]n-O—, —C(R.sub.a)═C(R.sub.b)—, —C(R.sub.a)═N—, —C(═NR.sub.a)—, —C(═O)—, —C(═S)—, —O—, —Si(R.sub.a).sub.2—, —S(═O)X—, and —N(R.sub.a)—; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R.sub.a and R.sub.b is, independently, H, a protecting group, hydroxyl, C.sub.1-C.sub.12 alkyl, substituted C.sub.1-C.sub.12 alkyl, C.sub.2-C.sub.12 alkenyl, substituted C.sub.2-C.sub.12 alkenyl, C.sub.2-C.sub.12 alkynyl, substituted C.sub.2-C.sub.12 alkynyl, C.sub.5-C.sub.20 aryl, substituted C.sub.5-C.sub.20 aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C.sub.5-C.sub.7 alicyclic radical, substituted C.sub.5-C.sub.7 alicyclic radical, halogen, OJ1, NJ1J2, SJ1, N3, COOJ1, acyl (C(═O)—H), substituted acyl, CN, sulfonyl (S(=0)2-J1), or sulfoxyl (S(═O)-J1); and each J1 and J2 is, independently, H, C.sub.1-C.sub.12 alkyl, substituted C.sub.1-C.sub.12 alkyl, C.sub.2-C.sub.12 alkenyl, substituted C.sub.2-C.sub.12 alkenyl, C.sub.2-C.sub.12 alkynyl, substituted C.sub.2-C.sub.12 alkynyl, C.sub.5-C.sub.20 aryl, substituted C.sub.5-C.sub.20 aryl, acyl (C(═O)—H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C.sub.1-C.sub.12 aminoalkyl, substituted C.sub.1-C.sub.12 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; Koshkin 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 a., 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(CH.sub.3)—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—CH.sub.3) 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-aminocthoxy)-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 (m.sup.5C), 5′fluoro-2′deoxyuridine, N-ethylpiperidine 7-EAA triazole modified adenine, N-ethylpiperidine 6′triazole modified adenine, 6-phenylpyrrolo-cytosine (PhpC), 2′,4′-difluorotoluyl 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 (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), methpxypropyl-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 sulfonamide backbones; amide backbones; and others having mixed N, O, S, and CH.sub.2 component parts.

[0672] Representative non-phosphorous containing internucleoside linking groups include but are not limited to methylenemethylimino (—CH.sub.2—N(CH.sub.3)—O—CH.sub.2—), thiodiester, thionocarbamate (—O—C(═O) (NH)—S—); siloxane (—O—SiH.sub.2—O—); and N,N′-dimethylhydrazine (—CH.sub.2—N(CH.sub.3)—N(CH.sub.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 (idT) 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 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 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 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.
[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 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.
[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.

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 an 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 moictics, polyethylene glycols, thioethers, polyethers, cholesterols, thiocholesterols, cholic acid moieties, folate, lipophilic groups, phospholipids, biotin, phenazine,

phenanthridine, anthraquinone, adamantane, 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 moities (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. Acid. Sci. USA, 1989, 86:6553-6556); cholic acid (see, e.g., Manoharan et al., Biorg. Med. Chem. Let., 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. Let., 1993, 3:2765-2770); thiocholesterols (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; Kabanov 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); adamantane 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:
##STR00002## ##STR00003## ##STR00004## ##STR00005##
##STR00006## ##STR00007## ##STR00008## ##STR00009## ##STR00010##
##STR00011## ##STR00012## ##STR00013## ##STR00014##
[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.

[0710] Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO2, SO2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkynyl, alkynylheteroarylalkenyl, alkylheterocyclylalkyl, alkylhererocyclylalkynyl, alkylheterocyclylalkenyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO.sub.2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic, or substituted aliphatic. In one embodiment, the linker is about 1-24 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-dioxaoctanoic 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 Ci-Cw 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 (—S—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 —O—P(O)(ORk)-O—, —OP(S)(ORk)-O—, —O—P(S)(SRk)-O—, —S—P(O)(ORk)-O—, —O—P(O)(ORk)-S—, —S—P(O)(ORk)-S—, —OP(S)(ORk)-S—, —S—P(S)(ORk)-O—, —O—P(O)(Rk)-O—, —O—P(S)(Rk)-O—, —S—P(O)(Rk)-O—, —S—P(S)(Rk)-O—, —S—P(O)(Rk)-S—, —O—P(S)(Rk)-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 —OP(O)(OH)—O—, —O—P(S)(OH)—O—, —O—P(S)(SH)—O—, —S—P(O)(OH)—O—, —O—P(O)(OH)—S—, —S—P(O)(OH)—S—, —O—P(S)(OH)—S—, —S—P(S)(OH)—O—, —O—P(O)(H)—O—, —O—P(S)(H)—O—, —S—P(O)(H)—O, —S—P(S)(H)—O—, —S—P(O)(H)—S—, or —O—P(S)(H)—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 —C═NN—, C(O) O, or —OC(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 at 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 at 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).
##STR00015##
[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:
##STR00016##
[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.
##STR00017##
[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:
##STR00018## ##STR00019## ##STR00020##
[0736] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula I:
##STR00021##
[0737] In specific embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XXXIX.
##STR00022##
[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.
##STR00023##
[0741] In specific preferred embodiments, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula XL, 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-US-00006 TABLE 11 Exemplary dsRNA Agent Conjugates. Corresponding Corresponding Unconjugated Unconjugated Unmodified Modified dsRNA dsRNA dsRNA Sense SEQ Antisense SEQ Agent Agent ID Agent ID Sequence ID Sequence ID ID (Table 2) (Table 3) 5′ to 3′ NO 5′ to 3′ NO 483 129 479 csasguauCfuAf 1193 (vinu)sCfsgag 1188 AfUfauaagcucg CfuuauauuAfgA a (GalNAc-TEG) fuacugsasc 484 129 481 csasguauCfuAf 1193 (vinu)sCfsgag 1190 AfUfauaagcucg CfuuauauuAfga a (GalNAc-TEG) uacugsasc 485 172 482 csasgaCfaguAf 1194 (vinu)sUfsauc 1191 CfAfggcuagaua UfagccuguAfcu a (GalNAc-TEG) gucugscsa 486 135 480 usasauauAfaGf 1195 (vinu)sCfsaaa 1189 CfUfcggaguuug CfuccgagcUfuA a (GalNAc-TEG) fuauuasgsa 487 173 409 asgsacagUfaCf 1196 (vinu)sUfsuau 1062 AfGfgcuagauaa CfuAfGfccugUf a (GalNAc-TEG) aCfugucusgsc
[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 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. (Edrs.), 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, parapoxivirus 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: pcDNA™, pCR3.1™, pCMV™, pFRT™, pVAX1™, pCI™, Nanoplasmid™, and Pcaggs. 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 embodiments, 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), 3β-[N—(N′,N′-dimethylaminoethyl)carbamoyl) cholesterol (DC-chol), 1,2-dioleoyloxy-3-[trimethylammonio]-propane (DOTAP), 1,2-dioctadecyloxy-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-dioleyloxy)propylamine (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,
##STR00024## ##STR00025## [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; I-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)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)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-phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (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, dicetylphosphate, 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 C.sub.10-C.sub.24 carbon chains, e.g., lauroyl, myristoyl, paimitoyl, 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 polyethyloxylated 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) (PFAG) 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-dialkyloxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanoloamine (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-distearoyl-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-I, 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-distearyloxypropyl. In some embodiments, the PEG-lipid includes one of the following:

##STR00026##

[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 of 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 octadecyldimethylbenzyl 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 dextrins; 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 TWEEN™, PLURONICS™ 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, triethanolamine 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 carboxymethylcelluose, 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; orsodium 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.Math.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.Math.kg, 1-3 mg/kg, 1-2 mg/kg, 1-2.5 mg/kg, 2-5 mg.Math.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.Math.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 sub eject 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 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.

[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, 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.

[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 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).

[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, steatotic 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 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.
[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 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). 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). 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 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.

[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 a 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

TABLE-US-00007 TABLE OF CONTENTS 5.1 Example 1. CIDEB selection in Nonalcoholic Steatohepatitis. 5.2 Example 2. Design of CIDEB Targeting RNAi Agents. 5.3 Example 3. Synthesis of CIDEB Targeting RNAi Agents. 5.4 Example 4. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Hep3B Cells. 5.5 Example 5. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes. 5.6 Example 6. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes. 5.7 Example 7. In Vitro dsRNA Agent Mediated Knockdown of hCIDEB in Primary Cyno Hepatocytes. 5.8 Example 8. In Vitro GalNAc-dsRNA Agent Mediated Knockdown of hCIDEB in Hep3B cells. 5.9 Example 9. In Vitro GalNAc-dsRNA Agent Mediated Knockdown of hCIDEB in Primary Human Hepatocytes. 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 A) 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 acetontrile: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-US-00008 TABLE 5 Range % hCIDEB mRNA Remaining (Normalized to GAPDH).

dsRNA 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 60-75 301 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 20-30 372 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 5-15 443 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-US-00009 TABLE 6 IC50, IC80, and Max % Inhibition of hCIDEB mRNA (Normalized to GAPDH). dsRNA % Maximum Agent IC50 [nM] IC80 [nM] 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, 388, 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-US-00010 TABLE 7 IC50, IC80, and Max % Inhibition of hCIDEB mRNA (Normalized to GAPDH). % Maximum DsRNA Agent IC50 [nM] IC80 [nM] 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 ≤ 90 380 >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 hCIDEB 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 hCIDEB 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 hCIDEB 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 CIDEB was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of cyno CIDEB was normalized to the expression of cyno GAPDH. Each treatment group was run in quadruplicate.

[0963] Table 8 shows the percent of cyno CIDEB mRNA remaining after treatment with the indicated dsRNA agent (normalized to GAPDH and relative to control treated cells set to 100%).

TABLE-US-00011 TABLE 8 Range % cyno CIDEB mRNA Remaining (Normalized to GAPDH).

dsRNA CIDEB/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
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 hCIDEB 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 hCIDEB 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 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.

[0967] Table 9 shows the percent of hCIDEB mRNA remaining after treatment with the indicated GalNAc-dsRNA Agent (normalized to GAPDH and relative to control treated cells set to 100%).

TABLE-US-00012 TABLE 9 Range % hCIDEB mRNA Remaining (Normalized to GAPDH).

CIDEB/GAPDH dsRNA Agent	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-US-00013 TABLE 10 IC50, IC80, and Max % Inhibition of hCIDEB mRNA (Normalized to GAPDH). DsRNA % Maximum Agent IC50 [nM] IC80 [nM] 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.

Claims

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 nucleotide 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)