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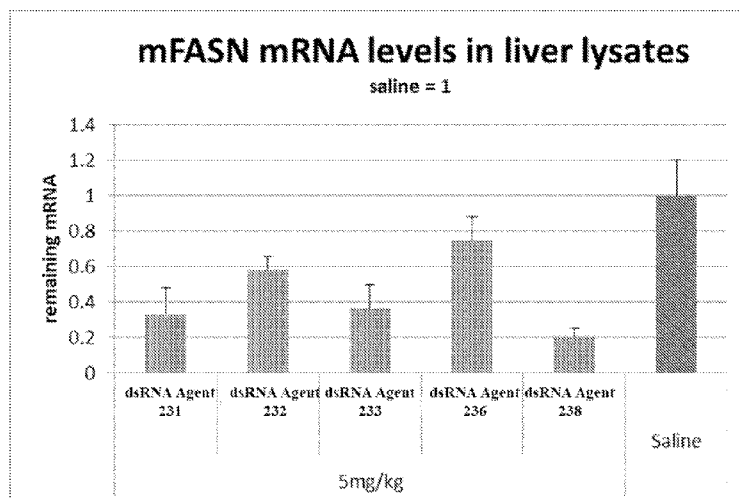


FIG. 2

(57) Abstract: Provided herein are, *inter alia*, agents (e.g., RNAi agents, dsRNA agents) comprising a sense strand and an antisense strand targeting FASN (e.g., hFASN); 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 FASN expression (e.g., mRNA expression), methods of treating FASN associated diseases, and methods of treating liver diseases (e.g., nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD)).

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RNAI AGENTS TARGETING FATTY ACID SYNTHASE AND RELATED METHODS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Serial No.: 63/497,568, filed April 21, 2023, the entire contents of each of which is incorporated herein by reference.

1. FIELD

[0002] This disclosure relates to RNAi agents (*e.g.*, double stranded RNA (dsRNA) agents comprising a sense strand and an antisense strand) targeting fatty acid synthase (FASN). The disclosure further relates to pharmaceutical compositions comprising the same; and methods of utilizing the same, including, *e.g.*, methods of treating FASN associated diseases (*e.g.*, liver diseases).

2. BACKGROUND

[0003] Fatty acids serve a multitude of functions within a cell, including, *e.g.*, as components of cell membranes, substrates in energy metabolism, and as secondary messengers in cell signaling pathways. Structurally, fatty acids comprise a carboxylic acid with a saturated or unsaturated aliphatic chain. Fatty acids can generally be grouped into two categories: essential fatty acids (those an organism cannot synthesize *de novo*) and non-essential fatty acids (those an organism can synthesize *de novo*). A critical enzyme in *de novo* fatty acid synthesis is fatty acid synthase (FASN). FASN is a multifunctional enzyme that catalyzes the *de novo* biosynthesis of long-chain saturated fatty acids starting from acetyl-CoA and malonyl-CoA, using nicotinamide adenine dinucleotide phosphate (NADPH) as a reducing agent. As such, FASN is primarily expressed by lipogenic tissues.

3. SUMMARY

[0004] Provided herein are, *inter alia*, agents (*e.g.*, RNAi agents, dsRNA agents) comprising a sense strand and an antisense strand targeting FASN (*e.g.*, hFASN); 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 FASN expression (*e.g.*, mRNA expression), methods of treating FASN associated diseases, and methods of treating liver diseases (*e.g.*, nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD)).

[0005] Accordingly, in one aspect provided herein are double stranded ribonucleic acid (dsRNA) agents for inhibiting expression of fatty acid synthase (FASN) (*e.g.*, human FASN (hFASN)), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein 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: 232-459 or 916-1143.

[0006] 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 any sense strand set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 4-231 or 688-915. 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 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: 4-231 or 688-915.

[0007] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0008] 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, 26-30, 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, 26-30, 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.

[0009] 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).

[0010] 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.

[0011] 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. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0012] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3; and wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 2 or Table 3.

[0013] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0014] 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, 26-30, 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, 26-30, 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.

[0015] 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).

[0016] 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.

[0017] 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. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0018] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from nucleotides 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-

2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 of SEQ ID NO: 1; wherein 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 corresponding complementary nucleotide sequence of SEQ ID NO: 2.

[0019] In some embodiments, 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: 232-459 or 916-1143. In some embodiments, 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 set forth in any one of SEQ ID NOS: 232-459. In some embodiments, 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 3 or set forth in any one of SEQ ID NOS: 916-1143.

[0020] 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 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: 4-231 or 688-915. 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 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: 4-231 or 688-915. 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 the nucleotide sequence of any one of the sense strands set forth in Table 2 or set forth in any one of SEQ ID NOS: 4-231. 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 the nucleotide sequence of the corresponding sense strand set forth in Table 2 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-231. 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 the nucleotide sequence of any one of the sense strands set forth in Table 3 or set forth in any one of SEQ ID NOS: 688-915. 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 the nucleotide sequence of the corresponding sense strand set forth in Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 688-915.

[0021] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0022] 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, 26-30, 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, 26-30, 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.

[0023] 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).

[0024] 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.

[0025] 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. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0026] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein 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 set forth in any one of SEQ ID NOS: 232-459.

[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 any sense strand set forth in Table 2 or set forth in any one of SEQ ID NOS: 4-231. 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 the corresponding sense strand set forth in Table 2 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-231.

[0028] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0029] 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, 26-30, 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, 26-30, 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.

[0030] 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).

[0031] 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.

[0032] 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. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0033] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 2; and wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 2.

[0034] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0035] 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, 26-30, 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, 26-30, 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.

[0036] 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).

[0037] 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.

[0038] 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). In some embodiments, the sense strand and the

antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0039] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0040] 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, 26-30, 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, 26-30, 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.

[0041] 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).

[0042] 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.

[0043] 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). In some embodiments, the sense strand and the

antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0044] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein 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 3 or set forth in any one of SEQ ID NOS: 916-1143.

[0045] 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 any sense strand set forth in Table 3 or set forth in any one of SEQ ID NOS: 688-915.

[0046] 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 the corresponding sense strand set forth in Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 688-915.

[0047] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0048] 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, 26-30, 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, 26-30, 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.

[0049] 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).

[0050] 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.

[0051] 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. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0052] In one aspect provided herein are dsRNA agents for inhibiting expression of FASN (*e.g.*, hFASN), wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 3; and wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 3.

[0053] 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, substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified. 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.

[0054] 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, 26-30, 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, 26-30, 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.

[0055] 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).

[0056] 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.

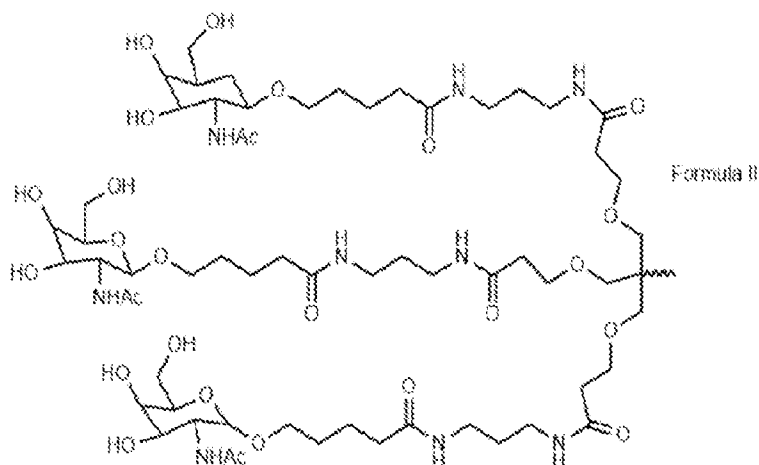
[0057] In some embodiments, the sense strand and the antisense strand are part of a single nucleic acid molecule (*e.g.*, wherein a hairpin loop is between the sense strand and the antisense strand of the single nucleic acid molecule. In some embodiments, the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

[0058] In one aspect, provided herein are conjugates comprising a dsRNA agent described herein and a heterologous moiety.

[0059] In some embodiments, the heterologous moiety is a peptide, protein, carbohydrate, lipid, polymer, or small molecule. In some embodiments, the heterologous moiety is carbohydrate. In some embodiments, the heterologous moiety comprises one or more GalNac.

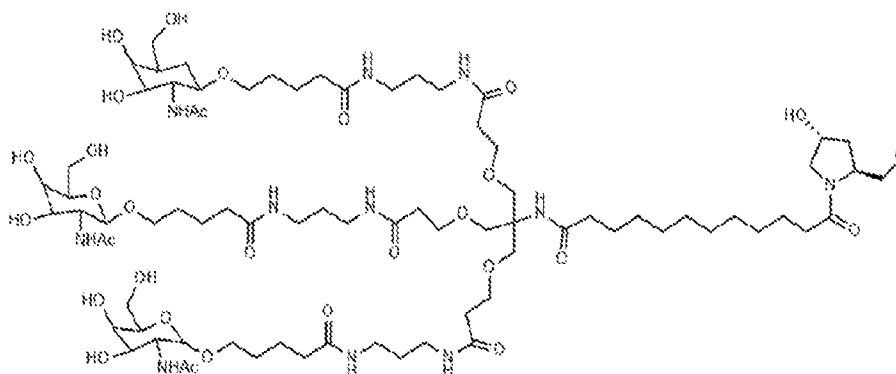
[0060] In some embodiments, the heterologous moiety is a targeting moiety. In some embodiments, the targeting moiety specifically binds to a moiety expressed by hepatocytes

(*e.g.*, on the surface of the hepatocytes). In some embodiments, the targeting moiety comprises GalNac. In some embodiments, the targeting moiety comprises Formula II:



; or

Formula I:



[0061] 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).

[0062] In some embodiments, the heterologous moiety is attached to the dsRNA agent via a linker. In some embodiments, the linker is cleavable.

[0063] 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.

[0064] In one aspect, provided herein are vectors (*e.g.*, a viral vector, a non-viral vector) encoding the antisense strand, the sense strand, or both the antisense and sense strand described herein.

[0065] In one aspect, provided herein are carriers comprising a dsRNA agent described herein or a vector described herein. 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.

[0066] In one aspect, provided herein are cells comprising a dsRNA described herein, a conjugate described herein, a vector described herein, or a carrier described herein.

[0067] In one aspect, provided herein are pharmaceutical compositions comprising a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, or a cell described herein, and a pharmaceutically acceptable excipient.

[0068] In one aspect, provided herein are kits comprising a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein.

[0069] In one aspect, provided herein are methods of delivering a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell 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). In some embodiments, the subject is a human.

[0070] In one aspect, provided herein are methods of delivering a dsRNA, conjugate, vector, carrier, or pharmaceutical composition to a subject, the method comprising administering to the subject a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein, to thereby deliver the dsRNA, conjugate, vector, carrier, or pharmaceutical composition to the subject. In some embodiments, the subject is a human.

[0071] In one aspect, provided herein are methods of reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell, the method comprising delivering into the cell a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein, to thereby reduce or inhibit expression of FASN (*e.g.*, hFASN) in the cell. In some embodiments, the subject is a human.

[0072] In one aspect, provided herein are methods of reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell in a subject, the method comprising administering to the subject a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein, to

thereby reduce or inhibit expression of FASN (*e.g.*, hFASN) in the cell in the subject. In some embodiments, the subject is a human.

[0073] In one aspect, provided herein are methods of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) associated disease in a subject, the method comprising administering to the subject a dsRNA described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the FASN (*e.g.*, hFASN) associated disease in the subject. In some embodiments, the FASN (*e.g.*, hFASN) associated disease is fatty liver, liver inflammation, nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD). In some embodiments, the FASN (*e.g.*, hFASN) associated disease is obesity-induced metabolic syndrome, insulin insensitivity, 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 and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), or cryptogenic SLD. In some embodiments, the subject is a human.

[0074] 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 described herein, a conjugate described herein, a vector described herein, a carrier described herein, a cell described herein, or a pharmaceutical composition described herein, to thereby treat, ameliorate, or prevent the liver disease in the subject. 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 subject is a human.

[0075] In one aspect, provided herein are methods of diagnosing a FASN (*e.g.*, hFASN) 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; and (b) detecting, or having detected, the presence or absence of one or more somatic FASN mutation in the DNA, RNA, or protein, wherein the presence of the one or more somatic mutation indicates that the subject has a FASN (*e.g.*, hFASN) associated disease.

[0076] In some embodiments, the FASN (*e.g.*, hFASN) associated disease is a liver disease. In some embodiments, the FASN (*e.g.*, hFASN) associated 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.

[0077] 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. In some embodiments, the subject is a human.

[0078] 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.

[0079] 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; and (b) detecting, or having detected, the presence or absence of one or more somatic FASN 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. In some embodiments, the liver disease 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.

[0080] 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 FASN mutation in the DNA.

[0081] In some embodiments, the method further comprises administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if a FASN 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, or a pharmaceutical composition described herein.

[0082] 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. In some embodiments, the subject is a human.

[0083] 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.

[0084] In one aspect, provided herein are methods of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of FASN, 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; and (b) detecting, or having detected, the presence or absence of one or more somatic FASN 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.

[0085] 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 FASN mutation in the DNA.

[0086] In some embodiments, the method further comprises administering to the subject the inhibitory nucleic acid molecule if the subject is selected. 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, or a pharmaceutical composition described herein.

[0087] 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. In some embodiments, the subject is a human.

[0088] 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.

[0089] In one aspect, provided herein are methods of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) 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 FASN mutation in the DNA, RNA, or protein, and (c) administering to the subject an inhibitory nucleic acid that inhibits expression of FASN if the one or more FASN somatic mutation is detected in the DNA, RNA, or protein.

[0090] In some embodiments, the FASN (*e.g.*, hFASN) associated disease is a liver disease. 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.

[0091] 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. In some embodiments, the subject is a human.

[0092] 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.

[0093] 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 FASN mutation in the DNA, RNA, or protein, and (c) administering to the subject an inhibitory nucleic acid that inhibits expression of FASN if the one or more FASN somatic mutation is detected in the DNA, RNA, or protein.

[0094] 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, or a pharmaceutical composition described herein.

[0095] 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.

[0096] 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 FASN mutation in the DNA.

[0097] 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. In some embodiments, the subject is a human.

[0098] 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.

[0099] In one aspect, provided herein are *in vitro* methods of screening a sample from a subject for one or more somatic FASN 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 FASN mutation in the DNA, RNA, or protein.

[00100] 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. In some embodiments, the subject is a human.

[00101] 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.

4. BRIEF DESCRIPTION OF THE FIGURES

[00102] FIG. 1A-1H is a bar graph showing the percent of hFASN mRNA remaining in Hep3B cells after 24 hour *in vitro* treatment with the indicated dsRNA agent (normalized to GAPDH and relative to control treated cells set to 100%). For the sake of additional clarity, it is noted that each dsRNA agent has two bars, the left bar shows the results utilizing 20nM of the dsRNA agent and the right bar shows the result utilizing 0.5nM of the dsRNA agent.

[00103] FIG. 2 is a bar graph showing the percent of mFASN mRNA remaining in liver cells from mice treated with the indicated dsRNA agent (normalized to GAPDH).

[00104] FIG. 3 is a bar graph showing the percent of mFASN mRNA remaining in liver cells from mice treated with the indicated dsRNA agent (normalized to GAPDH).

5. DETAILED DESCRIPTION

[00105] The inventors have, *inter alia*, discovered that FASN is increasingly expressed in the liver under conditions of increased fat accumulation (*e.g.*, in NASH). The inventors have further discovered, *inter alia*, RNAi agents that inhibit expression of FASN (*e.g.*, hFASN). As such, the RNAi agents described herein are useful for the treatment of FASN mediated diseases such as liver diseases (*e.g.*, fatty liver disease, NASH, nonalcoholic fatty liver disease (NAFLD)). As such, the current disclosure provides RNAi agents (*e.g.*, dsRNAi agents comprising a sense strand and an antisense strand) capable of inhibiting FASN 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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5.1 Definitions

[00106] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] 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).

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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).

[00115] 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN mRNA)).

[00116] 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.

[00117] As used herein, the term “bicyclic nucleoside” (“BNA”) is a nucleoside comprising a bicyclic sugar.

[00118] 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.

[00119] 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 *in 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).

[00120] 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.

[00121] As used herein, the term “differing by no more than X nucleotides” and the like (*e.g.*, differing by not 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 (as defined herein) 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.

[00122] 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).

[00123] 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.

[00124] As used herein, the term “fatty acid synthase” or “FASN” refers to the enzyme that functions, *inter alia*, to catalyze the synthesis of fatty acids (principally the long-chain saturated fatty acid palmitate) from acetyl-CoA and malonyl-CoA. The term FASN includes human FASN (hFASN). The mRNA sequence of reference hFASN gene is set forth in SEQ ID NO: 1 (NCBI Ref.: NM_004104.5). The amino acid sequence of a reference hFASN protein is set forth in SEQ ID NO: 3 (NCBI Ref.: NP_004095.4). The term FASN includes naturally occurring variants of FASN. FASN 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.

[00125] 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.

[00126] 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.

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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).

[00131] 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.*, §§ 5.3, 5.3.1. 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.

[00132] 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).

[00133] 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.

[00134] 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.

[00135] As used herein, the term “obtaining a sample” refers to the acquisition of a sample. The term includes the direct acquisition from a subject and the indirect acquisition through one or more third parties wherein one of the third parties directly acquired the sample from the subject.

[00136] 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).

[00137] 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.

[00138] 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 SF 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 SF 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.

[00139] 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.

[00140] 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).

[00141] The terms “polynucleotide” and “nucleic acid molecule” 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).

[00142] As used herein, the term “prognostication” and the like refers to the process of estimating/predicting the likely course and/or outcome of a disease in a subject, including, *e.g.*, the chance that a subject has of recovering from the disease.

[0001] 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 as well as polypeptides in the primary structure. Proteins can include more than one polypeptide (*e.g.*, customarily referred to as the quaternary structure).

[0002] 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.

[0003] 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.

[0004] 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.*, FASN) 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.

[0005] As used herein, the term “sample” encompasses a variety of biological specimens obtained from a subject. Exemplary sample types include, *e.g.*, blood, red blood cells, and other liquid samples of biological origin (including, but not limited to, whole-blood, red blood cells (*e.g.*, isolated from whole blood), peripheral blood mononuclear cells (PBMCs), serum, plasma, urine, saliva, amniotic fluid, stool, synovial fluid, etc.), nasopharyngeal swabs, solid tissue samples such as biopsies (or cells derived therefrom and the progeny thereof), tissue cultures (or cells derived therefrom and the progeny thereof), and cell cultures (or cells derived therefrom and the progeny thereof). The term also includes samples that have been manipulated in any way after their procurement from a subject, such as by centrifugation, filtration, washing, precipitation, dialysis, chromatography, lysis, treatment with reagents, enriched for certain cell populations, refrigeration, freezing, staining, etc.

[0006] 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).

[0007] As used herein, the term “somatic mutation” refers to one or more nucleotide alteration (*e.g.*, variation, modification (*e.g.*, variation)) in a genomic DNA sequence (*e.g.*, of a gene) that is acquired during the lifetime of a subject. It is understood in the art that somatic mutations are not present in the germline DNA of an individual and are therefore not inherited from a parent like germline polymorphisms. Somatic mutations may occur spontaneously due to *e.g.*, the infidelity of DNA replication occurring at each cell division creating substitutions, deletions, or additions of nucleotides into the DNA of a cell. A somatic mutation may also be caused by environmental factors such as *e.g.*, ultraviolet radiation, chemical exposure, or viral infections.

[0008] 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), Paleognathae (*e.g.*, ostriches, emus), Columbiformes (*e.g.*, pigeons, doves), or Psittaciformes (*e.g.*, parrots).

[0009] 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.

[0010] 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.

[0011] 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.*, FASN)). In some embodiments, the target nucleic acid sequence is an mRNA molecule formed during the transcription of a target gene (*e.g.*, FASN)). 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 FASN gene. In one embodiment, the target sequence is within the protein coding region of FASN.

[0012] 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.

[0013] 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.

5.2 RNAi Agents

[0014] Provided herein are, *inter alia*, agents (*e.g.*, RNAi agents, dsRNA agents), useful in, *inter alia*, inhibiting expression of fatty acid synthase (FASN) (*e.g.*, human FASN (hFASN)) (*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 FASN (*e.g.*, hFASN) mRNA).

[0015] FASN is a key enzyme in the endogenous lipogenesis pathway. FASN primarily catalyzes the synthesis of fatty acids (principally the long-chain saturated fatty acid palmitate) from acetyl-CoA and malonyl-CoA using NADPH as a reducing agent. The mRNA sequence of a reference hFASN gene is set forth in SEQ ID NO: 1. The reverse complement sequence of the hFASN mRNA is set forth in SEQ ID NO: 2. The amino acid sequence of the hFASN protein encoded by the hFASN reference gene is set forth in SEQ ID NO: 3. *See* Table 1, herein.

Table 1. The mRNA and Amino Acid Sequence of a Reference hFASN Protein.

Description	Amino Acid Sequence	SEQ ID NO
hFAS mRNA NCBI Ref.: NM_004104.5	GAGCCAGAGAGACGGCAGCGGCCCCGGCCUCCCUCCGCGCGCGCUUC AGCCUCCCGCUCCGCGCGCUCCAGCCUCCGCUCCGCGCGCGCGCACC GCCGCGCGCGCGCUCCAGAGCAGCAUGGAGGAGGUGGUGAUUGCC GGCAUGUCCGGGAAGCUGCCAGAGUCGGAGAACUUGCAGGAGUUCUGG GACAACCUCAUCGGCGGUGUGGACAUGGUCACGGACGAUGACCGUCGC UGGAAGGCGGGGCUACCGGCCUGCCCCGGCGGUCGGCAAGCUGAAG GACCUGUCUAGGUUUGAUGCCUCCUUCUCCGAGUCCACCCCAAGCAG GCACACACGAUGGACCCUCCAGCUGCGCGUCGUCGUGGAAGUCACCUAU GAAGCCAUCGUGGACGGAGGCAUCAACCCAGAUUCACUCCGAGGAACA CACACUGGCGUCUGGGUGGGCGUGAGCGGCUUGAGACCUCGGAGGCC CUGAGCCGAGACCCCGAGACACUCGUGGGCUACAGCAUGGUGGGCUGC CAGCGAGCGAUGAUGGCCAACCGGCUCUCCUUCUUCUUCGACUUCAGA GGGCCCAGCAUCGCACUGGACACAGCCUGCUCCUCCAGCCUGAUGGCC CUGCAGAACGCCUACCAGGCCAUCCACAGCGGGCAGUGCCCUGCCGCC AUCGUGGGGGGCAUCAUGUCCUGCUGAAGCCCAACACCUCCGUGCAG UUCUUGAGGCUGGGGAUGCUCAGCCCCGAGGGCACCUGCAAGGCCUUC GACACAGCGGGGAUUGGGUACUGCCGCUCCGAGGGUGUGGUGGCCGUC CUGCUGACCAAGAAGUCCUGGCCCGGGGUGUACGCCACCAUCCUG AACGCCGGCACCAAUACAGAUGGCUUCAAGGAGCAAGGCGUGACCUUC CCCUCCAGGGGAUUAUCCAGGAGCAGCUAUCCGCUCCUUGUACCAGUCG GCCGAGUGGGCCCUGAGUCAUUUGAAUACAUCGAAGCCACGGCACA GGCACCAAGGUGGGCGACCCCCAGGAGCUGAAUGGCAUACCCGAGCC CUGUGCGCCACCCGCCAGGAGCCGUCUCAUCGGCUCCACCAAGUCC AACAUUGGGGACCCGGAGCCAGCCUCGGGGCUGGCAGCCUGGGCAAG GUGCUGCUGUCCUGGAGCACGGGCUUGGGCCCCCAACCUGCACUUC CAUAGCCCCAACCUGAGAUCACAGCGCUGUUGGAUGGGCGGCUGCAG	1

	GUGGUGGACCAGCCCCUGCCCGUCCUGGCGGCAACGUGGGCAUCAAC UCCUUUGGCUUCGGGGGCUCCAACGUGCACAUAUCCUGAGGCCCAAC ACGCAGCCGCCCCCGCACCCGCCCAUAUGCCACCCUGCCCCGUCUG CUGCGGGCCAGCGGACGCACCCUGAGGCCGUGCAGAAGCUGCUGGAG CAGGGCCUCCGGCACAGCCAGGACCUGGCUUCCUGAGCAUGCUGAAC GACAUCGCGGGCUGUCCCCGCCACCGCCAUGCCCUUCCGUGGCUACGCU GUGCUGGGUGGUGAGCGCGGUGGCCAGAGGUGCAGCAGGUGCCCGCU GGCGAGCGCCCGCUCUGGUUCAUCUGCUCUGGGAUGGGCACACAGUGG CGCGGGAUGGGGCUAGGCCUCAUGCGCCUGGACCGCUUCCGAGAUUCC AUCCUACGCUCCGAUGAGGCUGUGAAGCCAUUCGGCCUGAAGGUGUCA CAGCUGCUGCUGAGCACAGACGAGAGCACC UUUGAUGACAUCGUCCA UCGUUUGUGAGCCUGACUGCCAUCAGAUAGGCCUCAUAGACCUGCUG AGCUGCAUGGGGCUAGAGCCAGAUUGCAUCGUCGGCCACUCCUGGGG GAGGUGGCCUGUGGCUACGCCGACGGCUGCCUGUCCAGGAGGAGGCC GUCCUCGCUGCCUACUGGAGGGGACAGUGCAUCAAAGAAGCCCAUCUC CCGCCGGGCGCCAUGGCAGCCGUGGGCUUGUCCUGGGAGGAGUGUAAA CAGCGCUGCCCCCGGGCGUGGUGCCCGCCUGCCACAACUCCAAGGAC ACAGUACCAUUCUGGGACCUCAGGCCCGGUGUUUGAGUUCGUGGAG CAGCUGAGGAAGGAGGGUGUGUUUGCCAAGGAGGUGCGGACCGGGCGU AUGGCCUUCACUCCUACUUAUGGAGGCCAU CGCACCCCCACUGCUG CAGGAGCUCAAGAAGGUGAUCCGGGAGCCGAAGCCACGUUCAGCCCGC UGGCU CAGCACCUCUAUCCCCGAGGCCAGUGGCACAGCAGCCUGGCA CGCACGUCUCCGCCGAGUACAAUGUCAACAACUGGUGAGCCUGUG CUGUUC CAGGAGGCCUGUGGCACGUGCCUGAGCACGCGGUGGUGCUG GAGAU CGCGCCCCACGCCUGCUGCAGGCUGUCCUGAAGCGUGGCCUG AAGCCGAGCUGCACC AUCAUCCCCUGAUGAAGAAGGAUCACAGGGAC AACCUGGAGUUCUCCUGGCCGGCAUCGGCAGGCUGCACCUCUCAGGC AUCGACGCCAACC CCAUGCCUUGUUCCACCUGUGGAGUUC CAGCU CCCCGAGGAACUCCCCU CAUCUCCCCACUCAUAAGUGGGACCACAGC CUGGCCUGGGACGUGCCGGCCGCCGAGGACUCCCCAACGGUUCAGGU UCCCCUCAGCCGCCAU CUACAACAUCGACACCAGCUC CAGUCUCCU GACCACUACCUGGUGGACCACACCUCGACGGUCGCGUCCUCUCCCC GCCACUGGCUACCUGAGCAUAGUGGGAAGACGCGGCCCGCGCCUG GGCCUGGGCGUCGAGCAGCUGCCUGUGGUGUUUGAGGAUGUGGUGCUG CACCAGGCCACCAUCCUGCCCAAGACUGGGACAGUGUCCUGGAGGUA CGGCUCCUGGAGGCCUCCCGUGCCUUCGAGGUGUCAGAGAACGGCAAC CUGGUAGUGAGUGGGAAGGUGUACCAGUGGGAUGACCCUGACCC CAGG CUCUUCGACCACCCGGAAGCCCCACCCCAACCCACGGAGCCCCUC UUCUGGCC CAGGCUGAAGUUACAAGGAGCUGCGUCUGCGUGGCCUAC GACUACGGCCCUCAUUC CAGGGCAUCCUGGAGGCCAGCCUGGAAGGU GACUCGGGGAGGCUGCUGUGGAAGGAUAACUGGGUGAGCUUCAUGGAC ACCAUGCUGCAGAUGUCCAUCCUGGGCUCGGCCAAGCACGGCCUGUAC CUGCCCACCCGUGUCACCGCCAUCCACAUCGACCCUGCCACCCACAGG CAGAAGCUGUACACACUGCAGGACAAGGCCCAAGUGGCUGACGUGGUG GUGAGCAGGUGGCUGAGGGUCACAGUGGCCGGAGGCGUCCACAUCUCC GGGCUCCACACUGAGUCGGCCCCGCGCGGCAGCAGGAGCAGCAGGUG CCCAUCCUGGAGAAGUUUUGCUUCACUCCCCACACGGAGGAGGGGUGC CUGUCUGAGCGCGCUGCCUGCAGGAGGAGCUGCAACUGUGCAAGGGG CUGGUGCAGGCACUGCAGACCAAGGUGACCCAGCAGGGGCGUAAGAUG GUGGUGCCCGGACUGGAUGGGGGCCAGAUCCCCGGGACCCUCACAG CAGGAACUGCCCCGGCUGUUGUGCGCUGCCUGCAGGCUUCAGCUCAAC GGGAACUGCAGCUGGAGCUGGCGCAGGUGCUGGCC CAGGAGAGGCC AAGCUGCCAGAGGACCCUCUGCUCAGCGGCCUCCUGGACUCCCCGGCA CUCAAGGCCUGCCUGGACACUGCCGUGGAGAAUAUGCCCAGCCUGAAG AUGAAGGUGGUGGAGGUGCUGGCCUGGCCACGGUCACCUGUAUCCCCG	
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	AGCCCGAGUGGAUGAGCAGCGUCUCCCCGGGGCGCACCCGCCACGCA CCACCAGCGCGUAGUAGGCCGUGCUGUAGACGACAGGCACCGAGGCCG CCUCCUCCAGCGUCCAGUUGGAAGGCACAUCCCAGAGGAAGUCCGGUG ACAGCAGGACAGAGGUGGCCAGGCCUUGGCAGGCACCAGUCCCAUCA CACGCUUGCCGCUGGCGUCUCGGCCCGAGAACUCCAUAACUAGCAGGC UGUCCUGGGAGGUCCACUCCUUGGGAUGGCAUCAGGGGACAGCUUGC CAGUGGCCAGCAUGAUGUCGCGGAAGUUGAGGGAGGCGUAGUAGACCG UGCAGAGCUGGGCGCCAGGGCAGGUGGGCUGGGCAUGGCGCAGCGAGG AGCAGACCCAGCGGAUGGAGGACAGGUCCCCCGGGUGAGGGUGCUCA CAAAGGCAUGUGCCGUCGGCUCCUAGGCUUUGUCCUCCUCCAGCAGGA AGUGGGCGAAAGCCCCCAGGCCCGUCGCGGUAGACGUUCAUCACCA GGUCUCCUGCAACACCUUCUGCAGUUCUGCGGAGCCCGGGUCCACCU CCGGGACGUGGGAGGUGCUGCUGAGGUUGGAGAGCAGCACACACCGGA GGCGGUUCCCGCCGGGCUUCGCGGGAGACAGUUCACCAAGCCACCA CGCCCGAGGUGGCACAGUUGAUGGCCUUCAGCCACACAGGCCGGGAAG AGUCUUCGUCAGCCAGGAUGCCUUCAGAGACUCCACCCAGCGGAAGC UGGUUAUCGUCCACCGGCAGGAAGAUUGGGGCUUCCUGCGGGGUGGGCC GGCGGCACAGGAAGAGCGUGGAGCCGUAGAAGGACUUCUUCAGGCCCA CCAGGCGCAGCGACACCCUGGAGAAGAGGCUUCCACGCGUCCUGGC UCAGGAUGCCUGGCCAUACUGCGGCUAGUGGAGGUGAGGAAGGCCA CGAUGUCCCCGAGGGGUGCCCCCGGAGCAGUGUGCAGGAGCAGAA AGCCCCUUCUCUAGGGCAGCCACCAUGUUGCUGAGAGCUGAGGCCG GGUCCCCGAGGGCAGCCACAGCACAGUUGCACACCAGGAGGUCGGCGC UGCCCGAGGGCGCUGGGGGCAGGGUCUGCGGGAUCCACUGGCCCUUGG CAACGUCGUGCUGCUGCAGCUCGGCCUGGGCAGCCUCCAGGGCCUGGG GGUGGGGUGCGGUGGCCGUGUAGCUCAGCUGCAGCAGGGGAUGGGGGC UGAGCAGGCCUGGGAUGCGGGAAUACAGGUGACCGUGGCCAGCCAGCA CCUCCACCACCUUCAUCUUCAGGCUUGGCAUGUUCUCCACGGCAGUGU CCAGGCAGGCCUUGAGUGCCGGGGAGUCCAGGAGGCCGUGAGCAGAG GGUCCUUCUGGCAGCUUGGGCCUUCUUGGGCCAGCACCUGCGCCAGCU CCAGCUGCAGGUUCCCGUUGAGCUGAAGCCUGCAGGCAGCCGACAACA GCCGGGGCAGUUCUUGCUGUGAGGGGUCCCGGGGAUCUGGGCCCCAU CCAGUCCGGGCACCACCAUCUUCAGCCCCUGCUGGGUACCUUGGUCU GCAGUGCCUGCACCAGCCCCUUGCACAGUUGCAGCUCCUCCUGCAGGG CAGCGCGCUCAGACAGGCACCCUCCUCCUGUGGGGAGUGAAGCAAA ACUUCUCCAGGAUGGGCACCUGCUGCUCCUGCUGCCGCCCGGGGGCCG ACUCAGUGUGGAGCCCGGAGAUGUGGACGCCUCCGGCCACUGUGACCC UCAGCCACCUGCUCACCACCAGUCAGCCACUUGGGCCUUGUCCUGCA GUGUGUACAGCUUCUGCCUGUGGGUGGCAGGGUCGAUGUGGAUGGCGG UGACACGGGUGGGCAGGUACAGGCCGUGCUUGGCCGAGCCAGGAUGG ACAUCUGCAGCAUGGUGUCCAUGAAGCUCACCCAGUUAUCCUCCACA GCAGCCUCCCCGAGUACCUUCCAGGCUUGCCUCCAGGAUGCCUGGA AAUGAGGGCCGUAGUCGUAGCCACGCAGACGCAGCUCCUUGUAAACUU CAGCCUGGGCCAGGAAGAGGGGCUCCGUGGGGUUGGGGUGGGGCUUU CCGGGUGGUCGAAGAGCCUGGGGUCAGGGUCAUCCACUGGUACACCU UCCCACUCACUACCAGGUUGCCGUUCUCUGACACCUCGAAGGCACGGG AGGCCUCCAGGAGCCGUACCUCAGGGACACUGUCCAGUCUUGGGCA GGAUGGUGGCCUGGUGCAGCACCACAUCUCAAACACCACAGGCAGCU GCUCGACGCCCAGGCCAGGGCGCGGGCCAGCGUCUCCACACUAUGC UCAGGUAGCCAGUGGCGGGGAAGAGGACGCGACCGUCGAGGGUGUGGU CCACCAGGUAGUGGUCAGGAGACUCGGAGCUGGUGUCGAUGUUGUAGA UGGCGGCUGAGGGGGAACCUGAACCGUUGGGGAAGUCCUGGCGGGCCG GCACGUCCAGGCCAGGCUUGGUUCCACUUGAUGAGUGGGGAGAUGA GGGGAGUUCUCGGGGAGCUGGGAACUCCACAGGUGGGAACAAGGCAU UGGGGUUGGCGUCGAUGCCUGAGAGGUGCAGCCUGCCGAUGCCGGCCA	
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	GGAAGAACUCCAGGUUGUCCUGUGAUCCUUCUUAUCAGGGGGAUGA UGGUGCAGCUCGGCUUCAGGCCACGCUUCAGGACAGCCUGCAGCAGGG CGUGGGGCGCGAUCUCCAGCACCACCGCGUCUCAGGCACGUGCCACA GGGCCUCCUGGAACAGCACAGGGCUACCAGGUUGUUGACAUUGUACU CGGCGGAGGACGUGCGUGCCAGGCUGCUGUGCCACUGGGCCUCGGGGA UAGAGGUGCUGAGCCAGCGGGCUGAACGUGGCUUCGGCUCCCGGAUC CCUUCUUGAGCUCUGCAGCAGUGGGGGUGCGAUGGCCUCCAUGAAGU AGGAGUGGAAGGCCAUACCGCCGGUCCGCACCUCUUGGCAAACACAC CCUCCUUCUCAGCUGCUCACGAAACUCAAACACCGGGGCCUGAGGUC CCGAGAUGGUGACUGUGUCCUUGGAGUUGGCGAGGCGGGCACCACGC CCGGGGGGCAGCGCUGUUACACUCCUCCAGGACAAGCCCACGGCUG CCAUGGCGCCCGGGGAGAUUGGGCUUCUUGAUGCACUGUCCCCUCC AGUAGGCAGCGAGGACGGCCUCCUCCUGGGACAGGCAGCCGUCGGCGU AGCCACAGGCCACCUCGCCAGGGAGUGGCCGACGAUGCCAUCUGGCC UCAGCCCCAUGCAGCUCAGCAGGUCUAUGAGGCCUAUCUGGAUGGCAG UCAGGCUCACAAACGAAUGGACGAUGUCAUCAAAGGUGCUCUCGUCUG UGCUCAGCAGCAGCUGUGACACCUUCAGGCCGAAUGGCUUCACAGCCU CAUCGGAGCGUAGGAUGGAAUCUCGGAAGCGGUCCAGGCGCAUGAGGC UCAGCCCCAUCCCGCGCCACUGUGGCCCAUCCAGAGCAGAUGAACC AGAGCGGGCGCUCGCCAGCGGGCACCUGCUGCACCUCUGGGCCACCGC GCUACACCACCCAGCACAGCGUAGCCACGGAAGGGCAUGGCGGUGGGCG GGACAGCCGCGAUGUCGUUCAGCAUGCUCAGGAAAGCCAGGUCCUGGC UGUGCCGGAGGCCUCCUCCAGCAGCUUCUGCACGGCCUCAGGGGUGC GUCCGCUGGCCCGCAGCAGACGGGGCAGGGUGGCAUGUGGGGCGGGUG CGGGGGGCGGCGUGCGUGUUGGGCCUCAGGAUGAUGUGCACGUUGGAGC CCCCGAAGCCAAAGGAGUUGAUGCCACGUUGCCGCCACGGACGGGCA GGGGCUGGUCCACCACCUGCAGCCGCCAUCCAACAGCGCUGGGAUUCU CAGGGUUGGGGCUAUGGAAGUGCAGGUUGGGGGCCAGAGCCCGUGCU CCAGGGACAGCAGCACCUGGCCAGGGCUGCCAGCCCCGAGGCUGGCU CCGGGUGCCCCAUGUUGGACUUGGUGGAGCCGAUGAGCAGCGGCUCCU GGCGGGUGGGCGCACAGGGCUCGGGUGAUGCCAUUCAGCUCUUGGGGU CGCCACCUCUGGUGCCUGUGCCGUGGGCUUCGAUGUAUCAAUGACU CAGGGGCCACUCCGGCCGACUGGUACAACGAGCGGAUGAGCUGCUCCU GGAUAUCCCUUGAGGGGAAGGUCACGCCUUGCUCUUGAAGCCAUCUG UAUUGGUGCCGGCGUUCAGGAUGGUGGCGUACACCCGCCGGGCCAGGG ACUUCUUGGUCAGCAGGACGGCCACCACACCCUCCGAGCGGCAGUACC CAUUCGCCGUGUGUCGAAGGCCUUGCAGGUGCCUCGGGGCUGAGCA UCCCCAGCCUCAAGAACUGCACGGAGGUGUUGGGCUUCAGCAGGACAU UGAUGCCCCCACGAUGGCGGCAGGGCACUGCCCGUGUGGAUGGCCU GGUAGGCGUUCUGCAGGGCCAUCAGGCUUGGAGGAGCAGGCUGUGUCCA GUGCGAUGCUGGGCCUCUGAAGUCGAAGAAGAAGGAGAGCCGGUUGG CCAUCAUCGCUCGCUGGCAGCCACCAUGCUGUAGCCACGAGUGUCU CGGGGUCUCGGCUCAGGGCCUCCGAGGUCUCAGAGCCGCUCACGCCCA CCCAGACGCCAGUGUGUGUUCUCGGAGUGAAUCUGGGUUGAUGCCUC CGUCCACGAUGGCUUCAUAGGUGACUUCAGCAGCAGCCGCAGCUGAG GGUCCAUCGUGUGGCCUGCUUGGGGUGGACUCCGAAGAAGGAGGCAU CAAACCUAGACAGGUCCUUCAGCUUGCCGGACCGCCGGGGCAGGCCGU AGAGCCCCGCCUUCAGCGACGGUCAUCGUCGUGACCAUGUCCACAC CGCCGAUGAGGUUGUCCAGAACUCCUGCAAGUUCUCCGACUCUGGCA GCUUCCCGGACAUGCCGGCAAUACCAACCUCUCCAUGGCUGCUCUGG UGAGGGCGCGGGCGGGGUGCGGGCGGGGAGAGCGAGGCUGGAGCGC GGCGGAGCGGGAGGCUGAAGCGCGGGGAGAGGGAGGCCGGGGCCGCU GCCGUCUCUCUGGCUC	
hFAS Protein	MEEVVIAGMSGKLPESENLQEFWDNLIIGVDMVTDDDRRWKAGLYGLP RRSGKLDLSRFDASFFGVHPKQAHMTDPQLRLLEVTYEAIVDGGIN	3

NCBI Ref.: NP_004095.4	PDSLGRGTHGTGVWVGVSGETSEALS RDPETLVGYSMVGCQRAMMANRL SFFFD FRGPSIALDTACSSSIMALQNA YQAIHSGQCPAAIVGGINVL KPNTSVQFLRLGMLSPEGTCKAFDTAGNGYCRSEGVVAVLLTKKSLAR RVYATILNAGTNTDGFKEQGVTFPSGDIQEQLIRSLYQSAGVAPESFE YIEAHGTGTKVGDPQELNGITRALCATRQEPLLI GSTKSNMGHPEPAS GLAALAKVLLSLEHGLWAPNLHFHSPNPEIPALLDGR LQVVDQPLPVR GGNVGINSFGFGGSNVHII LRPNTPPPAPAPHATLPRLLRASGRTP AVQKLEQGLRHSQDLAFLSMLNDIAAVPATAMPFRGYAVLGGERGGP EVQQVPAGERPLWFICSGMGTQWRGMGLSLMRLDRFRDSILRSDEAVK PFGLKVSQ LLLSTDESTFDDIVHSFVSLTAIQIGLIDL LSCMGLRPDG IVGHS LGEVACGYADGCLSQEEAVLAAYWRGQC I KEAHLPPGAMA AVG LSWEECKQRCPPGVVPACHNSKDTVTISGPQAPVFEFVEQLRKEGVFA KEVRTGGMAFHSYFMEAIA PPLLQELKKVIREPKPRSARWLSTSIPEA QWHSSLARTSSAEYNVNNLVSPVLFQEALWHVPEHAVVLEIAPHALLQ AVLKRGLKPSCTIIPLMKKDHRDNLEFFLAGIGRLHLSGIDANPNALF PPVEFPAPRGTP LISPLIKWDHSLAWDVPA AEDFPNGSGSPSAAIYNI DTSSSPDHYLVDHTLDGRVLF PATGYLSIVWKT LARALGLGVEQLPV VFEDVVLHQATILPKTGTVSLEVRLL EASRAFEVSENGNLVVS GKVYQ WDDPD PRLFDHPESPTPNPTEPLFLAQAEVYKELRLRGYDYGPHFQGI LEASLEGDSGRLLWKDNWVSFMDTMLQMSILGSAKHGLYLPTRVTAIH IDPATHRQKLYTLQDKAQVADVVSRLRVTVAGGVHISGLHTESAPR RQQEQQVP ILEKFCFTPHTEEGCLSERAA LQEELQLCKGLVQALQTKV TQQGLKMVVPGLDGAQIPRDP SQQELPRLLSAACRLQLNGNLQLELAQ VLAQERPKLPEDPLLSGLLSPALKACLD TAVENMPSLKMKVVEVLG HGHLYSRIPLGLSPHPLLQLSYATDRH FQALEAAQAE LQQHDVAQGG WDPADPAPSALGSADLLVCNCAVAALGDFASALSNMVAALREGGFLL HTLLRGHPLGDIVAFLTSTEPQYGGILSQDAWESLFSRVSLRLVGLK KSFYGSTLFLCRRPTPQDSPIFLPVDDTSFRWVESLKGILADEDSRP VWLKAINCATSGVGLVNCLRREP GGNRLRCVLLSNLSSTSHVPEVDP GSAELQKVLQGDLMNVYRDGAWGA FRHFLLEEDKPEEPTAHAFVSTL TRGDLSSIRWVCSSLRHAQPTCPGAQLCTVYYASLNFRDIMLATGKLS PDAIPGKWT SQD SLLGMEFSGRDASGKRV MGLVPAKGLATSVLLSPDF LWDVPSNWTLEEAASVPVYSTAYYALVVRGRVRPGETLLIHSGSGGV GQAAIAIALSLGCRVFTTVGSAEKRAYLQARFPQLDSTSFANSRDTSF EQHVLWHTGGKGVDLVNL SLAEKQLQASVRCLATHGRFLEIGKFDLSQ NHPLGMAIFLKNVTFHGVLLDAFFNESSADWREVWALVQAGIRDGVVR PLKCTVFHGAQVEDAFRYMAQ GKHIGKV VVQVLAE EPEAVLKGAKPKL MSAISKTFCPAHKSYIIAGGLGGFGL ELAQWLIQRGVQKLVLT SRSGI RTGYQAKQVRRWR RQGVQVQVSTSNIS SLEGARGLIAEAAQLGPVGGV FNLAVVLRDGLLENQTPEFFQDVCKPKYSGTLNLDRVTREACPELDYF VVFSSVSCGRGNAGQSNYGFANSAMERICEKRRHEGLPGLAVQWGAIG DVGILVETMSTNDTIVSGTLPQRMASCLEVLDFLNLQPHMVLSSFVLA EKAAAYRDRDSQRDLVEAVAHILGIRDLAAVNLDSS LADLGLDSLMSV EVRQTLERELNLVLSVREVRQLTLRKLQELSSKADEASELACPTPKED GLAQQTQLNLRSLVNPEGPTLMRLNSVQSSERPLFLVHP IEGSTTV FHSLASRLSIPTYGLQCTRAAPLDSIHS LAAYYIDCIRQVQPEGPYRV AGYSYGACVAFEMCSQLQAQQSPAPTHNSLFLFDGSPTYVLAYTQSYR AKLTPGCEAAEAE TEAICFFVQQFTDMEHNRVLEALLPLKGLEERVAAA VDLI IKSHQGLDRQELSFAARSFYYKLRAAEQYTPKAKYHGNVMLLRA KTGGAYGEDLGADYNLSQVCDGKVS VHVIEGDHRTLLEGGSGLESIISI IHSSLAEPVSVREG
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[0016] 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.

[0017] 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.

5.2.1 Antisense Strand

5.2.1.1 Targeting Region

[0018] 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN mRNA)).

[0019] 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN mRNA)).

[0020] 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN mRNA))).

[0021] 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.

[0022] 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 FASN mRNA). In some embodiments, the target nucleic acid molecule is a contiguous nucleotide sequence of a target mRNA (*e.g.*, a FASN 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).

[0023] In some embodiments, the target nucleic acid molecule is a target mRNA (*e.g.*, a FASN 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 FASN mRNA). In some embodiments, the target nucleic acid molecule is at least a portion (*e.g.*, a portion) of an mRNA (*e.g.*, a FASN 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 FASN gene). In some embodiments, the target nucleic acid molecule is at least a portion (*e.g.*, a portion) of a FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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).

[0024] In some embodiments, the target nucleic acid molecule comprises or consists of from about 19-30 nucleotides, *e.g.*, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24, 20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, 21-22, 22-30, 22-29, 22-28, 22-27, 22-26, 22-25, 22-24, 22-23, 23-30, 23-29, 23-28, 23-27, 23-26, 23-25, 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.

5.2.1.2 Overall Length

[0025] 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, 26-30, 27-30, 28-30, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides.

[0026] 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.

5.2.1.3 Exemplary Antisense Strands

[0027] 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.

[0028] 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.

[0029] 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.

[0030] Table 2 and Table 3 further identify the target nucleic acid molecule within the cited reference FASN 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 FASN mRNA transcript targeted by the select antisense strand.

[0031] 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: 232-459 or 916-1143. 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 NOS: 232-459 or 916-1143. 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: 232-459 or 916-1143. 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: 232-459 or 916-1143.

[0032] 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: 232-459 or 916-1143. 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: 232-459 or 916-1143. 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: 232-459 or 916-1143.

[0033] In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 232-459 or 916-1143 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: 232-459 or 916-1143. In some embodiments, the nucleotide sequence of the antisense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 232-459 or 916-1143.

[0034] As described above, Table 2 and Table 3 further identify the target nucleic acid molecule within the cited reference FASN 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: 232-459 or 916-1143 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 FASN mRNA transcript targeted by the select antisense strand.

[0035] 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 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0036] 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 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0037] 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 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0038] As described above, Table 2 and Table 3 further identify the target nucleic acid molecule within the cited reference FASN 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 1-228 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 FASN mRNA transcript targeted by the select antisense strand.

[0039] It is to be understood, that although the antisense strands set forth in Table 2 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 that is unmodified, unconjugated, modified (*e.g.*, as described herein), or conjugated (*e.g.*, as described herein).

[0040] It is to be understood, that the antisense strands set forth in Table 3 are modified (*e.g.*, comprising chemically modified nucleotides), conjugated, etc., the disclosure includes any antisense strand set forth in Table 3 that is unmodified, unconjugated, alternatively modified (*e.g.*, as described herein), or conjugated (*e.g.*, as described herein).

5.2.2 Sense Strand

5.2.2.1 Antisense Strand Complementarity

[0041] 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).

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

5.2.2.2 Overall Length

[0046] 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, 26-30, 27-30, 28-30-, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides.

[0047] 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 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.

5.2.2.3 Exemplary Sense Strands

[0048] 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.

[0049] 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.

[0050] 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.

[0051] Table 2 and Table 3 further identify the target nucleic acid molecule within the reference FASN 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 FASN mRNA transcript identical to the select sense strand.

[0052] 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: 4-231 or 688-915. 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: 4-231 or 688-915. 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: 4-231 or 688-915. 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: 4-231 or 688-915.

[0053] 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: 4-231 or 688-915. 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: 4-231 or 688-915. 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: 4-231 or 688-915.

[0054] In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-231 or 688-915 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: 4-231 or 688-915. In some embodiments, the nucleotide sequence of the sense strand comprises the nucleotide sequence set forth in any one of SEQ ID NOS: 4-231 or 688-915.

[0055] As described above, Table 2 and Table 3 further identify the target nucleic acid molecule within the reference FASN 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: 4-231 or 688-915 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 FASN mRNA transcript identical to the select sense strand.

[0056] 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 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0057] 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 1-228 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 of any one of dsRNA agents 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0058] 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 1-228 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 of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3.

[0059] As described above, Table 2 and Table 3 further identify the target nucleic acid molecule within the reference FASN 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 1-228 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 FASN mRNA transcript identical to the select sense strand.

[0060] 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-8461, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-

558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-

7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 of SEQ ID NO: 1.

[0061] 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720,

2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 of SEQ ID NO: 1.

[0062] As described above, Table 2 and Table 3 further identify the target nucleic acid molecule within the reference FASN 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-8461, or 8422-8471 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 FASN mRNA transcript identical to the select sense strand.

[0063] It is to be understood, that although the sense strands set forth in Table 2 are not described as being modified (*e.g.*, comprising chemically modified nucleotides), conjugated, etc., the disclosure includes any sense strand set forth in Table 2 that is unmodified, unconjugated, modified (*e.g.*, as described herein), or conjugated (*e.g.*, as described herein).

[0064] It is to be understood, that although the sense strands set forth in Table 3 are described as being modified (*e.g.*, comprising chemically modified nucleotides), conjugated, etc., the disclosure includes any sense strand set forth in Table 3 that is unmodified, unconjugated, alternatively modified (*e.g.*, as described herein), or conjugated (*e.g.*, as described herein).

5.2.3 dsRNA Agents

[0065] 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 § 5.2.1) and a sense strand (*e.g.*, described herein, *e.g.*, described in § 5.2.2) 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)).

[0066] 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 FASN mRNA), a portion of a target mRNA (*e.g.*, a FASN 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.

5.2.3.1 Single & Multiple Nucleic Acid Molecules

[0067] 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.

[0068] 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).

[0069] 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).

5.2.3.2 Length of Double Stranded Region

[0070] 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.

[0071] 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.

5.2.3.3 Nucleotide Overhangs & Blunt Ends

[0072] 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 §§ 5.3, 5.3.1).

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

5.2.3.4 Exemplary Structural Combinations of Sense & Antisense Strands

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

5.2.3.5 Exemplary Antisense Strands & Sense Strands

[0086] 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 § 5.2.1. In some

embodiments, the sense strand is a sense strand described in § 5.2.2. In some embodiments, the antisense strand is an antisense strand described in § 5.2.1; and the sense strand is a sense strand described in § 5.2.2. It is to be understood that any sense strand described herein (*e.g.*, in § 5.2.2); and be utilized in combination with any antisense strand in a dsRNA agent described herein (*e.g.*, in § 5.2.1). For the sake of clarity, the entire contents of in §§ 5.2.1 and § 5.2.2, are incorporated by reference into the instant section in § 5.2.3.5.

[0087] 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; 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. 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; 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. 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; 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. 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; 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. 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; 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.

[0088] 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; 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. 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; 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. 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; 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. 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; 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.

[0089] 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; 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. 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; 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. 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; 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. 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; 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. 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; 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. 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; 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. 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; 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.

[0090] 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 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the antisense strand set forth in Table 2; 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 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the sense strand set forth in Table 2.

[0091] 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; 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.

[0092] 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; 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. 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; 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. 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; 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. 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; 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. 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; 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.

[0093] 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; 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. 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; 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. 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; 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. 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; 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.

[0094] 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; 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. 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; 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. 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; 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. 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; 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. 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; 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. 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; 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. 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; 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.

[0095] 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 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the antisense strand set forth in Table 2; 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 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the corresponding sense strand set forth in Table 2.

[0096] 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; 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.

[0097] 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231.

[0098] 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231.

[0099] 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231. 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: 232-459; 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: 4-231.

[00100] 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: 232-459 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: 4-231; 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: 232-459 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: 4-231.

[00101] 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: 232-459; 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: 4-231.

[00102] 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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:

232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231).

[00103] 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231).

[00104] 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231). 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: 232-459; 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: 4-231).

[00105] 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: 232-459 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: 232-459; 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: 4-231) 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: 4-231.

[00106] 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: 232-459; 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: 4-231).

[00107] 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 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 3.

[00108] 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 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 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 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 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 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 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 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 3.

[00109] 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 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 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 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 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 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 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 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 3.

[00110] 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 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 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 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 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 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 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 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 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 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 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 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 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 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 3.

[00111] 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 3 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the antisense strand set forth in 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 3 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the sense strand set forth in Table 3.

[00112] 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 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 3.

[00113] 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 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 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 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 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 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 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 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 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 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 3.

[00114] 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 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 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 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 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 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 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 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 3.

[00115] 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 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 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 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 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 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 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 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 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 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 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 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 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 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 3.

[00116] 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 3 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the antisense strand set forth in 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 3 differing by no more than 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the corresponding sense strand set forth in Table 3.

[00117] 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 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 3.

[00118] 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: 916-1143;

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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915.

[00119] 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915.

[00120] 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915. 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: 916-1143; 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: 688-915.

[00121] 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: 916-1143 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: 688-915; 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: 916-1143 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: 688-915.

[00122] 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: 916-1143; 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: 688-915.

[00123] 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915).

[00124] 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915).

[00125] 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915). 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: 916-1143; 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: 688-915).

[00126] 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: 232-459 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: 232-459; 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: 688-915) 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: 688-915.

[00127] 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: 232-459; 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: 688-915).

[00128] 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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.

[00129] 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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.

[00130] 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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 1-228; 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.

[00131] 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 1-228 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 1-228; 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.

[00132] 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 1-228; 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.

[00133] 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-

3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-84711 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955,

4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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.

[00134] 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-

3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 nucleotides 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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.

[00135] 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 nucleotides 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925,

2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-8461, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-8461, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-

2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-8461, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973,

8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-

2570,2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235,2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 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.

5.2.3.6 Exemplary dsRNA Agents

[00136] The nucleotide sequence of exemplary unmodified dsRNA agents comprising a sense and antisense strand (*e.g.*, suitable for targeting hFASN, suitable for inhibiting hFASN expression)) are set forth in Table 2. More specifically, Table 2 sets forth the nucleotide sequence of exemplary sense strands, antisense strands, and dsRNA agent pairs of sense and antisense strands. It is to be understood that while the sense and antisense strands are set forth in pairs in Table 2, the disclosure encompasses dsRNA agents comprising any sense strand and any antisense set forth in Table 2 (*e.g.*, that are at least partially complementary (*e.g.*, as could be determined by a person of ordinary skill in the art)). It is to be understood that while the nucleotide sequence of the sense strands and antisense strands in Table 2 are set forth as unmodified (not containing any modified nucleotides), the disclosure encompasses the sense and antisense sense strands set forth in Table 2 comprising one or more modified nucleotide (*e.g.*, as described herein).

Table 2. Unmodified Sense and Antisense Strand Sequences of FASN dsRNA Agents.

dsRNA Agent ID	Sense Sequence 5'to 3'	SEQ ID NO	Range in NM_004 104.5	Antisense Sequence 5'to 3'	SEQ ID NO	Range in NM_004 104.5	mRNA Target Sequence	SEQ ID NO
1	CUCUACGGC CUGCCCCGG CGA	4	253-273	UCGCCGGGGC AGGCCGUAGA GCC	232	251-273	GGCUCUACGG CCUGCCCCGG CGG	460
2	GCCUGCCCC GGCGGUCCG GCA	5	260-280	UGCCGGACCG CCGGGGCAGG CCG	233	258-280	CGGCCUGCCC CGCGGUCCG GCA	461

3	CUGCCCCGG CGGUCCGGC AAA	6	262-282	UUUGCCGGAC CGCCGGGGCA GGC	234	260-282	GCCUGCCCCG GCGGUCCGGC AAG	462
4	ACUGGCGUC UGGGUGGGC GUA	7	436-456	UACGCCCACC CAGACGCCAG UGU	235	434-456	ACACUGGCGU CUGGGUGGGC GUG	463
5	AGCAUGGUG GGCUGCCAG CGA	8	514-534	UCGCGUGGAG CCCACCAUGC UGU	236	512-534	ACAGCAUGGU GGGCGGCCAG CGA	464
6	GCAUGGUGG GCUGCCAGC GAA	9	515-535	UUCGCGGGCA GCCCACCAUG CUG	237	513-535	CAGCAUGGUG GGCUGCCAGC GAG	465
7	CAUGGUGGG CUGCCAGCG AGA	10	516-536	UCUCGCGUGG AGCCACCAU GCU	238	514-536	AGCAUGGUGG GCUGCCAGCG AGC	466
8	AUGAUGGCC AACCGGCUC UCA	11	538-558	UGAGAGCCGG UUGGCCAUCA UCG	239	536-558	CGAUGAUGGC CAACCGGCUC UCC	467
9	GGCACCUGC AAGGCCUUC GAA	12	751-771	UUCGAAGGCC UUGCAGGUGC CCU	240	749-771	AGGGCACCUG CAAGGCCUUC GAC	468
10	UGGCCCGGC GGGUGUACG CCA	13	836-856	UGGCGUACAC CCGCCGGGCC AGG	241	834-856	CCUGGCCCGG CGGGUGUACG CCA	469
11	GGCCCGGCG GGUGUACGC CAA	14	837-857	UUGGCGUACA CCCGCCGGGC CAG	242	835-857	CUGGCCCGGC GGGUGUACGC CAC	470
12	GCCCGGCGG GUGUACGCC ACA	15	838-858	UGUGGCGUAC ACCGCCGGG CCA	243	836-858	UGGCCCGGCG GGUGUACGCC ACC	471
13	CCCGGCGGG UGUACGCCA CCA	16	839-859	UGGUGGCGUA CACCCGCCGG GCC	244	837-859	GGCCCGGCGG GUGUACGCCA CCA	472
14	CCGGCGGGU GUACGCCAC CAA	17	840-860	UUGGUGGCGU ACACCCGCCG GGC	245	838-860	GCCCGGCGGG UGUACGCCAC CAU	473
15	GGUGUACGC CACCAUCCU GAA	18	846-866	UUCAGGAUGG UGGCGUACAC CCG	246	844-866	CGGGUGUACG CCACCAUCCU GAA	474
16	GUGUACGCC ACCAUCCUG AAA	19	847-867	UUUCAGGAUG GUGGCGUACA CCC	247	845-867	GGGUGUACGC CACCAUCCUG AAC	475
17	GUACGCCAC CAUCCUGAA CGA	20	849-869	UCGUUCAGGA UGGUGGCGUA CAC	248	847-869	GUGUACGCCA CCAUCCUGAA CGC	476
18	CGCCACCAU CCUGAACGC CGA	21	852-872	UCGGCGUUCA GGAUGGUGGC GUA	249	850-872	UACGCCACCA UCCUGAACGC CGG	477
19	GCCACCAUC CUGAACGCC GGA	22	853-873	UCCGGCGUUC AGGAUGGUGG CGU	250	851-873	ACGCCACCAU CCUGAACGCC GGC	478
20	CCACCAUCC UGAACGCCG GCA	23	854-874	UGCCGGCGUU CAGGAUGGUG GCG	251	852-874	CGCCACCAUC CUGAACGCCG GCA	479
21	ACCAUCCUG AACGCCGGC ACA	24	856-876	UGUGCCGGCG UUCAGGAUGG UGG	252	854-876	CCACCAUCCU GAACGCCGGC ACC	480
22	CCUGAACGC CGGCACCAA UAA	25	861-881	UUAUUGGUGC CGGCGUUCAG GAU	253	859-881	AUCCUGAACG CCGGCACCAA UAC	481

23	UGAACGCCG GCACCAUA CAA	26	863-883	UUGUAUUGGU GCCGGCGUUC AGG	254	861-883	CCUGAACGCC GGCACCAUA CAG	482
24	AACGCCGGC ACCAUACA GAA	27	865-885	UUCUGUAUUG GUGCCGGCGU UCA	255	863-885	UGAACGCCGG CACCAUACA GAU	483
25	ACGCCGGCA CCAUAACAG AUA	28	866-886	UAUCUGUAUU GGUGCCGGCG UUC	256	864-886	GAACGCCGGC ACCAUAACAG AUG	484
26	CGCCGGCAC CAAUACAGA UGA	29	867-887	UCAUCUGUAU UGGUGCCGGC GUU	257	865-887	AACGCCGGCA CCAUAACAGA UGG	485
27	GCCGGCACC AAUACAGAU GGA	30	868-888	UCCAUCUGUA UUGGUGCCGG CGU	258	866-888	ACGCCGGCAC CAAUACAGAU GGC	486
28	GCCCACGGC ACAGGCACC AAA	31	997-1017	UUUGGUGCCU GUGCCGUGGG CUU	259	995-1017	AAGCCACGG CACAGGCACC AAG	487
29	ACCCGAGCC CUGUGCGCC ACA	32	1048- 1068	UGUGGCGCAC AGGGCUCGGG UGA	260	1046- 1068	UCACCCGAGC CCUGUGCGCC ACC	488
30	CCCUGUGCG CCACCGGCC AGA	33	1055- 1075	UCUGGCGGGU GGCGCACAGG GCU	261	1053- 1075	AGCCUGUGC GCCACCGGCC AGG	489
31	AAGUCCAAC AUGGGGCAC CCA	34	1099- 1119	UGGGUGCCCC AUGUUGGACU UGG	262	1097- 1119	CCAAGUCCAA CAUGGGGCAC CCG	490
32	CGUGGGCAU CAACUCCUU UGA	35	1284- 1304	UCAAAGGAGU UGAUGCCAC GUU	263	1282- 1304	AACUGGGGCA UCAACUCCUU UGG	491
33	GGACGCACC CCUGAGGCC GUA	36	1405- 1425	UACGGCCUCA GGGGUGCGUC CGC	264	1403- 1425	GCGGACGCAC CCCUGAGGCC GUG	492
34	CUGGCGAGC GCCCCUCUC GGA	37	1583- 1603	UCCAGAGCGG GCGCUCGCCA GCG	265	1581- 1603	CGCUGGCGAG CGCCCGCUCU GGU	493
35	UGGCGAGCG CCCGCUCUG GUA	38	1584- 1604	UACCAGAGCG GGCGCUCGCC AGC	266	1582- 1604	GCUGGCGAGC GCCCCCUCUG GUU	494
36	GGCGAGCGC CCGCUCUGG UUA	39	1585- 1605	UAACCAGAGC GGGCGCUCGC CAG	267	1583- 1605	CUGGCGAGCG CCCGCUCUGG UUC	495
37	GCGAGCGCC CGCUCUGGU UCA	40	1586- 1606	UGAACCAGAG CGGGCGCUCG CCA	268	1584- 1603	UGGCGAGCGC CCGCUCUGGU UCA	496
38	GCGCCCGCU CUGGUUCAU CUA	41	1590- 1610	UAGAUGAACC AGAGCGGGCG CUC	269	1588- 1610	GAGCGCCCGC UCUGGUUCAU CUG	497
39	CUCAUGCGC CUGGACCGC UUA	42	1651- 1671	UAAGCGGUCC AGGCGCAUGA GGC	270	1649- 1671	GCCUCAUGCG CCUGGACCGC UUC	498
40	GACUGCCAU CCAGAUAGG CCA	43	1791- 1811	UGGCCUAUCU GGAUGGCAGU CAG	271	1789- 1811	CUGACUGCCA UCCAGAUAGG CCU	499
41	AAGAAGCCC AUCUCCCGC CGA	44	1955- 1975	UCGGCGGGAG AUGGGCUUCU UUG	272	1953- 1975	CAAAGAAGCC CAUCUCCCGC CGG	500
42	AGCCCAUCU CCCGCCGGG CGA	45	1959- 1979	UCGCCCCGGC GGAGAUGGGC UUC	273	1957- 1979	GAAGCCCAUC UCCCGCCGGG CGC	501

43	GCCCAUCUC CCGCCGGGC GCA	46	1960- 1980	UGCGCCCGGC GGGAGAUGGG CUU	274	1958- 1980	AAGCCCAUCU CCCGCCGGGC GCC	502
44	CCAUCUCCC GCCGGGCGC CAA	47	1962- 1982	UUGGCGCCCG GCCGGAGAUG GGC	275	1960- 1982	GCCCAUCUCC CGCCGGGCGC CAU	503
45	AUGGCAGCC GUGGGCUUG UCA	48	1981- 2001	UGACAAGCCC ACGGCUGCCA UGG	276	1979- 2001	CCAUGGCAGC CGUGGGCUUG UCC	504
46	CUUGUCCUG GGAGGAGUG UAA	49	1995- 2015	UUACACUCCU CCCAGGACAA GCC	277	1993- 2015	GGCUUGUCCU GGGAGGAGUG UAA	505
47	UGGGAGGAG UGUAAACAG CGA	50	2002- 2022	UGCGUGUUUA CACUCCUCCC AGG	278	2000- 2022	CCUGGGAGGA GUGUAAACAG CGC	506
48	GAGGAGUGU AAACAGCGC UGA	51	2005- 2025	UCAGCGCUGU UUACACUCCU CCC	279	2003- 2025	GGGAGGAGUG UAAACAGCGC UGC	507
49	CAGUCACCA UCUCGGGAC CUA	52	2066- 2086	UAGGUCCCGA GAUGGUGACU GUG	280	2064- 2086	CACAGUCACC AUCUCGGGAC CUC	508
50	ACCAUCUCG GGACCUCAG GCA	53	2071- 2091	UGCCUGAGGU CCCGAGAUGG UGA	281	2069- 2091	UCACCAUCUC GGGACCUCAG GCC	509
51	UUCCACUCC UACUUCAUG GAA	54	2167- 2187	UUCCAUGAAG UAGGAGUGGA AGG	282	2165- 2187	CCUCCACUC CUACUUCAUG GAG	510
52	CUUCAUGGA GGCCAUCGC ACA	55	2178- 2198	UGUGCGAUGG CCUCCAUGAA GUA	283	2176- 2198	UACUUCAUGG AGGCCAUCGC ACC	511
53	UGAUCCGGG AGCCGAAGC CAA	56	2225- 2245	UUGGCUUCGG CUCCCGGAUC ACC	284	2223- 2245	GGUGAUCCGG GAGCCGAAGC CAC	512
54	AGCCGAAGC CACGUUCAG CCA	57	2234- 2254	UGGCUGAACG UGGCUUCGGC UCC	285	2232- 2254	GGAGCCGAAG CCACGUUCAG CCC	513
55	CCGAAGCCA CGUUCAGCC CGA	58	2236- 2256	UCCGGCUGAA CGUGGCUUCG GCU	286	2234- 2256	AGCCGAAGCC ACGUUCAGCC CGC	514
56	AAGCCACGU UCAGCCCGC UGA	59	2239- 2259	UCAGCGGGCU GAACGUGGCU UCG	287	2237- 2259	CGAAGCCACG UUCAGCCCGC UGG	515
57	CACGUUCAG CCCGCUGGC UCA	60	2243- 2263	UGAGCCAGCG GGCUGAACGU GGC	288	2241- 2263	GCCACGUUCA GCCCGCUGGC UCA	516
58	UCCUCCGCC GAGUACAAU GUA	61	2311- 2331	UACAUGUAC UCGGCGGAGG ACG	289	2309- 2331	CGUCCUCCGC CGAGUACAAU GUC	517
59	CCGCCGAGU ACAAUGUCA ACA	62	2315- 2335	UGUUGACAUU GUACUCGGCG GAG	290	2313- 2335	CUCCGCCGAG UACAAUGUCA ACA	518
60	CGCCGAGUA CAAUGUCAA CAA	63	2316- 2336	UUCUUGACAU UGUACUCGGC GGA	291	2314- 2336	UCCGCCGAGU ACAAUGUCAA CAA	519
61	UGCAGGCUG UCCUGAAGC GUA	64	2423- 2443	UACGCUUCAG GACAGCCUGC AGC	292	2421- 2443	GCUGCAGGCU GUCCUGAAGC GUG	520
62	AAGGAUCAC AGGGACAAC CUA	65	2482- 2502	UAGGVUGUCC CUGUGAUCCU UCU	293	2480- 2502	AGAAGGAUCA CAGGGACAAC CUG	521

63	GGAUCACAG GGACAACCU GGA	66	2484- 2504	UCCAGGUUGU CCCUGUGAUC CUU	294	2482- 2504	AAGGAUCACA GGGACAACCU GGA	522
64	CGGCAUCGG CAGGCUGCA CCA	67	2517- 2537	UGGUGCAGCC UGCCGAUGCC GGC	295	2515- 2537	GCCGGCAUCG GCAGGCUGCA CCU	523
65	UGCACCUCU CAGGCAUCG ACA	68	2531- 2551	UGUCGAUGCC UGAGAGGUGC AGC	296	2529- 2551	GCUGCACCUC UCAGGCAUCG ACG	524
66	CACCUCUCA GGCAUCGAC GCA	69	2533- 2553	UGCGUCGAUG CCUGAGAGGU GCA	297	2531- 2553	UGCACCUCUC AGGCAUCGAC GCC	525
67	ACCUCUCAG GCAUCGACG CCA	70	2534- 2554	UGGCGUCGAU GCCUGAGAGG UGC	298	2532- 2554	GCACCUCUCA GGCAUCGACG CCA	526
68	CCUCUCAGG CAUCGACGC CAA	71	2535- 2555	UUGGCGUCGA UGCCUGAGAG GUG	299	2533- 2555	CACCUCUCAG GCAUCGACGC CAA	527
69	CUCUCAGGC AUCGACGCC AAA	72	2536- 2556	UUUGGCGUCG AUGCCUGAGA GGU	300	2534- 2556	ACCUCUCAGG CAUCGACGCC AAC	528
70	GCAUCGACG CCAACCCCA AUA	73	2543- 2563	UAUUGGGGUU GGCGUCGAUG CCU	301	2541- 2563	AGGCAUCGAC GCCAACCCCA AUG	529
71	CAUCGACGC CAACCCCAA UGA	74	2544- 2564	UCAUUGGGGU UGGCGUCGAU GCC	302	2542- 2564	GGCAUCGACG CCAACCCCAA UGC	530
72	AUCGACGCC AACCCCAAU GCA	75	2545- 2565	UGCAUUGGGG UUGGCGUCGA UGC	303	2543- 2565	GCAUCGACGC CAACCCCAAU GCC	531
73	CUACAACAU CGACACCAG CUA	76	2706- 2726	UAGCUGGUGU CGAUGUUGUA GAU	304	2704- 2726	AUCTACAACA UCGACACCAG CUC	532
74	AGCAUAGUG UGGAAGACG CUA	77	2800- 2820	UAGCGUCUUC CACACUAUGC UCA	305	2798- 2820	UGAGCAUAGU GUGGAAGACG CUG	533
75	AGUGUCCCU GGAGGUACG GCA	78	2913- 2933	UGCCGUACCU CCAGGGACAC UGU	306	2911- 2933	ACAGUGUCCC UGGAGGUACG GCU	534
76	GUGUCCCU GAGGUACGG CUA	79	2914- 2934	UAGCCGUACC UCCAGGGACA CUG	307	2912- 2934	CAGUGUCCCU GGAGGUACGG CUC	535
77	UAGUGAGUG GGAAGGUGU ACA	80	2981- 3001	UGUACACCUU CCCACUCACU ACC	308	2979- 3001	GGUAGUGAGU GGGAAGGUGU ACC	536
78	AGUGAGUGG GAAGGUGUA CCA	81	2982- 3002	UGGUACACCU UCCCACUCAC UAC	309	2980- 3002	GUAGUGAGUG GGAAGGUGUA CCA	537
79	AGUUUACAA GGAGCUGCG UCA	82	3090- 3110	UGACGCAGCU CCUUGUAAAC UUC	310	3088- 3110	GAAGUUUACA AGGAGCUGCG UCU	538
80	ACAAGGAGC UGCUCUGC GUA	83	3095- 3115	UACGCAGACG CAGCUCUUG UAA	311	3093- 3115	UUACAAGGAG CUGCGUCUGC GUG	539
81	AGCUGCGUC UGCUGGCU ACA	84	3101- 3121	UGUAGCCACG CAGACGCAGC UCC	312	3099- 3121	GGAGCUGCGU CUGCGUGGCU ACG	540
82	GCUGCGUCU GCGUGGCUA CGA	85	3102- 3122	UCGUAGCCAC GCAGACGCAG CUC	313	3100- 3122	GAGCUGCGUC UGCGUGGCUA CGA	541

83	CUGCGUCUG CGUGGCUAC GAA	86	3103- 3123	UUCGUAGCCA CGCAGACGCA GCU	314	3101- 3123	AGCUGCGUCU GCGUGGCUAC GAC	542
84	GCGUCUGCG UGGCUACGA CUA	87	3105- 3125	UAGUCGUAGC CACGCAGACG CAG	315	3103- 3125	CUGCGUCUGC GUGGCUACGA CUA	543
85	UCCACAUCG ACCCUGCCA CCA	88	3287- 3307	UGGUGGCAGG GUCGAUGUGG AUG	316	3285- 3307	CAUCCACAUC GACCCUGCCA CCC	544
86	CACAUCGAC CCUGCCACC CAA	89	3289- 3309	UUGGGUGGCA GGGUCGAUGU GGA	317	3287- 3309	UCCACAUCGA CCCUGCCACC CAC	545
87	GCCCAAGUG GCUGACGUG GUA	90	3340- 3360	UACCACGUCA GCCACUUGGG CCU	318	3338- 3360	AGGCCCAAGU GGCUGACGUG GUG	546
88	CCCAAGUGG CUGACGUGG UGA	91	3341- 3361	UCACCACGUC AGCCACUUGG GCC	319	3339- 3361	GGCCCAAGUG GCUGACGUGG UGG	547
89	GGUGGUGCC CGGACUGGA UGA	92	3600- 3620	UCAUCCAGUC CGGGCACCAC CAU	320	3598- 3620	AUGGUGGUGC CCGGACUGGA UGG	548
90	UGGUGCCCG GACUGGAUG GGA	93	3602- 3622	UCCCAUCCAG UCCGGGCACC ACC	321	3600- 3622	GGUGGUGCCC GGACUGGAUG GGG	549
91	CUGCAGGCU UCAGCUCAA CGA	94	3678- 3698	UCGUUGAGCU GAAGCCUGCA GGC	322	3676- 3698	GCCUGCAGGC UUCAGCUCAA CGG	550
92	UGCAGGCUU CAGCUCAAC GGA	95	3679- 3699	UCCGUUGAGC UGAAGCCUGC AGG	323	3677- 3699	CCUGCAGGCU UCAGCUCAAC GGG	551
93	CAGGCUUCA GCUCAACGG GAA	96	3681- 3701	UUCCCGUUGA GCUGAAGCCU GCA	324	3679- 3701	UGCAGGCUUC AGCUCAACGG GAA	552
94	AGGCUUCAG CUCAACGGG AAA	97	3682- 3702	UUUCCCGUUG AGCUGAAGCC UGC	325	3680- 3702	GCAGGCUUCA GCUCAACGGG AAC	553
95	GCUUCAGCU CAACGGGAA CCA	98	3684- 3704	UGGUUCCCGU UGAGCUGAAG CCU	326	3682- 3704	AGGCUUCAGC UCAACGGGAA CCU	554
96	GACACUGCC GUGGAGAAC AUA	99	3808- 3828	UAUGUUCUCC ACGGCAGUGU CCA	327	3806- 3828	UGGACACUGC CGUGGAGAAC AUG	555
97	CUGAGCUAC ACGGCCACC GAA	100	3925- 3945	UUCGGUGGCC GUGUAGCUCA GCU	328	3923- 3945	AGCUGAGCUA CACGGCCACC GAC	556
98	GUACACGG CCACCGACC GCA	101	3929- 3949	UGCGGUCGGU GGCCGUGUAG CUC	329	3927- 3949	GAGCUACACG GCCACCGACC GCC	557
99	ACACGGCCA CCGACCGCC ACA	102	3932- 3952	UGUGGCGGUC GGUGGCCGUG UAG	330	3930- 3952	CUACACGGCC ACCGACCGCC ACC	558
100	CAGGACGCG UGGGAGAGC CUA	103	4243- 4263	UAGGCUCUCC CACGCGUCCU GGC	331	4241- 4263	GCCAGGACGC GUGGGAGAGC CUC	559
101	GGACGCGUG GGAGAGCCU CUA	104	4245- 4265	UAGAGGCUCU CCCACGCGUC CUG	332	4243- 4265	CAGGACGCGU GGGAGAGCCU CUU	560
102	ACCAGCUUC CGCUGGGUG GAA	105	4381- 4401	UUCCACCCAG CGGAAGCUGG UAU	333	4379- 4401	AUACCAGCUU CCGUGGGUG GAG	561

103	AGCUUCCGC UGGGUGGAG UCA	106	4384- 4404	UGACUCCACC CAGCGGAAGC UGG	334	4382- 4404	CCAGCUUCCG CUGGGUGGAG UCU	562
104	AACUGUGCC ACCUCGGGC GUA	107	4462- 4482	UACGCCCAG GUGGCACAGU UGA	335	4460- 4482	UCAACUGUGC CACCUCGGGC GUG	563
105	CUGUGCCAC CUCGGGCGU GGA	108	4464- 4484	UCCACGCCCC AGGUGGCACA GUU	336	4462- 4484	AACUGUGCCA CCUCGGGCGU GGU	564
106	CACCUCGGG CGUGGUGGG CUA	109	4470- 4490	UAGCCCACCA CGCCCGAGGU GGC	337	4468- 4490	GCCACCUCGG GCGUGGUGGG CUU	565
107	ACCUCGGGC GUGGUGGGC UUA	110	4471- 4491	UAAGCCCACC ACGCCCAGAG UGG	338	4469- 4491	CCACCUCGGG CGUGGUGGGC UUG	566
108	ACCUGGUGA UGAACGUCU ACA	111	4622- 4642	UGUAGACGUU CAUACCCAGG UCU	339	4620- 4642	AGACCUGGUG AUGAACGUCU ACC	567
109	CUGGUGAUG AACGUCUAC CGA	112	4624- 4644	UCGGUAGACG UUCAUACCA GGU	340	4622- 4644	ACCUGGUGAU GAACGUCUAC CGC	568
110	UGGUGAUGA ACGUCUACC GCA	113	4625- 4645	UGCUGUAGAC GUUCAUACCC AGG	341	4623- 4645	CCUGGUGAUG AACGUCUACC GCG	569
111	UGAUGAACG UCUACCGCG ACA	114	4628- 4648	UGUCGCGGUA GACGUUCAUC ACC	342	4626- 4648	GGUGAUGAAC GUCUACCGCG ACG	570
112	AUGAACGUC UACCGCGAC GGA	115	4630- 4650	UCCGUCGCGG UAGACGUUCA UCA	343	4628- 4650	UGAUGAACGU CUACCGCGAC GGG	571
113	GAACGUCUA CCGCGACGG GGA	116	4632- 4652	UCCCCGUCGC GGUAGACGUU CAU	344	4630- 4652	AUGAACGUCU ACCGCGACGG GGC	572
114	UCCAUCCGC UGGGUCUGC UCA	117	4750- 4770	UGAGCAGACC CAGCGGAUGG AGG	345	4748- 4770	CCUCCAUCCG CUGGGUCUGC UCC	573
115	CCCAGCUCU GCACGGUCU ACA	118	4805- 4825	UGUAGACCGU GCAGAGCUGG GCG	346	4803- 4825	CGCCCAGCUC UGCACGGUCU ACU	574
116	CGCCUCCCU CAACUUCG CGA	119	4827- 4847	UCGCGGAAGU UGAGGGAGGC GUA	347	4825- 4847	UACGCCUCCC UCAACUUCG CGA	575
117	UCCCUCAAC UUCGCGAC AUA	120	4831- 4851	UAUGUCGCGG AAGUUGAGGG AGG	348	4829- 4851	CCUCCCUCAA CUUCCGCGAC AUC	576
118	CCUCAACUU CCGCGACAU CAA	121	4833- 4853	UUGAUGUCGC GGAAGUUGAG GGA	349	4831- 4853	UCCCUCAACU UCCGCGACAU CAU	577
119	AACUUCCGC GACAUCAUG CUA	122	4837- 4857	UAGCAUGAUG UCGCGGAAGU UGA	350	4835- 4857	UCAACUUCG CGACAUCAUG CUG	578
120	ACUUCCGCG ACAUCAUGC UGA	123	4838- 4858	UCAGCAUGAU GUCGCGGAAG UUG	351	4836- 4858	CAACUUCCGC GACAUCAUGC UGG	579
121	UUCGCGGAC AUCAUGCUG GCA	124	4840- 4860	UGCCAGCAUG AUGUCGCGGA AGU	352	4838- 4860	ACUUCGCGCA CAUCAUGCUG GCC	580
122	UGGAGUUCU CGGGCCGAG ACA	125	4925- 4945	UGUCUCGGCC CGAGAACUCC AUA	353	4923- 4945	UAUGGAGUUC UCGGGCCGAG ACG	581

123	CUCUGUCCU GCUGUCACC GGA	126	4995- 5015	UCCGGUGACA GCAGGACAGA GGU	354	4993- 5015	ACCUCUGUCC UGCUGUCACC GGA	582
124	UCUGUCCUG CUGUCACCG GAA	127	4996- 5016	UCCGGUGAC AGCAGGACAG AGG	355	4994- 5016	CCUCUGUCCU GCUGUCACCG GAC	583
125	CUGUCCUGC UGUCACCGG ACA	128	4997- 5017	UGUCCGGUGA CAGCAGGACA GAG	356	4995- 5017	CUCUGUCCUG CUGUCACCGG ACU	584
126	CCAUCGCCA UCGCCCUCA GUA	129	5174- 5194	UACUGAGGGC GAUGGCCAUG GCG	357	5172- 5194	CGCCAUCGCC AUCGCCCUCA GUC	585
127	GGUCGCUUC CUGGAAAUA GGA	130	5413- 5433	UCCAAUUUCC AGGAAGCGAC CGU	358	5411- 5433	ACGGUCGCUU CCUGGAAAUA GGC	586
128	CCUGGAAAUA UGGCAAAUA CGA	131	5421- 5441	UCGAAUUUGC CAAUUUCCAG GAA	359	5419- 5441	UUCUGGAAA UUGGCAAAUA CGA	587
129	AAUUCGACC UUUCUCAGA ACA	132	5435- 5455	UGUUCUGAGA AAGGUCGAUA UUG	360	5433- 5455	CAAAUUCGAC CUUUCUCAGA ACC	588
130	GAAGAACGU GACAUUCCA CGA	133	5481- 5501	UCGUGGAAUG UCACGUUCUU CAG	361	5479- 5501	CUGAAGAACG UGACAUUCCA CGG	589
131	AGAACGUGA CAUUCCACG GGA	134	5483- 5503	UCCCUGGGAA UGUCACGUUC UUC	362	5481- 5503	GAAGAACGUG ACAUUCCACG GGG	590
132	GCAUCCGGG AUGGGGUGG UAA	135	5573- 5593	UUACCACCCC AUCCCGGAUG CCG	363	5571- 5593	CGGCAUCCGG GAUGGGGUGG UAC	591
133	CAUCCGGGA UGGGGUGGU ACA	136	5574- 5594	UGUACCACCC CAUCCCGGAU GCC	364	5572- 5594	GGCAUCCGGG AUGGGGUGGU ACG	592
134	CGCCUCCG CUACAUGGC CCA	137	5637- 5657	UGGGCCAUGU AGCGGAAGGC GUC	365	5635- 5657	GACGCCUUC GCUACAUGGC CCA	593
135	GCCUCCGC UACAUGGCC CAA	138	5638- 5658	UUGGGCCAUG UAGCGGAAGG CGU	366	5636- 5658	ACGCCUCCG CUACAUGGCC CAA	594
136	UUCAGGAC GUCUGCAAG CCA	139	6085- 6105	UGGCUUGCAG ACGUCCUGGA AGA	367	6083- 6105	UCUUCAGGA CGUCUGCAAG CCC	595
137	GAGAAACGC CGGCACGAA GGA	140	6259- 6279	UCCUUCGUGC CGGCGUUUCU CAC	368	6257- 6279	GUGAGAAACG CCGGCACGAA GGC	596
138	GAAACGCCG GCACGAAGG CCA	141	6261- 6281	UGGCCUUCGU GCCGGCGUUU CUC	369	6259- 6281	GAGAAACGCC GGCACGAAGG CCU	597
139	GUGCAGUGG GGCGCCAUC GGA	142	6295- 6315	UCCGAUGGCG CCCCACUGCA CGG	370	6293- 6315	CCGUGCAGUG GGGCGCCAUC GGC	598
140	UGCAGUGGG GCGCCAUCG GCA	143	6296- 6316	UGCCGAUGGC GCCCCACUGC ACG	371	6294- 6316	CGUGCAGUGG GGCGCCAUCG GCG	599
141	UGGGGCGCC AUCGGCGAC GUA	144	6301- 6321	UACGUCGCCG AUGGCGCCCC ACU	372	6299- 6321	AGUGGGGCGC CAUCGGCGAC GUG	600
142	GCGCCAUCG GCGACGUGG GCA	145	6305- 6325	UGCCACGUC GCCGAUGGCG CCC	373	6303- 6325	GGGCGCCAUC GGCGACGUGG GCA	601

143	CAUCGGCGA CGUGGGCAU UUA	146	6309- 6329	UAA AUGCCCA CGUCGCCGAU GGC	374	6307- 6329	GCCAUCGGCG ACGUGGGCAU UUU	602
144	CGGCGACGU GGGCAUUUU GGA	147	6312- 6332	UCCAAAUGC CCACGUCGCC GAU	375	6310- 6332	AUCGGCGACG UGGGCAUUUU GGU	603
145	ACCUGGACA GCUCACUGG CGA	148	6554- 6574	UCGCCAGUGA GCUGUCCAGG UUG	376	6552- 6574	CAACCUGGAC AGCUCACUGG CGG	604
146	GCGUGGAGG UGCGCCAGA CGA	149	6599- 6619	UCGUCUGGCG CACCUCACG CUC	377	6597- 6619	GAGCGUGGAG GUGCGCCAGA CGC	605
147	CCCACCCUG AUGCGGCUC AAA	150	6808- 6828	UUUGAGCCGC AUCAGGGUGG GGC	378	6806- 6828	GCCCCACCCU GAUGCGGCUC AAC	606
148	UCCUGGUGC ACCCAAUCG AGA	151	6857- 6877	UCUCGAUUGG GUGCACCAGG AAC	379	6855- 6877	GUUCCUGGUG CACCCAAUCG AGG	607
149	CCCAAUCGA GGGCUCCAC CAA	152	6867- 6887	UUGGUGGAGC CCUCGAUUGG GUG	380	6865- 6887	CACCCAAUCG AGGGCUCCAC CAC	608
150	GGCUCACC ACCGUGUUC CAA	153	6877- 6897	UUGGAACACG GUGGUGGAGC CCU	381	6875- 6897	AGGGCUCCAC CACCGUGUUC CAC	609
151	GGCUGCCUA CUACAUCGA CUA	154	6978- 6998	UAGUCGAUGU AGUAGGCAGC CAG	382	6976- 6998	CUGGCUGCCU ACUACAUCGA CUG	610
152	GCUGCCUAC UACAUCGAC UGA	155	6979- 6999	UCAGUCGAUG UAGUAGGCAG CCA	383	6977- 6999	UGGCUGCCUA CUACAUCGAC UGC	611
153	UGCCUACUA CAUCGACUG CAA	156	6981- 7001	UUGCAGUCGA UGUAGUAGGC AGC	384	6979- 7001	GCUGCCUACU ACAUCGACUG CAU	612
154	GCCUACUAC AUCGACUGC AUA	157	6982- 7002	UAUGCAGUCG AUGUAGUAGG CAG	385	6980- 7002	CUGCCUACUA CAUCGACUGC AUC	613
155	ACUACAUCG ACUGCAUCA GGA	158	6986- 7006	UCCUGAUGCA GUCGAUGUAG UAG	386	6984- 7006	CUACUACAUC GACUGCAUCA GGC	614
156	CUACAUCGA CUGCAUCAG GCA	159	6987- 7007	UGCCUGAUGC AGUCGAUGUA GUA	387	6985- 7007	UACUACAUCG ACUGCAUCAG GCA	615
157	CCCGAGGGC CCCUACCGC GUA	160	7015- 7035	UACGCGGUAG GGGCCUCUGG GCU	388	7013- 7035	AGCCCGAGGG CCCUACCGC GUG	616
158	CCCUACCG CGUGGCCGG CUA	161	7023- 7043	UAGCCGCCA CGCGUAGGG GCC	389	7021- 7043	GGCCCUACC GCGUGGCCGG CUA	617
159	CCCUACCGC GUGGCCGGC UAA	162	7024- 7044	UUAGCCGGCC ACGCGGUAGG GGC	390	7022- 7044	GCCCUACCG CGUGGCCGGC UAC	618
160	CCUGCGUGG CCUUUGAAA UGA	163	7055- 7075	UCAUUUCAA GGCCACGCAG GCC	391	7053- 7075	GGCCUGCGUG GCCUUUGAAA UGU	619
161	UACACCCAG AGCUACCGG GCA	164	7162- 7182	UGCCCGGUAG CUCUGGGUGU AGG	392	7160- 7182	CCUACACCCA GAGCUACCGG GCA	620
162	ACCCAGAGC UACCGGGCA AAA	165	7165- 7185	UUUUGCCGG UAGCUCUGGG UGU	393	7163- 7185	ACACCCAGAG CUACCGGGCA AAG	621

163	CCCAGAGCU ACCGGGCAA AGA	166	7166- 7186	UCUUUGCCCG GUAGCUCUGG GUG	394	7164- 7186	CACCCAGAGC UACCGGGCAA AGC	622
164	CCAGAGCUA CCGGGCAA GCA	167	7167- 7187	UGC UUUGCCC GGUAGCUCUG GGU	395	7165- 7187	ACCCAGAGCU ACCGGGCAA GCU	623
165	AGAGCUACC GGGCAAAGC UGA	168	7169- 7189	UCAGCUUUGC CCGGUAGCUC UGG	396	7167- 7189	CCAGAGCUAC CGGGCAAAGC UGA	624
166	GAGCUACCG GGCAAAGCU GAA	169	7170- 7190	UUCAGCUUUG CCC GGUAGCU CUG	397	7168- 7190	CAGAGCUACC GGGCAAAGCU GAC	625
167	AGCUACCGG GCAAAGCUG ACA	170	7171- 7191	UGUCAGCUUU GCCC GGUAGC UCU	398	7169- 7191	AGAGCUACCG GGCAAAGCUG ACC	626
168	UGAGACGGA GGCCAU AUG CUA	171	7212- 7232	UAGCAUAUGG CCUCCGUCUC AGC	399	7210- 7232	GCUGAGACGG AGGCCAU AUG CUU	627
169	AGACGGAGG CCAUAUGCU UCA	172	7214- 7234	UGAAGCAUAU GGCCUCCGUC UCA	400	7212- 7234	UGAGACGGAG GCCAU AUGCU UCU	628
170	GACGGAGGC CAUAUGCUU CUA	173	7215- 7235	UAGAAGCAUA UGGCCUCCGU CUC	401	7213- 7235	GAGACGGAGG CCAUAUGCUU CUU	629
171	GGAGGCCAU AUGCUUCUU CGA	174	7218- 7238	UCGAAGAAGC AUAUGGCCUC CGU	402	7216- 7238	ACGGAGGCCA UAUGCUUCUU CGU	630
172	GAGGCCAUA UGCUUCUUC GUA	175	7219- 7239	UACGAAGAAG CAUAUGGCCU CCG	403	7217- 7239	CGGAGGCCAU AUGCUUCUUC GUG	631
173	AGGCCAU AU GCUUCUUCG UGA	176	7220- 7240	UCACGAAGAA GCAUAUGGCC UCC	404	7218- 7240	GGAGGCCAU AU UGCUUCUUCG UGC	632
174	GGCCAUAUG CUUCUUCGU GCA	177	7221- 7241	UGCACGAAGA AGCAUAUGGC CUC	405	7219- 7241	GAGGCCAU AU GCUUCUUCGU GCA	633
175	GCCAUAUGC UUCUUCGUG CAA	178	7222- 7242	UUGCACGAAG AAGCAUAUGG CCU	406	7220- 7242	AGGCCAU AUG CUUCUUCGUG CAG	634
176	CAUAUGCUU CUUCGUGCA GCA	179	7224- 7244	UGCUGCACGA AGAAGCAUAU GGC	407	7222- 7244	GCCAUAUGCU UCUUCGUGCA GCA	635
177	AUGCUUCUU CGUGCAGCA GUA	180	7227- 7247	UACUGCUGCA CGAAGAAGCA UAU	408	7225- 7247	AUAUGCUUCU UCGUGCAGCA GUU	636
178	UUCUUCGUG CAGCAGUUC ACA	181	7231- 7251	UGUGAACUGC UGCACGAAGA AGC	409	7229- 7251	GCUUCUUCGU GCAGCAGUUC ACG	637
179	UCGUGCAGC AGUUCACGG ACA	182	7235- 7255	UGUCCGUGAA CUGCUGCACG AAG	410	7233- 7255	CUUCGUGCAG CAGUUCACGG ACA	638
180	UCACGGACA UGGAGCACA ACA	183	7247- 7267	UGUUGUGCUC CAUGUCCGUG AAC	411	7245- 7267	GUUCACGGAC AUGGAGCACA ACA	639
181	AGCCGCCGU GGACCUGAU CAA	184	7317- 7337	UUGAUCAGGU CCACGGCGGC UGC	412	7315- 7337	GCAGCCGCCG UGGACCUGAU CAU	640
182	UGGACCUGA UCAUCAAGA GCA	185	7325- 7345	UGCUCUUGAU GAUCAGGUCC ACG	413	7323- 7345	CGUGGACCUG AUCAUCAAGA GCC	641

183	CCUUCUACU ACAAGCUGC GUA	186	7388- 7408	UACGCAGCUU GUAGUAGAAG GAC	414	7386- 7408	GUCCUUCUAC UACAAGCUGC GUG	642
184	CUUCUACUA CAAGCUGCG UGA	187	7389- 7409	UCACGCAGCU UGUAGUAGAA GGA	415	7387- 7409	UCCUUCUACU ACAAGCUGCG UGC	643
185	UUCUACUAC AAGCUGCGU GCA	188	7390- 7410	UGCACGCAGC UUGUAGUAGA AGG	416	7388- 7410	CCUUCUACUA CAAGCUGCGU GCC	644
186	CUACUACAA GCUGCGUGC CGA	189	7392- 7412	UCGGCACGCA GCUUGUAGUA GAA	417	7390- 7412	UUCUACUACA AGCUGCGUGC CGC	645
187	GGCCAAGUA CCAUGGCAA CGA	190	7431- 7451	UCGUUGCCAU GGUACUUGGC CUU	418	7429- 7451	AAGGCCAAGU ACCAUGGCAA CGU	646
188	GCCAAGUAC CAUGGCAAC GUA	191	7432- 7452	UACGUUGCCA UGGUACUUGG CCU	419	7430- 7452	AGGCCAAGUA CCAUGGCAAC GUG	647
189	CCAAGUACC AUGGCAACG UGA	192	7433- 7453	UCACGUUGCC AUGGUACUUG GCC	420	7431- 7453	GGCCAAGUAC CAUGGCAACG UGA	648
190	CAAGUACCA UGGCAACGU GAA	193	7434- 7454	UUCACGUUGC CAUGGUACUU GGC	421	7432- 7454	GCCAAGUACC AUGGCAACGU GAU	649
191	UACCAUGGC AACGUGAUG CUA	194	7438- 7458	UAGCAUCACG UUGCCAUGGU ACU	422	7436- 7458	AGUACCAUGG CAACGUGAUG CUA	650
192	GCCAAGACG GGUGGCGCC UAA	195	7465- 7485	UUAGGCGCCA CCCGUCUUGG CGC	423	7463- 7485	GCGCCAAGAC GGGUGGCGCC UAC	651
193	CAAGACGGG UGGCGCCUA CGA	196	7467- 7487	UCGUAGGCGC CACCCGUCUU GGC	424	7465- 7487	GCCAAGACGG GUGGCGCCUA CGG	652
194	AGACGGGUG GCGCCUACG GCA	197	7469- 7489	UGCCGUAGGC GCCACCCGUC UUG	425	7467- 7489	CAAGACGGGU GGCGCCUACG GCG	653
195	ACGGGUGGC GCCUACGGC GAA	198	7471- 7491	UUCGCCCAGG GCGCCACCCG UCU	426	7469- 7491	AGACGGGUGG CGCCUACGGC GAG	654
196	UGGCGCCUA CGGCGAGGA CCA	199	7476- 7496	UGGUCCUCGC CGUAGGCGCC ACC	427	7474- 7496	GGUGGCGCCU ACGCGAGGGA CCU	655
197	AGGACCUGG GCGCGGACU ACA	200	7490- 7510	UGUAGUCCGC GCCCAGGUCC UCG	428	7488- 7510	CGAGGACCUG GGCGCGGACU ACA	656
198	GACUACAAC CUCUCCAG GUA	201	7504- 7524	UACCUGGGAG AGGUUGUAGU CCG	429	7502- 7524	CGGACUACAA CCUCUCCAG GUA	657
199	ACUACAACC UCUCCAGG UAA	202	7505- 7525	UUACCUGGGA GAGGUUGUAG UCC	430	7503- 7525	GGACUACAAC CUCUCCAGG UAU	658
200	UACAACCUC UCCCAGGUA UGA	203	7507- 7527	UCAUACCUGG GAGAGGUUGU AGU	431	7505- 7527	ACUACAACCU CUCCCAGGUA UGC	659
201	CAACCUCUC CCAGGUAUG CGA	204	7509- 7529	UCGCAUACCU GGGAGAGGUU GUA	432	7507- 7529	UACAACCUCU CCCAGGUAUG CGA	660
202	CUCUCCAG GUAUGCGAC GGA	205	7513- 7533	UCCGUCGCAU ACCUGGGAGA GGU	433	7511- 7533	ACCUCUCCCA GGUAUGCGAC GGG	661

203	CUCCCAGGU AUGCGACGG GAA	206	7515- 7535	UUCCCGUCGC AUACCUGGGA GAG	434	7513- 7535	CUCUCCCAGG UAUGCGACGG GAA	662
204	UCCCAGGUA UGCGACGGG AAA	207	7516- 7536	UUUCCCGUCG CAUACCUGGG AGA	435	7514- 7536	UCUCCCAGGU AUGCGACGGG AAA	663
205	CAGGUAUGC GACGGGAAA GUA	208	7519- 7539	UACUUUCCCG UCGCAUACCU GGG	436	7517- 7539	CCCAGGUAUG CGACGGGAAA GUA	664
206	UCCCACGGC ACCUCGGGG ACA	209	7836- 7856	UGUCCCCGAG GUGCCGUGGG AGG	437	7834- 7856	CCUCCCACGG CACCUCGGGG ACA	665
207	CCCACGGCA CCUCGGGGA CAA	210	7837- 7857	UUGUCCCCGA GGUGCCGUGG GAG	438	7835- 7857	CUCCCACGGC ACCUCGGGGA CAC	666
208	GCUGGGCCU CGUGCGCCC GUA	211	7925- 7945	UACGGGCGCA CGAGGCCCAG CCC	439	7923- 7945	GGGCUGGGCC UCGUGCGCCC GUG	667
209	CUGGGCCUC GUGCGCCCG UGA	212	7926- 7946	UCACGGGCGC ACGAGGCCCA GCC	440	7924- 7946	GGCUGGGCCU CGUGCGCCCG UGG	668
210	UGGGCCUCG UGCGCCCGU GGA	213	7927- 7947	UCCACGGGCG CACGAGGCC AGC	441	7925- 7947	GCUGGGCCUC GUGCGCCCGU GGG	669
211	GGCCUCGUG CGCCCGUGG GGA	214	7929- 7949	UCCCCACGGG CGCACGAGGC CCA	442	7927- 7949	UGGGCCUCGU GCGCCCGUGG GGU	670
212	GCCUCGUGC GCCCGUGGG GUA	215	7930- 7950	UACCCACGG GCGCACGAGG CCC	443	7928- 7950	GGGCCUCGUG CGCCCGUGGG GUC	671
213	CCUCGUGCG CCCGUGGGG UCA	216	7931- 7951	UGACCCACG GGCGCACGAG GCC	444	7929- 7951	GGCCUCGUGC GCCCGUGGGG UCU	672
214	CUCGUGCGC CCGUGGGGU CUA	217	7932- 7942	UAGACCCAC GGGCGCACGA GGC	445	7930- 7952	GCCUCGUGCG CCCGUGGGGU CUG	673
215	UCGUGCGCC CGUGGGGUC UGA	218	7933- 7953	UCAGACCCCA CGGGCGCACG AGG	446	7931- 7953	CCUCGUGCGC CCGUGGGGUC UGC	674
216	GUGCGCCCG UGGGGUCUG CGA	219	7935- 7955	UCGCAGACCC CACGGGCGCA CGA	447	7933- 7955	UCGUGCGCCC GUGGGGUCUG CGC	675
217	CGCCCGUGG GGUCUGCGC UUA	220	7938- 7958	UAAGCGCAGA CCCCACGGGC GCA	448	7936- 7958	UGC GCCCGUG GGGUCUGCGC UUG	676
218	GUGGGGUCU GCGCUUGGU CUA	221	7943- 7963	UAGACCAAGC GCAGACCCCA CGG	449	7941- 7963	CCGUGGGGUC UGCGCUUGGU CUU	677
219	UUCCCCGAU GUCCCCUGC GGA	222	8072- 8092	UCCGCAGGGG ACAUCGGGGA AAU	450	8070- 8092	AUUUCCCCGA UGUCCCCUGC GGG	678
220	UCCCCGAUG UCCCCUGCG GGA	223	8073- 8093	UCCCGCAGGG GACAUCGGGG AAA	451	8071- 8093	UUUCCCCGAU GUCCCCUGCG GGC	679
221	CCCCGAUGU CCCCUGCGG GCA	224	8074- 8094	UGCCCGCAGG GGACAUCGGG GAA	452	8072- 8094	UCCCCGAUG UCCCCUGCGG GCG	680
222	ACCCCGUUU CAUUUUUAC ACA	225	8388- 8408	UGUGUAAAAA UGAAACGGGG UCC	453	8386- 8408	GGACCCCGUU UCAUUUUUAC ACC	681

223	AGCCUCCCA CAAUUAAC CGA	226	8432- 8452	UCGGUUUAU UGUGGGAGG UGA	454	8430- 8452	UCAGCCUCCC ACAAUUAAC CGC	682
224	GCCUCCAC AAUUAAC GCA	227	8433- 8453	UGCGUUUA UUGUGGGAG CUG	455	8431- 8453	CAGCCUCCCA CAAUUAAC GCA	683
225	CCCACAAU AAACCGCAU GUA	228	8437- 8457	UACAUGCGG UUAUUGUGG GAG	456	8435- 8457	CUCCACAAU UAAACCGCAU GUG	684
226	CCACAAUA AACCGCAUG UGA	229	8438- 8458	UCACAUGCGG UUUAUUGUG GGA	457	8436- 8458	UCCACAAU AAACCGCAUG UGA	685
227	ACAAUAAA CCGCAUGUG AUA	230	8440- 8460	UAUCACAUGC GGUUAAUUG UGG	458	8438- 8460	CCACAAUAA ACCGCAUGUG AUC	686
228	CAAUUAAC CGCAUGUGA UCA	231	8441- 8461	UGAUCACAUG CGGUUAAU GUG	459	8439- 8461	CACAAUAAA CCGCAUGUGA UCU	687

[00137] The nucleotide sequence of exemplary modified versions of the dsRNA agents set forth in Table 2 are set forth in Table 3. More specifically, Table 3 sets forth the nucleotide sequence of exemplary sense strands, antisense strands, and dsRNA agent pairs of sense and antisense strands. It is to be understood that while the sense and antisense strands are set forth in pairs in Table 3, the disclosure encompasses dsRNA agents comprising any sense strand and any antisense set forth in Table 3 (*e.g.*, that are at least partially complementary (*e.g.*, as could be determined by a person of ordinary skill in the art)). It is to be understood that while the nucleotide sequence of the sense strands and antisense strands in Table 3 are set forth as modified (*i.e.*, contain at least one modified nucleotide), the disclosure encompasses the sense and antisense sense strands set forth in Table 3 comprising other nucleotide modifications (*e.g.*, as described herein) or that are unmodified.

Table 3. Modified Sense and Antisense Strand Sequences of FASN dsRNA Agents.

dsRNA Agent ID	Sense Sequence 5' to 3'	SEQ ID NO	Range in NM_004 104.5	Antisense Sequence 5' to 3'	SEQ ID NO	Range in NM_004 104.5	mRNA Target Sequence	SEQ ID NO
1	csuscuaacG fgCfCfUfg ccccggcga	688	253-273	usCfsgccGf gGfGfcaggC fcGfuagags csc	916	251-273	GGCUCUACGG CCUGCCCCGG CGG	460
2	gscscugcC fcCfGfGfc gguccgga	689	260-280	usGfsccgGf aCfCfGccgG fgGfcaggcs csg	917	258-280	CGGCCUGCCC CGGCGGUCCG GCA	461
3	csusgcccC fgGfCfGfg uccggcaaa	690	262-282	usUfsugcCf gGfAfccgcC fgGfggcags gsc	918	260-282	GCCUGCCCCG GCGGUCCGGC AAG	462
4	ascguggcG fuCfUfGfg gugggcgua	691	436-456	usAfscgcCf cAfCfccagA fcGfccagus gsu	919	434-456	ACACUGGCGU CUGGGUGGGC GUG	463

5	asgscaugG fuGfGfGfc ugccagcga	692	514-534	usCfsgcuGf gCfAfgeccA fcCfaugcus gsu	920	512-534	ACAGCAUGGU GGGUGCCAG CGA	464
6	gscsauggU fgGfGfCfu gccagcgaa	693	515-535	usUfscgcUf gGfCfagccC faCfcaugcs usg	921	513-535	CAGCAUGGUG GGCUGCCAGC GAG	465
7	csasugguG fgGfCfUfg ccagcgaga	694	516-536	usCfsucgCf uGfGfcagcC fcAfccaugs csu	922	514-536	AGCAUGGUGG GCUGCCAGCG AGC	466
8	asusgaugG fcCfAfAfc cggcucuca	695	538-558	usGfsagaGf cCfGfguugG fcCfaucaus csg	923	536-558	CGAUGAUGGC CAACCGGCUC UCC	467
9	gsgscaccU fgCfAfAfg gccuucgaa	696	751-771	usUfscgaAf gGfCfcuugC faGfgugccs csu	924	749-771	AGGGCACCUG CAAGGCCUUC GAC	468
10	usgsgcccG fgCfGfGfg uguacgcca	697	836-856	usGfsgcgUf aCfAfcccGf fcGfggccas gsg	925	834-856	CCUGGCCCCG CGGGUGUACG CCA	469
11	gsgscccG fcGfGfGfu guacgccaa	698	837-857	usUfsggcGf uAfCfaccC fcCfgggccc asg	926	835-857	CUGGCCCCGG GGGUGUACGC CAC	470
12	gscsccggC fgGfGfUfg uacgccaca	699	838-858	usGfsuggCf gUfAfcaccC fgCfcgggcs csa	927	836-858	UGGCCCCGGC GGUGUACGCC ACC	471
13	cscscggcG fgGfUfGfu acgccacca	700	839-859	usGfsgugGf cGfUfacacC fcGfccgggs csc	928	837-859	GGCCCCGGCG GUGUACGCCA CCA	472
14	cscsggcG fgUfGfUfa cgccaccaa	701	840-860	usUfsgguGf gCfGfuacaC fcCfgcgggs gsc	929	838-860	GCCCCGGCGG UGUACGCCAC CAU	473
15	gsgsuguaC fgCfCfAfc cauccugaa	702	846-866	usUfscagGf aUfGfguggC fgUfacaccs csg	930	844-866	CGGGUGUACG CCACCAUCCU GAA	474
16	gsusguacG fcCfAfCfc auccugaaa	703	847-867	usUfsucaGf gAfUfggugG fcGfuacacs csc	931	845-867	GGGUGUACGC CACCAUCCUG AAC	475
17	gsusacgcC faCfCfAfu ccugaacga	704	849-869	usCfsguuCf aGfGfaugG fgGfcguacs asc	932	847-869	GUGUACGCCA CCAUCCUGAA CGC	476
18	csgsccacC faUfCfCfu gaacgccga	705	852-872	usCfsggcGf uUfCfaggaU fgGfuggcgs usa	933	850-872	UACGCCACCA UCCUGAACGC CGG	477
19	gscscaccA fuCfCfUfg aacgccgga	706	853-873	usCfscggCf gUfUfcaggA fuGfguggcs gsu	934	851-873	ACGCCACCAU CCUGAACGCC GGC	478

20	cscsaccaU fcCfUfGfa acgccggca	707	854-874	usGfscggGf cGfUfucagG faUfgguggs csg	935	852-874	CGCCACCAUC CUGAACGCCG GCA	479
21	ascscaucC fuGfAfAfc gccggcaca	708	856-876	usGfsugcCf gGfCfGuucA fgGfauggus gsg	936	854-876	CCACCAUCCU GAACGCCGGC ACC	480
22	cscsugaaC fgCfCfGfg caccaauaa	709	861-881	usUfsauuGf gUfGfccggC fgUfucaggs asu	937	859-881	AUCCUGAACG CCGGCACCAA UAC	481
23	usgsaacgC fcGfGfCfa ccaauacaa	710	863-883	usUfsguaUf uGfGfugccG fgCfGuucas gsg	938	861-883	CCUGAACGCC GGCACCAUA CAG	482
24	asascgccG fgCfAfCfc aaucagaa	711	865-885	usUfscugUf aUfUfggugC fcGfgcguus csa	939	863-885	UGAACGCCGG CACCAAUACA GAU	483
25	ascsgccgG fcAfCfCfa auacagaua	712	866-886	usAfsucuGf uAfUfugguG fcCfggcgus usc	940	864-886	GAACGCCGGC ACCAAUACAG AUG	484
26	csgscggcC faCfCfAfa uacagauga	713	867-887	usCfsaucUf gUfAfuuggU fgCfeggcgs usu	941	865-887	AACGCCGGCA CCAAUACAGA UGG	485
27	gscscggcA fcCfAfAfu acagaugga	714	868-888	usCfscauCf uGfUfauugG fuGfccggcs gsu	942	866-888	ACGCCGGCAC CAAUACAGAU GGC	486
28	gscscacG fgCfAfCfa ggcaccaaa	715	997-1017	usUfsuggUf gCfCfugugC fcGfugggcs usu	943	995-1017	AAGCCACGG CACAGGCACC AAG	487
29	ascscgaG fcCfCfUfg ugcgccaca	716	1048- 1068	usGfsuggCf gCfAfcaggG fcUfcgggus gsa	944	1046- 1068	UCACCCGAGC CCUGUGCGCC ACC	488
30	cscscuguG fcGfCfCfa cccgccaga	717	1055- 1075	usCfsuggCf gGfGfuggcG fcAfcaggs csu	945	1053- 1075	AGCCUGUGC GCCACCCGCC AGG	489
31	asasguccA faCfAfUfg gggcacca	718	1099- 1119	usGfsgguGf cCfCfcaugU fuGfgacuus gsg	946	1097- 1119	CCAAGUCCAA CAUGGGGCAC CCG	490
32	csgsuggcC faUfCfAfa cuccuuuga	719	1284- 1304	usCfsaaaGf gAfGfuugaU fgCfccacgs usu	947	1282- 1304	AACGUGGGCA UCAACUCCUU UGG	491
33	gsgsacgcA fcCfCfCfu gaggccgua	720	1405- 1425	usAfsccgCf cUfCfagggG fuGfcguccs gsc	948	1403- 1425	GCGGACGCAC CCCUGAGGCC GUG	492
34	csusggcgA fgCfGfCfc cgcucugga	721	1583- 1603	usCfscagAf gCfGfggcgC fuCfgccags csg	949	1581- 1603	CGCUGGCGAG CGCCCGCUCU GGU	493

35	usgsgcgaG fcGfCfCfc gcucuggua	722	1584- 1604	usAfsccaGf aGfCfgggcG fcUfcgccas gsc	950	1582- 1604	GCUGGCGAGC GCCCCUCUG GUU	494
36	gsgscgagC fgCfCfCfcg cucugguua	723	1585- 1605	usAfsaccAf gAfGfcgggC fgCfucgccs asg	951	1583- 1605	CUGGCGAGCG CCCCUCUGG UUC	495
37	gscsgagcG fcCfCfGfc ucugguuca	724	1586- 1606	usGfsaacCf aGfAfgcggG fcGfcucgcs csa	952	1584- 1603	UGGCGAGCGC CCGCUCUGGU UCA	496
38	gscsgcccG fcUfCfUfg guucaucua	725	1590- 1610	usAfsgauGf aAfCfcagaG fcGfgggcgs usc	953	1588- 1610	GAGCGCCCGC UCUGGUUCAU CUG	497
39	csuscaugC fgCfCfUfg gaccgcuaa	726	1651- 1671	usAfsagcGf gUfCfcaggC fgCfaugags gsc	954	1649- 1671	GCCUCAUGCG CCUGGACCGC UUC	498
40	gsascugcC faUfCfCfa gauaggcca	727	1791- 1811	usGfsgccUf aUfCfuggaU fgGfcagucs asg	955	1789- 1811	CUGACUGCCA UCCAGAUAGG CCU	499
41	asasgaagC fcCfAfUfc ucccgccga	728	1955- 1975	usCfsggcGf gGfAfgaugG fgCfuucuus usg	956	1953- 1975	CAAAGAAGCC CAUCUCCCGC CGG	500
42	asgscccaU fcUfCfCfc gccgggcga	729	1959- 1979	usCfsgccCf gGfCfgggaG faUfgggcus usc	957	1957- 1979	GAAGCCCAUC UCCCGCCGGG CGC	501
43	gscsccauC fuCfCfCfcg ccgggcgca	730	1960- 1980	usGfscgcCf cGfGfcgggA fgAfugggcs usu	958	1958- 1980	AAGCCCAUCU CCCGCCGGGC GCC	502
44	cscsaucuC fcCfGfCfc gggcgcmaa	731	1962- 1982	usUfsggcGf cCfCfggcgG fgAfgauggs gsc	959	1960- 1982	GCCCAUCUCC CGCCGGGCGC CAU	503
45	asusggcaG fcCfGfUfg ggcuuguca	732	1981- 2001	usGfsacaAf gCfCfcacgG fcUfgccaus gsg	960	1979- 2001	CCAUGGCAGC CGUGGGCUUG UCC	504
46	csusugucC fuGfGfGfa ggaguguaa	733	1995- 2015	usUfsacaCf uCfCfuuccA fgGfacaags csc	961	1993- 2015	GGCUUGUCCU GGGAGGAGUG UAA	505
47	usgsggagG faGfUfGfu aaacagcga	734	2002- 2022	usCfsgcuGf uUfUfacacU fcCfucccas gsg	962	2000- 2022	CCUGGGAGGA GUGUAAACAG CGC	506
48	gsasggagU fgUfAfAfa cagcgcuca	735	2005- 2025	usCfsagcGf cUfGfuuaaC faCfuccucs csc	963	2003- 2025	GGGAGGAGUG UAAACAGCGC UGC	507
49	csasgucaC fcAfUfCfu cgggaccua	736	2066- 2086	usAfsgguCf cCfGfagauG fgUfgacugs usg	964	2064- 2086	CACAGUCACC AUCUCGGGAC CUC	508

50	ascscaucU fcGfGfGfa ccucagga	737	2071- 2091	usGfscuGf aGfGfuccG faGfauggus gsa	965	2069- 2091	UCACCAUCUC GGGACCUCAG GCC	509
51	ususcacU fcCfUfAfc uucagga	738	2167- 2187	usUfscUf gAfAfguagG faGfuggaas gsg	966	2165- 2187	CCUCCACUC CUACUUCAG GAG	510
52	csusucU fgAfGfGfc caucgcaca	739	2178- 2198	usGfsugGf aUfGfgccU fcAfugaags usa	967	2176- 2198	UACUUC AUGG AGGCCAUCGC ACC	511
53	usgsauccG fgGfAfGfc cgaagccaa	740	2225- 2245	usUfsggcUf uGfGfgcucC fcGfgaucas csc	968	2223- 2245	GGUGAUCCGG GAGCCGAAGC CAC	512
54	asgscgaA fgCfCfAfc guucagcca	741	2234- 2254	usGfsgcuGf aAfCfugugC fuUfcggcus csc	969	2232- 2254	GGAGCCGAAG CCACGUUCAG CCC	513
55	cscsgaagC fcAfCfGfu ucagcccga	742	2236- 2256	usCfsgggCf uGfAfacguG fgCfuucggs csu	970	2234- 2256	AGCCGAAGCC ACGUUCAGCC CGC	514
56	asasgccaC fgUfUfCfa gcccgcuga	743	2239- 2259	usCfsagcGf gGfCfugaaC fgUfggcuus csg	971	2237- 2259	CGAAGCCACG UUCAGCCCGC UGG	515
57	csascguuC faGfCfCfc gcuggcuca	744	2243- 2263	usGfsagcCf aGfCfgggcU fgAfacgugs gsc	972	2241- 2263	GCCACGUUCA GCCCCGUGGC UCA	516
58	uscscuccG fcCfGfAfg uacaaugua	745	2311- 2331	usAfscUf gUfAfucgG fcGfgaggas csg	973	2309- 2331	CGUCCUCCGC CGAGUACAAU GUC	517
59	cscsgccgA fgUfAfCfa augucaaca	746	2315- 2335	usGfsuugAf cAfUfuguaC fuCfggcggs asg	974	2313- 2335	CUCCGCCGAG UACAAUGUCA ACA	518
60	csgscgaG fuAfCfAfa ugucaacaa	747	2316- 2336	usUfsguuGf aCfAfuuguA fcUfcggcgs gsa	975	2314- 2336	UCCGCCGAGU ACAAUGUCAA CAA	519
61	usgscaggC fuGfUfCfc ugaagcgua	748	2423- 2443	usAfscgcUf uCfAfggacA fgCfcugcas gsc	976	2421- 2443	GCUGCAGGCU GUCCUGAAGC GUG	520
62	asasggauC faCfAfGfg gacaaccua	749	2482- 2502	usAfsgguUf gUfCfcccU fgAfuccuus csu	977	2480- 2502	AGAAGGAUCA CAGGGACAAC CUG	521
63	gsgsaucaC faGfGfGfa caaccugga	750	2484- 2504	usCfscagGf uUfGfuccU fgUfgauccs usu	978	2482- 2504	AAGGAUCACA GGGACAACCU GGA	522
64	csgsgcauC fgGfCfAfg gcugcacca	751	2517- 2537	usGfsgugCf aGfCfcugcC fgAfugccgs gsc	979	2515- 2537	GCCGGCAUCG GCAGGCUGCA CCU	523

65	usgscaccU fcUfCfAfG gcaucgaca	752	2531- 2551	usGfsucgAf uGfCfcugaG faGfgugcas gsc	980	2529- 2551	GCUGCACCUC UCAGGCAUCG ACG	524
66	csasccucU fcAfGfGfc aucgacgca	753	2533- 2553	usGfscguCf gAfUfgccuG faGfaggugs csa	981	2531- 2553	UGCACCUCUC AGGCAUCGAC GCC	525
67	ascscucuC faGfGfCfa ucgacgcca	754	2534- 2554	usGfsgcgUf cGfAfugccU fgAfaggus gsc	982	2532- 2554	GCACCUCUCA GGCAUCGACG CCA	526
68	cscsucucA fgGfCfAfu cgacgccaa	755	2535- 2555	usUfsggcGf uCfGfaugcC fuGfagaggs usg	983	2533- 2555	CACCUCUCAG GCAUCGACGC CAA	527
69	csuscucaG fgCfAfUfc gacgccaaa	756	2536- 2556	usUfsuggCf gUfCfgaugC fcUfgagags gsu	984	2534- 2556	ACCUCUCAGG CAUCGACGCC AAC	528
70	gscsaucgA fcGfCfCfa accccaaua	757	2543- 2563	usAfsuugGf gGfUfuggcG fuCfgaugcs csu	985	2541- 2563	AGGCAUCGAC GCCAACCCCA AUG	529
71	csasucgaC fgCfCfAfa ccccaaua	758	2544- 2564	usCfsauuGf gGfGfuugcG fgUfcgaugs csc	986	2542- 2564	GGCAUCGACG CCAACCCCAA UGC	530
72	asuscgacG fcCfAfAfc cccaaugca	759	2545- 2565	usGfscauUf gGfGfguugG fcGfucgaus gsc	987	2543- 2565	GCAUCGACGC CAACCCCAAU GCC	531
73	csusacaaC faUfCfGfa caccagcua	760	2706- 2726	usAfsfgcuGf gUfGfucgaU fgUfuguags asu	988	2704- 2726	AUCUACAACA UGCACACCAG CUC	532
74	asgscauaG fuGfUfGfg aagacgcua	761	2800- 2820	usAfsfgcuUf cUfUfccacA fcUfaugcus csa	989	2798- 2820	UGAGCAUAGU GUGGAAGACG CUG	533
75	asgsugucC fcUfGfGfa gguacggca	762	2913- 2933	usGfsccgUf aCfCfuccaG fgGfacacus gsu	990	2911- 2933	ACAGUGUCCC UGGAGGUACG GCU	534
76	gsusguccC fuGfGfAfg guacggcua	763	2914- 2934	usAfsgccGf uAfCfcuccA fgGfgacacs usg	991	2912- 2934	CAGUGUCCCU GGAGGUACGG CUC	535
77	usasgugaG fuGfGfGfa agguguaca	764	2981- 3001	usGfsuacAf cCfUfucccA fcUfcacuas csc	992	2979- 3001	GGUAGUGAGU GGGAAGGUGU ACC	536
78	asgsugagU fgGfGfAfa gguguacca	765	2982- 3002	usGfsguaCf aCfCfuuccC faCfucacus asc	993	2980- 3002	GUAGUGAGUG GGAAGGUGUA CCA	537
79	asgsuuuaC faAfGfGfa gcugcgua	766	3090- 3110	usGfsacgCf aGfCfuccuU fgUfaaacus usc	994	3088- 3110	GAAGUUUACA AGGAGCUGCG UCU	538

80	ascsaaggA fgCfUfGfc gucugcua	767	3095- 3115	usAfsccgCf gAfCfGcagC fuCfcuugus asa	995	3093- 3115	UUACAAGGAG CUGCGUCUGC GUG	539
81	asgscugcG fuCfUfGfc guggcuaca	768	3101- 3121	usCfsguagCf cAfCfGcagA fcGfcagcus csc	996	3099- 3121	GGAGCUGCGU CUGCGUGGCU ACG	540
82	gscsugcgU fcUfGfCfG uggcuacga	769	3102- 3122	usCfsguaGf cCfAfcgcaG faCfGcagcs usc	997	3100- 3122	GAGCUGCGUC UGCGUGGCUA CGA	541
83	csusgcguC fuGfCfGfu ggcuacgaa	770	3103- 3123	usUfscguAf gCfCfagcCA fgAfGcagcs csu	998	3101- 3123	AGCUGCGUCU GCGUGGCUAC GAC	542
84	gscsgucuC fcGfUfGfG cuacgacua	771	3105- 3125	usAfsugcGf uAfGfccacG fcAfGacgcs asg	999	3103- 3125	CUGCGUCUGC GUGGCUACGA CUA	543
85	uscscacaU fcGfAfCfc cugccacca	772	3287- 3307	usGfsgugGf cAfGfGgucG faUfguggas usg	1000	3285- 3307	CAUCCACAUC GACCCUGCCA CCC	544
86	csascaucG faCfCfCfu gccacccaa	773	3289- 3309	usUfsgggUf gGfCfagggU fcGfaugugs gsa	1001	3287- 3309	UCCACAUCGA CCCUGCCACC CAC	545
87	gscsccaaG fuGfGfCfu gacguggua	774	3340- 3360	usAfsccaCf gUfCfagccA fcUfugggcs csu	1002	3338- 3360	AGGCCCAAGU GGCUGACGUG GUG	546
88	cscscaaG fgGfCfUfg acgugguga	775	3341- 3361	usCfsaccAf cGfUfcagcC faCfuugggs csc	1003	3339- 3361	GGCCCAAGUG GCUGACGUGG UGG	547
89	gsgsugguG fcCfCfGfG acuggauga	776	3600- 3620	usCfsaucCf aGfUfccggG fcAfccaccs asu	1004	3598- 3620	AUGGUGGUGC CCGACUGGA UGG	548
90	usgsgugcC fcGfGfAfC uggauggga	777	3602- 3622	usCfscCaUf cCfAfguccG fgGfcaccas csc	1005	3600- 3622	GGUGGUGCCC GGACUGGAUG GGG	549
91	csusgcagG fcUfUfCfa gcucaacga	778	3678- 3698	usCfsguuGf aGfCfugaaG fcCfugcags gsc	1006	3676- 3698	GCCUGCAGGC UUCAGCUCAA CGG	550
92	usgscaggC fuUfCfAfg cucaacgga	779	3679- 3699	usCfscguUf gAfGfcugaA fgCfcugcas gsg	1007	3677- 3699	CCUGCAGGCU UCAGCUCAAC GGG	551
93	csasggcuU fcAfGfCfu caacgggaa	780	3681- 3701	usUfscCfGf uUfGfagcuG faAfGccugs csa	1008	3679- 3701	UGCAGGCUUC AGCUCAACGG GAA	552
94	asgsgcuuC faGfCfUfc aacgggaaa	781	3682- 3702	usUfsuccCf gUfUfagcuG fgAfagccus gsc	1009	3680- 3702	GCAGGCUUCA GCUCAACGGG AAC	553

95	gscsuucaG fcUfCfAfa cggaacca	782	3684- 3704	usGfsguuCf cCfGfuugaG fcUfgaagcs csu	1010	3682- 3704	AGGCUUCAGC UCAACGGGAA CCU	554
96	gsascacuG fcCfGfUfg gagaacaua	783	3808- 3828	usAfsuguUf cUfCfcacgG fcAfgugucs csa	1011	3806- 3828	UGGACACUGC CGUGGAGAAC AUG	555
97	csusgagcU faCfAfCfG gccaccgaa	784	3925- 3945	usUfscggUf gGfCfcgugU faGfcucags csu	1012	3923- 3945	AGCUGAGCUA CACGGCCACC GAC	556
98	gscsuacaC fgGfCfCfa ccgaccgca	785	3929- 3949	usGfscggUf cGfGfuggcC fgUfguagcs usc	1013	3927- 3949	GAGCUACACG GCCACCGACC GCC	557
99	ascscacggC fcAfCfCfG accgccaca	786	3932- 3952	usGfsuggCf gGfUfcgguG fgCfcgugus asg	1014	3930- 3952	CUACACGGCC ACCGACCGCC ACC	558
100	csasggacG fcGfUfGfg gagagccua	787	4243- 4263	usAfsggcUf cUfCfccacG fcGfuccugs gsc	1015	4241- 4263	GCCAGGACGC GUGGGAGAGC CUC	559
101	gsgsacgcG fuGfGfGfa gagccucua	788	4245- 4265	usAfsagagGf cUfCfucccA fcGfeguccs usg	1016	4243- 4265	CAGGACGCGU GGGAGAGCCU CUU	560
102	ascscagcU fuCfCfGfc uggguggaa	789	4381- 4401	usUfscCaCf cCfAfgcggA faGfcuggus asu	1017	4379- 4401	AUACCAGCUU CCGUGGGUG GAG	561
103	asgscuucC fgCfUfGfg guggaguca	790	4384- 4404	usGfsacuCf cAfCfccagC fgGfaagcus gsg	1018	4382- 4404	CCAGCUUCCG CUGGGUGGAG UCU	562
104	asascuguG fcCfAfCfc ucgggcgua	791	4462- 4482	usAfsccgcCf cGfAfggugG fcAfcaguus gsa	1019	4460- 4482	UCAACUGUGC CACCUCGGGC GUG	563
105	csusgugcC faCfCfUfc gggcgugga	792	4464- 4484	usCfscacGf cCfCfaggU fgGfcacags usu	1020	4462- 4484	AACUGUGCCA CCUCGGGCGU GGU	564
106	csasccucG fgGfCfGfu ggugggcua	793	4470- 4490	usAfsgccCf aCfCfacgcC fcGfaggugs gsc	1021	4468- 4490	GCCACCUCGG GCGUGGUGGG CUU	565
107	ascscucgG fgCfGfUfg gugggcuaa	794	4471- 4491	usAfsagcCf cAfCfcacgC fcCfaggus gsg	1022	4469- 4491	CCACCUCGGG CGUGGUGGGC UUG	566
108	ascscuggU fgAfUfGfa acgucuaca	795	4622- 4642	usGfsuagAf cGfUfucauC faCfcaggus csu	1023	4620- 4642	AGACCUGGUG AUGAACGUCU ACC	567
109	csusggugA fuGfAfAfc gucuaccga	796	4624- 4644	usCfsgguAf gAfCfguucA fuCfaccags gsu	1024	4622- 4644	ACCUGGUGAU GAACGUCUAC CGC	568

110	usgsgugaU fgAfAfCfG ucuaccgca	797	4625- 4645	usGfscggUf aGfAfcguuC faUfcaccas gsg	1025	4623- 4645	CCUGGUGAUG AACGUCUACC GCG	569
111	usgsaugaA fcGfUfCfu accgcgaca	798	4628- 4648	usCfsucgCf gGfUfagacG fuUfcacuas csc	1026	4626- 4648	GGUGAUGAAC GUCUACCGCG ACG	570
112	asusgaacG fuCfUfAfc cgcgacgga	799	4630- 4650	usCfscguCf gCfGfguagA fcGfuucuas csa	1027	4628- 4650	UGAUGAACGU CUACCGCGAC GGG	571
113	gsasacguC fuAfCfCfG cgacgggga	800	4632- 4652	usCfscggGf uCfGfCGguA fgAfCguucs asu	1028	4630- 4652	AUGAACGUCU ACCGCGACGG GGC	572
114	uscscaucC fgCfUfGfG gucugcuca	801	4750- 4770	usGfsagcAf gAfCfccagC fgGfauggas gsg	1029	4748- 4770	CCUCCAUCCG CUGGGUCUGC UCC	573
115	cscscagcU fcUfGfCfa cggucuaa	802	4805- 4825	usGfsuagAf cCfGfugcaG faGfcugggs csg	1030	4803- 4825	CGCCCAGCUC UGCACGGUCU ACU	574
116	csgscucC fcUfCfAfa cuuccgcga	803	4827- 4847	usCfsgcgGf aAfGfuugaG fgGfaggcgs usa	1031	4825- 4847	UACGCCUCCC UCAACUCCCG CGA	575
117	uscscucA faCfUfUfc cgcgacaua	804	4831- 4851	usAfsuguCf gCfGfgaagU fuGfagggas gsg	1032	4829- 4851	CCUCCCUCAA CUUCCGCGAC AUC	576
118	cscsucaaC fuUfCfCfG cgacaucaa	805	4833- 4853	usUfsgauGf uCfGfCGgaA fgUfugaggs gsa	1033	4831- 4853	UCCCUCAACU UCCGCGACAU CAU	577
119	asascuucC fgCfGfAfc aucaugcua	806	4837- 4857	usAfsagcUf gAfUfugucG fgGfaaguus gsa	1034	4835- 4857	UCAACUCCCG CGACAUCAUG CUG	578
120	ascsuuccG fcGfAfcfa ucaugcuga	807	4838- 4858	usCfsagcAf uGfAfcgucG fcGfgaagus usg	1035	4836- 4858	CAACUCCCGC GACAUCAUGC UGG	579
121	ususcgcG faCfAfUfc augcuggca	808	4840- 4860	usGfscgaGf cAfUfgaugU fcGfcggaas gsu	1036	4838- 4860	ACUUCGCGGA CAUCAUGCUG GCC	580
122	usgsgaguU fcUfCfGfG gccgagaca	809	4925- 4945	usGfsucuCf gGfCfccgaG faAfuccas usa	1037	4923- 4945	UAUGGAGUUC UCGGGCCGAG ACG	581
123	csuscuguC fcUfGfCfu gucaccgga	810	4995- 5015	usCfscggUf gAfCfagcaG fgAfCagags gsu	1038	4993- 5015	ACCUCUGUCC UGCUGUACCC GGA	582
124	uscugucC fuGfCfUfg ucaccgga	811	4996- 5016	usUfscggGf uGfAfcagcA fgGfacagas gsg	1039	4994- 5016	CCUCUGUCCU GCUGUACCCG GAC	583

125	csusguccU fgCfUfGfu caccggaca	812	4997- 5017	usGfsuccGf gUfGfacagC faGfgacags asg	1040	4995- 5017	CUCUGUCCUG CUGUCACCGG ACU	584
126	cscsaucgC fcAfUfCfG cccucagua	813	5174- 5194	usAfscugAf gGfGfcgauG fgCfgauggs csg	1041	5172- 5194	CGCCAUCGCC AUCGCCCUCA GUC	585
127	gsgsucgcU fuCfCfUfg gaaauugga	814	5413- 5433	usCfscaaUf uUfCfcaggA faGfcgaccs gsu	1042	5411- 5433	ACGGUCGCUU CCUGGAAAUU GGC	586
128	cscsuggaA faUfUfGfg caaaucga	815	5421- 5441	usCfsgaaUf uUfGfccaaU fuUfccaggs asa	1043	5419- 5441	UUCCUGGAAA UUGGCAAAU CGA	587
129	asasuucgA fcCfUfUfu cucagaaca	816	5435- 5455	usGfsuucUf gAfGfaaagG fuCfgaauus usg	1044	5433- 5455	CAAAUUCGAC CUUUCUCAGA ACC	588
130	gsasagaaC fgUfGfAfc auuccacga	817	5481- 5501	usCfsgugGf aAfUfgucaC fgUfucuucs asg	1045	5479- 5501	CUGAAGAACG UGACAUUCCA CGG	589
131	asgsaacgU fgAfCfAfu uccacggga	818	5483- 5503	usCfsccgUf gGfAfauguC faCfguucus usc	1046	5481- 5503	GAAGAACGUG ACAUUCACG GGG	590
132	gscsauccG fgGfAfUfg gggugguaa	819	5573- 5593	usUfsaccAf cCfCfcaucC fcGfgaugcs csg	1047	5571- 5593	CGGCAUCCGG GAUGGGGUGG UAC	591
133	csasuccgG fgAfUfGfg ggugguaca	820	5574- 5594	usGfsuacCf aCfCfccauC fcCfggauus csc	1048	5572- 5594	GGCAUCCGGG AUGGGGUGGU ACG	592
134	csgsccuuC fcGfCfUfa cauggccca	821	5637- 5657	usGfsggcCf aUfGfuageG fgAfaggcgs usc	1049	5635- 5657	GACGCCUUC GCUACAUGGC CCA	593
135	gscscuucC fgCfUfAfc auggcccaa	822	5638- 5658	usUfsgggCf cAfUfguagC fgCfaaggcs gsu	1050	5636- 5658	ACGCCUUCGG CUACAUGGCC CAA	594
136	ususccagG faCfGfUfc ugcaagcca	823	6085- 6105	usGfsgcuUf gCfAfgacgU fcCfuggaas gsa	1051	6083- 6105	UCUUCAGGA CGUCUGCAAG CCC	595
137	gsasgaaaC fgCfCfGfg cacgaagga	824	6259- 6279	usCfscuuCf gUfGfccggC fgUfuucucs asc	1052	6257- 6279	GUGAGAAACG CCGGCACGAA GGC	596
138	gsasaacgC fcGfGfCfa cgaaggcca	825	6261- 6281	usGfsgccUf uCfGfugccG fgCfguucus usc	1053	6259- 6281	GAGAAACGCC GGCACGAAGG CCU	597
139	gsusgcagU fgGfGfGfc gccaucgga	826	6295- 6315	usCfscgaUf gGfCfccccC faCfugcacs gsg	1054	6293- 6315	CCGUGCAGUG GGGCGCCAUC GGC	598

140	usgscaguG fgGfGfCfG ccaucggca	827	6296- 6316	usGfsccgAf uGfGfcgccC fcAfCugcas csg	1055	6294- 6316	CGUGCAGUGG GGCGCCAUCG GCG	599
141	usgsgggcG fcCfAfUfc ggcgacgua	828	6301- 6321	usAfscguCf gCfCfgaugG fcGfccccas csu	1056	6299- 6321	AGUGGGGCGC CAUCGGCGAC GUG	600
142	gscsgccaU fcGfGfCfG acgugggca	829	6305- 6325	usGfscCccAf cGfUfcgccG faUfggcgcs csc	1057	6303- 6325	GGGCGCCAUC GGCGACGUGG GCA	601
143	csasucggC fgAfCfGfu gggcauuua	830	6309- 6329	usAfSaauGf cCfCfacguC fgCfCgaugs gsc	1058	6307- 6329	GCCAUCGGCG ACGUGGGCAU UUU	602
144	csgsgcgaC fgUfGfGfG cauuuugga	831	6312- 6332	usCfscCaaAf aUfGfccccC fgUfcgccgs asu	1059	6310- 6332	AUCGGCGACG UGGGCAUUUU GGU	603
145	ascscuggA fcAfGfCfu cacuggcga	832	6554- 6574	usCfsgccAf gUfGfagcuG fuCfcaggus usg	1060	6552- 6574	CAACCUGGAC AGCUCACUGG CGG	604
146	gscsguggA fgGfUfGfc gccagacga	833	6599- 6619	usCfsgucUf gGfCfGcacC fuCfcacgcs usc	1061	6597- 6619	GAGCGUGGAG GUGCGCCAGA CGC	605
147	cscscaccC fuGfAfUfg cggcucaaa	834	6808- 6828	usUfsugaGf cCfGfcaucA fgGfgugggs gsc	1062	6806- 6828	GCCCCACCCU GAUGCGGCUC AAC	606
148	uscscuggU fgCfAfCfc caaucgaga	835	6857- 6877	usCfSUCgAf uUfGfggugC faCfcaggas asc	1063	6855- 6877	GUUCCUGGUG CACCCAAUCG AGG	607
149	cscscaauC fgAfGfGfG cuccaccaa	836	6867- 6887	usUfsgguGf gAfGfccccC fgAfuugggs usg	1064	6865- 6887	CACCCAAUCG AGGGCUCCAC CAC	608
150	gsgscuccA fcCfAfCfc guguuccaa	837	6877- 6897	usUfsggaAf cAfCfGgugG fuGfgagccs csu	1065	6875- 6897	AGGGCUCCAC CACCGUGUUC CAC	609
151	gsgscugcC fuAfCfUfa caucgacua	838	6978- 6998	usAfsgucGf aUfGfuaguA fgGfcagccs asg	1066	6976- 6998	CUGGCUGCCU ACUACAUCGA CUG	610
152	gscsugccU faCfUfAfc aucgacuga	839	6979- 6999	usCfsaguCf gAfUfGuagU faGfgcagcs csa	1067	6977- 6999	UGGCUGCCUA CUACAUCGAC UGC	611
153	usgscCuaC fuAfCfAfU cgacugcaa	840	6981- 7001	usUfsgcaGf uCfGfauguA fgUfaggcas gsc	1068	6979- 7001	GCUGCCUACU ACAUCGACUG CAU	612
154	gscscuacU faCfAfUfc gacugcaua	841	6982- 7002	usAfsugcAf gUfCfgaugU faGfuaggcs asg	1069	6980- 7002	CUGCCUACUA CAUCGACUGC AUC	613

155	ascsuacaU fcGfAfCfu gcaucagga	842	6986- 7006	usCfscugAf uGfCfagucG faUfguagus asg	1070	6984- 7006	CUACUACAUC GACUGCAUCA GGC	614
156	csusacauC fgAfCfUfg caucaggca	843	6987- 7007	usGfscuGf aUfGfagucC fgAfuguags usa	1071	6985- 7007	UACUACAUCG ACUGCAUCAG GCA	615
157	cscscgagG fgCfCfCfc uaccgcgua	844	7015- 7035	usAfscgcGf gUfAfggggC fcCfucgggs csu	1072	7013- 7035	AGCCCCAGGG CCCCUACCGC GUG	616
158	cscscuacC fcGfCfGfu ggccggcua	845	7023- 7043	usAfsgccGf gCfCfacgcG fgUfaggggs csc	1073	7021- 7043	GGCCCCUACC GCGUGGCCGG CUA	617
159	cscscuacC fgCfGfUfg gccggcuaa	846	7024- 7044	usUfsagcCf gGfCfcacgC fgGfuaggggs gsc	1074	7022- 7044	GCCCCUACCG CGUGGCCGGC UAC	618
160	cscsugcgU fgGfCfCfu uugaaauga	847	7055- 7075	usCfsauuUf cAfAfaggeC faCfgcaggs csc	1075	7053- 7075	GGCCUGCGUG GCCUUUGAAA UGU	619
161	usascaccC faGfAfGfc uaccgggca	848	7162- 7182	usGfscuGf gUfAfgcucU fgGfuguas gsg	1076	7160- 7182	CCUACACCCA GAGCUACCGG GCA	620
162	ascscagA fgCfUfAfc cgggcaaaa	849	7165- 7185	usUfsuugCf cCfGfaguagC fuCfugggus gsu	1077	7163- 7185	ACACCCAGAG CUACCGGGCA AAG	621
163	cscscagaG fcUfAfCfc gggcaaaga	850	7166- 7186	usCfsuuGf cCfCfagguaG fcUfcugggs usg	1078	7164- 7186	CACCCAGAGC UACCGGGCAA AGC	622
164	cscsagagC fuAfCfCfG ggcaaagca	851	7167- 7187	usGfscuUf gCfCfcggua fgCfucuggs gsu	1079	7165- 7187	ACCCAGAGCU ACCGGGCAAA GCU	623
165	asgsagcuA fcCfGfGfG caaagcuga	852	7169- 7189	usCfsagcUf uUfGfcccG fuAfgcucus gsg	1080	7167- 7189	CCAGAGCUAC CGGGCAAAGC UGA	624
166	gsasgcuaC fcGfGfGfc aaagcugaa	853	7170- 7190	usUfscagCf uUfUfgcccG fgUfagcucs usg	1081	7168- 7190	CAGAGCUACC GGGCAAAGCU GAC	625
167	asgscuacC fgGfGfCfa aagcugaca	854	7171- 7191	usGfsucaGf cUfUfugccC fgGfuagcus csu	1082	7169- 7191	AGAGCUACCG GGCAAAGCUG ACC	626
168	usgsagacG fgAfGfGfc cauagcua	855	7212- 7232	usAfsgcaUf aUfGfggcuC fcGfucucas gsc	1083	7210- 7232	GCUGAGACGG AGGCCAU AUG CUU	627
169	asgsacggA fgGfCfCfa uauugcuca	856	7214- 7234	usGfsaagCf aUfAfuggcC fuCfegucus csa	1084	7212- 7234	UGAGACGGAG GCCAU AUGCU UCU	628

170	gsascggaG fgCfCfAfu augcuucua	857	7215- 7235	usAfsgaaGf cAfUfauggC fcUfccgucs usc	1085	7213- 7235	GAGACGGAGG CCAU AUGCUU CUU	629
171	gsgsaggcC faUfAfUfg cuucuucga	858	7218- 7238	usCfsgaaGf aAfGfcauaU fgGfccuccs gsu	1086	7216- 7238	ACGGAGGCCA UAUGCUUCUU CGU	630
172	gsasggccA fuAfUfGfc uucuucgua	859	7219- 7239	usAfscgaAf gAfAfgcauA fuGfgccucs csg	1087	7217- 7239	CGGAGGCCAU AUGCUUCUUC GUG	631
173	asgsgccaU faUfGfCfu ucuucguga	860	7220- 7240	usCfsacgAf aGfAfagcaU faUfggccus csc	1088	7218- 7240	GGAGGCCAU UGCUCUUCG UGC	632
174	gsgsccauA fuGfCfUfu cuucgugca	861	7221- 7241	usGfscacGf aAfGfaagCA fuAfuggccs usc	1089	7219- 7241	GAGGCCAU GCUUCUUCGU GCA	633
175	gscscauaU fgCfUfUfc uucgugcaa	862	7222- 7242	usUfsgcaCf gAfAfgaagC faUfauggcs csu	1090	7220- 7242	AGGCCAU CUUCUUCGUG CAG	634
176	csasuaugC fuUfCfUfu cgugcagca	863	7224- 7244	usGfscugCf aCfGfaagaA fgCfauaugS gsc	1091	7222- 7244	GCCAU AUGCU UCUUCGUGCA GCA	635
177	asusgcuuC fuUfCfGfu gcagcagua	864	7227- 7247	usAfscugCf uGfCfacgaA fgAfagcaus asu	1092	7225- 7247	AUAUGCUUCU UCGUGCAGCA GUU	636
178	ususcuuC fuGfCfAfg caguucaca	865	7231- 7251	usGfsugaAf cUfGfcugcA fcGfaagaas gsc	1093	7229- 7251	GCUUCUUCGU GCAGCAGUUC ACG	637
179	uscsgugcA fgCfAfGfu ucacggaca	866	7235- 7255	usGfsuccGf uGfAfacugC fuGfcacgas asg	1094	7233- 7255	CUUCGUGCAG CAGUUCACGG ACA	638
180	uscsacggA fcAfUfGfg agcacaaca	867	7247- 7267	usGfsuugUf gCfUfccauG fuCfcgugas asc	1095	7245- 7267	GUUCACGGAC AUGGAGCACA ACA	639
181	asgsccgcC fgUfGfGfa ccugaucaa	868	7317- 7337	usUfsgauCf aGfGfuccaC fgGfcggcus gsc	1096	7315- 7337	GCAGCCGCCG UGGACCUGAU CAU	640
182	usgsgaccU fgAfUfCfa ucaagagca	869	7325- 7345	usGfscucUf uGfAfugauC faGfguccas csg	1097	7323- 7345	CGUGGACCUG AUCAUCAAGA GCC	641
183	cscsuucuA fcUfAfCfa agcugcgua	870	7388- 7408	usAfscgcAf gCfUfuguaG fuAfgaaggs asc	1098	7386- 7408	GUCCUUCUAC UACAAGCUGC GUG	642
184	csusucuaC fuAfCfAfa gcugcguga	871	7389- 7409	usCfsacgCf aGfCfuuguA fgUfagaags gsa	1099	7387- 7409	UCCUUCUACU ACAAGCUGCG UGC	643

185	ususcuaC faCfAfAfg cugcgugca	872	7390- 7410	usGfscacGf cAfGfcuugU faGfuagaas gsg	1100	7388- 7410	CCUUCUACUA CAAGCUGCGU GCC	644
186	csusacuaC faAfGfCfu gcgugccga	873	7392- 7412	usCfsggcAf cGfCfagcuU fgUfaguags asa	1101	7390- 7412	UUCUACUACA AGCUGCGUGC CGC	645
187	gsgsccaaG fuAfCfCfa uggcaacga	874	7431- 7451	usCfsguuGf cCfAfugguA fcUfuggccs usu	1102	7429- 7451	AAGGCCAAGU ACCAUGGCAA CGU	646
188	gscscaagU faCfCfAfU ggcaacgua	875	7432- 7452	usAfscguUf gCfCfauggU faCfuuggcs csu	1103	7430- 7452	AGGCCAAGUA CCAUGGCAAC GUG	647
189	cscsaaguA fcCfAfUfg gcaacguga	876	7433- 7453	usCfsacgUf uGfCfcaugG fuAfcuuggs csc	1104	7431- 7453	GGCCAAGUAC CAUGGCAACG UGA	648
190	csasaguaC fcAfUfGfg caacgugaa	877	7434- 7454	usUfscacGf uUfGfccauG fgUfacuugs gsc	1105	7432- 7454	GCCAAGUACC AUGGCAACGU GAU	649
191	usasccauG fgCfAfAfc gugaugcua	878	7438- 7458	usAfsagcaUf cAfCfguugC fcAfugguas csu	1106	7436- 7458	AGUACCAUGG CAACGUGAUG CUA	650
192	gscscaagA fcGfGfGfu ggcgccuaa	879	7465- 7485	usUfsaggCf gCfCfaccCG fuCfuuggcs gsc	1107	7463- 7485	GCGCCAAGAC GGGUGGCGCC UAC	651
193	csasagacG fgGfUfGfg cgccuacga	880	7467- 7487	usCfsguaGf gCfGfccacC fcGfucuugs gsc	1108	7465- 7487	GCCAAGACGG GUGGCGCCUA CGG	652
194	asgsacggG fuGfGfCfG ccuacggca	881	7469- 7489	usGfscCGUf aGfGfCGccA fcCfCGucus usg	1109	7467- 7489	CAAGACGGGU GGCGCCUACG GCG	653
195	ascsgggUg fgCfGfCfc uacggcgaa	882	7471- 7491	usUfscgcCf gUfAfggcgC fcAfcccgus csu	1110	7469- 7491	AGACGGGUGG CGCCUACGGC GAG	654
196	usgsgcgcC fuAfCfGfg cgaggacca	883	7476- 7496	usGfsgucCf uCfGfccguA fgGfCGccas csc	1111	7474- 7496	GGUGGCGCCU ACGGCGAGGA CCU	655
197	asgsgaccU fgGfGfCfG cggacuaca	884	7490- 7510	usGfsuagUf cCfGfCGccC faGfguccus csg	1112	7488- 7510	CGAGGACCUG GGCGCGGACU ACA	656
198	gsascuaC faCfCfUfc ucccaggua	885	7504- 7524	usAfscCGUf gGfAfgaggU fuGfuagucs csg	1113	7502- 7524	CGGACUACAA CCUCUCCCAG GUA	657
199	ascsuacaA fcCfUfCfu cccagguaa	886	7505- 7525	usUfsaccUf gGfGfagagG fuUfaguags csc	1114	7503- 7525	GGACUACAAC CUCUCCCAGG UAU	658

200	usascaacC fuCfUfCfc cagguauga	887	7507- 7527	usCfsauaCf cUfGfggagA fgGfuuguas gsu	1115	7505- 7527	ACUACAACCU CUCCCAGGUA UGC	659
201	csasaccuC fuCfCfCfa gguaugcga	888	7509- 7529	usCfsgcaUf aCfCfugggA fgAfggguugs usa	1116	7507- 7529	UACAACCUCU CCCAGGUAUG CGA	660
202	csuscuccC faGfGfUfa ugcgacgga	889	7513- 7533	usCfscguCf gCfAfuaccU fgGfgagags gsu	1117	7511- 7533	ACCUCUCCCA GGUAUGCGAC GGG	661
203	csuscccaG fgUfAfUfg cgacgggaa	890	7515- 7535	usUfscggGf uCfGfcauaC fcUfgggags asg	1118	7513- 7535	CUCUCCCAGG UAUGCGACGG GAA	662
204	uscscagG fuAfUfGfc gacgggaaa	891	7516- 7536	usUfsuccCf gUfCfGcauA fcCfugggas gsa	1119	7514- 7536	UCUCCCAGGU AUGCGACGGG AAA	663
205	csasgguaU fgCfGfAfc gggaaagua	892	7519- 7539	usAfscuuUf cCfCfGucgC faUfaccugs gsg	1120	7517- 7539	CCCAGGUAUG CGACGGGAAA GUA	664
206	uscscacG fgCfAfCfc ucggggaca	893	7836- 7856	usGfsuccCf cGfAfggugC fcGfugggas gsg	1121	7834- 7856	CCUCCACGG CACCUCGGGG ACA	665
207	cscscacG fcAfCfCfu cggggacaa	894	7837- 7857	usUfsgucCf cCfGfagguG fcCfuggggs asg	1122	7835- 7857	CUCCACGGC ACCUCGGGGA CAC	666
208	gscsugggC fcUfCfGfu gcgcccgua	895	7925- 7945	usAfscggGf cGfCfacgaG fgCfccagcs csc	1123	7923- 7945	GGGUGGGCC UCGUGCGCCC GUG	667
209	csusgggcC fuCfGfUfg cgcccguaga	896	7926- 7946	usCfsacgGf gCfGfcaagA fgGfcccags csc	1124	7924- 7946	GGCUGGGCCU CGUGCGCCCG UGG	668
210	usgsggccU fcGfUfGfc gcccguaga	897	7927- 7947	usCfscacGf gGfCfGcacG faGfgcccas gsc	1125	7925- 7947	GCUGGGCCUC GUGCGCCCGU GGG	669
211	gsgscucG fuGfCfGfc ccgugggga	898	7929- 7949	usCfscggAf cGfGfGcgA fcGfaggccs csa	1126	7927- 7949	UGGGCCUCGU GCGCCCGUGG GGU	670
212	gscscucG fgCfGfCfc cguggggua	899	7930- 7950	usAfscggCf aCfGfGcgC faCfaggcs csc	1127	7928- 7950	GGGCCUCGUG CGCCCGUGGG GUC	671
213	cscsucguG fcGfCfCfc guggggua	900	7931- 7951	usGfsaccCf aCfCfGggcG fcAfGagggs csc	1128	7929- 7951	GGCCUCGUGC GCCCGUGGGG UCU	672
214	csuscgugC fgCfCfCfc uggggucua	901	7932- 7942	usAfsgacCf cCfAfcgggC fgCfacgags gsc	1129	7930- 7952	GCCUCGUGCG CCCUGGGGU CUG	673

215	uscsgugcG fcCfCfGfu ggggucuga	902	7933- 7953	usCfsagaCf cCfCfacggG fcGfcacgas gsg	1130	7931- 7953	CCUCGUGCGC CCGUGGGGUC UGC	674
216	gsusgcgcC fcGfUfGfg ggucugcga	903	7935- 7955	usCfsgcaGf aCfCfccacG fgGfcgcacs gsa	1131	7933- 7955	UCGUGCGCCC GUGGGGUCUG CGC	675
217	csgscccG fgGfGfGfu cugcgcuaa	904	7938- 7958	usAfsagcGf cAfGfaccC faCfgggcs csa	1132	7936- 7958	UGC GCCGUG GGGUCUGCGC UUG	676
218	gsusggggU fcUfGfCfG cuuggucua	905	7943- 7963	usAfsagcCf aAfGfGcgaG faCfcccacs gsg	1133	7941- 7963	CCGUGGGGUC UGCGCUUGGU CUU	677
219	ususcG faUfGfUfc cccugcgga	906	8072- 8092	usCfscgcAf gGfGfgacaU fcGfggggaas asu	1134	8070- 8092	AUUUCCCCGA UGUCCCCUGC GGG	678
220	uscscG fuGfUfCfc ccugcgga	907	8073- 8093	usCfscgcCf aGfGfggaC fuCfggggas asa	1135	8071- 8093	UUUCCCCGAU GUCCCCUGCG GGC	679
221	cscscgaU fgUfCfCfc cugcgga	908	8074- 8094	usGfscgcGf cAfGfgggaC faUfGfgggs asa	1136	8072- 8094	UUUCCCCGAU UCCCCUGCGG GCG	680
222	ascscG fuUfCfAfu uuuuacaca	909	8388- 8408	usGfsuguAf aAfAfaugaA faCfggggus csc	1137	8386- 8408	GGACCCCGUU UCAUUUUUAC ACC	681
223	asgscucC fcAfCfAfa uuaaaccga	910	8432- 8452	usCfsgguUf uAfAfuuguG fgGfaggcus gsa	1138	8430- 8452	UCAGCCUCCC ACAAUUAAAC CGC	682
224	gscscuccC faCfAfaFu uaaaccgca	911	8433- 8453	usGfscggUf uUfAfauguU fgGfaggcs usg	1139	8431- 8453	CAGCCUCCCA CAAUUAAACC GCA	683
225	cscscacaA fuUfAfaAfa ccgcaugua	912	8437- 8457	usAfscauGf cGfGfuuuA fuUfgugggs asg	1140	8435- 8457	CUCCACAAU UAAACCGCAU GUG	684
226	cscsacaaU fuAfaAfaC cgcauguga	913	8438- 8458	usCfsacaUf gCfGfguuA faUfuguggs gsa	1141	8436- 8458	UCCACAAUU AAACCGCAUG UGA	685
227	ascsaauuA faAfCfCfG caugugaua	914	8440- 8460	usAfsucaCf aUfGfGguU fuAfaugus gsg	1142	8438- 8460	CCACAAUUA ACCGCAUGUG AUC	686
228	csasaauaA faCfCfGfC augugauc	915	8441- 8461	usGfsaucAf cAfUfGcggu fuUfaauugs usg	1143	8439- 8461	CACAAUUA CCGCAUGUGA UCU	687

[00138] The nucleotide sequence presented in Table 3, utilize the following abbreviations set forth in Table 4.

Table 4. Abbreviations of Nucleotide Modifications.

Abbreviation	Nucleotide(s)
a	2'-O-methyladenosine-3'-phosphate
A	adenosine-3'-phosphate
Aam	2'-O-(N-methylacetamide)adenosine-3'-phosphate
Aams	2'-O-(N-methylacetamide)adenosine-3'-phosphorothioate
Ab	beta-L-adenosine-3'-phosphate
Ab s	beta-L-adenosine-3'-phosphorothioate
Af	2'-fluoroadenosine-3'-phosphate
Af s	2'-fluoroadenosine-3'-phosphorothioate
Agn	Adenosine-glycol nucleic acid (GNA), S-isomer
Ahd	2'-O-hexadecyl adenosine-3'-phosphate
Ahds	2'-O-hexadecyl-adenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
as	2'-O-methyladenosine-3'- phosphorothioate
dA	2'-deoxyadenosine-3'-phosphate
dAs	2'-deoxyadenosine-3'-phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
C	cytidine-3'-phosphate
Cb	beta-L-cytidine-3-phosphate
Cbs	beta-L-cytidine-3'-phosphorothioate
Cf	2'-fluorocytidine-3'-phosphate
Cf s	2'-fluorocytidine-3'-phosphorothioate
Cgn	Cytidine-glycol nucleic acid (GNA), S-isomer
Chd	2'-O-hexadecyl cytidine-3'-phosphate
Chds	2'-O-hexadecyl-cytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
cs	2'-O-methylcytidine-3'- phosphorothioate
dC	2'-deoxycytidine-3'-phosphate
dCs	2'-deoxycytidine-3'-phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
G	guanosine-3'-phosphate
Gam	2'-O-(N-methylacetamide)guanosine-3'-phosphate
Gams	2'-O-(N-methylacetamide)guanosine-3'-phosphorothioate
Gb	beta-L-guanosine-3'-phosphate
Gbs	beta-L-guanosine-3'-phosphorothioate
Gf	2'-fluoroguanosine-3'-phosphate
Gf s	2'-fluoroguanosine-3'-phosphorothioate
Ggn	Guanosine-glycol nucleic acid (GNA), S-isomer
Ghd	2'-O-hexadecyl guanosine-3'-phosphate
Ghds	2'-O-hexadecyl-guanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
gs	2'-O-methylguanosine-3'- phosphorothioate
dG	2'-deoxyguanosine-3'-phosphate
dGs	2'-deoxyguanosine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
U	uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate

Ufs	2'-fluorouridine -3'-phosphorothioate
Uhd	2'-O-hexadecyl uridine-3'-phosphate
Uhds	2'-O-hexadecyl-uridine-3'-phosphorothioate
Us	uridine -3'-phosphorothioate
us	2'-O-methyluridine-3'-phosphorothioate
dU	2'-deoxyuridine
dUs	2'-deoxyuridine-3'-phosphorothioate
s	phosphorothioate linkage
N	Any nucleotide (A, G, C, U, T) modified or unmodified

[00139] 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.

5.3 Modified RNAi Agents

[00140] 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 FASN mRNA)), or any combination thereof.

5.3.1 Nature of Nucleotide Modifications

[00141] 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.

[00142] 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.

5.3.1.1 Modified Nucleosides

[00143] 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

[00144] 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.

[00145] 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).

[00146] 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.

[00147] Exemplary substituents include, for example, but are not limited to, substitution (*e.g.*, at any position of the sugar (*e.g.*, ribose) (*e.g.*, at position 2')) with any one of the following: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Additional exemplary substitutions (*e.g.*, at any position of the sugar (*e.g.*, ribose) (*e.g.*, at position 2')) include, for example, but are not limited to, substitution with any one of the following: O[(CH₂)_nO]_m, CH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10.

[00148] 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))).

[00149] In some embodiments, the agent (or any component thereof) comprises any of the following substituents at the 2'-position of the sugar (*e.g.*, ribose): C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, or a substituted silyl. In some embodiments, the agent (or any component thereof) comprises a 2'-methoxyethoxy (2'-O—CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (*see, e.g.*, Martin et al., *Helv. Chim. Acta*, 1995, 78:486-504, the entire contents of which is incorporated by reference herein for all purposes) (*i.e.*, an alkoxy-alkoxy group). In some embodiments, the agent (or any component thereof) comprises a 2'-dimethylaminoethoxyethoxy, *i.e.*, a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE; a 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O—CH₂—O—CH₂—N(CH₃)₂; a 5'-Me-2'-F nucleotide, a 5'-Me-2'-OMe nucleotide, a 5'-Me-2'-deoxynucleotide, (both R and S isomers in these three families); a 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

[00150] 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.

(a) Non-Bicyclic Sugar Modifications

[00151] 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.

[00152] In some embodiments, non-bicyclic modified sugar moiety comprises a substituent group at the 2'-position of the sugar (*e.g.*, ribose). Examples of 2'- substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-O-MOE), 2'-deoxy-2'-fluoro (2'-F), 2'-arabino-fluoro (2'-Ara-F), 2'-O-benzyl, 2'-O-methyl-4-pyridine (2'-O-methyl-4-pyridine (2'-O-CH₂Py(4))), and 2'-O-N-alkyl acetamide (*e.g.*, 2'-O-N-methyl acetamide ("NMA"), 2'-O-N-dimethyl acetamide, 2'-O-N-ethyl acetamide, and 2'-O-N-propyl acetamide). For example, *see, e.g.*, U.S. 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.

[00153] In some embodiments, the 2'-substituent group is a halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O- alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)- N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, or a 2'-substituent group described in any one of the following: Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087, the entire contents of which are incorporated herein by reference for all purposes. In some embodiments, these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl.

[00154] In some embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)-N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl. In some embodiments, a 2'-substituted non-bicyclic

modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF, OCH₃, OCH₂CH₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, and OCH₂C(=O)-N(H)CH₃ ("NMA"). In some embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, OCH₂CH₂OCH₃, and OCH₂C(=O)-N(H)CH₃.

[00155] 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).

[00156] 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.

[00157] 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).

[00158] 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.

[00159] 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- deoxyribose 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.

[00160] 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 Fluiters 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

[00161] In some embodiments, the modified sugar (*e.g.*, ribose) moiety comprises a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar (*e.g.*, ribose) moiety. In some embodiments, the bicyclic sugar (*e.g.*, ribose) moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt"), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.*, Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (*see, e.g.*, Prakash et al., U.S. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (*see, e.g.*, Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (*see, e.g.*, Zhou, et al., J. Org. Chem., 2009, 74, 118-134), 4'-CH₂-C(=CH₂)-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672). The entire contents of all of the foregoing references is incorporated by reference herein for all purposes.

[00162] In some embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from: -[C(R_a)(R_b)]_n-, -[C(R_a)(R_b)]_n-O-, -C(R_a)=C(R_b)-, -C(R_a)=N-, -C(=NR_a)-, -C(=O)-, -C(=S)-, -O-, -Si(R_a)₂-, -S(=O)X-, and -N(R_a)-, wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical,

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

[00163] Additional bicyclic sugar moieties are known in the art, *see*, for example: Freier *et al.*, *Nucleic Acids Research*, 1997, 25(22), 4429-4443; Albaek *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 al.*, U.S. 7,053,207; Imanishi *et al.*, U.S. 6,268,490; Imanishi *et al.*, U.S. 6,770,748; Imanishi *et al.*, U.S. RE44,779; Wengel *et al.*, U.S. 6,794,499; Wengel *et al.*, U.S. 6,670,461; Wengel *et al.*, U.S. 7,034,133; Wengel *et al.*, U.S. 8,080,644; Wengel *et al.*, U.S. 8,034,909; Wengel *et al.*, U.S. 8,153,365; Wengel *et al.*, U.S. 7,572,582; Ramasamy *et al.*, U.S. 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. 7,547,684; Seth *et al.*, U.S. 7,666,854; Seth *et al.*, U.S. 8,088,746; Seth *et al.*, U.S. 7,750,131; Seth *et al.*, U.S. 8,030,467; Seth *et al.*, U.S. 8,268,980; Seth *et al.*, U.S. 8,546,556; Seth *et al.*, U.S. 8,530,640; Migawa *et al.*, U.S. 9,012,421; Seth *et al.*, U.S. 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.

[00164] In some embodiments, the modified sugar (*e.g.*, ribose) comprises a constrained ethyl nucleotide comprising a 4'-CH(CH₃)—O-2' bridge. In some embodiments, the constrained ethyl nucleotide is in the S conformation (S-cEt). In some embodiments, the modified sugar (*e.g.*, ribose) comprises a conformationally restricted nucleotide (CRN). CRNs are nucleotide analogs with a linker connecting the C2' and C4' carbons of ribose or the C3 and —C5' carbons of ribose. Representative publications that teach the preparation of certain of the above include, but are not limited to, US2013/0190383; and WO2013/036868, the entire contents of each of which are hereby incorporated herein by reference.

[00165] 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).

[00166] 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

[00167] 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.

[00168] 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.

[00169] 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, deoxythymidine (dT), 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl (-C≡C-CH₃) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases

may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 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.

[00170] In some embodiments, the modified nucleobase comprises a pseudouridine, 2-thiouridine (s2U), N6'-methyladenosine, 5'-methylcytidine (m⁵C), 5'-fluoro-2'-deoxyuridine, N-ethylpiperidine 7-EAA triazole modified adenine, N-ethylpiperidine 6'-triazole modified adenine, 6-phenylpyrrolo-cytosine (PhpC), 2',4'-difluorotoluy l 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.

[00171] Representative U.S. Patents and 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. 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.

5.3.1.2 Internucleoside Linkage Modifications

[00172] 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).

[00173] 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'.

[00174] The two main classes of modified internucleoside linking can be defined by the presence or absence of a phosphorous atom.

(i) Modified Phosphorous Containing Internucleoside Linkages

[00175] In some embodiments, the modified internucleoside linkage comprises a phosphorous atom. Representative modified phosphorus-containing internucleoside linkages include but are not limited to phosphorothioates (PS (Rp isomer or Sp isomer)) (*e.g.*, 5'phosphorothioate), phosphotriesters, phosphoramidates (*e.g.*, 3'-amino phosphoramidate and aminoalkylphosphoramidates), chiral phosphorothioates, phosphorodithioates (PS2), aminoalkylphosphotriesters, methyl and other alkyl phosphonates (*e.g.*, methylphosphonate (MP), 3'-alkylene phosphonates), methoxypropyl-phosphonates (MOP), 5'-(E)-vinylphosphonates, 5'methyl phosphonates, (S)-5'C-methyl with phosphates, phosphinates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, boranophosphates, and peptide nucleic acids (PNAs).

[00176] 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.

(ii) Modified Non-Phosphorous Containing Internucleoside Linkages

[00177] 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 CH₂ component parts.

[00178] Representative non-phosphorous containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-); siloxane (-O-SiH₂-O-); and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-).

[00179] 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.

5.3.1.3 Additional Exemplary Nucleotide Modifications

[00180] 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.

[00181] 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.

5.3.2 Extent of Modified Nucleotides

[00182] 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, 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 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 modified.

[00183] 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. 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.

[00184] 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.

[00185] 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.

[00186] 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.

[00187] 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.

5.4 Conjugates

[00188] In some embodiments, the agent (*e.g.*, described herein) (*e.g.*, RNAi agent, dsRNA agent, antisense strand, sense strand) comprises a heterologous moiety (*e.g.*, operably connected to the agent). Therefore, further provided herein are conjugates comprising an agent (*e.g.*, described herein) (*e.g.*, RNAi agent, dsRNA agent, antisense strand, sense strand) and a heterologous moiety (*e.g.*, operably connected to the agent). It is clear from the disclosure, but for the sake of clarity, the conjugate can comprise a modified agent (*e.g.*, described herein, *see, e.g.*, § 5.3).

[00189] 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).

[00190] 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).

[00191] 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 FASN mRNA), inhibition of expression of a target gene (*e.g.*, a FASN gene), and/or reduction in the expression of a target gene (*e.g.*, a FASN gene).

[00192] 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).

[00193] 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).

[00194] 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.

5.4.1 Heterologous Moieties

[00195] Heterologous moieties, include for example, but are not limited to, carbohydrates, peptides, proteins (*e.g.*, antibodies or functional fragments or variants thereof; ligands (*e.g.*, of a target receptor)), lipids, polymers, small molecules, intercalators, reporter molecules, polyamines, polyamides, vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipophilic groups, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

[00196] 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.

[00197] Exemplary heterologous moieties (*e.g.*, targeting moieties), further include but are not limited, to carbohydrate moieties (*e.g.*, GalNAc and GalNAc derivatives (*See, e.g.*, U.S. Patent No. 8,106,022 and WO2019055633)); lipid moieties such as a cholesterol moiety (*see, e.g.*, Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556); cholic acid (*see, e.g.*, Manoharan et al., *Biorg. Med. Chem. Lett.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (*see, e.g.*, Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan et al., *Biorg. Med. Chem. Lett.*, 1993, 3:2765-2770); 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.

5.4.1.1 Targeting Moieties

[00198] 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).

[00199] 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

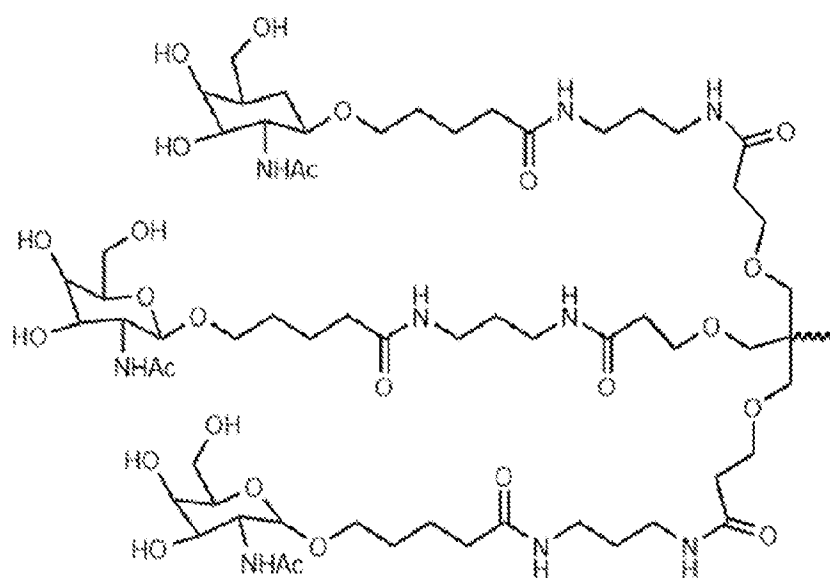
[00200] In some embodiments, the targeting moiety specifically binds to a target molecule (*e.g.*, protein, carbohydrate, lipid, etc.) expressed by hepatocytes (*e.g.*, on the surface of the surface of hepatocytes). In some embodiments, the targeting moiety specifically binds to a target molecule protein (*e.g.*, receptor) expressed on the surface of hepatocytes.

[00201] 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.

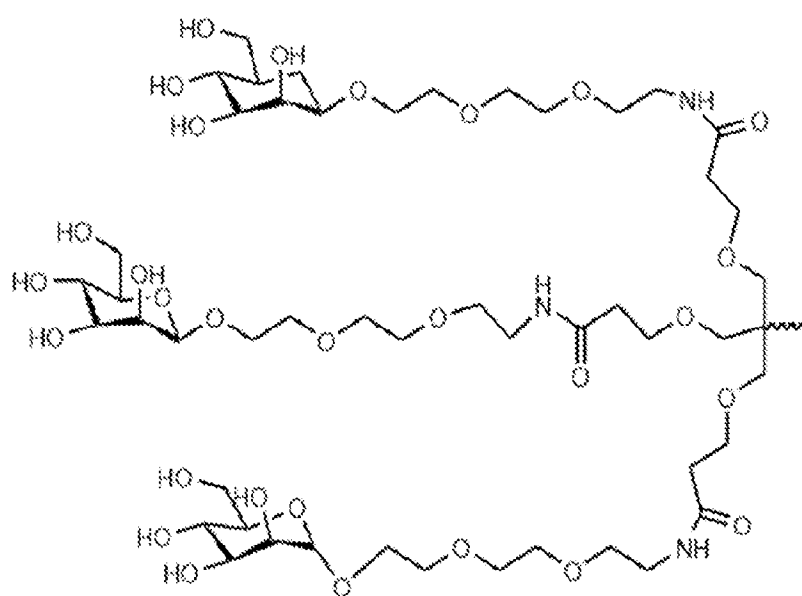
[00202] In some embodiments, the targeting moiety comprises at least one (*e.g.*, at least 2, 3, 4, or more) N-acetylgalactosamine (GalNAc) or GalNAc derivative. In some embodiments, the targeting moiety comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) of GalNAc moieties and/or GalNAc derivatives. In 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.

[00203] Exemplary GalNAc conjugates, which comprise one or more GalNAc and/or derivative thereof, are known the art. *See, e.g.*, in U.S. Patent 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.

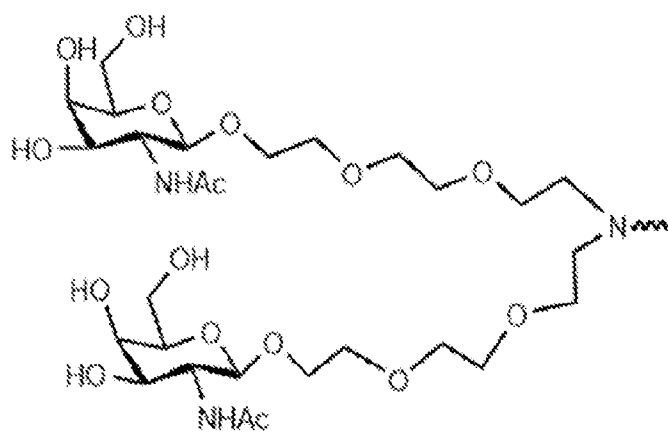
[00204] In some embodiments, the targeting moiety (*e.g.*, GalNAc targeting moiety) comprises any one of the following formulas:



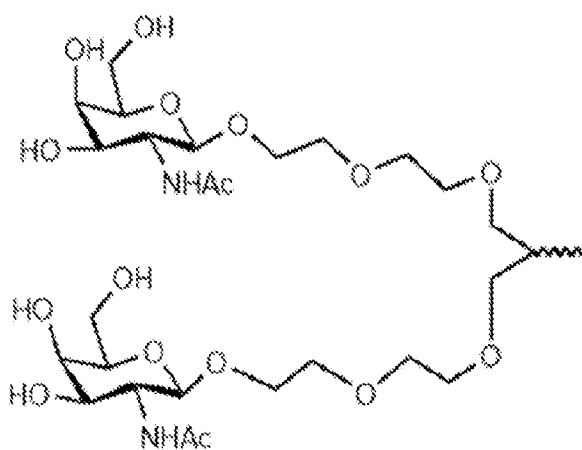
Formula II



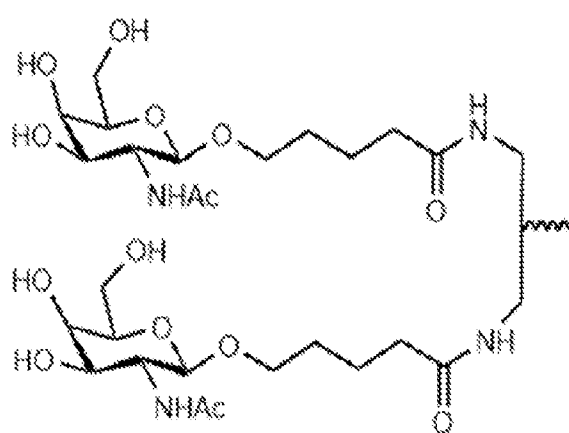
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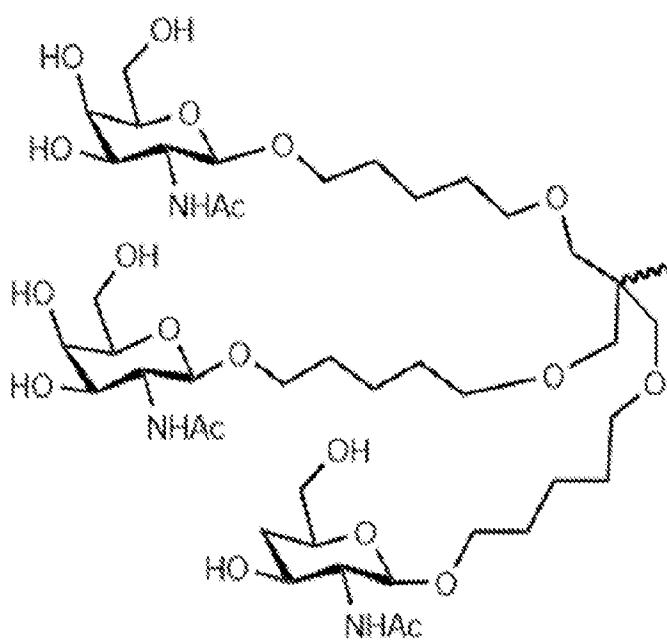
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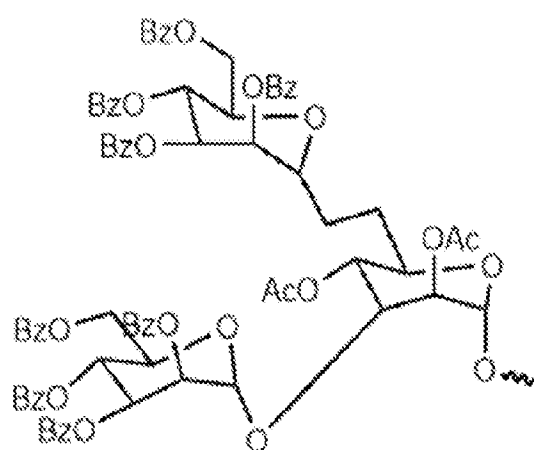
Formula V



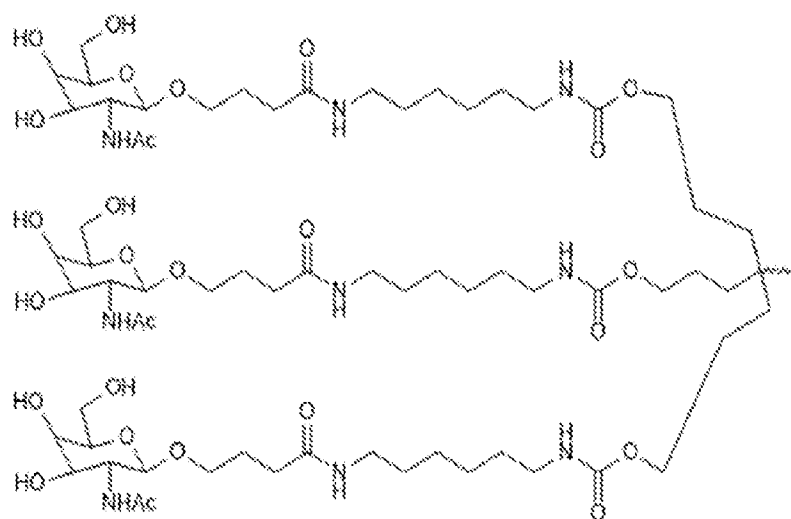
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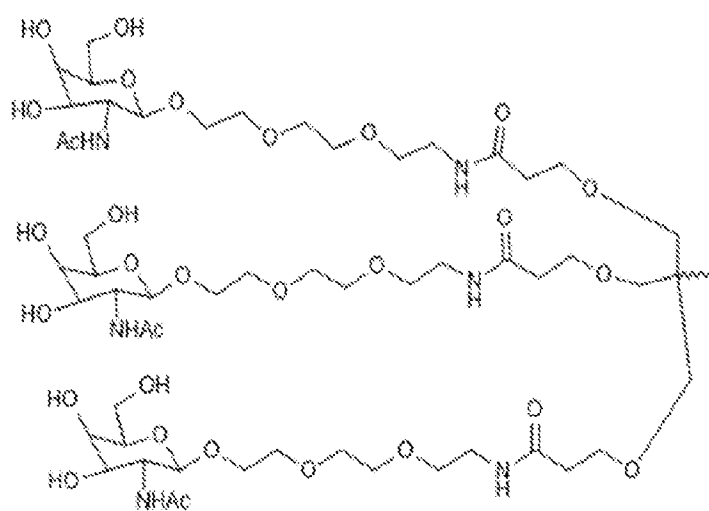
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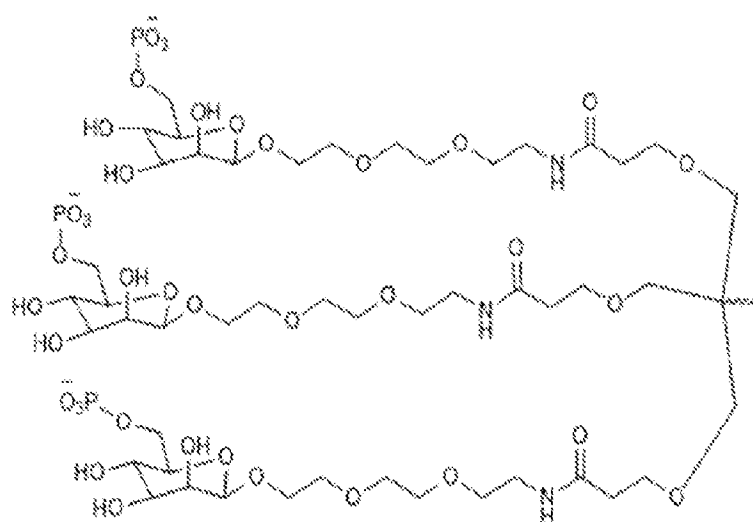
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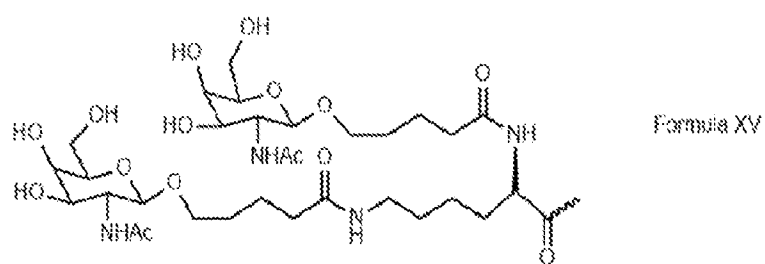
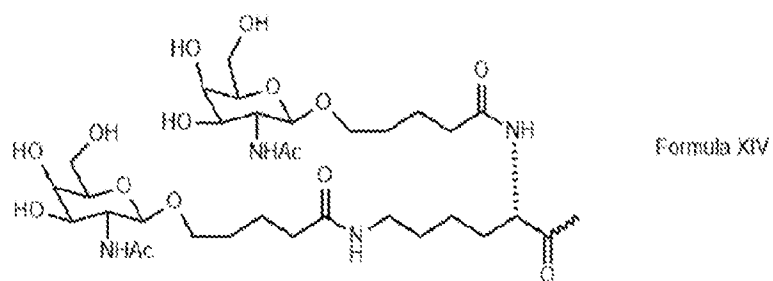
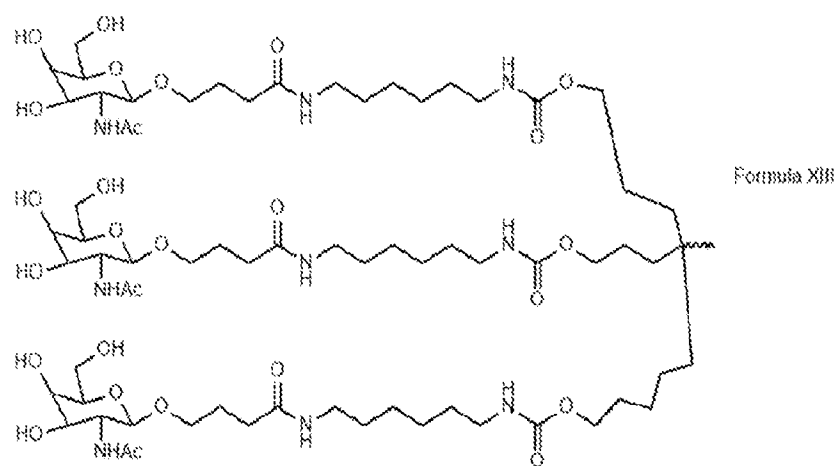
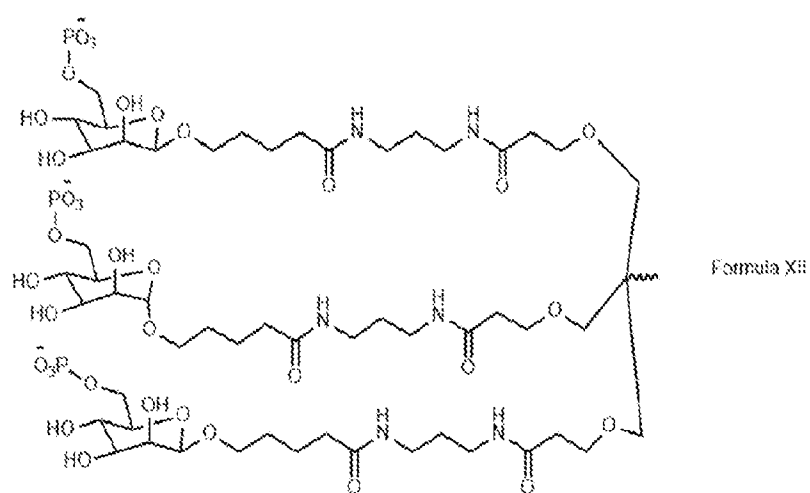
Forma X

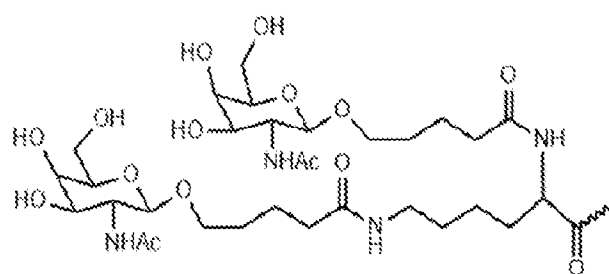


Formula X

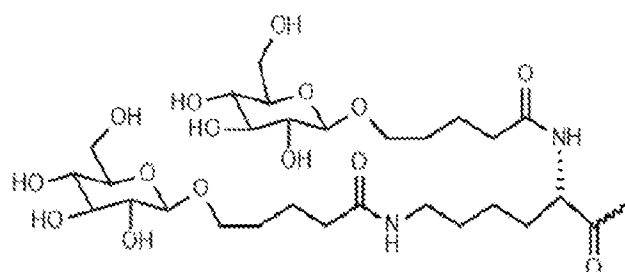


Formula XI

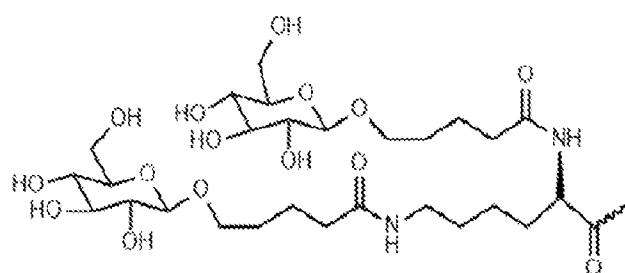




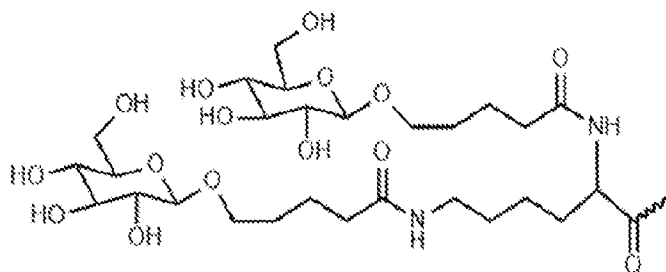
Formula XVI



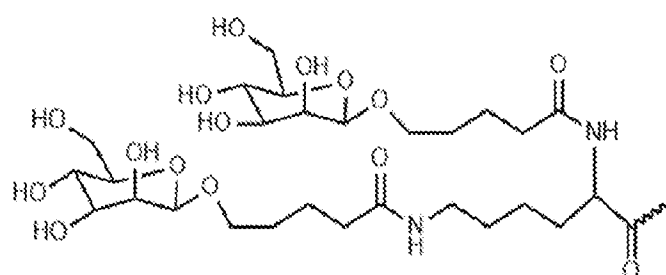
Formula XVII



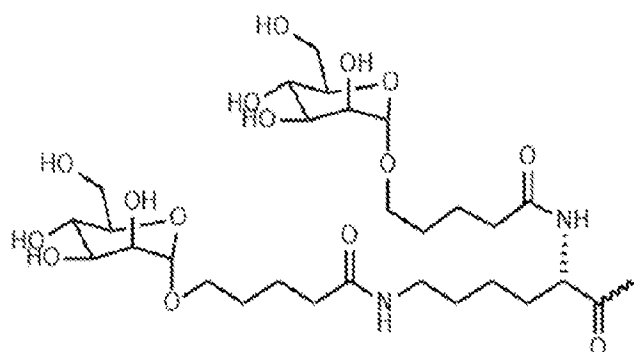
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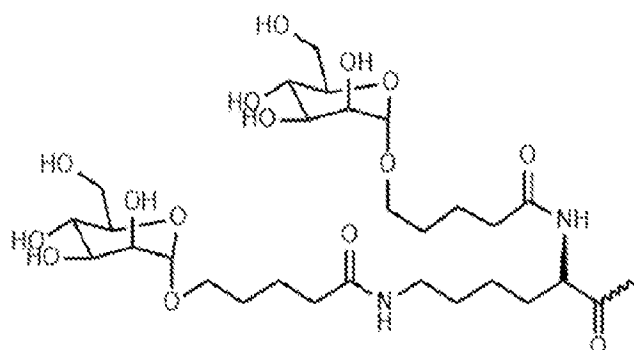
Formula XIX



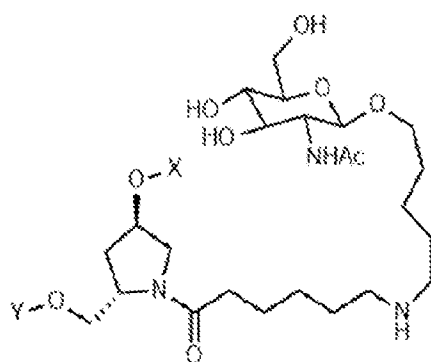
Formula XX



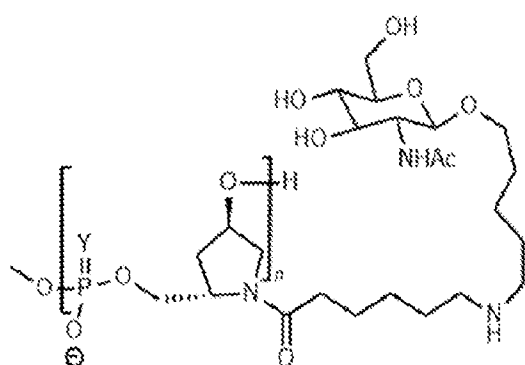
Formula XXI



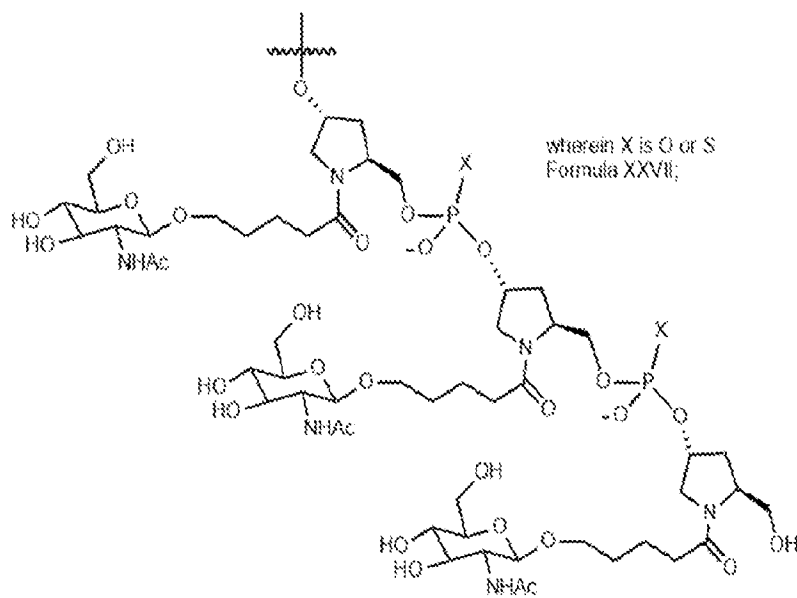
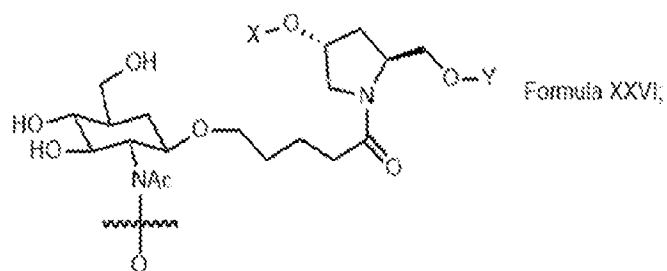
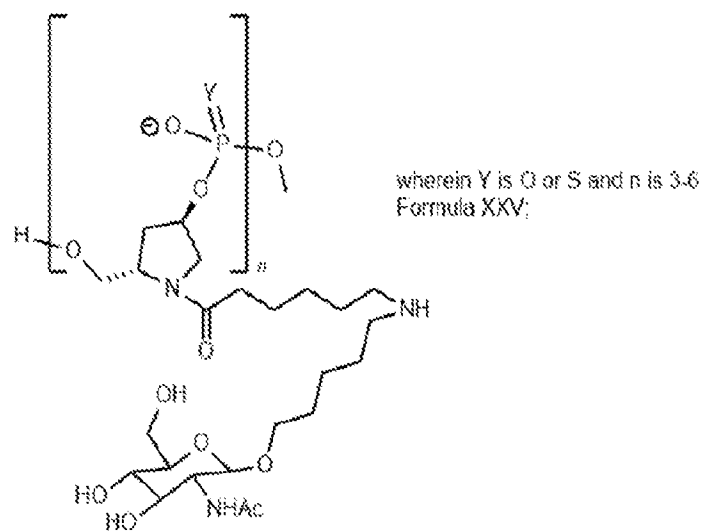
Formula XXII

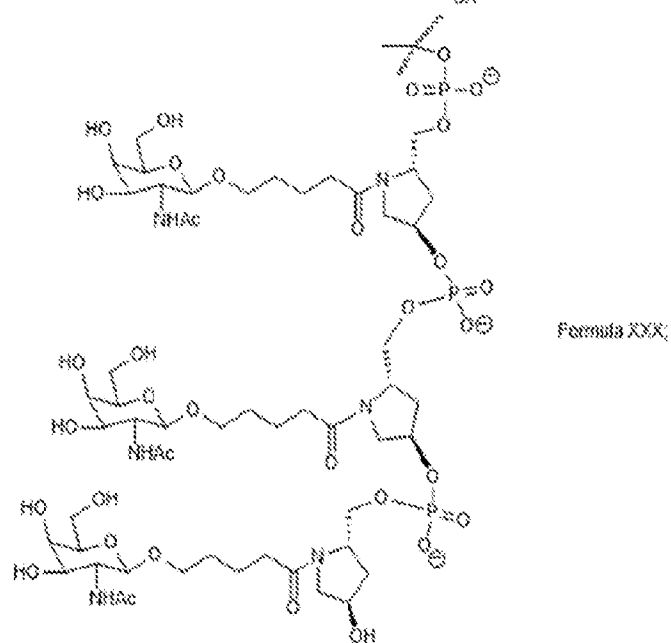
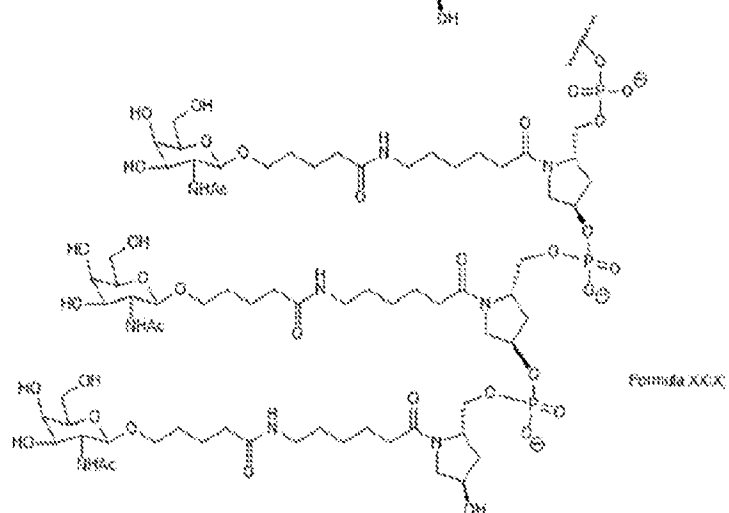
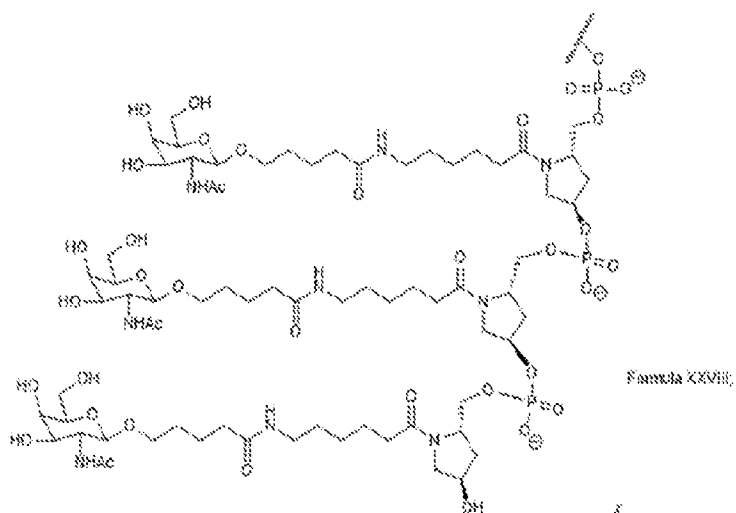


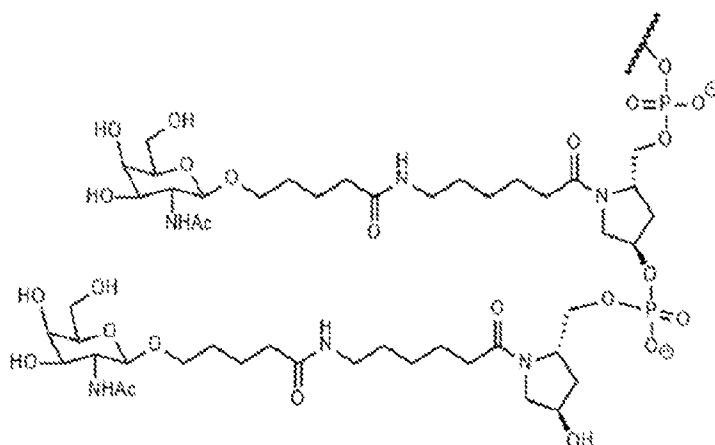
Formula XXIII



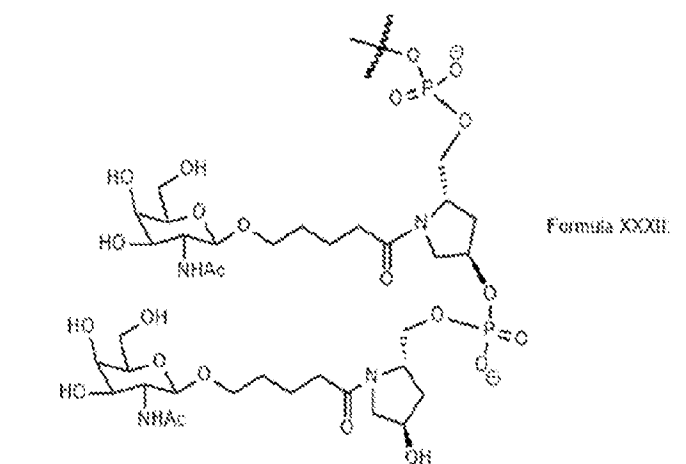
wherein Y is O or S and n is 3-6
Formula XXIV;



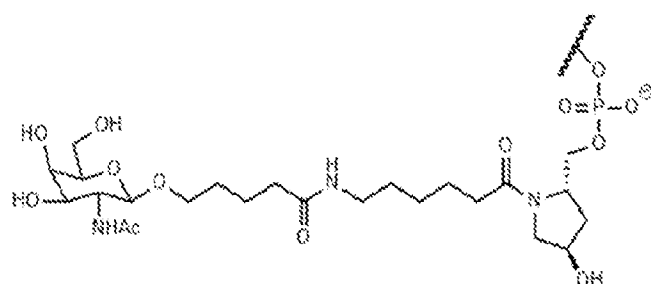




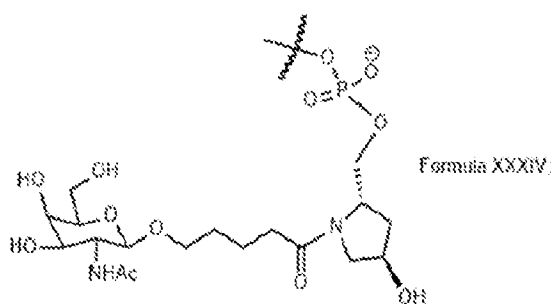
Formula XXXI.



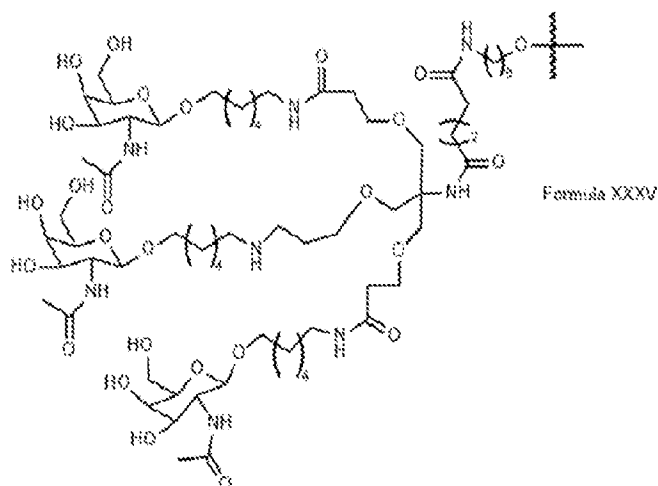
Formula XXXII.



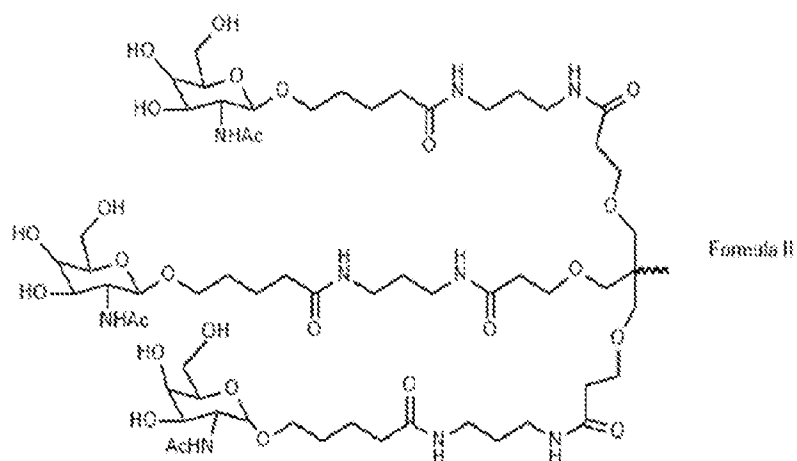
Formula XXXIII.



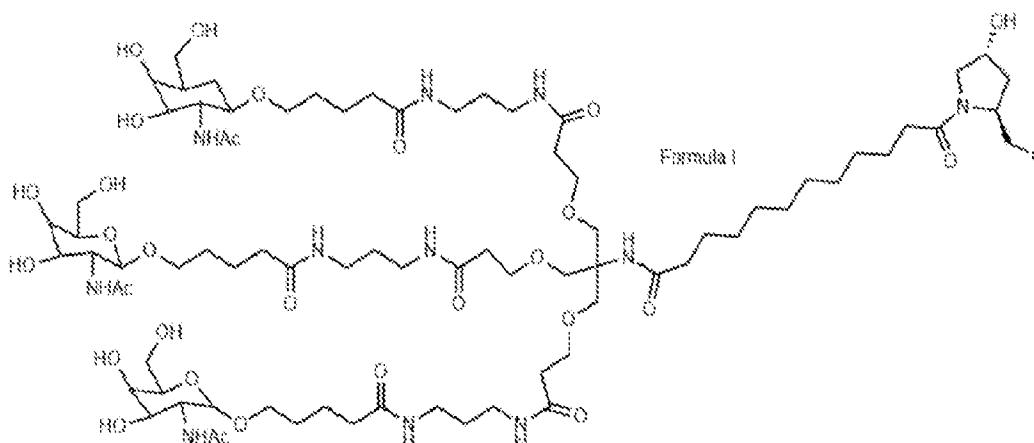
Formula XXXIV.



[00205] In one embodiment, the targeting moiety comprises the GalNAc targeting moiety set forth in below in Formula II:



[00206] In one embodiment, the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula I:



[00207] In one embodiment, the targeting moiety comprises N-[tris(GalNAc)-amido-dodecanoyl]-4-hydroxyprolinol [Hyp-(GalNAc-alkyl)3].

[00208] 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.

5.4.2 Linkers

[00209] 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.

[00210] 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.

[00211] 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, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, 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.

[00212] In some embodiments, the linker comprises ethylene 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 ether 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 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 C_i-C_w alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl or substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[00213] 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.

[00214] In some embodiments, the linker is a monovalent linker, a bivalent linker, a trivalent linker, or a tetravalent linker.

[00215] In some embodiments, the linker comprises or consists of the linker set forth above in Formula I.

5.4.2.1 Cleavable Linkers

[00216] 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.

[00217] 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).

[00218] 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).

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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.

5.4.3 Orientation

[00224] 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).

[00225] 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).

[00226] 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.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] 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

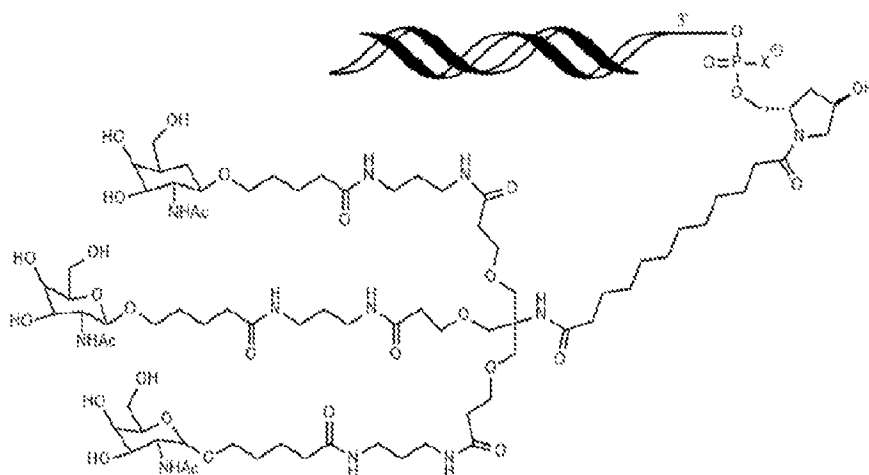
the sense strand and a second heterologous moiety is conjugated to the 5' end of the antisense strand. The first and second heterologous moieties can be the same or different.

[00231] 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.

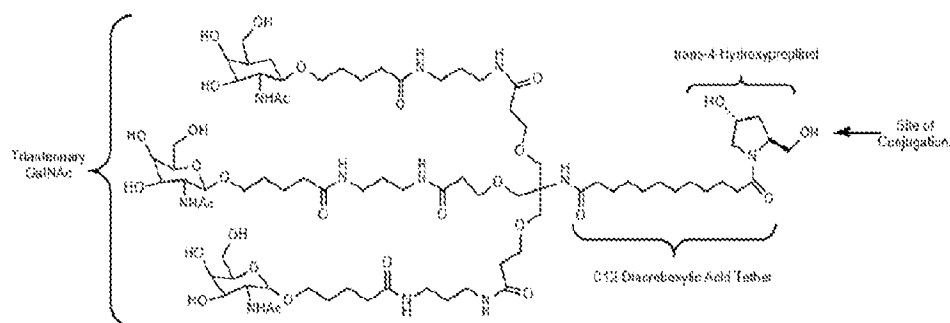
5.4.4 Exemplary Conjugates

[00232] 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.

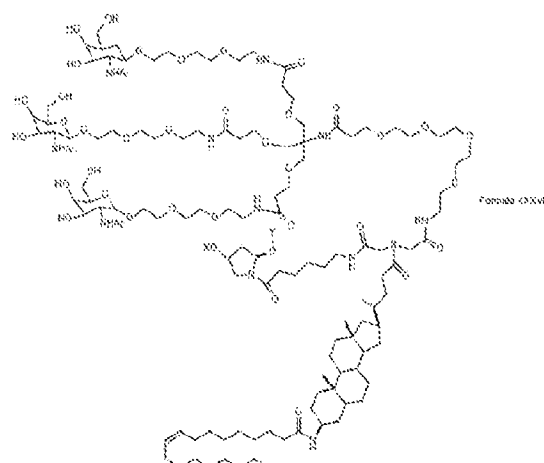
[00233] For example, in some embodiments, the agent (*e.g.*, RNAi agent, dsRNA agent, antisense strand, sense strand) is conjugated to a GalNAc targeting moiety through a linker *e.g.*, as shown in the following schematic, wherein X is O or S (and further described in § 5.4.2).



[00234] 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:

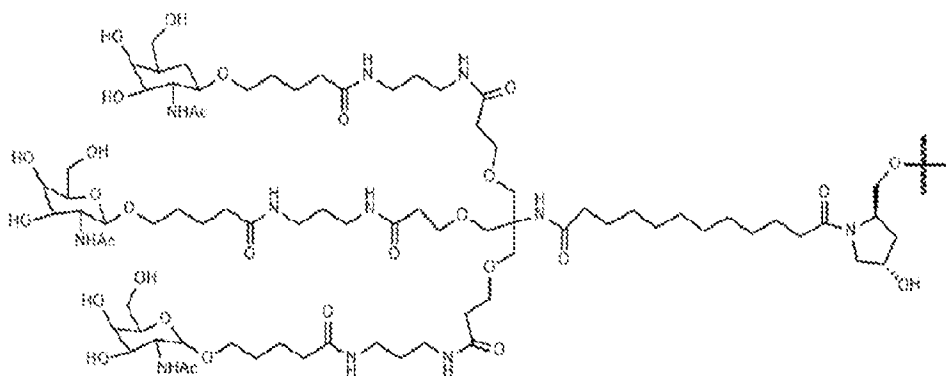


[00235] In some embodiments, the GalNAc targeting moiety and linker comprises that set forth below in Formula XXXVI wherein one of X or Y is a polynucleotide, the other is a hydrogen.

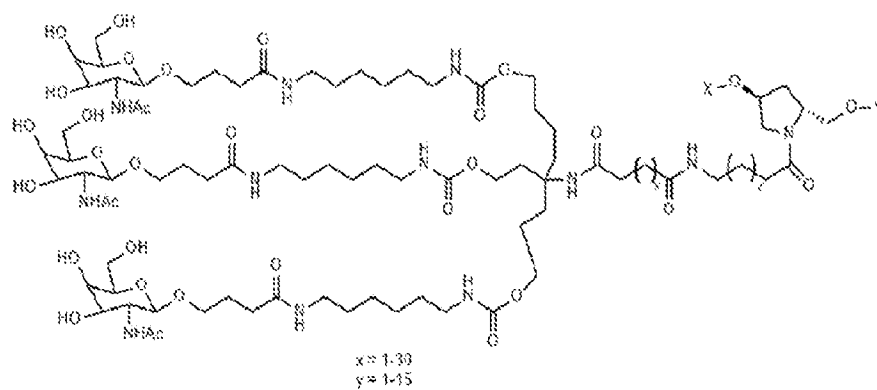


[00236] In some embodiments, the GalNAc targeting moiety and linker comprises that set forth in any one of the following formulas, wherein in any of the following formulas wherein one of X or Y is a polynucleotide, the other is a hydrogen:

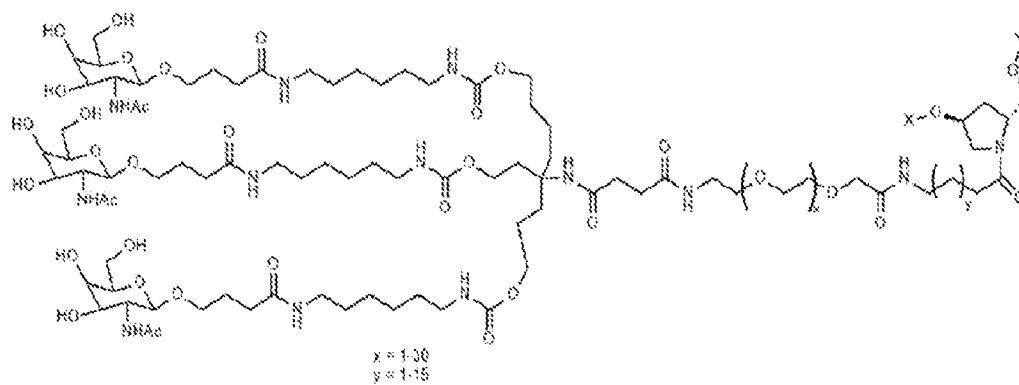
Formula XXXVIII



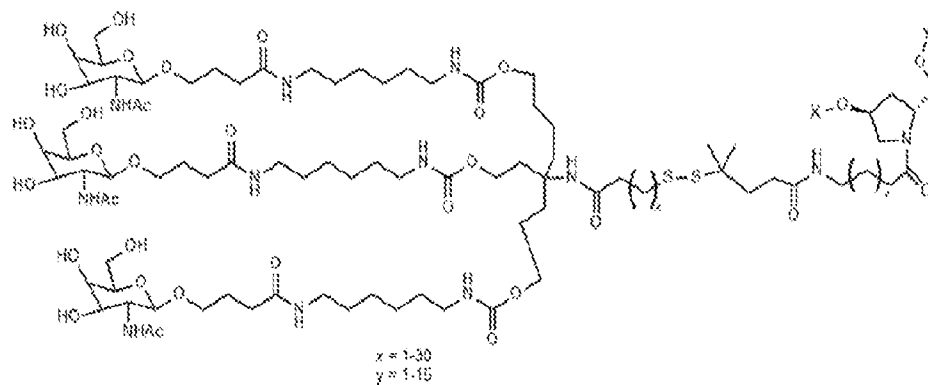
Formula XXXIX



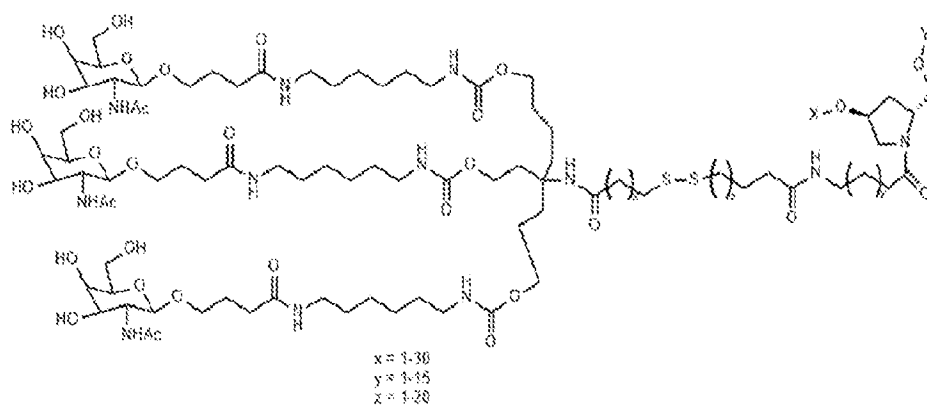
Formula XL



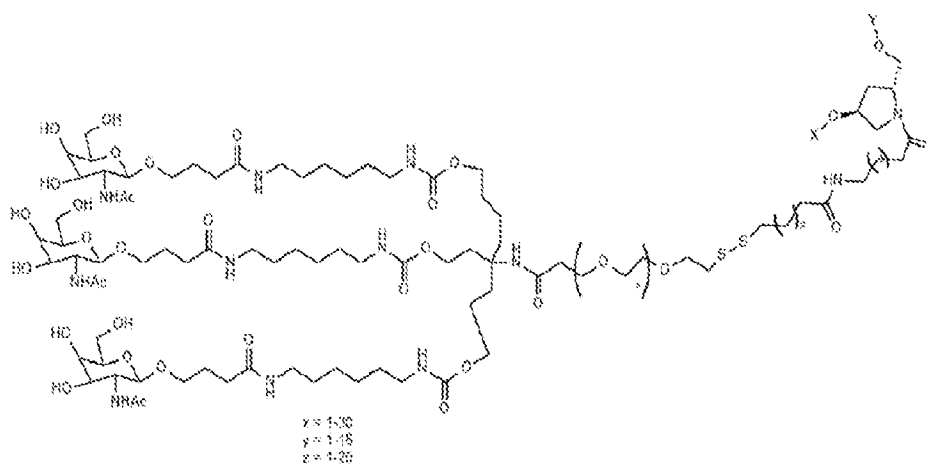
Formula XLI



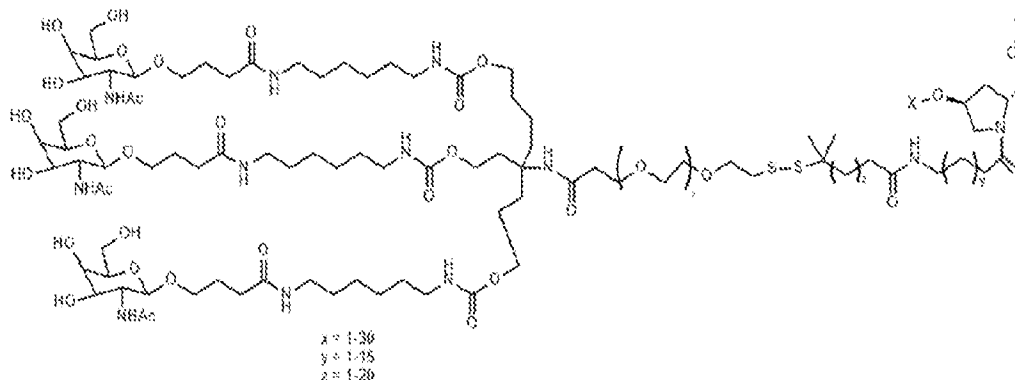
Formula XLII



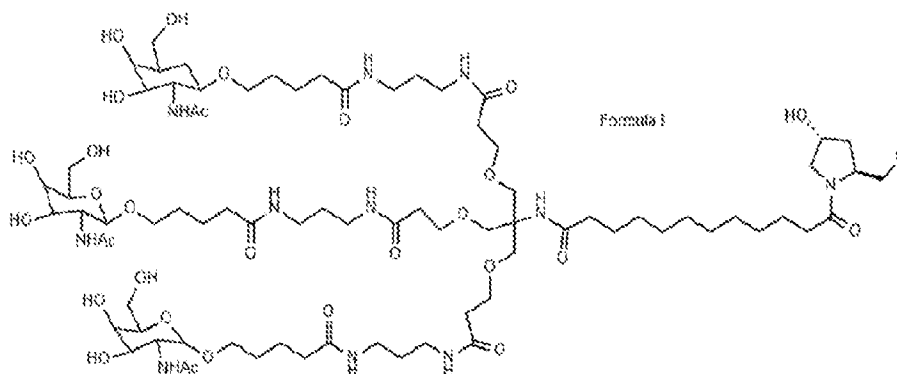
Formula XLIII



Formula XLIV



[00237] the targeting moiety comprises the GalNAc targeting moiety and linker set forth below in Formula I:



[00238] In one embodiment, the targeting moiety comprises N-[tris(GalNAc)-amido-dodecanoyl]-4-hydroxyprolinol [Hyp-(GalNAc-alkyl)3].

[00239] 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.

5.5 Activity of RNAi Agents & Conjugates Thereof

[00240] In some embodiments, the agent (*e.g.*, RNAi agent, *e.g.*, dsRNA agent) inhibits expression of a target gene (*e.g.*, FASN). In some embodiments, the agent (*e.g.*, RNAi agent, *e.g.*, dsRNA agent) inhibits expression of a target gene (*e.g.*, FASN) in a cell. In some embodiments, the agent (*e.g.*, RNAi agent, *e.g.*, dsRNA agent) inhibits expression of a target gene (*e.g.*, FASN) 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.*, FASN) 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) inhibits expression of a target gene (*e.g.*, FASN) 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.*, FASN) 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.*, FASN) 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.*, FASN) 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.*, FASN) 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.*, FASN) 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.*, FASN) 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.*, FASN) 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%. In some embodiments, the agent (*e.g.*, RNAi agent, *e.g.*, dsRNA agent) mediates degradation of a target mRNA (*e.g.*, a FASN (*e.g.*, hFASN) mRNA).

[00241] 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.*, FASN (*e.g.*, hFASN)) expression is determined by qPCR.

5.6 Methods of Making RNAi Agents & Conjugates Thereof

[00242] An agent (*e.g.*, described herein) (*e.g.*, RNAi agent, dsRNA agent, antisense strand, sense strand) can be synthesized by standard methods known in the art (*e.g.*, chemical synthesis (*e.g.*, solid phase synthesis)). *See, e.g.*, “Current protocols in nucleic acid chemistry,” Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, and *See, e.g.*, Dong Y, Siegwart DJ, Anderson DG. Strategies, design, and chemistry in siRNA delivery systems. *Adv Drug Deliv Rev.* 2019 Apr;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).

[00243] 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.

[00244] Likewise, conjugates (*e.g.*, described herein) can be synthesized utilizing standard methods known in the art. *See, e.g.*, Dong Y, Siegwart DJ, Anderson DG. Strategies, design, and chemistry in siRNA delivery systems. *Adv Drug Deliv Rev.* 2019 Apr;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.

5.7 Vectors

[00245] 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.*, §§ 5.2, 5.3) 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.*, §§ 5.2, 5.3). 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.*, §§ 5.2, 5.3).

[00246] 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.

[00247] 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).

[00248] 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.*, W02005071093 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.*, W02005071093, the entire contents of which is incorporated by reference herein for all purposes) or AdCh68.

[00249] 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.

[00250] 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 W02009150222A2 and as defined in PCT claims 1 to 33, the disclosure relating to claim 1 to 33 of W02009150222A2 the entire contents of which is incorporated by reference herein for all purposes.

5.8 Host Cells

[00251] Provided herein is a cell (*e.g.*, host cell) or population of cells (*e.g.*, a population of 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.*, §§ 5.2, 5.3); a vector described herein (*see, e.g.*, § 5.6); a conjugate described herein (*see, e.g.*, § 5.4); a carrier described herein (*see, e.g.*, § 5.8); a pharmaceutical composition described herein (*see, e.g.*, § 5.10), and/or a cell described herein (*see, e.g.*, § 5.8); or any combination thereof. In some embodiments, the cell or population of cells is *in vitro*. In some embodiments, the cell or population of cells is *in vivo*. In some embodiments, the cell or population of cells is *ex vivo*. In some embodiments, the cell or population of cells are derived from a subject (*e.g.*, a human subject. In some embodiments, the subject is a human, mouse, rat, primate, or non-human primate.

5.9 Carriers

[00252] 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.

[00253] 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.

[00254] 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).

[00255] 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 § 5.9.1.

5.9.1 Lipid Based Carriers/Lipid Nanoformulations

[00256] 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.

[00257] 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).

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] One or more naturally occurring and/or synthetic lipid compounds may be used in the preparation of the lipid-based carrier (or lipid nanoformulation).

[00264] The lipid-based carrier (or lipid nanoformulation) may contain positively charged (cationic) lipids, neutral lipids, negatively charged (anionic) lipids, or a combination thereof.

5.9.1.1 Cationic Lipids (Positively Charged) and Ionizable Lipids

[00265] 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.

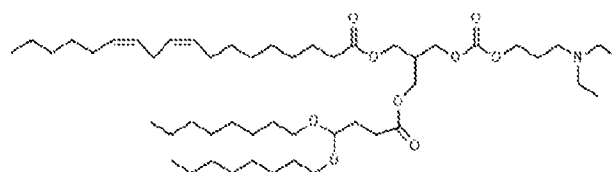
[00266] Exemplary cationic lipids include one or more amine group(s) which bear the positive charge. Examples of positively charged (cationic) lipids include, but are not limited to, N,N'-dimethyl-N,N'-dioctacyl ammonium bromide (DDAB) and chloride DDAC), N-(1-

(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), 3 β -[N-(N',N'-dimethylaminoethyl)carbamoyl] cholesterol (DC-chol), 1,2-dioleoyloxy-3-[trimethylammonio]-propane (DOTAP), 1,2-dioctadecyloxy-3-[trimethylammonio]-propane (DSTAP), and 1,2-dioleoyloxypropyl-3-dimethyl-hydroxy ethyl ammonium chloride (DORI), N,N-dioleoyl-N,N-dimethylammonium chloride (DODAC), N,N-dimethyl-2,3-dioleoyloxy)propylamine (DODMA), 1,2-Dioleoyl-3-Dimethylammonium-propane (DODAP), 1,2-Dioleoylcarbamyl-3-Dimethylammonium-propane (DOCDAP), 1,2-Dioleoyl-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 (CpLinDMA), N,N-Dimethyl-3,4-dioleoyloxybenzylamine (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.

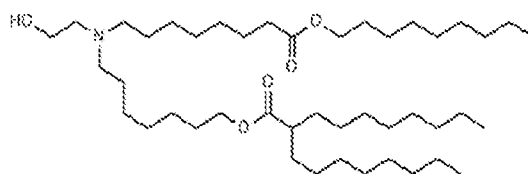
[00267] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises a cationic lipid having an effective pKa over 6.0. In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises a second cationic lipid having a different effective pKa (*e.g.*, greater than the first effective pKa) than the first cationic lipid.

[00268] 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.

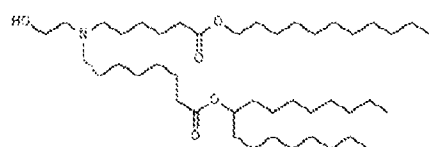
[00269] In some embodiments, the cationic lipid is an ionizable lipid (*e.g.*, a lipid that is protonated at low pH, but that remains neutral at physiological pH). In some embodiments, the lipid-based carrier (or lipid nanoformulation) may comprise one or more additional ionizable lipids, different than the ionizable lipids described herein. Exemplary ionizable lipids include, but are not limited to,



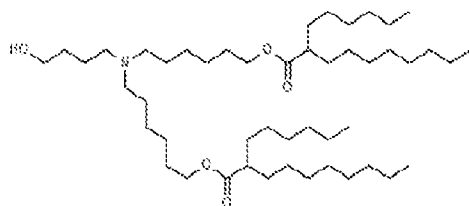
(LP01),



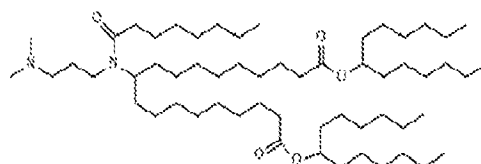
(SM-086),



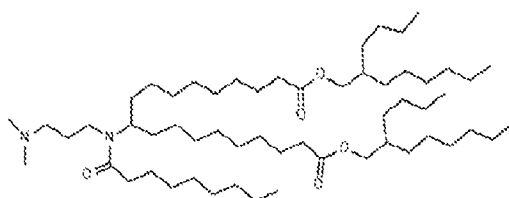
(SM-102),



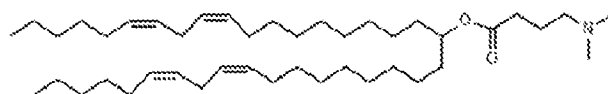
(ALC-0315),



(Lipid 10),



(Lipid A9), and



(DLin-MC3-DMA),

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

[00270] 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.

[00271] 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).

[00272] 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 US 20150376115 or in US 2016/0376224; Compound 5 or Compound 6 in US 2016/0376224; I, IA, or II of US 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 US 10,221,127; III-3 of WO 2018/081480; I-5 or I-8 of WO 2020/081938; I of WO 2015/199952 (*e.g.*, compound 6 or 22) and Table 1 therein; 18 or 25 of US 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 US 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 S9,708,628; 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.

[00273] 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.

5.9.1.2 Non-Cationic Lipids (*e.g.*, Phospholipids)

[00274] 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.

[00275] 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-l-trans PE, 1-stearoyl-2-oleoyl-phosphatidylethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierycoylphosphatidylcholine (DEPC), palmitoyloleoylphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), 1,2-dilauroyl- sn-glycero-3-phosphocholine (DLPC), Sodium 1,2- ditetradecanoyl-sn-glycero-3-phosphate (DMPA), phosphatidylcholine (lecithin), phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), phosphatidylethanolamine (cephalin), cardiolipin, phosphatidic acid, cerebrosides, 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 C₁₀-C₂₄ carbon chains, *e.g.*, lauroyl, myristoyl, palmitoyl, stearoyl, or oleoyl. Additional exemplary lipids, in certain embodiments, include, without limitation, those described in Kim et al. (2020) [dx.doi.org/10.1021/acs.nanolett.0c01386](https://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).

[00276] 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.

[00277] Other examples of suitable non-cationic lipids include, without limitation, nonphosphorous lipids such as, *e.g.*, stearylamine, dodecylamine, hexadecylamine, acetyl palmitate, glycerol ricinoleate, hexadecyl stearate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethoxylated fatty acid amides, dioctadecyl dimethyl ammonium bromide, ceramide, sphingomyelin, and the like. Other non-cationic lipids are described in WO 2017/099823 or US 2018/0028664, the entire contents of each of which are incorporated by reference herein for all purposes.

[00278] 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.

[00279] 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.

[00280] 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).

[00281] In some embodiments, the lipid-based carrier (or lipid nanoformulation) does not include any phospholipids.

[00282] 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).

5.9.1.3 Structural Lipids

[00283] 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.

[00284] 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.

[00285] 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).

[00286] 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.

[00287] In some embodiments, the structural lipid is a cholesterol derivative. Non-limiting examples of cholesterol derivatives include polar analogues such as 5 α -cholestanol, 5 β -coprostanol, cholesteryl-(2'-hydroxy)-ethyl ether, cholesteryl-(4'-hydroxy)-butyl ether, and 6-ketocholestanol; non-polar analogues such as 5 α -cholestane, cholestenone, 5 α -cholestanone, 5 β -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.

[00288] 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.

5.9.1.4 Polymers and Polyethylene Glycol (PEG) - Lipids

[00289] 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) (PLGA) nanoparticles.

[00290] 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)-350] (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)-5000] (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.

[00291] 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).

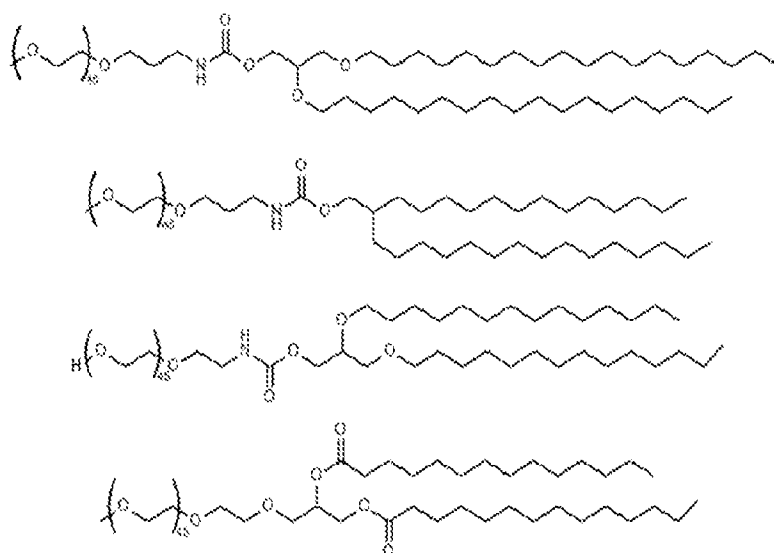
[00292] The PEG conjugate can comprise a PEG-dilaurylglycerol (C12), a PEG-dimyristylglycerol (C14), a PEG-dipalmitoylglycerol (C16), a PEG-disterylglycerol (C18), PEG-dilaurylglycamide (C12), PEG-dimyristylglycamide (C14), PEG-dipalmitoylglycamide (C16), and PEG-disterylglycamide (C18).

[00293] 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-dialkylxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanolamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl)-1-0-(ω-methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypylcarbam, 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.

[00294] Additional exemplary PEG-lipid conjugates are described, for example, in US 5,885,613, US 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.

[00295] In some embodiments, the PEG-lipid is a compound of Formula III, III-a-1, III-a-2, III-b-1, III-b-2, or V of US 2018/0028664, which is incorporated herein by reference in its entirety. In some embodiments, the PEG-lipid is of Formula II of US 2015/0376115 or US 2016/0376224, the entire contents of each of which are incorporated by reference herein for all purposes. In some embodiments, the PEG-DAA conjugate can be, for example, PEG-dilauryloxypropyl, PEG-dimyristyloxypropyl, PEG-dipalmitoyloxypropyl, or PEG-distearoyloxypropyl. In some embodiments, the PEG-lipid includes one of the following:



[00296] 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.

[00297] 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.

[00298] 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.

[00299] 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).

[00300] 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.

5.9.1.5 Percentages of Lipid Nanoformulation Components

[00301] In some embodiments, the lipid-based carrier (or lipid nanoformulation) comprises one or more of the agents described herein (e.g., RNAi agents, double stranded RNA (dsRNA) agents, sense strands, antisense strands (or a conjugate comprising the same)) (or a vector comprising any of the foregoing), optionally a non-cationic lipid (e.g., a phospholipid), a sterol, a neutral lipid, and optionally conjugated lipid (e.g., a PEGylated lipid) that inhibits aggregation of particles. In some embodiments, the lipid-based carrier (or lipid nanoformulation) further comprises an agent (e.g., an agent described herein (e.g., RNAi agent, double stranded RNA (dsRNA) agent, sense strand, antisense strand (or a conjugate comprising the same)) (or a vector comprising any of the foregoing))). The amounts of these components can be varied independently and to achieve desired properties. For example, in some embodiments, the ionizable lipid including the lipid compounds described herein is present in an amount from about 20 mol% to about 100 mol% (e.g., 20-90 mol%, 20-80 mol%, 20-70 mol%, 25-100 mol%, 30-70 mol%, 30-60 mol%, 30-40 mol%, 40-50 mol%, or 50-90 mol%) of the total lipid components; a non-cationic lipid (e.g., phospholipid) is present in an amount from about 0 mol% to about 50 mol% (e.g., 0-40 mol%, 0-30 mol%, 5-50 mol%, 5-40 mol%, 5-30 mol%, or 5-10 mol%) of the total lipid components, a conjugated lipid (e.g., a PEGylated lipid) in an amount from about 0.5 mol% to about 20 mol% (e.g., 1-10 mol% or 5-10%) of the total lipid components, and a sterol in an amount from about 0 mol % to about 60 mol% (e.g., 0-50 mol%, 10-60 mol%, 10-50 mol%, 15-60 mol%, 15-50 mol%, 20-50 mol%, 20-40 mol%) of the total lipid components, provided that the total mol% of the lipid component does not exceed 100%.

[00302] 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.

[00303] 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%.

[00304] 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.

[00305] 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%.

[00306] 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.

[00307] 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%.

[00308] 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%).

[00309] 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%.

[00310] 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).

[00311] 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%.

[00312] 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.

[00313] 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.

[00314] 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.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] 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%.

5.10 Pharmaceutical Compositions

[00319] 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.*, §§ 5.2, 5.3); a vector described herein (*see, e.g.*, § 5.6); a conjugate described herein (*see, e.g.*, § 5.4); a carrier described herein (*see, e.g.*, § 5.8); and/or a cell described herein (*see, e.g.*, § 5.8); 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).

[00320] 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.*, §§ 5.2, 5.3); a vector described herein (*see, e.g.*, § 5.6); a conjugate described herein (*see, e.g.*, § 5.4); a carrier described herein (*see, e.g.*, § 5.8); and/or a cell described herein (*see, e.g.*, § 5.8); and formulating it into a pharmaceutically acceptable composition by the addition of one or more pharmaceutically acceptable excipient.

[00321] 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.

[00322] 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 dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[00323] 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.

[00324] 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.

[00325] Pharmaceutically acceptable excipients used in the parenteral preparations described herein include for example, aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents or other pharmaceutically acceptable substances. Examples of aqueous vehicles, which can be incorporated in one or more of the formulations described herein, include sodium chloride injection, Ringer's injection, isotonic dextrose injection, sterile water injection, dextrose or lactated Ringer's injection. Nonaqueous parenteral vehicles, which can be incorporated in one or more of the formulations described herein, include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil or peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to the parenteral preparations described herein and packaged in multiple-dose containers, which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride or benzethonium chloride. Isotonic agents, which can be incorporated in one or more of the formulations described herein, include sodium chloride or dextrose. Buffers, which can be incorporated in one or more of the formulations described herein, include phosphate or citrate. Antioxidants, which can be incorporated in one or more of the formulations described herein, include sodium bisulfate. Local anesthetics, which can be incorporated in one or more of the formulations described herein, include procaine hydrochloride. Suspending and dispersing agents, which can be incorporated in one or more of the formulations described herein, include sodium carboxymethylcellulose, hydroxypropyl methylcellulose or polyvinylpyrrolidone. Emulsifying agents, which can be incorporated in one or more of the formulations described herein, include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions, which can be incorporated in one or more of the formulations described herein, is EDTA. Pharmaceutical carriers, which can be incorporated in one or more of the formulations described herein, also include ethyl alcohol, polyethylene glycol or propylene glycol for water miscible vehicles; or sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00326] 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.

5.11 Methods of Use

[00327] 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.*, §§ 5.2, 5.3); a vector described herein (*see, e.g.*, § 5.6); a conjugate described herein (*see, e.g.*, § 5.4); a carrier described herein (*see, e.g.*, § 5.9); a host cell described herein (*see, e.g.*, § 5.8); and/or a pharmaceutical composition described herein (*see, e.g.*, § 5.10); or any combination thereof.

[00328] 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.

[00329] 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.

[00330] In some embodiments, the agent described herein (*e.g.*, an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (*see, e.g.*, §§ 5.2, 5.3) or a conjugate thereof (*see, e.g.*, § 5.4) is administered to a subject at a dose of from about 1-10 mg/kg, 2-10 mg/kg, 3-10 mg/kg, 4-10 mg/kg, 5-10 mg/kg, 6-10 mg/kg, 7-10 mg/kg, 8-10 mg/kg, 9-10 mg/kg, 1-5 mg/kg, 1-4 mg/kg, 1-3 mg/kg, 1-2 mg/kg, 1-2.5 mg/kg, 2-5 mg/kg, 2-4 mg/kg, 2-3 mg/kg, or 2-2.5 mg/kg. In some embodiments, the agent described herein (*e.g.*, an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (*see, e.g.*, §§ 5.2, 5.3) or a conjugate thereof (*see, e.g.*, § 5.4) is administered to a subject at a dose of about 1 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, or 10 mg/kg. In some embodiments, the agent described herein (*e.g.*, an RNAi agent, a dsRNA agent, an antisense strand, a sense strand) (*see, e.g.*, §§ 5.2, 5.3) or a conjugate thereof (*see, e.g.*, § 5.4) 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.

5.11.1 Methods of Delivery

[00331] 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.

[00332] 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*.

[00333] 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.

[00334] 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.

5.11.2 Methods of Reducing or Inhibiting FASN Expression

[00335] In one aspect, provided herein are methods of reducing or inhibiting expression of FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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*.

[00336] In some embodiments, the level of FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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).

[00337] In one aspect, provided herein are methods of reducing or inhibiting expression of FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) in the cell in the subject. In some embodiments, the level of FASN (*e.g.*, hFASN) 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).

[00338] 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 FASN

(*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) in the cell in the subject. In some embodiments, the level of FASN (*e.g.*, hFASN) 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).

[00339] 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 the reduction or inhibition of FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) in the cell in the subject. In some embodiments, the level of FASN (*e.g.*, hFASN) 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).

[00340] 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) in the cell in the subject. In some embodiments, the level of FASN (*e.g.*, hFASN) 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).

5.11.3 Methods of Treating, Ameliorating, or Preventing a FASN Associated Disease

[00341] 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.

[00342] In one aspect, provided herein are methods of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) associated disease in the subject.

[00343] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD). In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, alcoholic fatty liver disease (AFLD), or cirrhosis. In some embodiments, the disease is metabolic dysfunction associated steatotic liver disease (MASLD), metabolic-associated steatohepatitis (MASH), metabolic dysfunction and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), 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.

[00344] 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) associated disease in the subject.

[00345] 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 FASN (*e.g.*, hFASN) associated disease in the subject.

[00346] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00347] 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 the treatment, amelioration, or prevention of a FASN (*e.g.*, hFASN) associated disease in a subject.

[00348] 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 treat, ameliorate, or prevent the FASN (*e.g.*, hFASN) associated disease in the subject.

[00349] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00350] 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 FASN (*e.g.*, hFASN) 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 FASN (*e.g.*, hFASN) associated disease in the subject.

[00351] 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 FASN (*e.g.*, hFASN) associated disease in the subject.

[00352] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00353] 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 FASN (*e.g.*, hFASN) associated disease, more preferably a liver disease.

[00354] In one aspect, provided herein are dsRNA agents, conjugates, vectors, carriers, and pharmaceutical compositions for use for use in treating a disease in a subject (preferably a FASN (*e.g.*, hFASN) associated disease, more preferably a liver disease) by reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell.

5.11.4 Methods of Treating, Ameliorating, or Preventing a Liver Disease

[00355] 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.

[00356] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00357] 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.

[00358] 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.

[00359] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00360] 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.

[00361] 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 treat, ameliorate, or prevent the liver disease in the subject.

[00362] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00363] 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.

[00364] 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.

[00365] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

5.11.5 Methods of Diagnosing and/or Prognosticating a Liver Disease

[00366] 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 FASN mutation in the DNA, RNA, or protein, wherein the presence of the somatic mutation indicates that the subject has a liver disease.

[00367] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00368] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00369] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00370] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00371] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00372] 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 FASN 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.

[00373] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00374] 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 FASN if one or more somatic FASN 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.

[00375] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00376] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00377] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00378] 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 FASN 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.

[00379] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00380] 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 FASN if one or more somatic FASN 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.

[00381] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00382] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample

is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00383] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

5.11.6 Methods of Screening, Identifying, and Selecting a Subject for Treatment with a FASN Inhibitory Agent

[00384] In one aspect, provided herein are methods of screening a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of FASN, 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 FASN 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 FASN if the somatic mutation is present.

[00385] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00386] 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.

[00387] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00388] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00389] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00390] In one aspect, provided herein are methods of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of FASN, 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 FASN 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 FASN if the somatic mutation is present.

[00391] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00392] 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.

[00393] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00394] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00395] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00396] In one aspect, provided herein are methods of identifying a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of FASN, 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 FASN 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 FASN.

[00397] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00398] 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.

[00399] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00400] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00401] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00402] 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 FASN, 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 FASN 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 FASN if the somatic mutation is present.

[00403] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00404] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00405] 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.

[00406] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00407] In some embodiments, the method further comprises (c) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00408] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

[00409] 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 FASN, 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 FASN 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 FASN if the somatic mutation is present.

[00410] In some embodiments, the FASN associated disease is fatty liver, liver inflammation, NASH or NAFLD. In some embodiments, the disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, or cirrhosis. In some embodiments, the disease is MASLD, MASH, MetALD, SLD, cryptogenic SLD.

[00411] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00412] 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.

[00413] In some embodiments, the method further comprises (d) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more

somatic FASN 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.

[00414] In some embodiments, the method further comprises (d) withholding administration of an inhibitory nucleic acid molecule that inhibits expression of FASN to the subject if one or more somatic FASN 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 FASN to the subject if a somatic FASN mutation in the sample is not detected. In some embodiments, the different therapeutic agent is a standard of care agent for the disease.

[00415] 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 FASN and/or function of FASN. In some embodiments, the treatment with the different therapeutic agent is discontinued if a somatic FASN mutation in the sample is detected and/or the inhibitory nucleic acid molecule that inhibits expression of FASN is administered to the subject.

5.11.7 *In Vitro* Methods of Screening Samples for Somatic FASN Mutations

[00416] In one aspect, provided herein are methods of screening a sample from a subject for the presence or absence of one or more somatic FASN 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 FASN mutation in the DNA, RNA, or protein.

[00417] 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 FASN 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 FASN 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 FASN mutation in the protein.

[00418] In some embodiments, the method further comprises (c) administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if one or more somatic FASN 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.

[00419] 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 FASN gene in the DNA); and (c) determining the presence or absence of a somatic FASN mutation in the DNA molecule.

[00420] 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 FASN mutation in the DNA; and (c) characterizing the liver disease as somatic FASN mutation positive or somatic FASN mutation negative based on the detection.

5.12 Kits

[00421] 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.*, §§ 5.2, 5.3); a vector described herein (*see, e.g.*, § 5.6); a conjugate described herein (*see, e.g.*, § 5.4); a carrier described herein (*see, e.g.*, § 5.9); a host cell described herein (*see, e.g.*, § 5.8); and/or a pharmaceutical composition described herein (*see, e.g.*, § 5.10); 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.

[00422] 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).

[00423] 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).

[00424] In one aspect, provided herein are *in vitro* test kits for use in a method described herein (*e.g.*, diagnostic method, prognostic method, subject screening, subject identification, subject selection, sample screening). In some embodiments, the kit comprises one or more reagents for detecting one or more somatic FASN mutation in a sample from a subject (*e.g.*, in DNA, RNA, or protein from a sample from a subject).

[00425] Any of the kits described herein may be used in any of the methods described herein (*see, e.g.*, § 5.11).

6. EXAMPLES

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6.1 Example 1. FASN Expression in Nonalcoholic Steatohepatitis

[00426] The expression of FASN in the context of nonalcoholic steatohepatitis (NASH) or alcohol related liver disease (ARLD) was evaluated. Briefly, liver samples from 29 subjects with either NASH or ARLD and liver samples from 5 subjects without liver disease were sequenced using laser capture microscopy and whole genome sequencing at a depth of 40x. Nucleotide mutations were called using standard bioinformatics algorithms and analyzed using the expected to observed ratio of nonsynonymous to synonymous SNPs. The results were replicated in an independent sample of 20 NASH liver tissue samples that underwent whole exome sequencing using Nanoseq at a sequencing depth of 200X Dx per sample; 10 of these samples also underwent laser capture microscopy with whole exome sequencing at a sequencing depth of 100x. Results of interest in the primary sample (defined as a global q-value<0.1) were restricted hypothesis tested in the replication samples.

[00427] In the primary sample, FASN had an enrichment ratio of 51 and a global q-value=0.024; there was no indication of selection in the normal liver samples. In the Nanoseq replication cohort, FASN had an enrichment ratio of 11.4 and a global p-value of 4.6×10^{-3} . In the LCM replication cohort, FASN had an enrichment ratio of 61.4 and a global p-value of 1.1×10^{-3} . Taken together, these findings indicate that FASN is positively selected for in NASH, meaning that cell clones with mutations in the FASN gene proliferate under NASH disease conditions.

6.2 Example 2. Design of FASN Targeting RNAi Agents

[00428] dsRNA agents targeting hFASN (NCBI Ref.: NM_004104.5) were designed and the nucleotide sequence of the unmodified FASN sense and antisense strands of each of the dsRNA agents are set forth in Table 2.

6.3 Example 3. Synthesis of FASN Targeting RNAi Agents

[00429] The dsRNA agents set forth in Table 2 or Table 3 are synthesized using standard methods known in the art and described herein. Briefly, the dsRNA agents are synthesized using a Mermade 192 synthesizer (BioAutomation) on controlled pore glass (500-1000 Å) solid supports loaded with a first nucleotide of interest. Upon completion of the solid phase synthesis, solid-supported polynucleotides are 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 are precipitated by the addition of 1 mL of 9:1 acetonitrile:ethanol or 1:1 ethanol:isopropanol. The plates are then centrifuged at 4°C for 45 minutes and the supernatant removed. The polynucleotide pellet is 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 are collected in 96 well plates and then analyzed by LC-MS and UV spectrometry to confirm identity and quantify the amount of material, respectively.

[00430] Duplexing of single strands is performed on a Tecan liquid handling robot. Sense and antisense single strands are combined in an equimolar ratio to a final concentration of 10 µM in 1x PBS in 96 well plates, the plate is sealed, incubated at 100 °C for 10 minutes, and is subsequently allowed to return slowly to room temperature over a period of 2-3 hours. The concentration and identity of each duplex is confirmed and is then subsequently utilized for screening assays.

6.4 Example 4. *In Vitro* dsRNA Agent Mediated Knockdown of hFASN

[00431] Each of dsRNA Agents 1-228 set forth in Table 3 (the modified versions) above were evaluated for their ability to knockdown hFASN expression *in vitro*.

[00432] 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 hFASN targeting dsRNA agent (either 0.5 nM or 20 nM) or the indicated control (AHSA1 (Activator Of HSP90 ATPase Activity 1

(referred to in **FIG. 1H** as “Control A”)) targeting siRNA) using Lipofectamine RNAiMax (0.3µl/well) (Thermo Fisher Scientific) according to the manufacturer’s instructions and incubated for 24 hours. The level of hFASN was assessed utilizing a standard branched DNA (bDNA) assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to the manufacturer’s instructions. The expression of hFASN was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate, the mean and standard deviation calculated.

[00433] **FIGS. 1A-1H** and Table 5 shows the percent of hFASN mRNA remaining after treatment with the indicated dsRNA agent (normalized to GAPDH and relative to control treated cells set to 100%).

Table 5. Range % hFASN mRNA Remaining (Normalized to GAPDH; Control Treated Cells = 100%).

dsRNA Agent ID	FASN/GAPDH	
	20 nM	0.5 nM
1	81-90	92-120
2	69-78	94-109
3	95-103	94-120
4	86-96	92-112
5	52-54	86-104
6	46-55	78-100
7	42-46	80-117
8	47-53	74-83
9	57-63	78-94
10	90-94	100-103
11	95-109	94-113
12	81-97	91-104
13	80-86	90-98
14	68-81	87-96
15	28-35	45-53
16	28-34	49-55
17	19-22	55-63
18	28-31	52-61
19	61-67	79-97
20	86-91	88-109
21	61-69	85-90
22	36-42	59-66
23	65-73	83-89
24	25-32	62-67
25	59-70	83-92
26	38-46	81-85
27	32-41	90-95
28	31-35	47-51

29	69-77	89-98
30	92-104	99-110
31	81-92	93-98
32	16-18	39-42
33	56-64	80-87
34	37-42	83-90
35	60-70	89-94
36	60-71	85-93
37	43-49	83-90
38	30-36	75-83
39	25-29	33-37
40	36-40	91-101
41	60-66	91-99
42	76-85	100-109
43	77-96	103-111
44	78-93	102-117
45	50-59	97-103
46	16-18	29-30
47	16-20	48-56
48	21-25	44-52
49	73-86	92-99
50	90-105	96-103
51	44-54	91-101
52	30-51	73-92
53	43-47	69-99
54	22-25	72-89
55	18-20	66-93
56	60-68	83-103
57	28-32	65-88
58	32-36	66-76
59	24-26	48-58
60	17-18	27-28
61	24-24	43-49
62	22-36	50-56
63	27-29	84-97
64	71-77	100-113
65	28-30	36-46
66	52-56	95-116
67	54-60	60-72
68	39-44	58-67
69	23-25	40-44
70	58-69	74-81
71	38-47	60-65
72	64-75	87-96

73	26-27	50-79
74	31-37	48-68
75	25-30	68-88
76	44-50	77-93
77	31-36	36-48
78	29-38	64-75
79	34-40	57-69
80	45-48	83-88
81	39-43	72-79
82	62-67	96-107
83	18-23	28-31
84	80-88	100-114
85	78-87	105-121
86	22-24	41-48
87	18-20	30-34
88	31-33	87-97
89	75-77	95-110
90	86-93	101-108
91	44-47	75-78
92	46-52	91-92
93	30-37	52-65
94	27-31	35-37
95	51-76	99-107
96	62-71	84-94
97	55-64	78-99
98	81-90	100-104
99	87-97	95-98
100	90-93	95-103
101	45-51	67-74
102	16-20	56-61
103	72-84	96-104
104	75-93	95-102
105	41-51	96-101
106	26-32	76-88
107	54-64	81-89
108	20-28	36-43
109	14-19	29-33
110	26-28	47-56
111	30-35	53-56
112	63-79	88-91
113	61-73	86-97
114	34-39	73-92
115	22-25	31-39
116	28-33	74-79
117	44-52	62-82

118	29-36	32-43
119	17-21	21-26
120	28-48	70-87
121	19-23	50-56
122	70-82	80-94
123	20-25	52-58
124	27-32	50-54
125	57-68	84-96
126	87-106	94-99
127	18-20	40-45
128	17-20	34-36
129	24-28	36-42
130	24-27	67-73
131	25-29	73-79
132	70-78	85-87
133	76-84	88-97
134	79-86	89-99
135	68-73	87-90
136	30-34	56-61
137	59-69	99-109
138	81-90	98-111
139	82-95	103-109
140	61-67	101-110
141	80-96	85-95
142	53-87	85-99
143	23-37	33-39
144	39-44	83-93
145	23-30	78-85
146	67-82	93-100
147	51-64	77-87
148	19-23	72-79
149	48-54	83-91
150	55-62	77-89
151	31-34	47-51
152	44-51	72-77
153	13-17	23-25
154	9-19	18-20
155	23-25	72-77
156	33-39	89-99
157	29-34	73-81
158	26-30	82-87
159	43-47	74-83
160	23-26	78-88
161	80-87	100-101

162	80-85	89-99
163	69-72	92-99
164	39-43	92-98
165	53-60	92-99
166	56-67	84-94
167	54-59	85-92
168	16-18	33-36
169	42-50	78-82
170	19-27	16-42
171	21-25	58-64
172	51-55	68-69
173	18-21	24-27
174	14-16	43-45
175	15-17	28-34
176	12-13	27-32
177	13-14	13-26
178	16-18	19-20
179	14-20	32-33
180	78-85	84-102
181	29-33	57-61
182	15-17	45-50
183	35-38	63-74
184	15-17	34-39
185	17-20	54-58
186	9-15	32-39
187	19-23	62-64
188	19-23	18-19
189	10-18	46-48
190	30-36	61-68
191	13-15	22-25
192	34-37	65-75
193	80-85	97-108
194	61-71	95-103
195	34-39	70-76
196	88-90	89-102
197	82-89	87-102
198	14-15	34-39
199	15-18	47-50
200	22-24	48-53
201	15-17	67-76
202	20-24	71-78
203	24-28	84-91
204	24-27	60-62
205	13-15	43-47

206	76-83	92-104
207	77-84	91-99
208	74-81	86-102
209	68-80	92-103
210	89-102	91-99
211	86-88	96-113
212	73-79	86-104
213	84-95	88-106
214	62-68	80-97
215	77-85	90-103
216	77-82	92-104
217	37-44	61-72
218	48-52	69-76
219	34-39	81-87
220	75-76	91-102
221	86-98	98-102
222	50-58	56-61
223	64-72	82-90
224	49-54	56-60
225	68-71	66-92
226	48-50	75-103
227	48-55	77-107
228	59-66	78-103
Control	9-11	8-9

6.5 Example 5. *In Vitro* dsRNA Agent Mediated Knockdown of murine FASN

[00434] A set of dsRNA agents targeting murine FASN (mFASN) were designed and generated using standard methods known in the art. The nucleotide sequence of the sense and anti-sense strand of each of the dsRNA agents is set forth in Table 6. The abbreviations utilized in the nucleotide sequence set forth in Table 6 are set forth above in Table 4 above.

Table 6. Modified Sense and Antisense Strand Sequences of mFASN Targeting dsRNA

Agents.

dsRNA Agent ID	Sense Sequence 5' to 3'	SEQ ID NO	Antisense Sequence 5' to 3'	SEQ ID NO
229	csasguUfcUfGfCfugacuaagaa	1144	usUfscuuAfgucagcaGfaAfcu gscsu	1156
230	csgsccCfaCfUfCfugguucauca	1145	usGfsaugAfaccagagUfgGfgc gscsu	1157
231	gsasagAfaCfGfUfcacuuuccaa	1146	usUfsggaAfagugacgUfuCfu csasa	1158
232	csgsgcUfuCfGfCfcaacucuaca	1147	usGfsuagAfguuggcgAfaGfcc gsusa	1159

233	csusguGfuAfGfCfcuucgagaua	1148	usAfsucuCfgaaggcuAfcAfca gsgsc	1160
234	gsusguAfgCfCfUfucgagaugua	1149	usAfscauCfucgaaggCfuAfca csasg	1161
235	csasccAfgAfGfAfugcuccgaua	1150	usAfsucgGfagcaucuCfuGfgu gsgsc	1162
236	cscsggCfaCfCfAfaucacagauga	1151	usCfsaucUfguauuggUfgCfcg gscsa	1163
237	cscsgaGfuAfCfAfaugucaacaa	1152	usUfsguuGfacauuguAfcUfcg gscsa	1164
238	csasagUfaCfCfAfuggcaacgua	1153	usAfsccguUfgccauggUfaCfu gsgsc	1165
239	asasguAfcCfAfUfggcaacguga	1154	usCfsacgUfugccaugGfuAfcu usgsg	1166
240	csusacAfaCfCfUfcucccaggua	1155	usAfscuGfggagaggUfuGfua gsusc	1167

[00435] Each dsRNA agent generated above was evaluated for their ability to knockdown mFASN expression *in vitro*. Briefly, Hepa1-6 cells (ATCC) were seeded at 20,000 cells per well in a standard 96 well plate. The cells were transfected with the indicated mFASN targeting dsRNA agent (20 nM, 3.3 nM, 0.55 nM, 0.09 nM, or 0.02 nM) or the indicated control (AHSA1-directed siRNA) using Lipofectamine RNAiMax (0.3µl/well) (Thermo Fisher Scientific) according to the manufacturer's instructions and incubated for 24 hours. The level of mFASN was assessed utilizing a standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The expression of mFASN was normalized to the expression of human GAPDH. Each treatment group was run in quadruplicate.

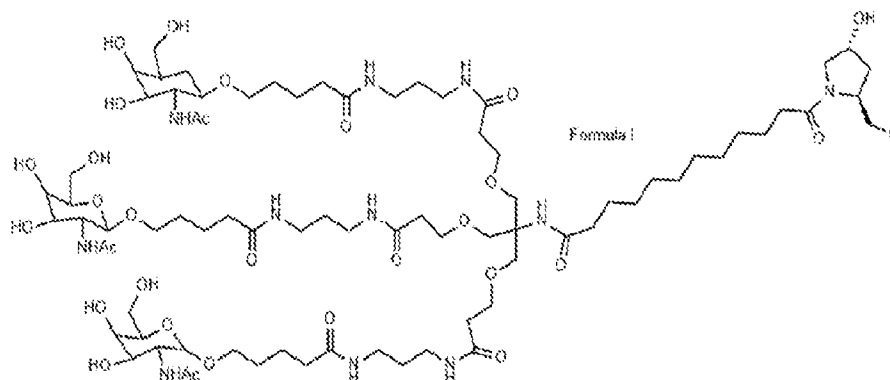
[00436] Table 7 shows the calculated IC₅₀ (nM) and the remaining mFASN mRNA percent (normalized to GAPDH).

Table 7. IC₅₀ and Max % Inhibition of mFASN mRNA (Normalized to GAPDH).

DsRNA Agents	IC ₅₀ [nM]	% Maximum Inhibition
229	>0.01≤0.05	>70≤80
230	>0.05≤0.1	>70≤80
231	>0.01≤0.05	>80≤90
232	>0.01≤0.05	>80≤90
233	>0.1≤0.5	>80≤90
234	>0.1≤0.5	>70≤80
235	>0.1≤0.5	>70≤80
236	>0.1≤0.5	>80≤90
237	>0.1≤0.5	>70≤80
238	>0.05≤0.1	>80≤90
239	>0.1≤0.5	>70≤80
240	>5.0≤10.0	>60≤70

6.6 Example 6. Generation of GalNac-Conjugated dsRNA Agents Targeting mFASN

[00437] A subset of the dsRNA agents described in Example 5 targeting mFASN were conjugated to a GalNac targeting moiety and linker comprising Formula I:



N-[tris(GalNac)-amido-dodecanoyl]-4-hydroxyprolinol [Hyp-(GalNac-alkyl)3].

[00438] The sense strand of the dsRNA agent was conjugated to the GalNac targeting moiety using standard methods.

6.7 Example 7. *In Vivo* GalNac-Conjugated dsRNA Agent Mediated Knockdown of mFASN

[00439] The ability of each of the conjugates generated in Example 6 was evaluated for their ability to knockdown mFASN expression *in vivo*.

[00440] Briefly, 9 week old female C57Bl6N mice (4 per treatment or control group) were administered a single dose of the indicated conjugate (5mg/kg) (or saline control) via subcutaneous injection and treated for seven days. During treatment, the mice were observed daily, and weight measurements taken. No adverse events were observed. Liver samples were taken seven days post administration (snap frozen in liquid nitrogen). Liver lysate was prepared from approximately 50mg of liver tissue by sonication in 1ml of lysis buffer. mFASN mRNA was quantified from liver lysate using standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The level of mFASN mRNA was normalized to GAPDH.

[00441] All conjugates showed knockdown of mFASN mRNA, with dsRNA conjugates 231, 233, and 238 showing the largest percent knockdown (FIG. 2).

6.8 Example 8. *In Vivo* GalNac-Conjugated dsRNA Agent Mediated Knockdown of mFASN

[00442] The ability of dsRNA conjugates 231, 233, and 238 were evaluated for their ability to knockdown mFASN expression *in vivo* at various dosages.

[00443] Briefly, 9 week old female C57Bl6N mice (4 per treatment or control group) were administered a single dose of the indicated conjugate (dsRNA conjugate 231 dosed at 2.5 mg/kg or 10 mg/kg, dsRNA conjugate 233 dosed at 2.5 mg/kg or 10 mg/kg, and 238 dosed at 1.25mg/kg, 2.5 mg/kg, 5 mg/kg, or 10 mg/kg, negative control conjugate dosed at 5 mg/kg) (or saline control) via subcutaneous injection and treated for 14 or 21 days. During treatment, the mice were observed daily, and weight measurements taken. No adverse events were observed. Liver samples were taken seven days post administration (snap frozen in liquid nitrogen). Liver lysate was prepared from approximately 50mg of liver tissue by sonication in 1ml of lysis buffer. mFASN mRNA was quantified from liver lysate using standard bDNA assay (Quantigene 2.0 (Thermo Fisher Scientific)) according to manufacturer's instructions. The level of mFASN mRNA was normalized to GAPDH.

[00444] FIG. 3 shows a dose dependent knockdown of mFASN mRNA with dsRNA conjugates 231, 233, and 238.

* * *

[00445] 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.

[00446] 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.

[00447] Other embodiments are within the following claims.

CLAIMS

What is claimed is:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of fatty acid synthase (FASN) (*e.g.*, human FASN (hFASN)),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,
wherein 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: 232-459 or 916-1143.
2. The dsRNA agent of claim 1, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from any sense strand set forth in Table 2 or Table 3 or set forth in any one of SEQ ID NOS: 4-231 or 688-915.
3. The dsRNA agent of claim 1 or 2, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from 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: 4-231 or 688-915.
4. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and
wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 2 or Table 3; and
wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 2 or Table 3.
5. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from

nucleotides 250-285, 253-282, 430-440, 436-456, 510-565, 510-560, 514-558, 745-775, 751-771, 830-895, 830-890, 836-888, 990-1025, 997-1017, 1045-1080, 1048-1075, 1050-1080, 1055-1075, 1095-1025, 1099-1119, 1280-1310, 1284-1304, 1400-1430, 1405-1425, 1575-1620, 1583-1610, 1651-1671, 1791-1811, 1945-2015, 1950-2010, 1955-2001, 1990-2030, 1995-2025, 2060-2095, 2066-2091, 2160-2195, 2160-2190, 2167-2187, 2220-2270, 2225-2263, 2300-2340, 2311-2336, 2415-2435, 2423-2443, 2875-2495, 2482-2504, 2510-2530, 2517-2537, 2520-2570, 2525-2570, 2531-2565, 2695-2720, 2706-2726, 2790-2830, 2800-2820, 2905-2925, 2913-2934, 2975-3235, 2981-3215, 3270-3315, 3287-3309, 3330-3370, 3340-3361, 3590-3630, 3600-3622, 3670-3715, 3678-3704, 3795-3835, 3808-3828, 3915-4275, 3925-4265, 4375-4415, 4381-4404, 4455-4500, 4462-4491, 4615-4660, 4622-4652, 4740-4780, 4750-4770, 4795-4870, 4805-4860, 4915-4955, 4925-4945, 4985-5030, 4995-5017, 5174-5194, 5164-5184, 5413-5455, 5410-5465, 5481-5503, 5471-5490, 5573-5594, 5565-5605, 5637-5658, 5657-5648, 6085-6105, 6087-6115, 6259-6281, 6249-6291, 6295-6332, 6285-6343, 6554-6574, 6544-6584, 6599-6619, 6589-6629, 6808-6828, 6790-6838, 6857-7007, 6847-7017, 7015-7044, 7005-7054, 7055-7075, 7045-7085, 7212-7267, 7202-7277, 7317-7345, 7307-7355, 7388-7458, 7278-7468, 7465-7496, 7455-7506, 7490-7539, 7480-7529, 7836-7857, 7826-7867, 7925-7963, 7915-7973, 8072-8094, 8062-8104, 8388-8408, 8378-8418, 8432-4861, or 8422-8471 of SEQ ID NO: 1;

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

6. The dsRNA agent of claim 5, wherein 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: 232-459 or 916-1143.

7. The dsRNA agent of claim 5 or 6, 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 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: 4-231 or 688-915.

8. The dsRNA agent of any one of claims 5-7, 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 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: 4-231 or 688-915.

9. The dsRNA agent of claim 5, wherein 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 set forth in any one of SEQ ID NOS: 232-459.

10. The dsRNA agent of claim 9, 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 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 set forth in any one of SEQ ID NOS: 4-231.

11. The dsRNA agent of any one of claims 9-10, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 2 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-231.

12. The dsRNA agent of claim 5, wherein 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 3 or set forth in any one of SEQ ID NOS: 916-1143.

13. The dsRNA agent of claim 12, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the nucleotide sequence of any one of the sense strands set forth in Table 3 or set forth in any one of SEQ ID NOS: 688-915.

14. The dsRNA agent of any one of claims 12-13, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the nucleotide sequence of the corresponding sense strand set forth in Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 688-915.

15. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein 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 set forth in any one of SEQ ID NOS: 232-459.

16. The dsRNA agent of claim 15, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from any sense strand set forth in Table 2 or set forth in any one of SEQ ID NOS: 4-231.

17. The dsRNA agent of claim 15 or 16, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from the corresponding sense strand set forth in Table 2 or the corresponding sense strand set forth in one of SEQ ID NOS: 4-231.

18. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and

wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 2; and

wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 2.

19. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein 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 3 or set forth in any one of SEQ ID NOS: 916-1143.

20. The dsRNA agent of claim 19, 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 3 (*e.g.*, 0, 1, 2, or 3) nucleotides from any sense strand set forth in Table 3 or set forth in any one of SEQ ID NOS: 688-915.

21. The dsRNA agent of claim 19 or 20, 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 3 (*e.g.*,

0, 1, 2, or 3) nucleotides from the corresponding sense strand set forth in Table 3 or the corresponding sense strand set forth in one of SEQ ID NOS: 688-915.

22. A dsRNA agent for inhibiting expression of FASN (*e.g.*, hFASN),
wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, and

wherein 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 the antisense strands of any one of dsRNA agents 1-228 set forth in Table 3; and

wherein the sense 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 the sense strand of the corresponding dsRNA agent set forth in Table 3.

23. The dsRNA agent of any one of the preceding claims, wherein the sense strand comprises at least one modified nucleotide and/or the antisense strand comprises at least one modified nucleotide.

24. The dsRNA agent of any one of the preceding claims, wherein 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.

25. The dsRNA agent of any one of the preceding claims, wherein substantially all (or all) of the nucleotides in the sense strand and/or antisense strand are modified.

26. The dsRNA agent of any one of the preceding claims, wherein at least one of the modified nucleotides comprises a modified sugar (*e.g.*, ribose moiety).

27. The dsRNA agent of any one of the preceding claims, wherein at least one of the modified nucleotides comprises a modified nucleobase.

28. The dsRNA agent of any one of the preceding claims, wherein the sense strand comprises at least one modified internucleoside linkage and/or the antisense strand comprises at least one modified internucleoside linkage.

29. The dsRNA agent of any one of the preceding claims, wherein 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.

30. The dsRNA agent of any one of the preceding claims, wherein 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, 26-30, 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, 26-30, 27-30, 28-30, 29-30, 19-20, 19-21, 19-22, 19-23, 19-24, or 19-25 nucleotides.

31. The dsRNA agent of any one of the preceding claims, wherein antisense strand comprises from about 19-23 nucleotides; and/or the sense strand comprises from about 19-23 nucleotides.

32. The dsRNA agent of any one of the preceding claims, wherein antisense strand comprises or consists of about 23 nucleotides; and/or the sense strand comprises or consists of about 21 nucleotides.

33. The dsRNA agent of any one of the preceding claims, wherein the sense strand and/or the antisense strand comprises a 3' and/or 5' overhang of 1, 2, or 3 nucleotides.

34. The dsRNA agent of any one of the preceding claims, wherein the antisense strand comprises a 3' overhang of 1, 2, or 3 nucleotides (*e.g.*, 2 nucleotides).

35. The dsRNA agent of any one of the preceding claims, wherein 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.

36. The dsRNA agent of any one of the preceding claims, wherein the double stranded region is from about 19-23 or 19-21 nucleotide pairs in length.

37. The dsRNA agent of any one of the preceding claims, wherein the double stranded region is about 21 nucleotide pairs in length.

38. The dsRNA agent of any one of the preceding claims, wherein 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).

39. The dsRNA agent of any one of the preceding claims, wherein the sense strand and the antisense strand are separate nucleic acid molecules (*i.e.*, connected only through the double stranded region).

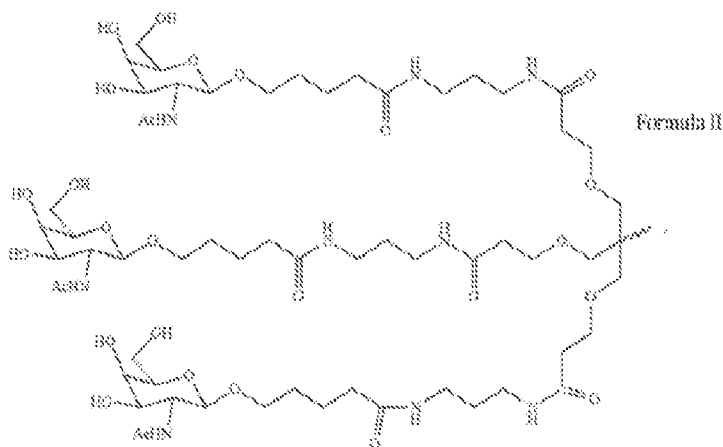
40. A conjugate comprising the dsRNA agent of any one of claims 1-39 and a heterologous moiety.

41. The conjugate of claim 40, wherein the heterologous moiety is a peptide, protein, carbohydrate, lipid, polymer, or small molecule.

42. The conjugate of claim 41, wherein the heterologous moiety is carbohydrate.

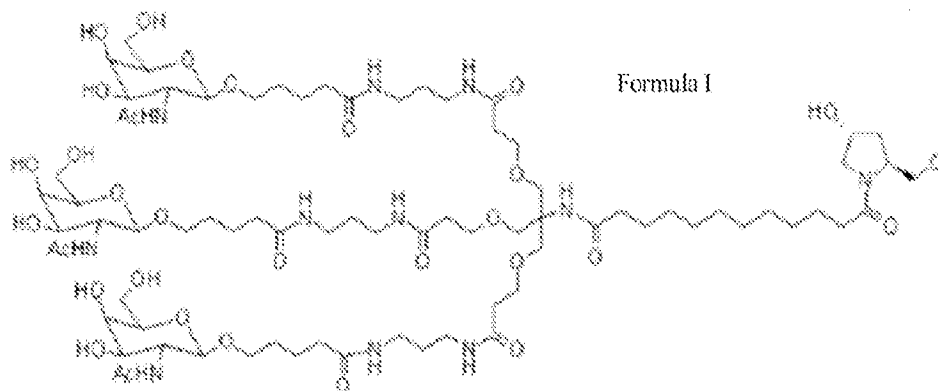
43. The conjugate of claim 42, wherein the heterologous moiety comprises one or more GalNac.

44. The conjugate of any one of claims 40-43, wherein the heterologous moiety is a targeting moiety.
45. The conjugate of claim 44, wherein the targeting moiety specifically binds to a moiety expressed by hepatocytes (*e.g.*, on the surface of the hepatocytes).
46. The conjugate of any one of claims 44-45, wherein the targeting moiety comprises GalNac.
47. The conjugate of any one of claims 44-46, wherein the targeting moiety comprises Formula II:



; or

Formula I:



48. The conjugate of any one of claims 44-47, wherein the targeting moiety directs the agent to hepatocytes through specific binding to the asialoglycoprotein receptor (*e.g.*, expressed on the surface of hepatocytes).
49. The conjugate of any one of claims 40-48, wherein the heterologous moiety is attached to the dsRNA agent via a linker.
50. The conjugate of claim 49, wherein the linker is cleavable.

51. The conjugate of any one of claims 40-50, wherein 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.
52. A vector (*e.g.*, a viral vector, a non-viral vector) encoding the antisense strand, the sense strand, or both the antisense and sense strand of any one of claims 1-39.
53. A carrier comprising the dsRNA agent of any one of claims 1-39 or the vector of claim 52.
54. The carrier of claim 53, wherein the carrier comprises a nanoparticle, a polymer, a lipid-based delivery system, as dendrimer, a cationic delivery system, or a hydrogel.
55. The carrier of claim 54, wherein the lipid-based delivery system is a lipid nanoparticle (LNP), liposome, lipoplex, nanoliposome, an exosome, or a micelle.
56. A cell comprising the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, or the carrier of any one of claims 53-55.
57. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the cell of claim 56, and a pharmaceutically acceptable excipient.
58. A kit comprising the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, the cell of claim 56, or the pharmaceutical composition of claim 57.
59. A method of delivering a dsRNA agent, conjugate, vector, carrier, or pharmaceutical composition to a cell, the method comprising introducing into a cell the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby deliver the dsRNA, conjugate, vector, carrier, or pharmaceutical composition into the cell.
60. The method of claim 59, wherein the cell is *in vitro*, *ex vivo*, or *in vivo*.
61. The method of claim 59 or 60, wherein the cell is a subject (*e.g.*, a human subject).
62. A method of delivering a dsRNA agent, conjugate, vector, carrier, or pharmaceutical composition to a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby deliver the dsRNA, conjugate, vector, carrier, or pharmaceutical composition to the subject.
63. A method of reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell, the method comprising delivering into the cell the dsRNA agent of any one of claims 1-39, the

conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby reduce or inhibit expression of FASN (*e.g.*, hFASN) in the cell.

64. A method of reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby reduce or inhibit expression of FASN (*e.g.*, hFASN) in the cell in the subject.

65. A dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 for use in a method of reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby reduce or inhibit expression of FASN (*e.g.*, hFASN) in the cell in the subject.

66. A use of the dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 in the manufacture of a medicament for reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell in a subject.

67. A method of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) associated disease in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby treat, ameliorate, or prevent the FASN (*e.g.*, hFASN) associated disease in the subject.

68. The method of claim 67, wherein the FASN (*e.g.*, hFASN) associated disease is fatty liver, liver inflammation, nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD).

69. The method of claim 67, wherein the FASN (*e.g.*, hFASN) associated disease is 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 and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), or cryptogenic SLD.

70. A dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 for use in treating a disease in a subject, preferably a FASN (*e.g.*, hFASN) associated disease, more preferably a liver disease.

71. A dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 for use in treating a disease in a subject (preferably a FASN (*e.g.*, hFASN) associated disease, more preferably a liver disease) by reducing or inhibiting expression of FASN (*e.g.*, hFASN) in a cell.

72. A dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 for use in a method of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) associated disease in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby treat, ameliorate, or prevent the FASN (*e.g.*, hFASN) associated disease in the subject.

73. The dsRNA, agent conjugate, vector, carrier, or pharmaceutical composition for use of claim 72, wherein the FASN (*e.g.*, hFASN) associated disease is fatty liver, liver inflammation, NASH or NAFLD.

74. The dsRNA agent, conjugate, vector, carrier, or pharmaceutical composition for use of claim 72, wherein the FASN (*e.g.*, hFASN) associated disease is 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 and alcohol associated steatotic liver disease (MetALD), steatotic liver disease (SLD), or cryptogenic SLD.

75. Use of the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57 in the manufacture of a medicament for use in a method of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) associated disease in a subject.

76. The use of claim 75, wherein the FASN (*e.g.*, hFASN) associated disease is fatty liver, liver inflammation, NASH or NAFLD.

77. The use of claim 75, wherein the FASN (*e.g.*, hFASN) associated disease is obesity-induced metabolic syndrome, insulin insensitivity, obesity, type-2 diabetes, AFLD, cirrhosis, MASLD, MASH, MetALD, SLD, or cryptogenic SLD.

78. A method of treating, ameliorate, or preventing a liver disease in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby treat, ameliorate, or prevent the liver disease in the subject.

79. The method of claim 78, wherein 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.

80. A dsRNA agent of any one of claims 1-39, a conjugate of any one of claims 40-51, a vector of claim 52, a carrier of any one of claims 53-55, or a pharmaceutical composition of claim 57 for use in a method of treating, ameliorating, or preventing a liver disease in a subject, the method comprising administering to the subject the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57, to thereby treat, ameliorate, or prevent the liver disease in the subject.

81. The dsRNA agent, conjugate, vector, carrier, or pharmaceutical composition for use of claim 80, wherein 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.

82. Use of the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57 in the manufacture of a medicament for treating, ameliorating, or preventing a liver disease in a subject.

83. The use of claim 82, wherein 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.

84. A method of diagnosing a FASN (*e.g.*, hFASN) 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 FASN mutation in the DNA, RNA, or protein,
wherein the presence of the one or more somatic mutation indicates that the subject has a FASN (*e.g.*, hFASN) associated disease.

85. The method of claim 84, wherein the FASN (*e.g.*, hFASN) associated disease is a liver disease.

86. The method of any one of claims 84-85, wherein the FASN (*e.g.*, hFASN) associated 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.

87. A method 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 FASN 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.

88. The method of claim 87, wherein the liver disease 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.

89. The method of any one of claims 84-88, wherein (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 FASN mutation in the DNA.

90. The method of any one of claims 84-89, further comprising administering to the subject an inhibitory nucleic acid molecule that inhibits expression of FASN if a FASN somatic mutation is detected in the DNA, RNA, or protein.

91. The method of claim 90, wherein the inhibitory nucleic acid molecule comprises the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57.

92. A method of selecting a subject for administration of an inhibitory nucleic acid molecule that inhibits expression of FASN, 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 FASN 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.

93. The method of claim 92, wherein (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 FASN mutation in the DNA.

94. The method of any one of claims 92-93, further comprising administering to the subject the inhibitory nucleic acid molecule if the subject is selected.

95. The method of claim 94, wherein the inhibitory nucleic acid molecule comprises the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57.

96. A method of treating, ameliorating, or preventing a FASN (*e.g.*, hFASN) 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 FASN mutation in the DNA, RNA, or protein, and

(c) administering to the subject an inhibitory nucleic acid that inhibits expression of FASN if the one or more FASN somatic mutation is detected in the DNA, RNA, or protein.

97. The method of claim 96, wherein the FASN (*e.g.*, hFASN) associated disease is a liver disease.

98. The method of any one of claims 96-97, wherein 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.

99. A method 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 FASN mutation in the DNA, RNA, or protein, and

(c) administering to the subject an inhibitory nucleic acid that inhibits expression of FASN if the one or more FASN somatic mutation is detected in the DNA, RNA, or protein.

100. The method of claim 99, wherein 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.

101. The method of any one of claims 96-100, wherein (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 FASN mutation in the DNA.

102. The method of any one of claims 96-101, wherein the inhibitory nucleic acid molecule comprises the dsRNA agent of any one of claims 1-39, the conjugate of any one of claims 40-51, the vector of claim 52, the carrier of any one of claims 53-55, or the pharmaceutical composition of claim 57.

103. An *in vitro* method of screening a sample from a subject for one or more somatic FASN 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 FASN mutation in the DNA, RNA, or protein.

104. The method of any one of claims 84-103, wherein the sample is a blood, tissue, or cell sample.

105. The method of any one of claims 84-104, wherein the sample is biopsy.

106. The method of any one of claims 84-105, wherein the sample is a liver biopsy.

107. The method of any one of claims 84-106, wherein at least one of the one or more somatic mutation is a loss of function mutation.

108. The method of any one of claims 84-107, wherein at least one of the one or more somatic mutation is a gain of function mutation.

109. The method, use, dsRNA agent for use, conjugate for use, vector for use, carrier for use, or pharmaceutical composition for use of any one of claims 59-108, wherein the subject is a human.

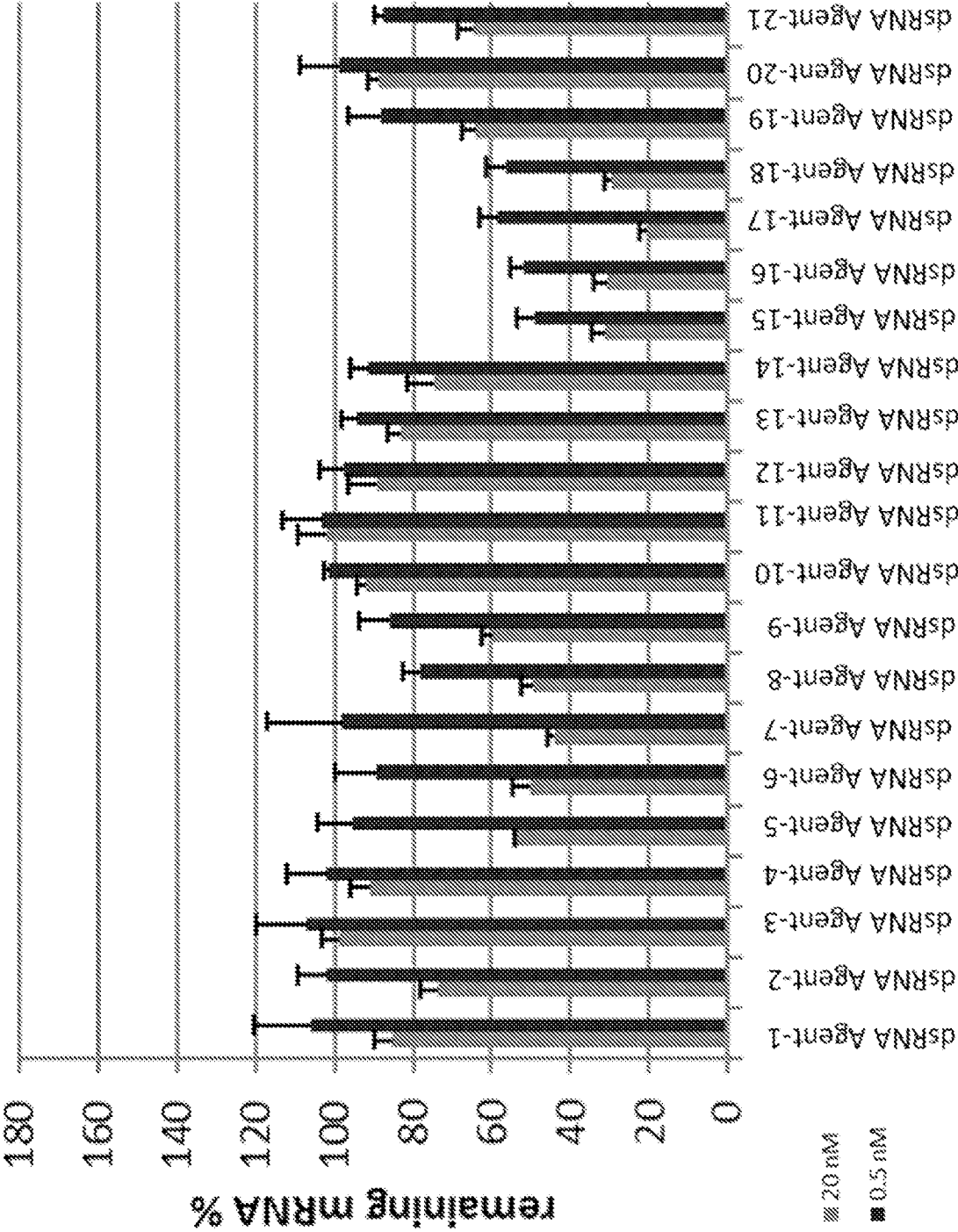


FIG. 1A

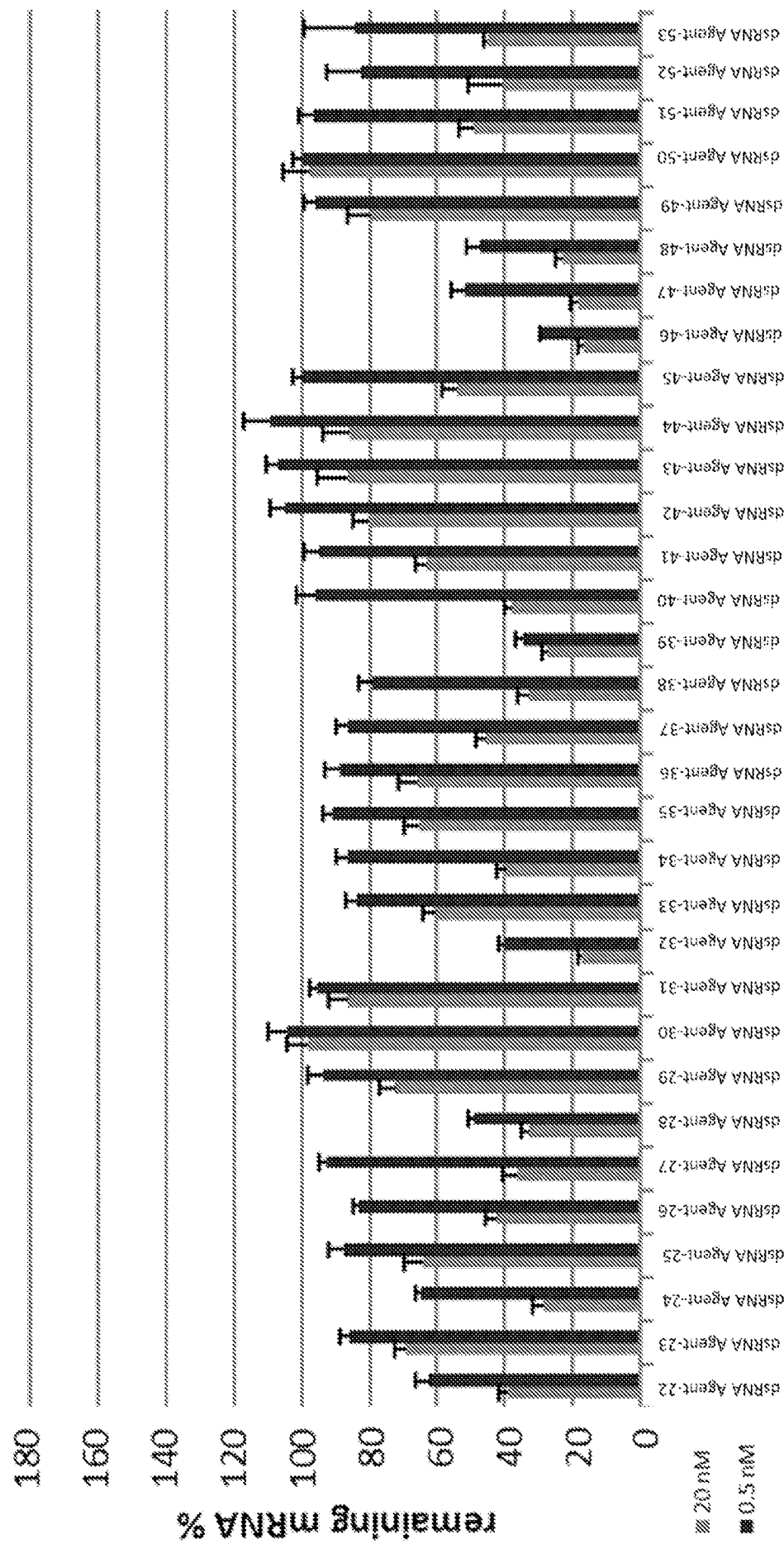


FIG. 1B

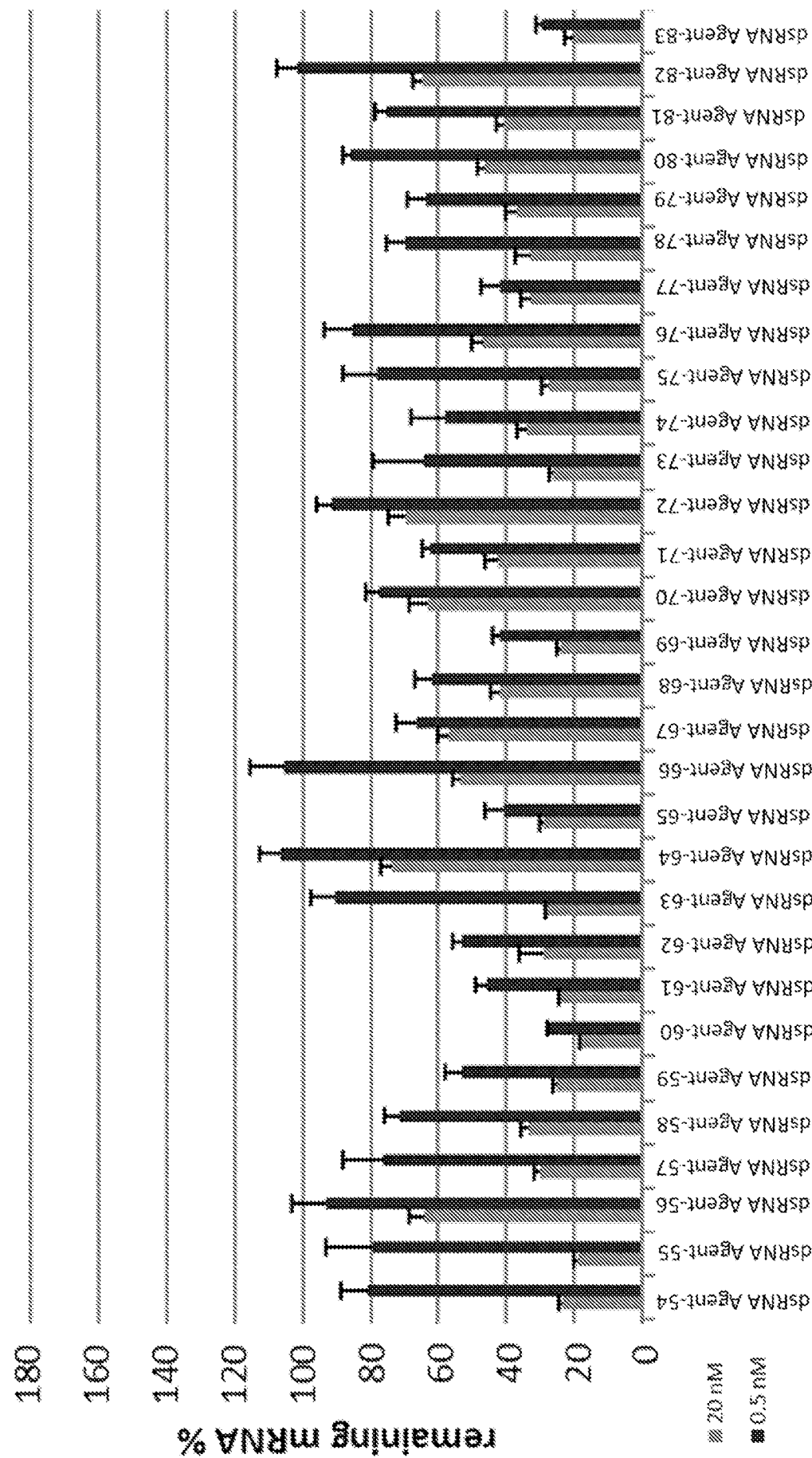


FIG. 1C

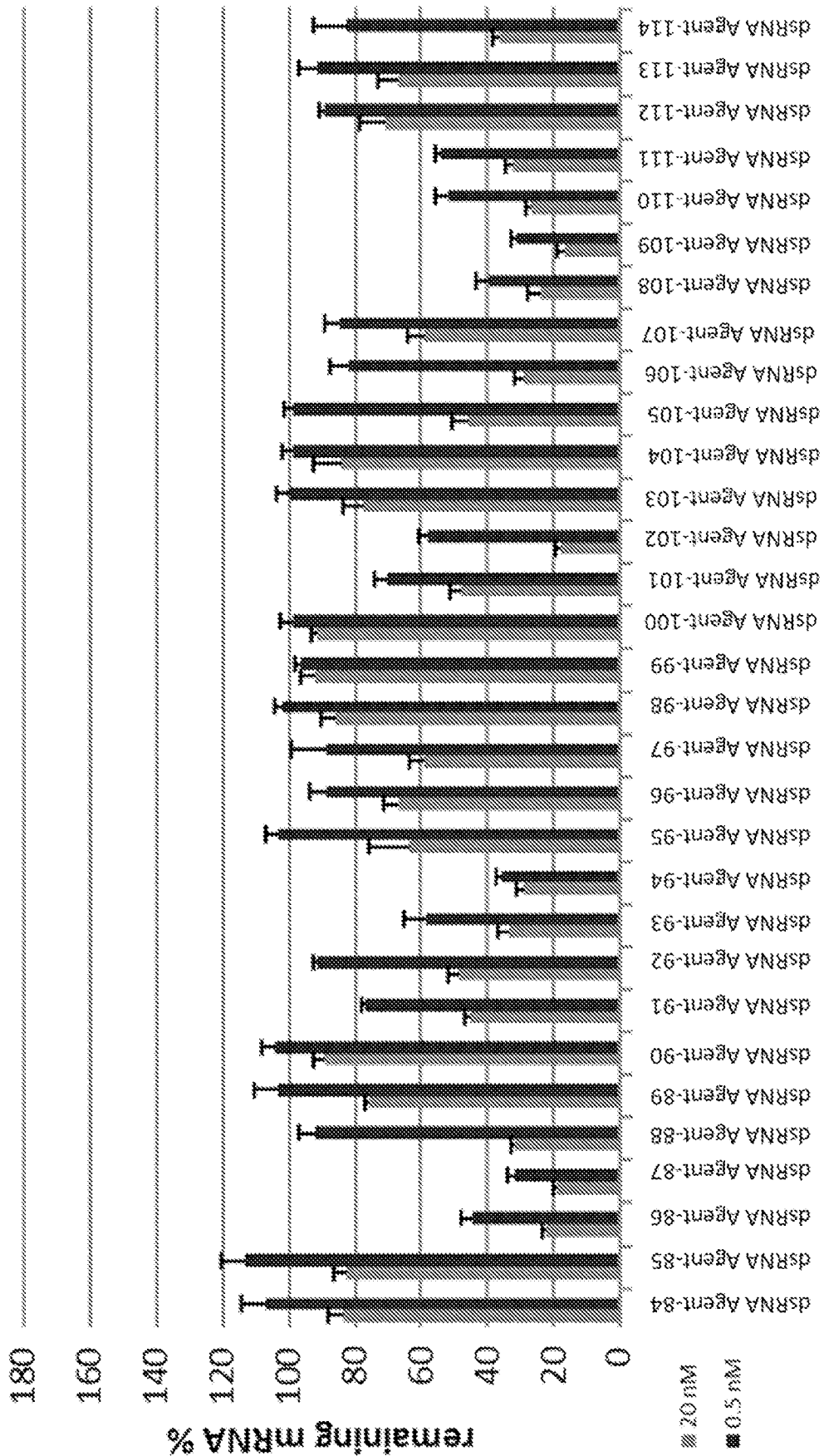


FIG. 1D

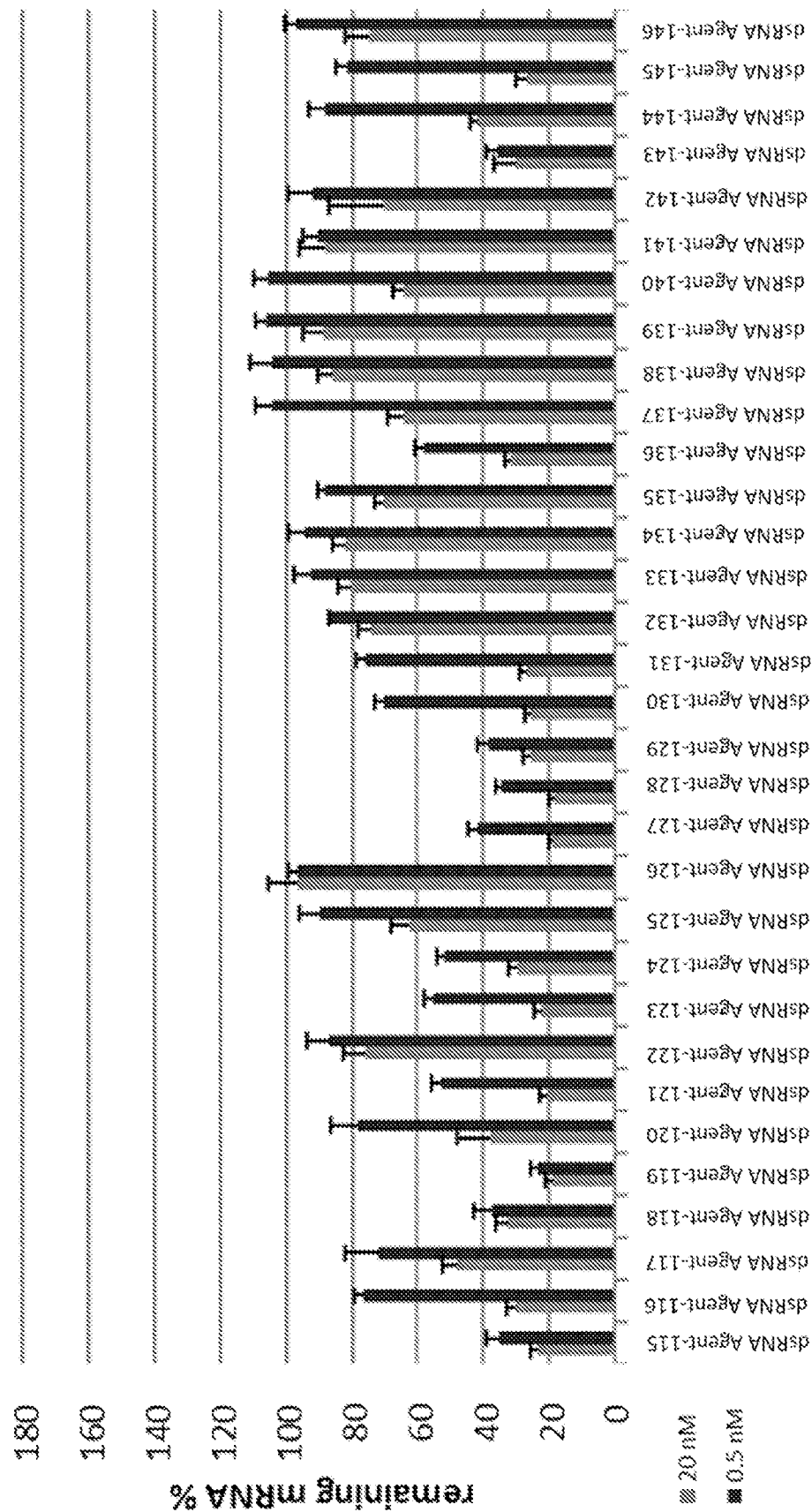


FIG. 1E

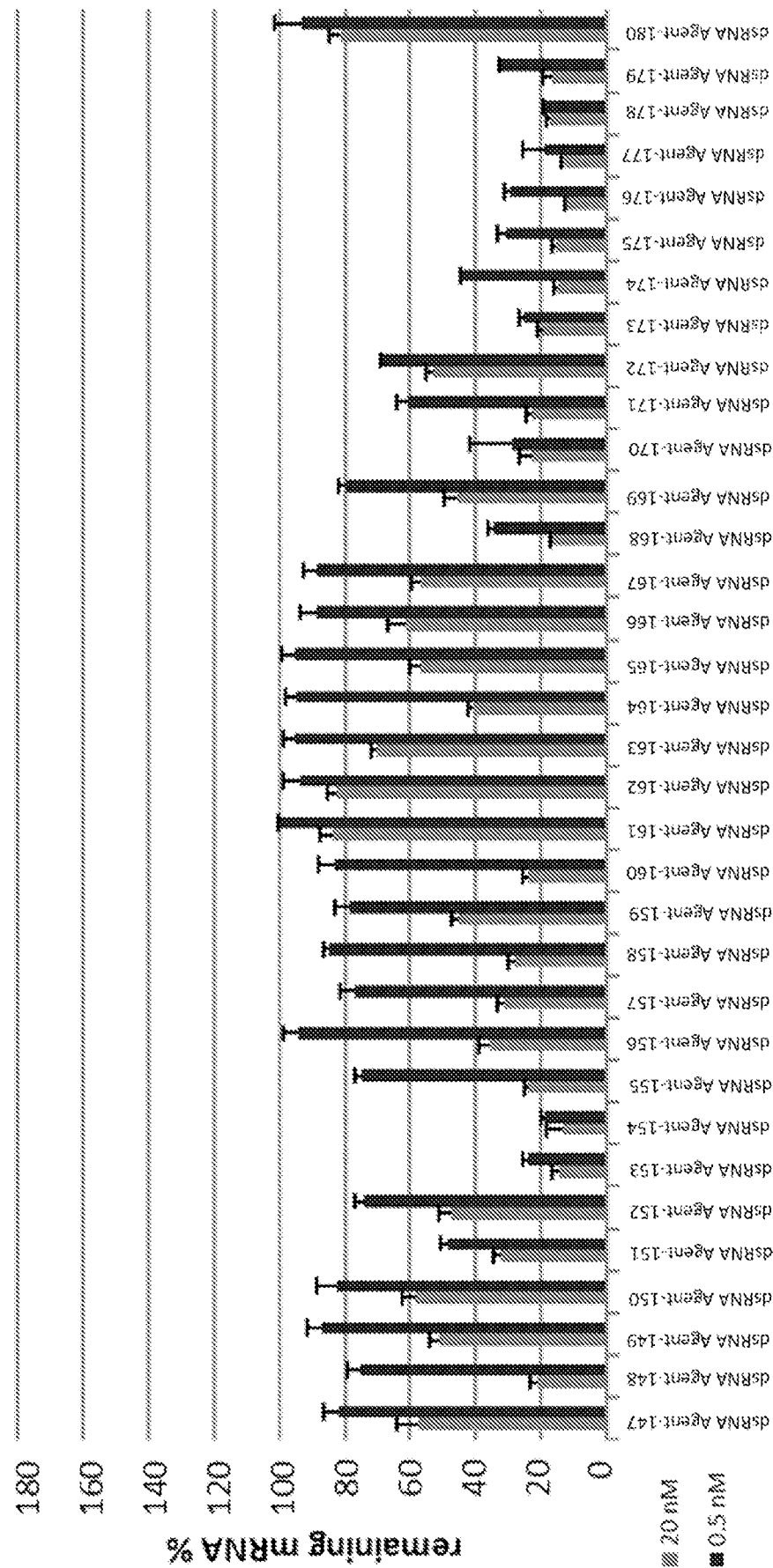


FIG. 1F

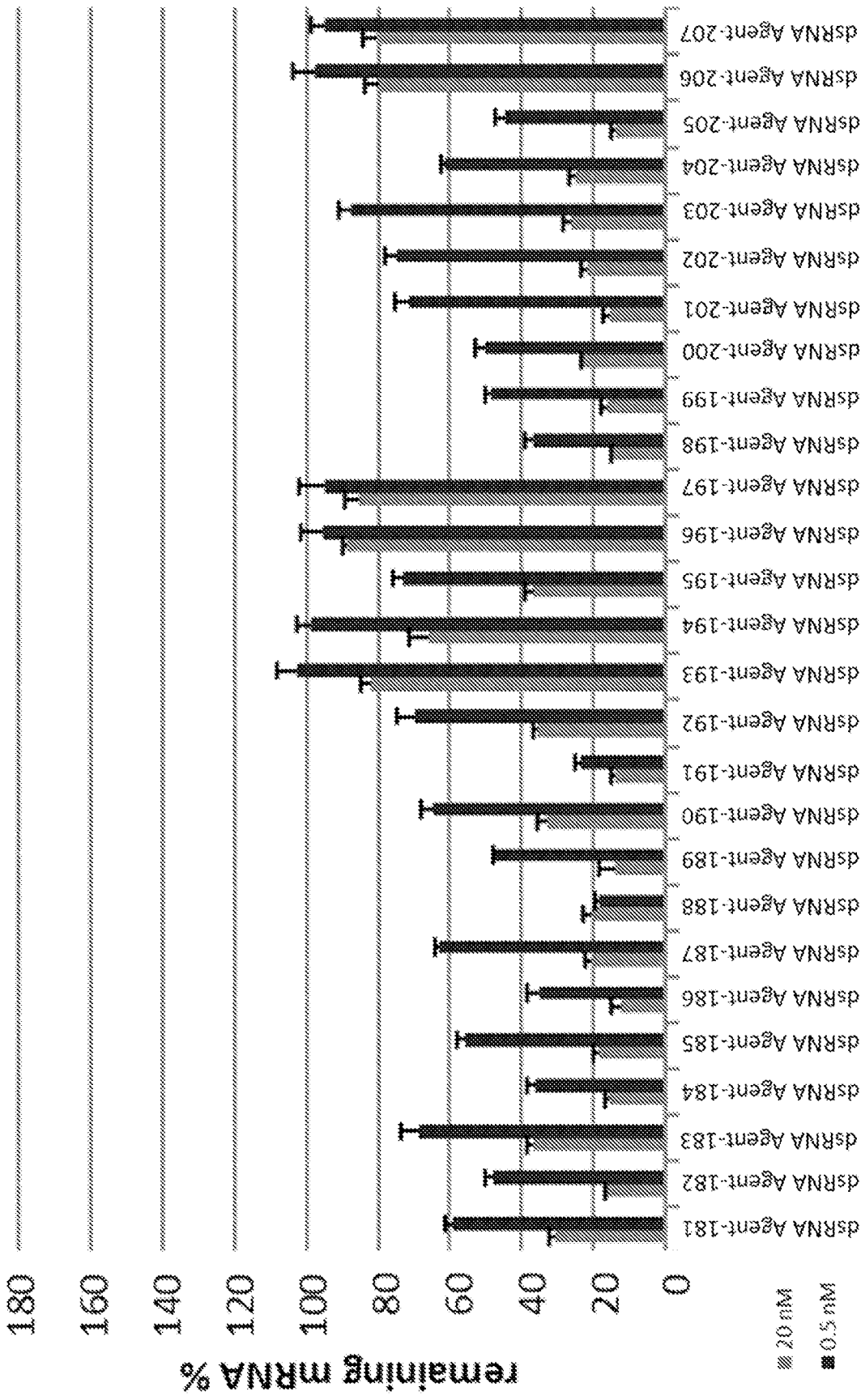


FIG. 1G

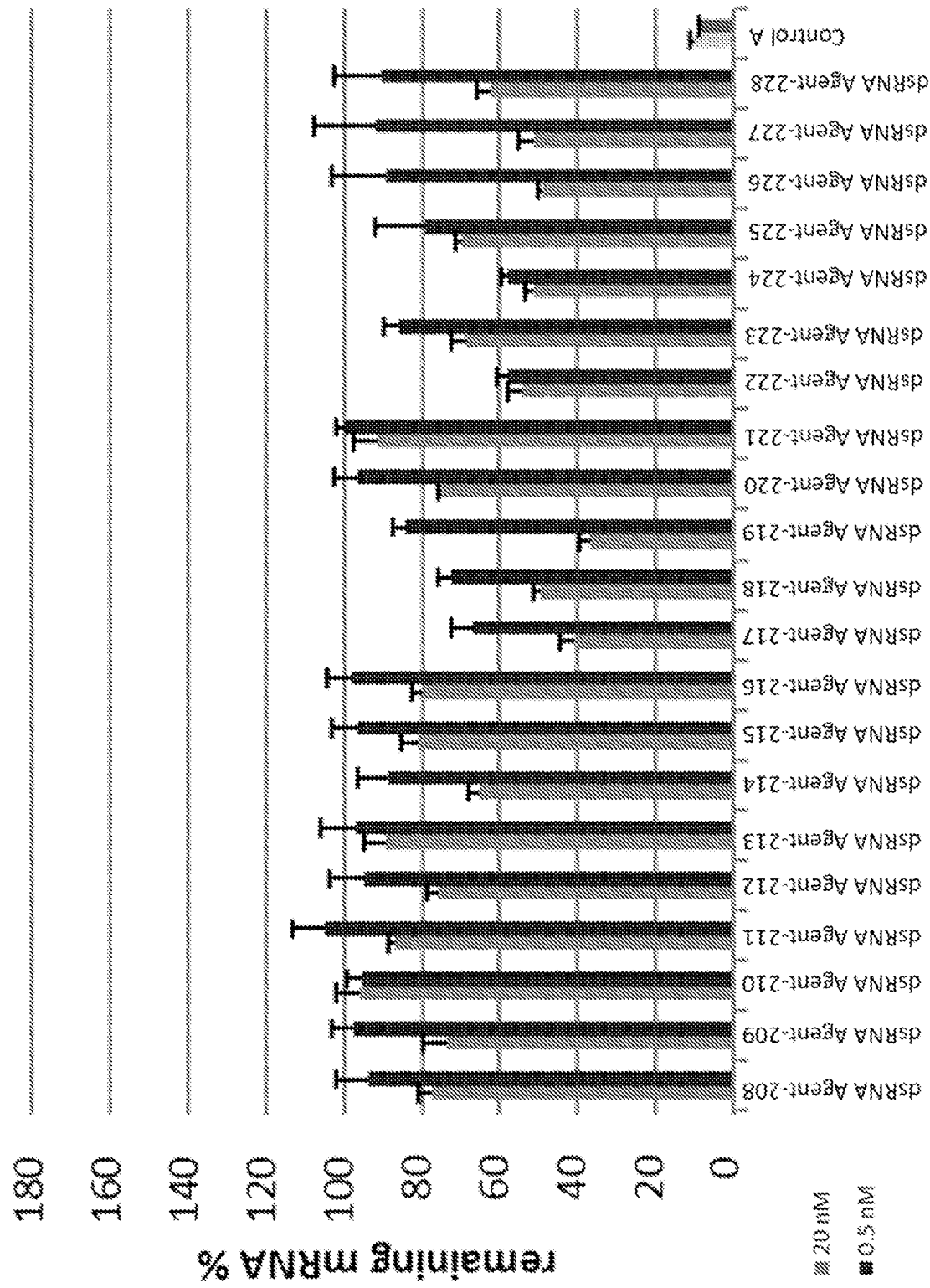


FIG. 1H

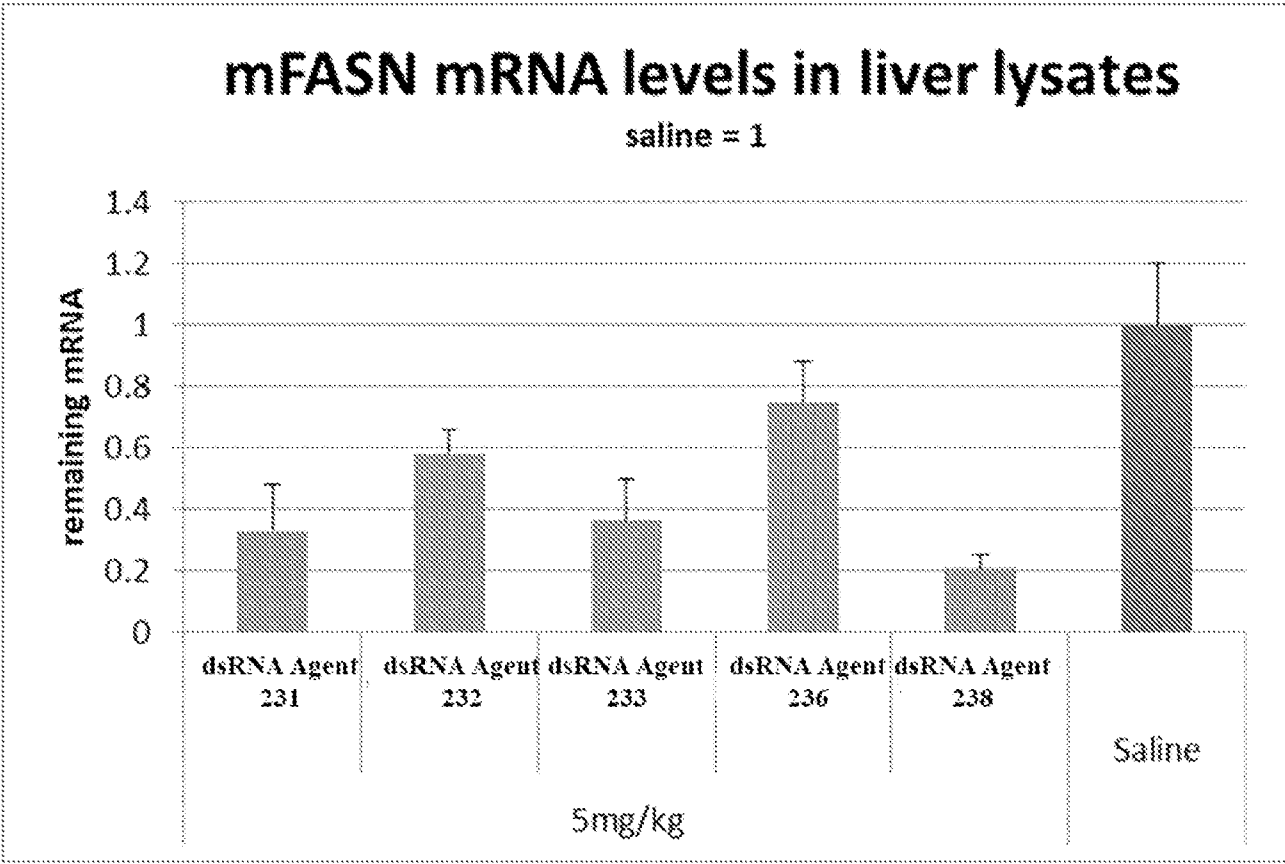


FIG. 2

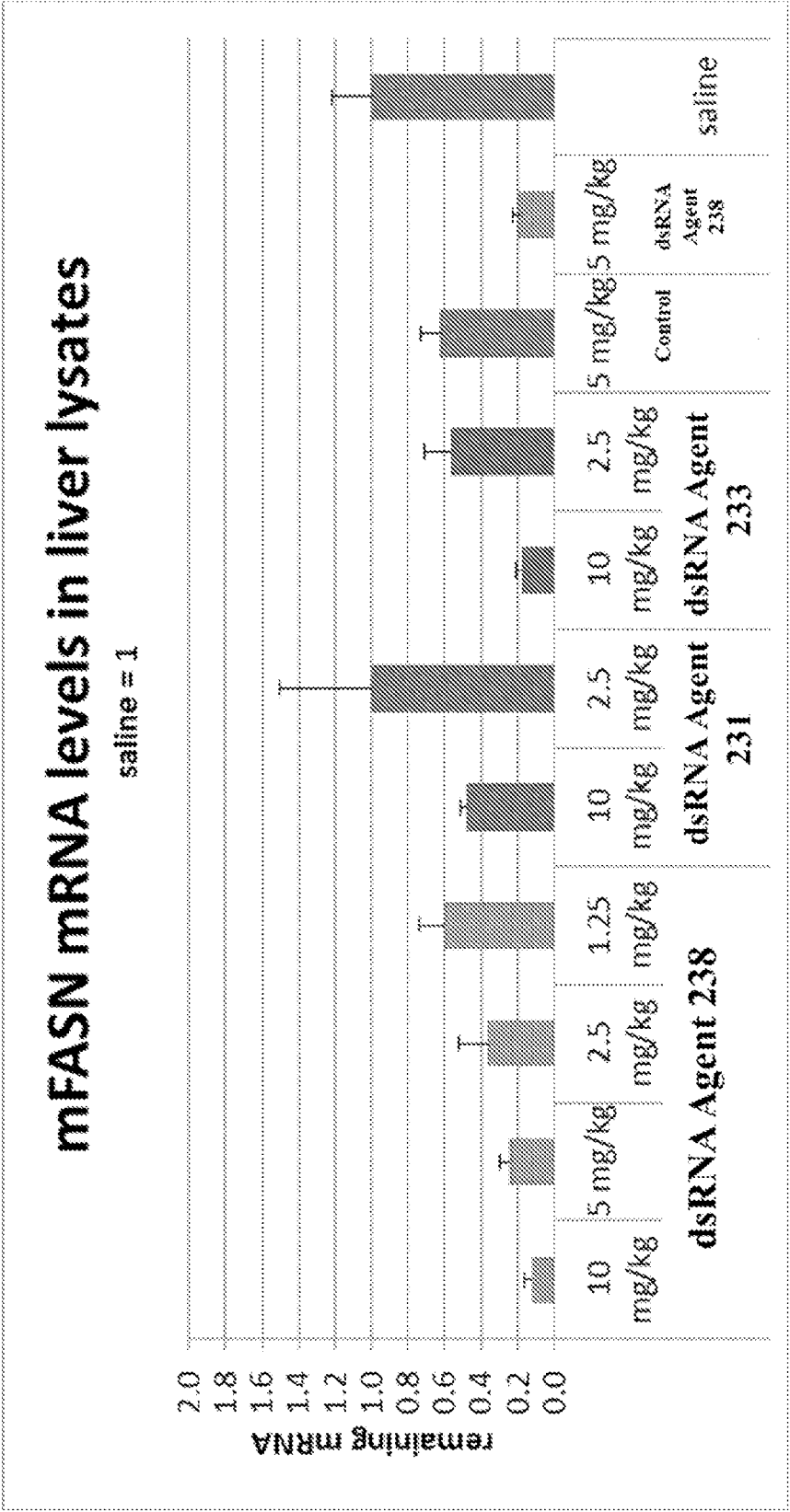


FIG. 3