

COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF 3-HYDROXY-3-METHYLGLUTARYL-COA REDUCTASE (HMGCR)

Field of the Invention

5 The invention relates, in part, to compositions and methods that can be used to inhibit 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) gene expression.

Background

High levels of cholesterol and in particular high levels of low-density lipoprotein (LDL) are well-recognized risk factors for the development of cardiovascular disease. Certain mutations in the gene encoding the low-density lipoprotein receptor (LDLR) reduce or prevent LDLR-mediated removal of LDL-C from the blood. HMG-CoA reductase (also known as 3-hydroxy-3-methylglutaryl-Coenzyme A reductase, HMGCR, hydroxymethylglutaryl-CoA reductase) is a transmembrane glycoprotein that catalyzes the rate-limiting, committed step in cholesterol biosynthesis, i.e., the conversion of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) to mevalonate, a crucial intermediate in the formation of cholesterol and many nonsteroidal isoprenoid compounds including isopentenyladenine, ubiquinone, dolichol and prenyl groups which posttranslationally modify cell proteins (Aboushadi et al., *Biochemistry*, 2000, 39, 237-247; Asslan et al., *Biochem. Biophys. Res. Commun.*, 1999, 260, 699-706; Istvan and Deisenhofer, *Biochim. Biophys. Acta*, 2000, 1529, 9-18). HMG-CoA reductase translation and degradation rates are controlled by sterol compounds and nonsterol metabolites derived from mevalonate, and short term regulation is achieved by a bicyclic cascade involving reversible phosphorylation of both HMG-CoA reductase and reductase kinases (Asslan et al., *Biochem. Biophys. Res. Commun.*, 1999, 260, 699-706).

25 Since the reaction catalyzed by HMG-CoA reductase is the rate-limiting step in
cholesterol synthesis, this enzyme represents the major drug target for contemporary
cholesterol-lowering drugs in humans. Statins are widely used drugs for cholesterol lowering
and have been found to reduce cardiovascular disease and mortality in those who are at high
risk. However, some patients experience side effects of statins including muscle pain,
30 increased risk of hyperlipidemia mellitus, and abnormalities in liver enzyme tests (Naci H, *et al.* (2013). *Circ Cardiovasc Qual Outcomes* 6 (4): 390-9).

Accordingly, novel therapeutics targeting HMGCR are needed for treatment of HMGCR-related diseases, such as disorders of lipid metabolism.

35 Summary of the Invention

In general, the present disclosure features novel HMGCR gene-specific RNAi agents, compositions that include HMGCR RNAi agents, and methods for inhibiting expression of an HMGCR gene in vitro and/or in vivo using the HMGCR RNAi agents and compositions that include HMGCR RNAi agents described herein. The HMGCR RNAi agents described herein

can selectively and efficiently decrease, inhibit, or silence expression of an HMGCR gene in a subject, e.g., a human or animal subject.

According to an aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1, 3 or 5 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2, 4 or 6, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to part of an mRNA encoding HMGCR which comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides with 0, 1, 2, 3, 4 or 5 mismatches. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to a target region of HMGCR mRNA transcript which comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides with 0, 1, 2, 3, 4 or 5 mismatches.

In some embodiments, the HMGCR RNA transcript is SEQ ID NO: 1.

In some embodiments, the target region of HMGCR mRNA transcript is any one of nucleotides 96-116, 97-117, 98-116, 99-117, 99-119, 101-121, 103-121, 103-123, 105-123, 104-124, 106-124, 105-125, 107-125, 106-126, 108-126, 107-127, 109-127, 108-128, 110-128, 109-129, 111-129, 110-130, 112-130, 113-133, 115-133, 120-140, 122-140, 150-170, 152-170, 181-201, 183-201, 185-205, 187-205, 186-206, 188-206, 188-208, 190-208, 189-209, 191-209, 191-211, 193-211, 193-213, 194-214, 195-213, 196-216, 198-216, 197-217, 199-217, 199-219, 201-219, 202-222, 204-222, 203-223, 205-223, 204-224, 206-224, 205-225, 207-225, 206-226, 208-226, 207-227, 209-227, 208-228, 210-228, 210-230, 212-230, 211-231, 213-231, 212-232, 214-232, 214-234, 216-234, 215-235, 217-235, 216-236, 218-236, 217-237, 219-237, 218-238, 220-238, 221-241, 223-241, 222-242, 224-242, 223-243, 225-243, 224-244, 226-244, 225-245, 227-245, 226-246, 228-246, 227-247, 229-247, 228-248, 230-248, 229-249, 231-249, 230-250, 232-250, 234-254, 236-254, 236-256, 238-256, 237-257, 239-257, 238-258, 240-258, 240-260, 242-260, 243-263, 245-263, 244-264, 246-264, 246-266, 248-266, 247-267, 249-267, 249-269, 251-269, 253-273, 255-273, 257-277, 259-277, 263-283, 265-283, 265-285, 267-285, 269-289, 271-289, 270-290, 272-290, 271-291, 273-291, 272-292, 274-292, 273-293, 275-293, 275-295, 277-295, 278-298, 280-298, 279-299, 281-299, 280-300, 282-300, 281-301, 283-301, 282-302, 284-302, 283-303, 285-303, 284-304, 286-304, 285-305, 287-305, 287-307, 289-307, 293-313, 295-313, 294-314, 296-314, 295-315, 297-315, 296-316, 298-316, 298-318, 300-318, 299-319, 301-319, 320-340, 322-340, 324-344, 326-344, 325-345, 327-345, 326-346, 328-346, 327-347, 329-347, 330-350, 332-350, 331-351, 333-351, 332-352, 334-352, 334-354, 336-354, 335-355,

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In some embodiments, the dsRNA agent targets a corresponding portion of an HMGCRC mRNA transcript disclosed in Table 1 and/or the target region of HMGCRC mRNA transcript described above.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCRC, wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the complement of any one of nucleotides 96-116, 97-117, 98-116, 99-117, 99-119, 101-121, 103-121, 103-123, 105-123, 104-124, 106-124, 105-125, 107-125, 106-126, 108-126, 107-127, 109-127, 108-128, 110-128, 109-129, 111-129, 110-130, 112-130, 113-133, 115-133, 120-140, 122-140, 150-170, 152-170, 181-201, 183-201, 185-205, 187-205, 186-206, 188-206, 188-208, 190-208, 189-209, 191-209, 191-211, 193-211, 193-213, 194-214, 195-213, 196-216, 198-216, 197-217, 199-217, 199-219, 201-219, 202-222, 204-222, 203-223, 205-223, 204-224, 206-224, 205-225, 207-225, 206-226, 208-226, 207-227, 209-227, 208-228, 210-228, 210-230, 212-230, 211-231, 213-231, 212-232, 214-232, 214-234, 216-234, 215-235, 217-235, 216-236, 218-236, 217-237, 219-237, 218-238, 220-238, 221-241, 223-241, 222-242, 224-242, 223-243, 225-243, 224-244, 226-244, 225-245, 227-245, 226-246, 228-246, 227-247, 229-247, 228-248, 230-248, 229-249, 231-249, 230-250, 232-250, 234-254, 236-254, 236-256, 238-256, 237-257, 239-257, 238-258, 240-258, 240-260, 242-260, 243-263, 245-263, 244-264, 246-264, 246-266, 248-266, 247-267, 249-267, 249-269, 251-269, 253-273, 255-273, 257-277, 259-277, 263-283, 265-283, 265-285, 267-285, 269-289, 271-289, 270-290, 272-290, 271-291, 273-291, 272-292, 274-292, 273-293, 275-293, 275-295, 277-295, 278-298, 280-298, 279-299, 281-299, 280-300, 282-300, 281-301, 283-301, 282-302, 284-302, 283-303, 285-303, 284-304, 286-304, 285-305,

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20 In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGR, wherein the region of complementarity comprises at least 15, 16, 17, 18 or 19 contiguous nucleotides from the complement of any one of nucleotides 96-116, 97-117, 98-116, 99-117, 99-119, 101-121, 103-121, 103-123, 105-123, 25 104-124, 106-124, 105-125, 107-125, 106-126, 108-126, 107-127, 109-127, 108-128, 110-128, 109-129, 111-129, 110-130, 112-130, 113-133, 115-133, 120-140, 122-140, 150-170, 152-170, 181-201, 183-201, 185-205, 187-205, 186-206, 188-206, 188-208, 190-208, 189-209, 191-209, 191-211, 193-211, 193-213, 194-214, 195-213, 196-216, 198-216, 197-217, 199-217, 199-219, 201-219, 202-222, 204-222, 203-223, 205-223, 204-224, 206-224, 205-225, 207-225, 206-226, 30 208-226, 207-227, 209-227, 208-228, 210-228, 210-230, 212-230, 211-231, 213-231, 212-232, 214-232, 214-234, 216-234, 215-235, 217-235, 216-236, 218-236, 217-237, 219-237, 218-238, 220-238, 221-241, 223-241, 222-242, 224-242, 223-243, 225-243, 224-244, 226-244, 225-245, 227-245, 226-246, 228-246, 227-247, 229-247, 228-248, 230-248, 229-249, 231-249, 230-250, 232-250, 234-254, 236-254, 236-256, 238-256, 237-257, 239-257, 238-258, 240-258, 240-260, 35 242-260, 243-263, 245-263, 244-264, 246-264, 246-266, 248-266, 247-267, 249-267, 249-269, 251-269, 253-273, 255-273, 257-277, 259-277, 263-283, 265-283, 265-285, 267-285, 269-289, 271-289, 270-290, 272-290, 271-291, 273-291, 272-292, 274-292, 273-293, 275-293, 275-295, 277-295, 278-298, 280-298, 279-299, 281-299, 280-300, 282-300, 281-301, 283-301, 282-302, 284-302, 283-303, 285-303, 284-304, 286-304, 285-305, 287-305, 287-307, 289-307, 293-313,

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2426, 2409-2429, 2411-2429, 2412-2432, 2414-2432, 2413-2433, 2415-2433, 2414-2434, 2416-2434, 2416-2436, 2418-2436, 2422-2442, 2424-2442, 2430-2450, 2432-2450, 2432-2452, 2434-2452, 2437-2457, 2439-2457, 2457-2477, 2459-2477, 2483-2503, 2485-2503, 2488-2508, 2490-2508, 2491-2511, 2493-2511, 2492-2512, 2494-2512, 2572-2592, 2574-2592, 2586-2606, 2588-2606, 2647-2667, 2649-2667, 2679-2699, 2681-2699, 2681-2701, 2683-2701, 2714-2734, 2716-2734, 2718-2738, 2720-2738, 2721-2741, 2723-2741, 2810-2830, 2812-2830, 2817-2837, 2819-2837, 2820-2840, 2822-2840, 2822-2842, 2824-2842, 2828-2848, 2830-2848, 2917-2937, 2919-2937, 2966-2986, 2968-2986, 2974-2994, 2976-2994, 2976-2996, 2978-2996, 3033-3053, 3035-3053, 3035-3055, 3037-3055, 3082-3102, 3084-3102, 3088-3108, 3090-3108, 3089-3109, 3091-3109, 3090-3110, 3092-3110, 3098-3118, 3100-3118, 3100-3120, 3102-3120, 3103-3123, 3105-3123, 3106-3126, 3108-3126, 3109-3129, 3111-3129, 3110-3130, 3112-3130, 3184-3204, 3186-3204, 3187-3207, 3189-3207, 3189-3209, 3191-3209, 3190-3210, 3192-3210, 3201-3221, 3203-3221, 3210-3230, 3212-3230, 3224-3244, 3226-3244, 3232-3252, 3234-3252, 3233-3253, 3235-3253, 3234-3254, 3236-3254, 3236-3256, 3238-3256, 3318-3338, 3320-3338, 3335-3355, 3337-3355, 3349-3369, 3351-3369, 3378-3398, 3380-3398, 3380-3400, 3382-3400, 3445-3465, 3447-3465, 3448-3468, 3450-3468, 3458-3478, 3460-3478, 3462-3482, 3464-3482, 3463-3483, 3465-3483, 3464-3484, 3466-3484, 3465-3485 or 3467-3485 of SEQ ID NO: 1.

In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.

In some embodiments, the dsRNA agent including a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand including a region of complementarity to an HMGCR RNA transcript, wherein the region of complementarity includes at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally including a targeting ligand.

In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the antisense strand of the dsRNA agent is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is at least substantially

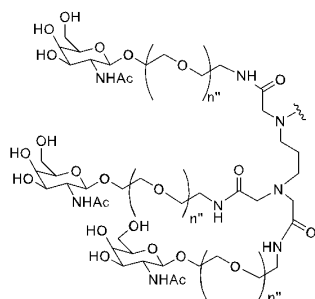
complementary to the antisense strand sequence in the dsRNA agent. In certain embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some embodiments, the dsRNA agent includes an antisense strand sequence set forth in any one of Tables 1-3. In some embodiments, the dsRNA agent includes the sequences set forth as a duplex sequence in any of Tables 1-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide. In certain embodiments, all or substantially all of the nucleotides of the antisense strand are modified nucleotides. In certain embodiments, all or substantially all of the nucleotides of the sense strand are modified nucleotides. In some embodiments, at least one of the modified nucleotides comprises: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, isomannide nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide including a 5'-phosphorothioate group, a 5'-phosphonate modified nucleotide, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidite, or a non-natural base including nucleotide. In some embodiments, the dsRNA agent includes an E-vinylphosphonate nucleotide at the 5' end of the guide strand. In certain embodiments, the dsRNA agent includes at least one phosphorothioate internucleoside linkage. In certain embodiments, the sense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the antisense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the sense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide, a 2'-fluoro nucleotide and an UNA modified nucleotide, wherein less than 6 modified nucleotides are 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 3 or 5 2'-fluoro nucleotides, preferably, the antisense strand comprises 5 2'-fluoro nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein less than 4 modified nucleotides are 2'-fluoro nucleotides. In certain embodiments, the sense strand comprises 3 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least 14 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 2, 5,

7, 12, 14, 16 and/or 18 counting from the first matching position from the 5' end of the antisense strand are independently a 2'-fluoro nucleotide. In some embodiments, the antisense strand comprises at least one UNA modified nucleotide and 5 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 16 counting from the first matching position from the 5' end, and the rest are 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 7, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest are 2'-O-methyl nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, preferably, wherein at least 18 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 9, 11 and/or 13 counting from the first matching position from the 3' end of the sense strand are 2'-fluoro nucleotides. In some embodiments, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3. In some embodiments, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide and further includes one or more targeting groups or linking groups. In some embodiments, the one or more targeting groups or linking groups are conjugated to the sense strand. In some embodiments, the targeting group or linking group includes N-acetyl-galactosamine (GalNAc).

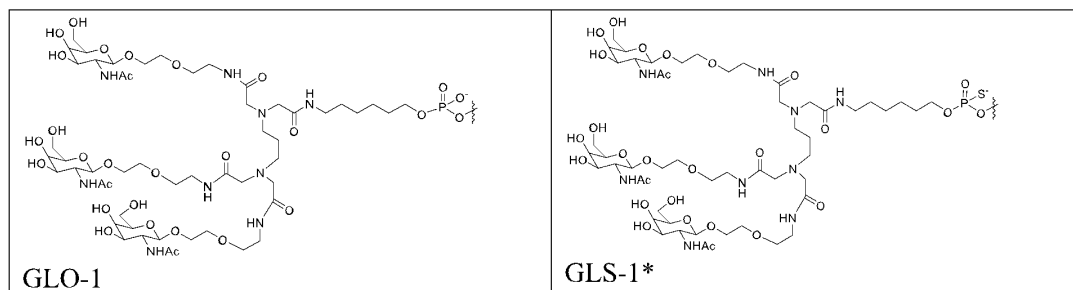
In some embodiments, the targeting group has a structure as Formula (X):

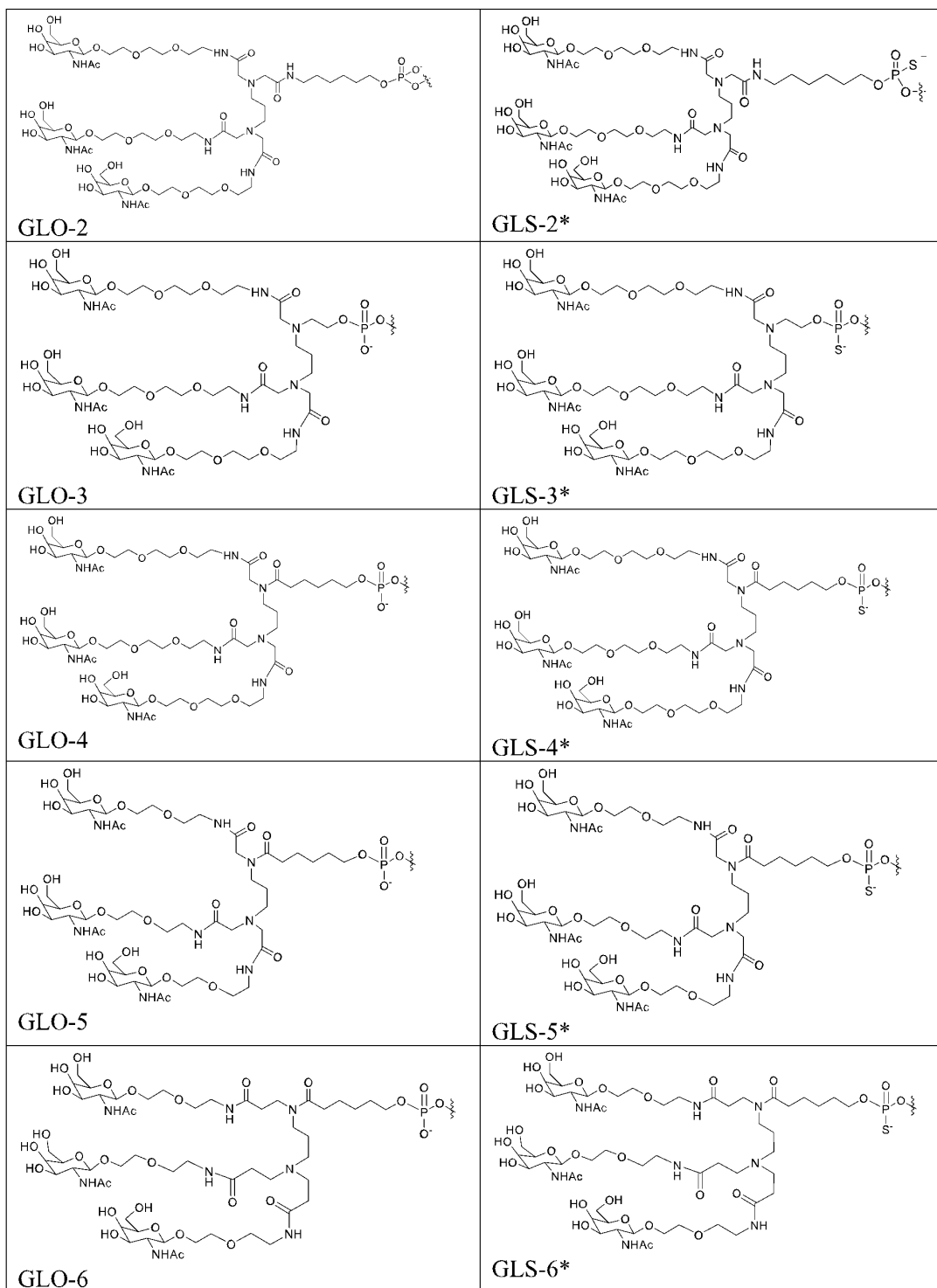


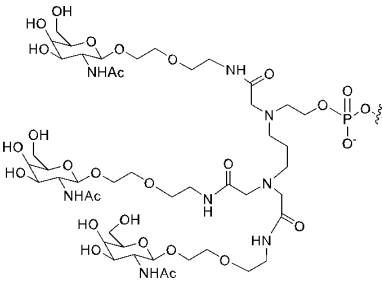
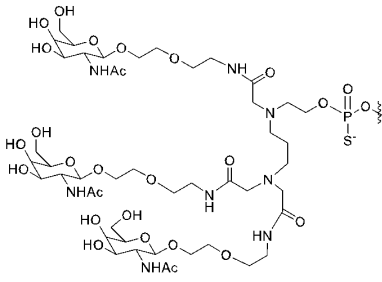
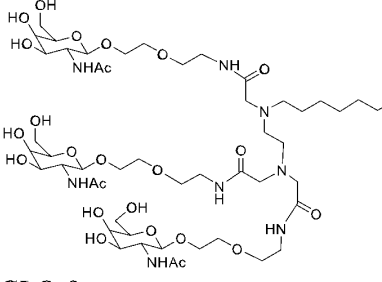
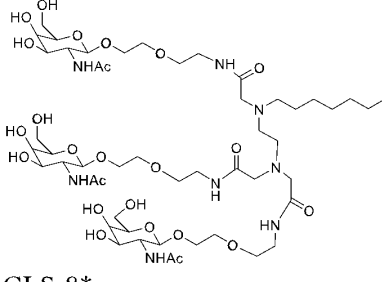
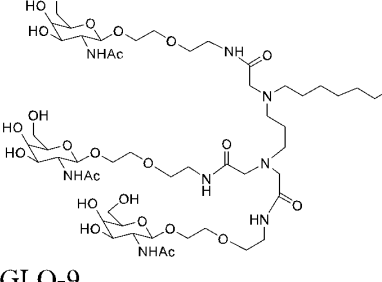
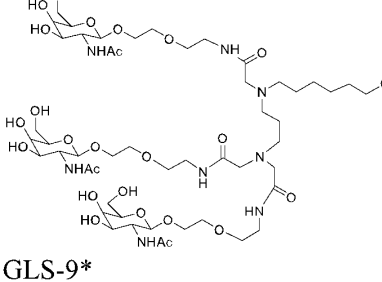
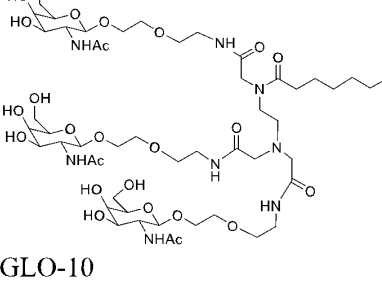
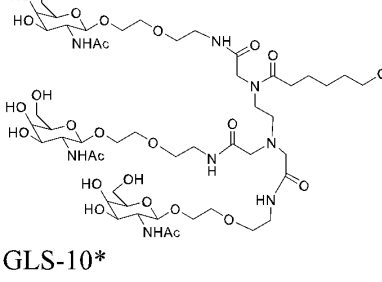
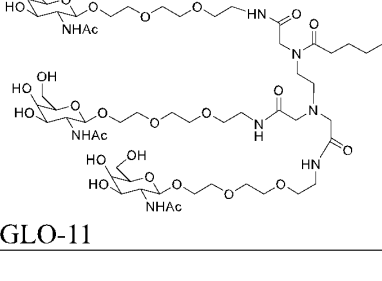
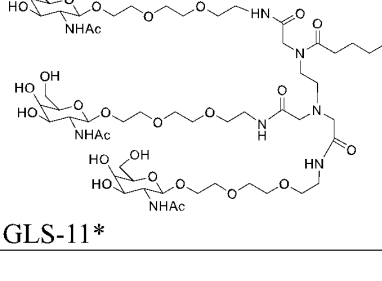
Formula (X)

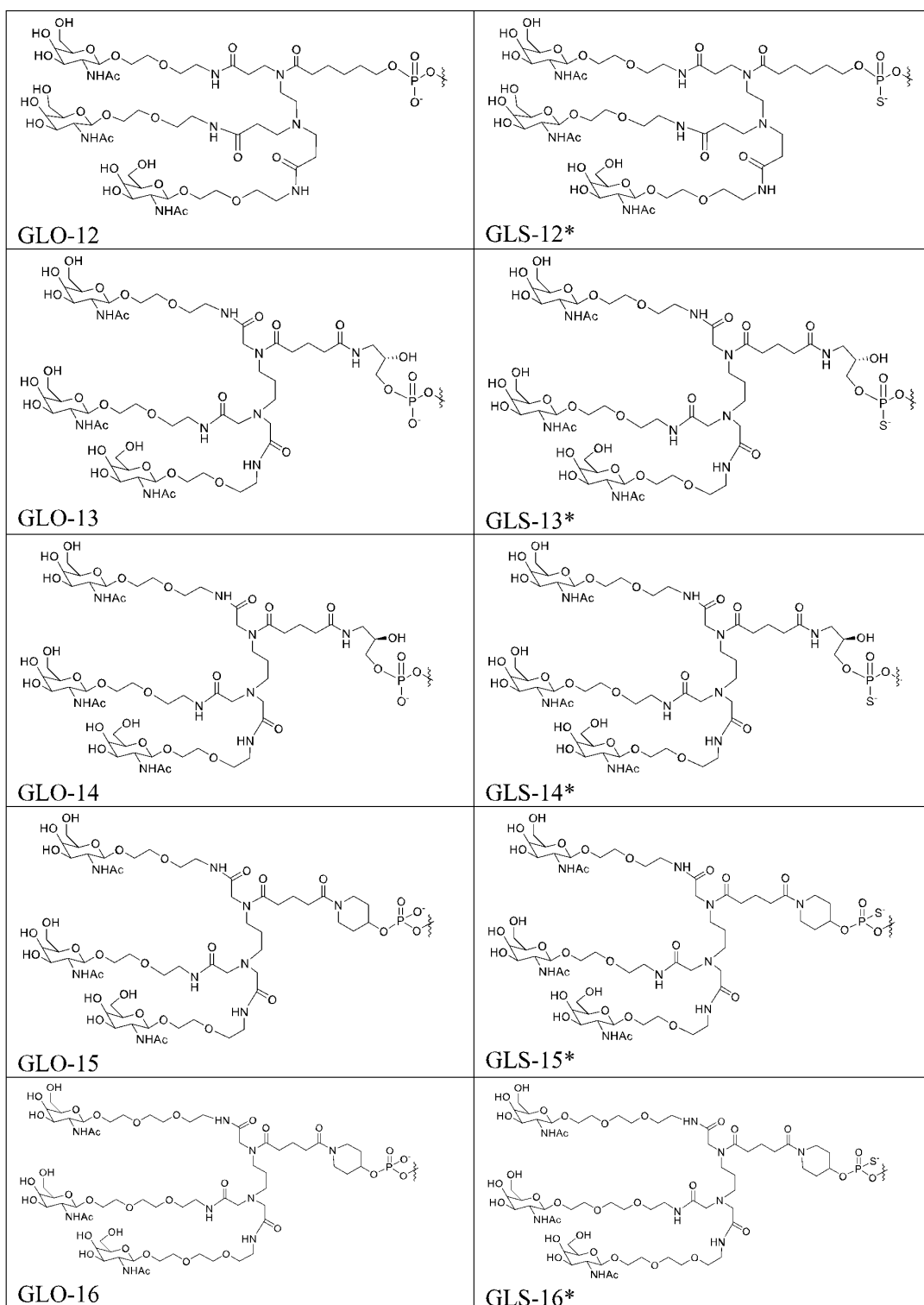
Each n'' is independently selected from 1 or 2.

In some embodiments, the targeting group has a structure:





 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*



In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In some embodiments, the dsRNA agent includes a

- targeting group that is conjugated to the 3'-terminal end of the sense strand. In some embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each end of the sense strand includes one inverted abasic residue. In certain embodiments, 3'-end of the sense strand includes one inverted abasic residue. In certain embodiments, each end of the sense strand includes one imann residue. In some embodiments, the dsRNA agent has two blunt ends. In some embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides. In certain embodiments, the dsRNA comprises a duplex selected from the group consisting of AD00608, AD00609, AD00610, AD00611, AD00612, AD00613, AD00614, AD00615, AD00616, AD00617, AD00618, AD00619, AD00620, AD00621, AD00622, AD00623, AD00624, AD00625, AD00626, AD00627, AD00628, AD00629, AD00630, AD00631, AD00632, AD00842, AD00843, AD00844, AD00845, AD00846, AD00847, AD00848, AD00849, AD00850, AD00851, AD00852, AD00853, AD00854, AD00855, AD00856, AD00857, AD00858, AD00859, AD00860, AD00861, AD00862, AD00863, AD01021, AD01022, AD01023, AD01024, AD01025, AD01026, AD02602, AD02603, AD02604, AD02605, AD02606, AD02607, AD02608, AD02609, AD02610, AD02611, AD02612, AD02613, AD02614, AD02615, AD02616.
- In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HMGCR, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand sequence may be represented by formula (I):
- $$5'-(N'_L)_{n'} N'_L N'_L N'_{N1} N'_{N2} N'_{N3} N'_{N4} N'_L N'_F N'_L N'_{N5} N'_{N6} N'_L N'_L N'_L (N'_L)_{m'}-3' \quad (I)$$
- wherein:
- each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} , N'_{N2} , N'_{N3} , N'_{N4} , N'_{N5} , and N'_{N6} independently represents a modified or unmodified nucleotide; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' and n' are each independently an integer of 0 to 7.
- In some embodiments, N'_{N2} and N'_{N4} each independently represents a 2'-fluoro-modified nucleotide;
- In some embodiments, m' is 2 and n' is 3, or m' is 2 and n' is 4, m' is 2 and n' is 5.
- In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a

targeting group that is conjugated to the 3'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, 3' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, 3'-end of the sense strand includes an inverted abasic residue and 5' terminal end is conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, each end of the sense strand includes an inverted abasic residue and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, each end of the sense strand includes an imann residue and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HMGCR, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand sequence may be represented by formula (II):



wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N_{M6} , N_{M7} and N_{M8} independently represents a modified or unmodified nucleotide; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide;

In some embodiments, N_{M2} , N_{M3} and N_{M7} each independently represents a 2'-fluoro-modified nucleotide and N_{M6} represents an UNA modified nucleotide;

In some embodiments, n is 1, or n is 2, or n is 3.

In some embodiments, N_{M6} , N_{M3} and N_{M2} are all 2'-fluoro-modified nucleotides.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to an

mRNA encoding HMGCR, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex represented by formula (III):

sense: 5'-(N'_L)_nN'_LN'_LN'_{N1}N'_{N2}N'_{N3}N'_{N4}N'_LN'_FN'_LN'_{N5}N'_{N6}N'_LN'_LN'_L(N'_L)_{m'}-3'

antisense: 3'-(N_L)_nN_{M1}N_LN_{M2}N_LN_FN_LN_{M3}N_LN_{M4}N_LN_{M5}N_{M6}N_LN_{M7}N_{M8}N_LN_FN_L-5'

5 (III)

wherein:

each strand is independently about 17 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1}, N_{M2}, N_{M3},

10 N_{M4}, N_{M5}, N_{M6}, N_{M7}, N_{M8}, N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} each independently represents a modified or unmodified nucleotide; each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m', n' and n are each independently an integer of 0 to 7.

In some embodiments, m' is 2 and n' is 3, or m' is 2 and n' is 4, m' is 2 and n' is 5.

15 In some embodiments, N'_{N2} and N'_{N4} each independently represents a 2'-fluoro-modified nucleotide;

In some embodiments, n is 1, or n is 2, or n is 3.

In some embodiments, N_{M2}, N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide; in certain embodiment, N_{M2}, N_{M3} and N_{M6} are all 2'-fluoro-modified nucleotides.

20 In some embodiments, N_{M2}, N_{M3} and N_{M7} each independently represents a 2'-fluoro-modified nucleotide and N_{M6} represents an UNA modified nucleotide.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*.

25 In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, 3' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments,

30 each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, each 3' and 5' terminal end of the sense strand includes an inverted abasic residue and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*.

35 In certain embodiments, 3'-end of the sense strand includes an inverted abasic residue and 5' terminal end is conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, each 3' and 5' terminal end of the sense strand includes an imann residue and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the dsRNA agent has two blunt

ends. In certain embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In certain embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

In some embodiments, at least one linkage of the sense strand and/or the antisense strand is a phosphodiester (PO) linkage. In some embodiments, at least one linkage of the sense strand and/or the antisense strand is a modified linkage. In some embodiments, at least one linkage of the sense strand and/or the antisense strand is a phosphorothioate (PS) linkage. In some embodiments, at least one phosphorothioate (PS) linkage is introduced at the 5'-end, 3'-end or both ends of the sense strand and/or the antisense strand. In some embodiments, 1, 2, 3, 4, 5, or 6 phosphorothioate (PS) linkages are introduced at the 5'-end, 3'-end or both ends of the sense strand and/or the antisense strand. In some embodiments, at least the terminal two modified or unmodified nucleotides at one end or both ends of the antisense strand are linked through phosphorothioate linkages. In some embodiments, the terminal three modified or unmodified nucleotides at one end or both ends of the antisense strand are linked through phosphorothioate linkages. In some embodiments, at least the terminal two modified or unmodified nucleotides at one end or both ends of the sense strand are linked through phosphorothioate linkages. In some embodiments, the terminal three modified or unmodified nucleotides at one end or both ends of the sense strand are linked through phosphorothioate linkages. In some embodiments, the terminal three modified or unmodified nucleotides at 5' end of the sense strand are linked through phosphorothioate linkages and the terminal two modified or unmodified nucleotides at 3' end of the sense strand are linked through phosphorothioate linkages. In some embodiments, the sense strand comprises phosphorothioate linkages between the targeting group and the inverted abasic residue or the imann residue, and between the inverted abasic residue or the imann residue and the terminal modified or unmodified nucleotide at 5' end of the sense strand. In some embodiments, the sense strand comprises phosphorothioate linkage between the targeting group and the terminal modified or unmodified nucleotide at 5' end of the sense strand, and between the inverted abasic residue and the terminal modified or unmodified nucleotide at 3' end of the sense strand.

In some embodiments, any one of the sense strands in Table 1 may further be modified in a pattern shown in aforesaid Formula (I) or (III). In some embodiments, any one of the antisense strands in Table 1 may further be modified in a pattern shown in aforesaid Formula (II) or (III). In some embodiments, any one of the duplexes in Table 1 may further be modified in a pattern shown in aforesaid Formula (III). In some embodiments, the modified sense strand has a modification pattern set forth in any one of Tables 2-3. In some embodiments, the modified antisense strand has a modification pattern set forth in any one of Tables 2-3.

According to an aspect of the invention, a composition is provided that includes any embodiment of the aforementioned dsRNA agent aspect of the invention. In certain embodiments, the composition also includes a pharmaceutically acceptable carrier. In some

embodiments, the composition also includes one or more additional therapeutic agents. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In some embodiments, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

5 According to another aspect of the invention a cell is provided that includes any embodiment of an aforementioned dsRNA agent aspect of the invention. In some embodiments, the cell is a mammalian cell, optionally a human cell.

 According to another aspect of the invention, a method of inhibiting the expression of an HMGR gene in a cell, is provided, the method including: (i) preparing a cell including an
10 effective amount of any embodiment of the aforementioned dsRNA agent aspect of the invention or any embodiment of an aforementioned composition of the invention. In certain embodiments, the method also includes: (ii) maintaining the prepared cell for a time sufficient to obtain degradation of the mRNA transcript of an HMGR gene, thereby inhibiting
15 expression of the HMGR gene in the cell. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject by IV administration. In certain embodiments, the method also includes assessing inhibition of the HMGR gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of an HMGR-
20 associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGR-associated disease or condition and/or to a control physiological characteristic of the HMGR-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HMGR gene in the subject. In some embodiments,
25 the physiological characteristic is one or more of: the HMGR mRNA level and the HMGR protein level. A reduction in the expression of HMGR may also be assessed indirectly by measuring a decrease in biological activity of HMGR, e.g., a decrease in one or more of: cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), free fatty acid level and lipid level in blood or serum, level of 3-hydroxy-3-methylglutaryl-CoA reductase expression in the cytoplasm. And the expression of an
30 HMGR may also be assessed indirectly based on other variables associated with HMGR gene expression, e.g. nuclear localization of 3-hydroxy-3-methylglutaryl-CoA reductase, or
35 expression of certain target genes such as Jun, c-Myc and CyclinD-1 or other oncogenes under transcription control of 3-hydroxy-3-methylglutaryl-CoA reductase.

 According to another aspect of the invention, a method of inhibiting expression of an HMGR gene in a subject, is provided, the method including administering to the subject an effective amount of an embodiment of the aforementioned dsRNA agent aspect of the

invention or an embodiment of an aforementioned composition of the invention. In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the method also includes: assessing inhibition of the HMGCR gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of an HMGCR-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition and/or to a control physiological characteristic of the HMGCR-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HMGCR gene in the subject. In some embodiments, expression of the HMGCR gene can be assessed based on the level or change in level of any variable associated with HMGCR gene expression, such as the HMGCR mRNA level and the HMGCR protein level. A reduction in the expression of HMGCR may also be assessed indirectly by measuring a decrease in biological activity of HMGCR, e.g., a decrease in one or more of: cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), free fatty acid and lipid level in blood or serum. The expression of an HMGCR may also be assessed indirectly based on other variables associated with HMGCR gene expression, e.g., level of 3-hydroxy-3-methylglutaryl-CoA reductase expression in the cytoplasm, nuclear localization of 3-hydroxy-3-methylglutaryl-CoA reductase, or expression of certain target genes such as Jun, c-Myc and CyclinD-1 or other oncogenes under transcription control of 3-hydroxy-3-methylglutaryl-CoA reductase.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of HMGCR protein is provided, the method including: administering to a subject an effective amount of an embodiment of any aforementioned dsRNA agent aspect of the invention or an embodiment of any aforementioned composition of the invention, to inhibit HMGCR gene expression. In some embodiments, the disease, disorder or condition associated with HMGCR is selected from the group consisting of: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, congestive heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1), polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other disorders of lipid metabolism related to HMGCR.

In some embodiments, the method also includes: administering an additional therapeutic regimen to the subject. In some embodiments, the additional therapeutic regimen includes a treatment for the HMGCR-associated disease or condition. In certain embodiments, the additional therapeutic regimen comprises: administering to the subject one or more

5 HMGCR antisense polynucleotides of the invention, administering to the subject a non-HMGCR dsRNA therapeutic agent, and a behavioral modification in the subject. In some embodiments, the non-HMGCR dsRNA therapeutic agent is one or more of: an HMG-CoA reductase inhibitor (e.g., a statin), a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist (e.g., losartan

10 potassium, such as Merck & Co. 's Cozaar®), an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene -based therapy, a composite vascular protectant (e.g., AGT 1067, from

15 Atherogenics), a glycoprotein IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor (e.g., S-8921, from Shionogi), a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor, or a combination of any of the foregoing, wherein HMG-CoA reductase inhibitors include, but are not limited to, atorvastatin (Pfizer's Lipitor®/Tahor/Sortis/Torvast/Cardyl), pravastatin (Bristol-Myers Squibb 's Pravachol,

20 Sankyo's Mevalotin/Sanapprav), simvastatin (Merck's Zocor®/Sinvacor, Boehringer Ingelheim's Denan, Banyu's Lipovas), lovastatin (Merck's Mevacor/Mevinacor, Bexal's Lovastatina, Cepa; Schwarz Pharma's Liposcler), fluvastatin (Novartis' Lescol®/Locol/Lochol, Fujisawa's Cranoc, Solvay's Digaril), cerivastatin (Bayer's Lipobay/GlaxoSmithKline's Baycol), rosuvastatin (AstraZeneca's Crestor®), and pitivastatin (itavastatin/risivastatin) (Nissan Chemical, Kowa

25 Kogyo, Sankyo, and Novartis), wherein fibrates include, but are not limited to, bezafibrate (e.g., Roche's Befizal®/Cedur®/Bezalip®, Kissei's Bezatol), clofibrate (e.g., Wyeth's Atromid-S®), fenofibrate (e.g., Founder's Lipidil/Lipantil, Abbott's Tricor®, Takeda's Lipantil, generics), gemfibrozil (e.g., Pfizer's Lopid/Lipur) and ciprofibrate (Sanofi-Synthelabo's Modalim®), wherein bile acid sequestrants include, but are not limited to, cholestyramine

30 (Bristol-Myers Squibb's Questran® and Questran Light™), colestipol (e.g., Pharmacia's Colestid), and colesvelam (Genzyme/Sankyo's WelChol™), wherein niacin therapies include, but are not limited to, immediate release formulations, such as Aventis' Nicobid, Upsher-Smith's Niacor, Aventis' Nicolar, and Sanwakagaku's Perycit, wherein Niacin extended release formulations include, e.g., Kos Pharmaceuticals' Niaspan and Upsher-Smith's SIO- Niacin,

35 wherein antiplatelet agents include, but are not limited to, aspirin (e.g., Bayer's aspirin), clopidogrel (Sanofi-Synthelabo/Bristol-Myers Squibb's Plavix), and ticlopidine (e.g., Sanofi-Synthelabo's Ticlid and Daiichi's Panaldine), wherein aspirin-like compounds include, but are not limited to, Asacard (slow-release aspirin, by Pharmacia) and Pamicrogel (Kanebo/Angelini Ricerche/CEPA), wherein angiotensin-converting enzyme inhibitors

include, but are not limited to, ramipril (e.g., Aventis' Altace) and enalapril (e.g., Merck & Co.'s Vasotec), wherein acyl CoA cholesterol acetyltransferase (ACAT) inhibitors include, but are not limited to, avasimibe (Pfizer), eflucimibe (BioMérieux Pierre Fabre/Eli Lilly), CS-505 (Sankyo and Kyoto), and SMP-797 (Sumito), wherein cholesterol absorption inhibitors

5 include, but are not limited to, ezetimibe (Merck/Schering-Plough Pharmaceuticals Zetia®) and Pamaqueside (Pfizer), wherein CETP inhibitors include, but are not limited to, Torcetrapib (also called CP-529414, Pfizer), JTT-705 (Japan Tobacco), and CETi-I (Avant Immunotherapeutics), wherein microsomal triglyceride transfer protein (MTTP) inhibitors

10 include, but are not limited to, implitapide (Bayer), R-103757 (Janssen), and CP-346086 (Pfizer), wherein cholesterol modulators include, but are not limited to, NO-1886 (Otsuka/TAP Pharmaceutical), CT 1027 (Pfizer), and WAY-135433 (Wyeth-Ayerst), wherein bile acid modulators include, but are not limited to, HBS-107 (Hisamitsu/Banyu), Btg-511 (British Technology Group), BARI-1453 (Aventis), S-8921 (Shionogi), SD-5613 (Pfizer), and AZD-7806 (AstraZeneca), wherein peroxisome proliferation activated receptor (PPAR) agonists

15 include, but are not limited to, tesaglitazar (AZ-242) (AstraZeneca), Netoglitazone (MCC-555) (Mitsubishi/Johnson & Johnson), GW-409544 (Ligand Pharmaceuticals/GlaxoSmithKline), GW-501516 (Ligand Pharmaceuticals/GlaxoSmithKline), LY-929 (Ligand Pharmaceuticals and Eli Lilly), LY-465608 (Ligand Pharmaceuticals and Eli Lilly), LY-518674 (Ligand Pharmaceuticals and Eli Lilly), and MK-767 (Merck and Kyorin),

20 wherein gene-based therapies include, but are not limited to, AdGWEGF 121.10 (GenVec), ApoA1 (UCB Pharma/Groupe Fournier), EG-004 (Trinam) (Ark Therapeutics), and ATP-binding cassette transporter-1 (ABCA1) (CV Therapeutics/Incyte, Aventis, Xenon), wherein Glycoprotein IIb/IIIa inhibitors include, but are not limited to, roxifiban (also called DMP754, Bristol-Myers Squibb), Gantofiban (Merck KGaA/Yamanouchi), and Cromafiban (Millennium Pharmaceuticals), wherein squalene synthase inhibitors include, but are not limited to, BMS-1884941 (Bristol-Myers Squibb), CP-210172 (Pfizer), CP-295697 (Pfizer), CP-294838 (Pfizer), and TAK-475 (Takeda), wherein MCP-I inhibitor include, but are not limited to, RS-504393 (Roche Bioscience), wherein anti-atherosclerotic agent include, but are not limited to, BO-653 (Chugai Pharmaceuticals), wherein the nicotinic acid derivative include, but are not

30 limited to, Nyclin (Yamanouchi Pharmaceuticals). Exemplary combination therapies suitable for administration with a dsRNA targeting HMGCR include, but are not limited to, advicor (Niacin/lovastatin from Kos Pharmaceuticals), amlodipine/atorvastatin (Pfizer), and ezetimibe/simvastatin (e.g., Vytorin® 10/10, 10/20, 10/40, and 10/80 tablets by Merck/Schering-Plough Pharmaceuticals). In some embodiments, the dsRNA agent is

35 administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the method also includes determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject. In some embodiments, a means of determining an efficacy of the treatment in the subject comprises: (i) determining one or more physiological characteristics of

the HMGCR-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded
5 ribonucleic acid (dsRNA) agent to the subject. In some embodiments, expression of the HMGCR gene can be assessed based on the level or change in level of any variable associated with HMGCR gene expression, such as HMGCR mRNA level, HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C),
10 low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.

According to another aspect of the invention, a method of decreasing a level of HMGCR protein in a subject compared to a baseline pre-treatment level of HMGCR protein in the subject, is provided, the method including administering to the subject an effective amount
15 of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to decrease the level of HMGCR gene expression. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

According to another aspect of the invention, a method of altering a physiological
20 characteristic of an HMGCR-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to alter the physiological
25 characteristic of the HMGCR-associated disease or condition in the subject. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration. In certain embodiments, the physiological characteristic is one or more of: HMGCR mRNA level, HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density
30 lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), free fatty acid level and lipid level in blood or serum.

According to another aspect of the invention, the aforementioned dsRNA agent for use in a method of treating a disease or condition associated with the presence of HMGCR protein
35 is provided. In some embodiments, the disease or condition is one or more of: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, congestive heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1),

polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other disorders of lipid metabolism related to HMGCR.

5 According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of HMGCR protein is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1. In
10 some embodiments, the equivalent region is any one of the target regions of SEQ ID NO: 1 and the complementary sequence is one provided in one of Tables 1-3. In certain embodiments, the antisense polynucleotide agent includes one of the antisense sequences provided in one of Tables 1-3.

 According to another aspect of the invention, a composition including an embodiment
15 of any aforementioned antisense polynucleotide agents is provided. In some embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents for treatment of an HMGCR-associated disease or condition. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In certain embodiments, the
20 composition is formulated for subcutaneous or IV administration.

 According to another aspect of the invention a cell that includes an embodiment of any of the aforementioned antisense polynucleotide agents is provided. In some embodiments, the cell is a mammalian cell, optionally a human cell.

 According to another aspect of the invention, a method of inhibiting the expression of
25 an HMGCR gene in a cell is provided, the method including: (i) preparing a cell including an effective amount of an embodiment of any aforementioned antisense polynucleotide agents. In some embodiments, the method also includes (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of an HMGCR gene, thereby inhibiting expression of the HMGCR gene in the cell.

30 According to another aspect of the invention, a method of inhibiting expression of an HMGCR gene in a subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agent.

 According to another aspect of the invention, a method of treating a disease or
35 condition associated with the presence of HMGCR protein, the method including administering to a subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to inhibit HMGCR gene expression. In certain embodiments, the disease or condition is one or more of: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia,

mixed hyperlipidemia, congestive heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1), polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other disorders of lipid metabolism related to HMGCR.

According to another aspect of the invention, a method of decreasing a level of HMGCR protein in a subject compared to a baseline pre-treatment level of HMGCR protein in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to decrease the level of HMGCR gene expression. In certain embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of HMGCR gene, is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% or about 85% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1.

According to another aspect of the invention, a method of altering a physiological characteristic of an HMGCR-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to alter the physiological characteristic of the HMGCR disease or condition in the subject. In some embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration. In some embodiments, the physiological characteristic is one or more of: HMGCR mRNA level, HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.

Brief Description of the Sequences

SEQ ID NO: 1 and SEQ ID NO: 2 (reverse complement) are Homo sapiens 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) mRNA [NCBI Reference Sequence: NM_000859.3].

SEQ ID NO: 3 and SEQ ID NO: 4 (reverse complement) are Predicted *Macaca fascicularis* 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) mRNA [NCBI Reference Sequence: XM_005557177.3].

- 5 SEQ ID NO: 5 and SEQ ID NO: 6 (reverse complement) are *Macaca mulatta* 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) mRNA [NCBI Reference Sequence: XM_001104607.4].

10 SEQ ID NOs: 7-876, 3157-3164, 3181-3388 are shown in Table 1 and are sense strand sequences.

SEQ ID NOs: 877-1746, 3165-3172, 3389-3596 are shown in Table 1 and are antisense strand sequences.

- 15 SEQ ID NOs: 1747-2616, 2723-3024, 3173-3180 are shown in Table 2 with chemical modifications, it can be understood by person skilled in the art that "*" is a symbol for indication of linkage relationship, wherein the presence of "*" means that monomers are mutually linked via a phosphorothioate diester linkage, wherein the absence of "*" between two monomers indicates that the monomers are mutually linked via a phosphodiester linkage.

- 20 SEQ ID NOs: 2617-2722, 3025-3156 are shown in Table 3. A delivery molecule is indicated as "GLX-__" at the 3' end or 5' end of each sense strand, it can be understood by person skilled in the art that "*" is a symbol for indication of linkage relationship, wherein the presence of "*" means that monomers are mutually linked via a phosphorothioate diester linkage, wherein the absence of "*" between two monomers indicates that the monomers are mutually linked via a phosphodiester linkage.
- 25

Detailed Description

- 30 The invention in part, includes RNAi agents, for example, though not limited to double stranded (ds) RNAi agents, which are capable of inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) gene expression. The invention, in part also includes compositions comprising HMGCR RNAi agents and methods of use of the compositions. HMGCR RNAi agents disclosed herein may be attached to delivery compounds for delivery to cells, including to hepatocytes. Pharmaceutical compositions of the invention may include at least one dsRNA
- 35 HMGCR agent and a delivery compound. In some embodiments of compositions and methods of the invention, the delivery compound is a GalNAc-containing delivery compound. HMGCR RNAi agents delivered to cells are capable of inhibiting HMGCR gene expression, thereby reducing activity in the cell of the HMGCR protein product of the gene. DsRNAi agents of the invention can be used to treat HMGCR-associated diseases and conditions.

In some embodiments of the invention reducing HMGCR expression in a cell or subject treats a disease or condition associated with HMGCR expression in the cell or subject, respectively. Non-limiting examples of diseases and conditions that may be treated by reducing HMGCR activity are: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, congestive heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1), polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other diseases for which reducing a level and activity of HMGCR protein is medically beneficial.

As used herein, "G," "C," "A" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, and uracil as a base, respectively. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person understands that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

As used herein, "3-hydroxy-3-methylglutaryl-CoA reductase" used interchangeably with the term "HMGCR" refers to the naturally occurring gene that encodes a 3-hydroxy-3-methylglutaryl-CoA reductase protein from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise. The term also refers to fragments and variants of native HMGCR that maintain at least one in vivo or in vitro activity of a native HMGCR. The amino acid and complete coding sequences of the reference sequence of the human HMGCR gene may be found in, for example, GenBank Ref Seq Accession No. NM_000859.3 (SEQ ID NO: 1 and SEQ ID NO:2). Mammalian orthologs of the human HMGCR gene may be found in, for example, GenBank Ref Seq Accession No. XM_005557177.3, Cynomolgus monkey (SEQ ID NO:3 and SEQ ID NO:4), GenBank Ref Seq Accession No. XM_001104607.4, Rhesus monkey (SEQ ID NO:5 and SEQ ID NO:6). Additional examples of HMGCR mRNA sequences are readily available using publicly available databases, e.g., GenBank, UniProt, Ensembl and OMIM.

The following describes how to make and use compositions comprising HMGCR single-stranded (ssRNA) and dsRNA agents to inhibit HMGCR gene expression, as well as

compositions and methods for treating diseases and conditions caused by or modulated by HMGCRC gene expression. The term “RNAi” is also known in the art, and may be referred to as “siRNA”.

As used herein, the term “RNAi” refers to an agent that comprises RNA and mediates targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. As is known in the art, an RNAi target region, which is also defined as “target region” or “target portion”, refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, including messenger RNA (mRNA) that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion. A target sequence may be from 8-30 nucleotides long (inclusive), from 10 - 30 nucleotides long (inclusive), from 12 - 25 nucleotides long (inclusive), from 15 - 23 nucleotides long (inclusive), from 16 -23 nucleotides long (inclusive), or from 18 – 23 nucleotides long (inclusive), including all shorter lengths within each stated range. In some embodiments of the invention, a target sequence is 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides long. In certain embodiment a target sequence is between 9 and 26 nucleotides long (inclusive), including all sub-ranges and integers there between. For example, though not intended to be limiting, in certain embodiments of the invention a target sequence is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides long, with the sequence fully or at least substantially complementary to at least part of an RNA transcript of an HMGCRC gene. Some aspects of the invention include pharmaceutical compositions comprising one or more HMGCRC dsRNA agents and a pharmaceutically acceptable carrier. In certain embodiments of the invention, an HMGCRC RNAi as described herein inhibits expression of HMGCRC protein.

As used herein, a “dsRNA agent” means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. Although not wishing to be limited to a particular theory, dsRNA agents of the invention may operate through the RNA interference mechanism (i.e., inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). Methods for silencing genes in plant, invertebrate, and vertebrate cells are well known in the art [see, for example, (Sharp et al., *Genes Dev.* 2001, 15:485; Bernstein, et al., (2001) *Nature* 409:363; Nykanen, et al., (2001) *Cell* 107:309; and Elbashir, et al., (2001) *Genes Dev.* 15:188)], the disclosure of each of which is incorporated herein by reference in its entirety.]. Art-known gene silencing procedures can be used in conjunction with the disclosure provided herein to inhibit expression of HMGCRC.

DsRNA agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: short interfering RNAs (siRNAs), RNAi agents,

micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the dsRNA agents described herein is at least partially complementary to the mRNA being targeted. It is understood in the art that different lengths of dsRNA duplex structure can be used to inhibit target gene expression. For example, dsRNAs having a duplex structure of 19, 20, 21, 22, and 23 base pairs are known to be effective to induce RNA interference (Elbashir et al., EMBO 2001, 20:6877-6888). It is also known in the art that shorter or longer RNA duplex structures are also effective to induce RNA interference. It is also known in the art that shorter or longer RNA duplex structures are also effective to induce RNA interference. As used herein, the terms “double stranded region”, “duplex region” and “the region of complementarity” can be used interchangeably, and refer to the region that the sense strand is complementary or substantially complementary to the antisense strand as is known in the art. In some embodiments, the sense strand and the antisense strand may be the same length or different lengths. In some embodiments, each strand is no more than 40 nucleotides in length. In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, each strand is no more than 25 nucleotides in length. In some embodiments, each strand is no more than 23 nucleotides in length. In some embodiments, each strand is no more than 21 nucleotides in length. In some embodiments, the sense and antisense strands of the RNAi agents can each be 15 to 49 nucleotides in length. In some embodiments, the antisense strand is independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the length of the sense strand is independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49 nucleotides. In some embodiments, the sense strand and the antisense strand are both 21 nucleotides in length. In some embodiments, the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 15 and 23 nucleotides in length. In some embodiments, the region of complementarity is 19-21 nucleotides in length. In some embodiments, the region of complementarity is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. HMGCRC dsRNAs in certain embodiments of the invention can include at least one strand of a length of minimally 21 nt or may have shorter duplexes based on one of the sequences set forth in any one of Tables 1-3, but minus 1, 2, 3, or 4 nucleotides on one or both ends may also be effective as compared to the dsRNAs set forth in Tables 1-3, respectively. In some embodiments of the invention, HMGCRC dsRNA agents may have a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one or more sequences of Tables 1-3, and differ in their ability to inhibit the expression of an HMGCRC gene by not more than 5%, 10%, 15%, 20%, 25%, or 30% from the level of inhibition resulting from a dsRNA comprising the full sequence. A sense sequence, an antisense sequence and a duplex disclosed in Tables 1-3 may be referred to herein as a “parent” sequence, meaning that the sequences disclosed in Tables 1-3 may be modified, shorten, lengthened, include substitutions, etc. as set forth herein, with the resulting sequences retaining

all or at least a portion of the efficacy of their parent sequences in methods and compositions of the invention. Sense and antisense strands included in a dsRNA of the invention are independently selected. As used herein the term “independently selected” means each of two or more like elements can be selected independent of the selection of the other elements. For example, though not intended to be limiting, in preparing a dsRNA of the invention, one may select the “elements” of the two strands to include in the duplex. One selected element, the sense sequence may be SEQ ID NO: 1747 (shown in Table 2) and the other selected element, the antisense sequence, may be SEQ ID NO: 2182, or may be SEQ ID NO: 2182 that is modified, shortened, lengthened, and/or includes 1, 2, or 3 substitutions as compared to its parent sequence SEQ ID NO: 2182. It will be understood that a duplex of the invention need not include both sense and antisense sequences shown as paired in duplexes in Tables 1-3. Each sense and antisense strand sequence in the tables is immediately followed by its SEQ ID NO.

Certain embodiments of compositions and methods of the invention comprise a single-strand RNA in a composition and/or administered to a subject. For example, an antisense strand such as one listed in any one of Tables 1-3 may be a composition or in a composition administered to a subject to reduce HMGCGR polypeptide activity and/or expression of HMGCGR gene in the subject. Tables 1 shows certain HMGCGR dsRNA agent antisense strand and sense strand core stretch base sequences. A single-strand antisense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand antisense agent” or an “antisense polynucleotide agent”. A single-strand sense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand sense agent” or a “sense polynucleotide agent”. The term “base sequence” is used herein in reference to a polynucleotide sequence without chemical modifications or delivery compounds. For example, the sense strand GUUGUCAAGACUUUUUCGAAA (SEQ ID NO: 7) shown in Table 1 is the base sequence for SEQ ID NO: 1747 in Table 2 and for SEQ ID NO: 2642 in Table 3, with SEQ ID NO: 1747 and SEQ ID NO: 2642 shown with their chemical modifications and a delivery compound. Sequences disclosed herein may be assigned identifiers. For example, a single-stranded sense sequence may be identified with a “Sense strand SS#”; a single stranded antisense sequence may be identified with an “Antisense strand AS#” and a duplex that includes a sense strand and an antisense strand may be identified with a “Duplex AD#/AV#”.

Table 1 includes sense and antisense strands and provides the identification number of duplexes formed from the sense and antisense strand on the same line in Table 1. In certain embodiments of the invention an antisense sequence includes nucleobase u or nucleobase a in position 1 of the antisense sequence. In certain embodiments of the invention an antisense sequence includes nucleobase u in position 1 of the antisense sequence. As used herein, the term “matching position” in a sense and an antisense strand are the positions in each strand that

“pair” when the two strands are duplexed strands. For example, in a 21 nucleobases sense strand and a 21 nucleobases antisense strand, nucleobase in position 1 of the sense strand and position 21 in the antisense strand are in “matching positions”. In yet another non-limiting example in a 23 nucleobases sense strand and a 23 nucleobases antisense strand, nucleobase 2 of the sense strand and position 22 of the antisense strand are in matching positions. In another non-limiting example, in an 18 nucleobases sense strand and an 18 nucleobases antisense strand, nucleobase in position 1 of the sense strand and nucleobase 18 in the antisense strand are in matching positions, and nucleobase 4 in the sense strand and nucleobase 15 in the antisense strand are in matching positions. A skilled artisan will understand how to identify matching positions in sense and antisense strands that are or will be duplexed strands and paired strands.

The first column in Table 1 indicates a Duplex AD# for a duplex that includes the sense and antisense sequences in the same table row. For example, Table 1 discloses the duplex assigned Duplex AD# AD00810.um, which includes sense strand SEQ ID NO: 7 and antisense strand SEQ ID NO: 877. Thus, each row in Table 1 identifies a duplex of the invention, each comprising the sense and antisense sequences shown in the same row, with the assigned identifier for each duplex shown in the first column in the row.

In some embodiments of methods of the invention, an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is administered to a subject.

In some embodiments of the invention an RNAi agent administered to a subject comprises a duplex comprising at least one of the base sequences set forth in Table 1, including 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 sequence modifications. In some embodiments of methods of the invention an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is attached to a delivery molecule, a non-limiting example of which is a delivery compound comprising a GalNAc compound, or a GLS-1 5* compound.

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Table 1: Unmodified HMGCR RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3' direction. Duplex AD#s are the number assigned to the duplex of the two strands in the same row in the table.

Duplex AD#	Sense strand	SEQ ID NO.	Antisense strand	SEQ ID NO.	Range in HMGCR mRNA NM 000859.3
AD00810.um	GUUGUCAAGACUUUUUCGAAA	7	UUUCGAAAAAGUCUUGACAAAC	877	107-127
AD00811.um	UGUCAAGACUUUUUCGAAUGA	8	UCAUUCGAAAAAGUCUUUGACA	878	109-129
AD00812.um	CAUCUGCAUGAUGUCCAUGAA	9	UUC AUGGACAUCAUGCAGAUG	879	188-208
AD00813.um	GAUGUCCAUGAACAUUUUUA	10	UUAAACAUGUUCAUGGACAUC	880	197-217
AD00814.um	CCAUGAACAUUUUACUGGUA	11	UACCAGUAAACAUGUUUCAUGG	881	202-222
AD00815.um	CAUGAACAUUUUACUGGUAA	12	UUACCAGUAAACAUGUUUCAUG	882	203-223
AD00816.um	AUGAACAUUUUACUGGUAAA	13	UUUACCAGUAAACAUGUUUCAU	883	204-224
AD00817.um	AACAUUUUUACUGGUAAACAA	14	UUUGUUACCAGUAAACAUGUU	884	207-227
AD00818.um	UAAGAUUCUGUGGUUGGAAUUA	15	UAAUCCAAACCACAGAUUUUA	885	227-247
AD00819.um	AGAUUCUGUGGUUGGAAUUAUA	16	UAUAAUCCAAACCACAGAUUCU	886	229-249
AD00820.um	AGAUUCUGUGGUUGGAAUUAUA	17	UAUAAUCCAAACCACAGAUUCU	887	229-249
AD00821.um	AAUU AUGAAUGUCCAAAGUUA	18	UAAUUUUGGACAUUCAUAAUU	888	243-263
AD00822.um	AAAGUUUGAAGAGGAUGUUUA	19	UAAACAUCUUCUUCAAACUUU	889	257-277
AD00823.um	GUUUUGAGCAGUGACAUUAUA	20	UAUAAUGUCACUCUCUCAAAC	890	273-293
AD00824.um	CAGUGACAUUAUAAUUCUGAA	21	UUCAGAAUUUAUAAUGUCACUG	891	281-301
AD00825.um	GACAUUAUAAUUCUGACAAUA	22	UAUUGUCAGAAUUUAUAAUGUC	892	285-305
AD00826.um	AAUUCUGACAAUAAACACGAUA	23	UAUCGUGUUUAUUGUCAGAAUU	893	293-313
AD00827.um	CAUCCUGUAUUAUUACUCCCA	24	UGGAAGUAAAUUAUACAGGAUG	894	320-340
AD00828.um	CAGUCCAGAAUUUAACGUCAA	25	UUGACGUAAAUUCUGGAACUG	895	339-359
AD00829.um	AGUCCAGAAUUUAACGUCAAA	26	UUUGACGUAAAUUCUGGAACU	896	340-360
AD00830.um	GUUCCAGAAUUUAACGUCAAAC	27	UGUUGACGUAAAUUCUGGAAC	897	341-361
AD00831.um	UUUACGUCAAAUUGGAUCAAA	28	UUUGAUCCAAAGUUGACGUAAA	898	350-370
AD00832.um	UUACGUCAAAUUGGAUCAAAA	29	UUUUGAUCCAAAGUUGACGUAAA	899	351-371
AD00833.um	UUUGUAUUCAGUACAGUUUGUA	30	UACAAUGUACUGAAUACAAA	900	414-434

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AD00834.um	AUUCAGUACAGUUGUCAUUA	31	UGAAUGACAAACUGUACUGAAU	901	419-439
AD00835.um	UUCAGUACAGUUGUCAUUA	32	UUGAAUGACAAACUGUACUGAA	902	420-440
AD00836.um	UACAGUUGUCAUUCACUUA	33	UAGAAGUGAAUUGACAAACUGUA	903	425-445
AD00837.um	ACAGUUGUCAUUCACUUA	34	UAAGAAAGUGAAUUGACAAACUGU	904	426-446
AD00838.um	UUGUCAUUCACUUCUAGACA	35	UGUCUAAAGAAUGUAAUGACAA	905	430-450
AD00839.um	UGUCAUUCACUUCUAGACA	36	UUGUCUAAAGAAUGUAAUGACA	906	431-451
AD00840.um	UUCUUAGACAAAGAAUUGACA	37	UGUCAAUUCUUUGUCUAAAGAA	907	441-461
AD00841.um	GAAUGAAGCUUUGCCCUUA	38	UAAAAGGGCAAAAGCUUUAUUC	908	467-487
AD00842.um	UCAGUUCCAAACUCACAGUA	39	UAUCCUUGUGAGUUGGAAACUGA	909	538-558
AD00843.um	GAAAAUUAUUGCUGUGGAAUA	40	UAUCCACGAGCAAUAUUUUC	910	567-587
AD00844.um	UGCUCUGGAAUGGCAAUUA	41	UAAAUUGCCAUUCCACGAGCA	911	575-595
AD00845.um	CUCGAUGCUCUUGUUGAAUGA	42	UCAUUAACAAGAGCAUCGAG	912	612-632
AD00846.um	GAUGCUCUUGUUGAAUGUCA	43	UAGACAUUCAACAAGAGCAUC	913	615-635
AD00847.um	CUUGUUGAAUGUCUUGUGUA	44	UAUCACAAGACAUUCAACAAG	914	621-641
AD00848.um	GUUGAAUGUCUUGUGAUUGGA	45	UCCAUCACAAGACAUUCAAAC	915	624-644
AD00849.um	UCUUGUGAUUGGAGUUGGUAA	46	UUACCAACUCCAUCACAAGA	916	632-652
AD00850.um	UCAGCUUGAAAAUUAUGUCUA	47	UAGCACAUAAUUUCAAGCUGA	917	668-688
AD00851.um	UUUGGCGCAUGUCAGUUCUA	48	UAGAACUGACAUGCAGCCAAA	918	690-710
AD00852.um	ACUACUUCGUGUUCAGACUA	49	UAGUCAUGAAACGAAAGUAGU	919	715-735
AD00853.um	CUUCGUGUUCAGACUUCUA	50	UAGAAAGUCAUGAACACGAAAG	920	719-739
AD00854.um	UUGUGUCCUUGGUUAUUGA	51	UCUAAUACCAAGGACACACAA	921	746-766
AD00855.um	CUAGGCUUGGUUCUUGUUCAA	52	UUGAACAAAGAACCAAGCCUAG	922	888-908
AD00856.um	GAUCCUUCUCCUCAAACAGA	53	UCUGUUUUGAGGAGAAAGGAGC	923	930-950
AD00857.um	AAAACAGUACAGCAGAUACUA	54	UAGUAUCUGCUGUACUGUUUU	924	943-963
AD00858.um	AGUACAGCAGAUACUUCUAAA	55	UUUAGAAGUAUCUGCUGUACU	925	948-968
AD00859.um	ACAGCAGAUACUUCUAAAGGUA	56	UACCUUAGAAGUAUCUGCUGU	926	951-971
AD00860.um	CAGCAGAUACUUCUAAAGGUUA	57	UAACCUUAGAAGUAUCUGCUG	927	952-972
AD00861.um	GCAGAUACUUCUAAAGGUUUA	58	UGAAACCUUAGAAGUAUCUGC	928	954-974
AD00862.um	UUAGGACUGGAUGAAAAUGUA	59	UACAUUUUCAUCCAGUCCUAA	929	975-995
AD00863.um	AUCAGCAUGGAUAUUGAACAA	60	UUGUCAAUAUCCAUGCUGAU	930	1050-1070

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AD00864.um	GAACAAGUUAUUACCCUAAAGA	61	UCUUAGGGUAAUAAACUUGUUC	931	1065-1085
AD00865.um	AGUUAUUACCCUAAAGUUUAGA	62	UCUAAACUUAAGGGUAAUAAACU	932	1070-1090
AD00866.um	UUACCCUAAAGUUUAGCUCUCA	63	UGAGAGCUAAACUUAGGGUAA	933	1075-1095
AD00867.um	CAAGUACAUCUCUCUUUGAACA	64	UGUCAAAGAAGAUUGUACUUG	934	1106-1126
AD00868.um	CCUUAUCACUCCUUGUAGUA	65	UACUACAGGAGAUUGUAUAGG	935	1161-1181
AD00869.um	UAGAGGAAGAGACAGGGAUAA	66	UUAUCCUGUCUUCUCCUCUA	936	1258-1278
AD00870.um	UAAACCGAGAAAGAAAAGUUA	67	UAAUUUUUUUUUCUGGUUUA	937	1276-1296
AD00871.um	AAAGUUGAGGUUAUAAAACCA	68	UGGUUUUUAUAAACCUCAACUU	938	1290-1310
AD00872.um	CAGAGCUACAUUUGUGGUUGA	69	UCAACCAAAAUUGUAGCUCUG	939	1337-1357
AD00873.um	AGCUACAUUUGUGGUUGUAA	70	UUACCAACCACAAAUGUAGCU	940	1340-1360
AD00874.um	CUCUCCUUACUCGAUACUUA	71	UAAGUUCGAGUAAAGGAGGAG	941	1361-1381
AD00875.um	ACACAGGAACCCUGAAAUUGAA	72	UUCAAUUUCAGGUUCCUGUGU	942	1395-1415
AD00876.um	AAGGUGCAAAAUUCCUUAGUA	73	UACUAAAGGAAUUUUUGCACCU	943	1474-1494
AD00877.um	AGGUGCAAAAUUCCUUAGUGA	74	UCACUAAAGGAAUUUUUGCACCU	944	1475-1495
AD00878.um	CUUAGUGAUGCUGAGAUCAUA	75	UAUGAUCUCAGCAUCACUAAAG	945	1488-1508
AD00879.um	AGAUCAUCCAGUUAGUCAAUUA	76	UAUUGACUAAACUGGAUGAUCU	946	1501-1521
AD00880.um	GAUCAUCCAGUUAGUCAAUUGA	77	UCAUUGACUAAACUGGAUGAUC	947	1502-1522
AD00881.um	CAUCCAGUUAGUCAAUUGCUAA	78	UUAGCAUUGAGCUAAACUGGAUG	948	1505-1525
AD00882.um	CAGUUAAGUCAAUUGCUAAGCAA	79	UUGCUUAGCAUUGACUAAACUG	949	1509-1529
AD00883.um	UUAGUCAAUUGCUAAGCAUUA	80	UAUAUGCUUAGCAUUGACUAA	950	1512-1532
AD00884.um	AGCCUACAAGUUGGAAAACUCA	81	UGAGUUUCCAAACUUGUAGGCU	951	1535-1555
AD00885.um	GUUGGAAAACUCUGAUGGAAAA	82	UUUCCAUACAGAGUUUCCAAAC	952	1544-1564
AD00886.um	ACUC AUGAGCGUGGUGUAUCA	83	UGAUACACCCAGCUCUAGAGU	953	1563-1583
AD00887.um	UUUCAGAAACCUUCUUCUCUCA	84	UGAGAGAAAGAGGUUCUGAAA	954	1612-1632
AD00888.um	UACAGGGAUUAUAAUUAUACUCA	85	UGAGUAAUUUAUAAUCCUUGUA	955	1644-1664
AD00889.um	GCUUGAGACUCUGCAGAAAGUA	86	UACUUCUGCAGAGUCACAAAGC	956	1899-1919
AD00890.um	UUUGACAGCACUAGCAGAUUA	87	UAAUCUGCUAGUGCUGUCAAA	957	1968-1988
AD00891.um	AUUUGCACGUCUACAGAAACA	88	UGUUUCUGUAGACGUGCAAAU	958	1985-2005
AD00892.um	CAGAAACUUCUAUACAAGUAUA	89	UAUACUUGUAUGAAAGUUUCUG	959	1998-2018
AD00893.um	GGACGCAACCUUUUAUUAUCCGA	90	UCGGAUUAUAAAGGUUGCGUCC	960	2022-2042

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AD00894.um	UUUCCUUGAAAAUGCAGAUUCA	91	UGAAUCUGCAUUUCAGGGAAA	961	2126-2146
AD00895.um	UUAGUGGUAAACUAAUUGUACUA	92	UAGUACAAUAGUUACACUAA	962	2152-2172
AD00896.um	GGUAACUAUUGUACUGACAAA	93	UUUGUCAGUACAAUAGUUACC	963	2157-2177
AD00897.um	AAGAAACCUCGCGCUAUAAAA	94	UUUUUAGCAGCAGGUUUUCUU	964	2175-2195
AD00898.um	AUCUGUUGUUUGUAGGCUA	95	UAGCUUCACAAAACAACAGAUU	965	2215-2235
AD00899.um	UCUGUUGUUUGUAGGCGUA	96	UACAGCUUCACAAAACAACAGA	966	2217-2237
AD00900.um	UCAGAGAAGUAUUAAAAGACUA	97	UAGUCUUUAAUACUUCUCUGA	967	2254-2274
AD00901.um	UGAGGUCAAACAUUAAACAAGAA	98	UUCUUGUUAAUGUUGACCUCU	968	2291-2311
AD00902.um	CCCAUGCAGCAAAACAUUGUCA	99	UGACAAUGUUUUGCUUGCAUGG	969	2356-2376
AD00903.um	UUCAAGGAGCAUGCAAAAGUA	100	UAUCUUUGCAUGCUCCUUGAA	970	2572-2592
AD00904.um	CUGGGAAUUGUCACUUAUGA	101	UCAUAAUGAGACAAAUUCCCCAG	971	2647-2667
AD00905.um	AGGACAUUCUUGUCAAAAAGUCA	102	UGACUUUUUGACAAAGAUGUCCU	972	2681-2701
AD00906.um	CAGGUCGAAGAUCAAUUUACA	103	UGUAAAUUUGAUUUUCGACCUG	973	2714-2734
AD00907.um	UCGAAGAUCAAUUUACAAGAA	104	UUCUUGUAAAUUUGAUUUUCGA	974	2718-2738
AD00908.um	GGACUACAUAAAACUUGUGA	105	UCACAGAUUUUUUGUUAGUCC	975	2817-2837
AD00909.um	UCAGAGAGGUCUCAGGUUCUA	106	UAGAACUUGAGAGCCUCUCUGA	976	2917-2937
AD00910.um	GCUUUAUCAUGCUGUGUCUCUA	107	UAAGAGCACAGCAUGUAAAAGC	977	2974-2994
AD00911.um	AGAUGGUAAUUCUACAGCUCAA	108	UUGAGCUGUAGAUUACCAUCU	978	3035-3055
AD00912.um	UUUGAUGAAAUUUCUUGAAGUA	109	UACUUCAGAAAUUUCAUCAAA	979	3088-3108
AD00913.um	AUGGUGAUCAGUGCAAUUGAA	110	UUCAAUUGCACUCUGAUCACCAU	980	3110-3130
AD01321.um	GUAGCUACAAUGUUGUCAAGA	111	UCUUGACAAACAUUGUAGCUAC	981	96-116
AD01322.um	AAUGUUGUCAAGACUUUUUCA	112	UGAAAAAGUCUUUGACAAACAU	982	104-124
AD01323.um	AUGUUGUCAAGACUUUUUCGA	113	UCGAAAAAGUCUUUGACAAACAU	983	105-125
AD01324.um	UGUUGUCAAGACUUUUUCGAA	114	UUCGAAAAAGUCUUUGACAAAC	984	106-126
AD01325.um	UUGUCAAGACUUUUUCGAAUA	115	UAUUCGAAAAAGUCUUUGACAA	985	108-128
AD01326.um	AAGACUUUUUCGAAUGCAUGA	116	UCAUGCAUUCGAAAAAGUCUU	986	113-133
AD01327.um	CAUCCUGGGGAAGUCAUAGUA	117	UACUAUGACUUUCCAGGGGAUG	987	150-170
AD01328.um	CACUGACCAUCUGCAUGAUGA	118	UCAUCAUGCAGAUUGGU'CAGUG	988	181-201
AD01329.um	ACCAUCUGCAUGAUGUCCAUA	119	UAUGGACAUCAUGCAGAUUGGU	989	186-206
AD01330.um	AUCUGCAUGAUGUCCAUGAAA	120	UUUCAUGGACAUCAUGCAGAU	990	189-209

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AD01331.um	CUGCAUGAUGUCCAUGAACAA	121	UUGUUC AUGGACAUC AUGCAG	991	191-211
AD01332.um	GCAUGAUGUCCAUGAACAU GA	122	UCAUGUUC AUGGACAUC AUGC	992	193-213
AD01333.um	UGAUGUCCAUGAACAU GUUUA	123	UAAACAUGUUC AUGGACAUC A	993	196-216
AD01334.um	UGUCCAUGAACAU GUUUUACUA	124	UAGUAAACAUGUUC AUGGACA	994	199-219
AD01335.um	UGAACAU GUUUUACUGGUAA CA	125	UGUUACCAAGUAAACAUGUU CA	995	205-225
AD01336.um	GAACAUGUUUACUGGUAA CA	126	UUGUUACCAAGUAAACAUGUUC	996	206-226
AD01337.um	ACAUGUUUACUGGUAA CAAUA	127	UAUUGUUACCAAGUAAACAUGU	997	208-228
AD01338.um	AUGUUUACUGGUAA CAAUAAA	128	UUUAUUUGUUACCAAGUAAACA U	998	210-230
AD01339.um	UGUUUACUGGUAA CAAUAGA	129	UCUUAAUUGUUACCAAGUAAACA	999	211-231
AD01340.um	GUUUACUGGUAA CAAUAGAA	130	UUCUUAAUUGUUACCAAGUAAAC	1000	212-232
AD01341.um	UUACUGGUAA CAAUAGAUCA	131	UGAUCUUAAUUGUUACCAAGUAA	1001	214-234
AD01342.um	UGGUAACAAU AAGAUUCUGUGA	132	UCACAGAUCUUAAUUGUUACCA	1002	218-238
AD01343.um	AAUAAAGAUUCUGGUUGGAAA	133	UUTCCAACCAACAGAUUCUUAU U	1003	225-245
AD01344.um	AUAAGAUUCUGGUUGGAAUA	134	UAUCCAACCAACAGAUUCUUAU	1004	226-246
AD01345.um	AAGAUUCUGGUUGGAAUUA	135	UUAUUCCAACCAACAGAUUCU U	1005	228-248
AD01346.um	GAUCUGGUUGGAAUUAUGA	136	UCAUAAUCCAACCAACAGAUUC	1006	230-250
AD01347.um	UAUAUUUACUUC CAGUUCCAA	137	UUGGAACUGGAAAGUAAAUUAU A	1007	327-347
AD01348.um	AUUUACUUC CAGUUC CAGAAA	138	UUUCUGGAAACUGGAAAGUAAAU	1008	330-350
AD01349.um	ACUCCAGUUC CAGAAUUUA	139	UUAAAUUCUGGAAACUGGAAAGU	1009	334-354
AD01350.um	CUUCCAGUUC CAGAAUUUACA	140	UGUAAAUUCUGGAAACUGGAAAG	1010	335-355
AD01351.um	UCCAGUUC CAGAAUUUACGA	141	UCGUAAAUUCUGGAAACUGGAA	1011	336-356
AD01352.um	UCCAGUUC CAGAAUUUACGUA	142	UACGUAAAUUCUGGAAACUGGA	1012	337-357
AD01353.um	CCAGUUC CAGAAUUUACGUA	143	UGACGUAAAUUCUGGAAACUGG	1013	338-358
AD01354.um	UCCAGAAUUUACGUAACUA	144	UAGUUGACGUAAAUUCUGGAA	1014	342-362
AD01355.um	CCAGAAUUUACGUAACUUGA	145	UCAAGUUGACGUAAAUUCUGG	1015	344-364
AD01356.um	AGAAUUUACGUAACUUGGAA	146	UUCCAAGUUGACGUAAAUUCU	1016	346-366
AD01357.um	GAAUUUACGUAACUUGGAUA	147	UAUCCAAGUUGACGUAAAUUC	1017	347-367
AD01358.um	AAUUUACGUAACUUGGAUCA	148	UGAUCCAAGUUGACGUAAAUU	1018	348-368
AD01359.um	UACGUCAACUUGGAUCAA AAA	149	UUUUUGAUCCAAGUUGACGU A	1019	352-372
AD01360.um	ACGUCAACUUGGAUCAAAAUA	150	UAUUUUGAUCCAAGUUGACGU	1020	353-373

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AD01361.um	CGUCAACUUGGAUCAAUA	151	UUUUUUUAUCCAAUUUGACG	1021	354-374
AD01362.um	CUUUUCACAAUUUUCUCAA	152	UCUUGAGAAAAUUUGAAAA	1022	393-413
AD04242.um	GAGCUACAAUUGUUGCAAG	153	UUCUUGACAAACAUUGUAG	1023	97-117
AD04243.um	GACAAUGUUGUCAAGACUU	154	UAAAGUCUUGACAAACAUUG	1024	101-121
AD04244.um	GAAUGUUGUCAAGACUUUU	155	UAAAAAGUCUUGACAAACAU	1025	103-123
AD04245.um	CUCAAGACUUUUCGAAUG	156	UGCAUUCGAAAAAGUCUUG	1026	110-130
AD04246.um	GUUCGAAUGCAUGGCCUCU	157	UAAGAGGCCAUGCAUUCGAA	1027	120-140
AD04247.um	CACCAUCUGCAUGAUGUCCA	158	UUGGACAUCAUAGCAGAU	1028	185-205
AD04248.um	GACUGGUAACAAUAAGAU	159	UAGAUCUUUUAUGUUAACCA	1029	215-235
AD04249.um	GCUGGUAACAAUAAGAU	160	UCAGAUCUUUUAUGUUAACCA	1030	216-236
AD04250.um	GUGGUAACAAUAAGAU	161	UACAGAUCUUUUAUGUUAACCA	1031	217-237
AD04251.um	GAACAAUAAGAUUCUGUGG	162	UAACCAACAGAUUUUAUUGU	1032	221-241
AD04252.um	GACAAUAAGAUUCUGUGG	163	UCAACCAACAGAUUUUAUUG	1033	222-242
AD04253.um	GCAAAUAAGAUUCUGUGG	164	UCCAACCAACAGAUUUUAUUG	1034	223-243
AD04254.um	GAAUAAGAUUCUGUGG	165	UUCCAACCAACAGAUUUUAU	1035	224-244
AD04255.um	GGUGGUUGAAUUUAUGAA	166	UCAUUCAAUAAUCCAAACCA	1036	234-254
AD04256.um	GGGUUGAAUUUAUGAAUG	167	UGACAUUCAAUAAUCCAAAC	1037	236-256
AD04257.um	CGUUGGAAUUUAUGAAUG	168	UGGACAUUCAAUAAUCCAA	1038	237-257
AD04258.um	CUUGGAAUUUAUGAAUG	169	UUGGACAUUCAAUAAUCCAA	1039	238-258
AD04259.um	GGGAAUUUAUGAAUGUCCA	170	UUUUGGACAUUCAAUAAUCC	1040	240-260
AD04260.um	GUUAUGAAUGUCCAAAGU	171	UAAACUUUGGACAUUCAUAA	1041	244-264
AD04261.um	GAUGAAUGUCCAAAGUUUG	172	UUCAAAACUUUGGACAUUC	1042	246-266
AD04262.um	GUGAAUGUCCAAAGUUUG	173	UUUCAAAACUUUGGACAUUC	1043	247-267
AD04263.um	CAUUGUCCAAAGUUUGAAG	174	UUCUCAAACUUUGGACAUUG	1044	249-269
AD04264.um	CUCCAAGUUUGAAGAGGA	175	UAUCCUUCUCAAACUUUGG	1045	253-273
AD04265.um	GGAAGAGGAUGUUUUGAG	176	UUGUCAAAACAUUCCUUC	1046	263-283
AD04266.um	GAGAGGAUGUUUUGAGCA	177	UACUGCUCAAAACAUUCCU	1047	265-285
AD04267.um	CGAUGUUUUGAGCAGUGA	178	UUGUCACUGCUCAAAACAU	1048	269-289
AD04268.um	CAUGUUUUGAGCAGUGA	179	UAUGUCACUGCUCAAAACAU	1049	270-290
AD04269.um	GUGUUUUGAGCAGUGA	180	UAAUGUCACUGCUCAAAAC	1050	271-291

AD04270. um	GGUUUUGAGCAGUGACAUIUAA	181	UUAAUGUCACUGCUCAAAACC	1051	272-292
AD04271. um	GUUGAGCAGUGACAUIUA AAA	182	UUUAUAAUGUCACUCUAAC	1052	275-295
AD04272. um	CAGCAGUGACAUIUA AUUCA	183	UGAAUUAUAAUGUCACUGCUG	1053	278-298
AD04273. um	GGCAGUGACAUIUA AUUUCUA	184	UAGA UUAUAAUGUCACUGCC	1054	279-299
AD04274. um	CCAGUGACAUIUA AUUUCUGA	185	UCAGA UUAUAAUGUCACUGG	1055	280-300
AD04275. um	GGUGACAUIUA AUUUCUGACA	186	UGUCAGAAUUAUAAUGUCACC	1056	282-302
AD04276. um	CUGACAUIUA AUUUCUGACAA	187	UUUCAGAAUUAUAAUGUCAG	1057	283-303
AD04277. um	GGACAUIUA AUUUCUGACAAA	188	UUUGCAGAAUUAUAAUGUCC	1058	284-304
AD04278. um	GAUUAUAAUUCUGACAAUAAA	189	UUUAUUGUCAGAAUUAUUAUC	1059	287-307
AD04279. um	GUUCUGACAAUAACACGAUGA	190	UCAUCGUGUUAUUGUCAGAAC	1060	294-314
AD04280. um	GUUCGACAAUAACACGAUGCA	191	UGCAUCGUGUUAUUGUCAGAC	1061	295-315
AD04281. um	GCUGACAAUAACACGAUGCAA	192	UUGCAUCGUGUUAUUGUCAGC	1062	296-316
AD04282. um	GGACAAUAACACGAUGCAUAA	193	UU AUGCAUCGUGUUAUUGUCC	1063	298-318
AD04283. um	CACAAUAACACGAUGCAUAGA	194	UCUAUGCAUCGUGUUAUUGUG	1064	299-319
AD04284. um	GUGUAUAUUACUUC CAGUUA	195	UAA CUGGAAGUAAAUAUACAC	1065	324-344
AD04285. um	GGUAUAUUUA CUUCCAGUUA	196	UGAACUGGAAGUAAAUAUACC	1066	325-345
AD04286. um	CUAUAUUUA CUUCCAGUCCA	197	UGGAA CUGGAAGUAAAUAUAG	1067	326-346
AD04287. um	GUUA CUUCCAGUCCAGAAUA	198	UAUUCUGGAA CUGGAAGUAA C	1068	331-351
AD04288. um	GUACUUC CAGUUC CAGAAUUA	199	UAUUCUGGAA CUGGAAGUAA C	1069	332-352
AD04289. um	GAGAAUUA CUGUAACUUGGA	200	UGCAA GUUGACGUAAAUAUCUC	1070	345-365
AD04290. um	GUUUA CUGUAACUUGGAUCA	201	UUGAUCCAAGUUGACGUAAAAC	1071	349-369
AD04291. um	GCUUUUCACAAUUUUCUCAAA	202	UUUGAGAAAAUUUGUAAAAGC	1072	392-412
AD04292. um	CUUUUGUAUUCAGUACAGUUA	203	UAACUGUACUGAAUACAAAAG	1073	412-432
AD04293. um	GUUUUGUAUUCAGUACAGUUGA	204	UCAACUGUACUGAAUACAAAAC	1074	413-433
AD04294. um	GUGUAUUCAGUACAGUUGUCA	205	UGACAACUGUACUGAAUACAC	1075	415-435
AD04295. um	GGUAUUCAGUACAGUUGUCA	206	UUGACAACUGUACUGAAUACCC	1076	416-436
AD04296. um	GAUUCAGUACAGUUGUCAUUA	207	UAAUGACAACUGUACUGAAUUC	1077	418-438
AD04297. um	GAGUA CAGUUGUCAUUCACUA	208	UAGUGAAUGACAACUGUACUC	1078	422-442
AD04298. um	GGUA CAGUUGUCAUUCACUUA	209	UAAUGUAAUGACAACUGUACC	1079	423-443
AD04299. um	CUACAGUUGUCAUUCACUUA	210	UGAAGUAAUGACAACUGUAG	1080	424-444

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AD04300.um	GAGUUGUCAUUCACUUCUUA	211	UUAAGAAGUGAAUAGACAAUC	1081	427-447
AD04301.um	GGUUGUCAUUCACUUCUUAAGA	212	UCUAAGAAGUGAAUAGACAAACC	1082	428-448
AD04302.um	CUUGUCAUUCACUUCUUAAGAA	213	UUCUAAGAAGUGAAUAGACAAAG	1083	429-449
AD04303.um	CUCAUUCACUUCUUAAGACAAA	214	UUUGUCUAAAGAGUGAAUGAG	1084	432-452
AD04304.um	GCAUUCACUUCUUAAGACAAA	215	UUUUGUCUAAAGAGUGAAUGC	1085	433-453
AD04305.um	GAUUCACUUCUUAAGACAAAAGA	216	UCUUUGUCUAAAGAGUGAAUUC	1086	434-454
AD04306.um	GUUCACUUCUUAAGACAAAAGAA	217	UUCUUUGUCUAAAGAGUGAAC	1087	435-455
AD04307.um	GUCACUUCUUAAGACAAAAGAAA	218	UUUCUUUGUCUAAAGAGUGAC	1088	436-456
AD04308.um	GCACUUCUUAAGACAAAAGAAUA	219	UAUUCUUUGUCUAAAGAGUGC	1089	437-457
AD04309.um	GACUUCUUAAGACAAAAGAAUUA	220	UAUUCUUUGUCUAAAGAGUUC	1090	438-458
AD04310.um	GCUUCUUAAGACAAAAGAAUUGA	221	UCAUUCUUUGUCUAAAGAGC	1091	439-459
AD04311.um	GUUCUUAAGACAAAAGAAUUGAA	222	UUCAAUUCUUUGUCUAAAGAAC	1092	440-460
AD04312.um	GCUUAGACAAAAGAAUUGACAA	223	UUGUCAUUCUUUGUCUAAAGC	1093	442-462
AD04313.um	GAAGAAUUGACAGGCUUGAAA	224	UUUCAAGCCUGUCAAUUCUUC	1094	450-470
AD04314.um	GAGAAUUGACAGGCUUGAAUA	225	UAUUCAAGCCUGUCAAUUCUC	1095	451-471
AD04315.um	GGAAUUGACAGGCUUGAAUUGA	226	UCAUCAAAGCCUGUCAAUUCC	1096	452-472
AD04316.um	GAUUGACAGGCUUGAAUUGAAA	227	UUUCAUCAAAGCCUGUCAAUUC	1097	454-474
AD04317.um	GUUGACAGGCUUGAAUUGAAGA	228	UCUUCAUUCAAGCCUGUCAAC	1098	455-475
AD04318.um	CACAGGCUUGAAUUGAAGCUUA	229	UAAGCUUCAUUCAAGCCUGUG	1099	458-478
AD04319.um	GGGCUUGAAUUGAAGCUUUGCA	230	UGCAAAGCUUCAUUCAAGCCC	1100	461-481
AD04320.um	GUGAAGCUUUGCCCUUUUUCUA	231	UGAAAAAGGGCAAAAGCUUCAC	1101	469-489
AD04321.um	CCUUUGCCCUUUUUCUUCUA	232	UAGUAGGAAAAAGGGCAAAAGG	1102	474-494
AD04322.um	GUUUGCCCUUUUUCUUCUUA	233	UAAGUAGGAAAAAGGGCAAAAC	1103	475-495
AD04323.um	GGCAAAGUUGCCCUUCAGUUA	234	UAACUGAGGGCAAAACUUGCC	1104	524-544
AD04324.um	GAAGUUGCCCUUCAGUUCCAA	235	UUGGAACUGAGGGCAAAACUUC	1105	527-547
AD04325.um	GUGCCCUUCAGUUCCAACUCAA	236	UUGAGUUGGAAACUGAGGGCAC	1106	532-552
AD04326.um	GGUCCCAACUCACAGGAUGAA	237	UUCAUCCUGUGAGUUGGAACC	1107	540-560
AD04327.um	CUUCCAAACUCACAGGAUGAAA	238	UUUCAUCCUGUGAGUUGGAAG	1108	541-561
AD04328.um	GAACUCACAGGAUGAAGUAAA	239	UUUACUUCAUCCUGUGAGUUC	1109	545-565
AD04329.um	GAGGAUGAAGUAGGGAAAAA	240	UUUUUCCCUUACUUCAUCCUC	1110	552-572

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AD04330.um	CAUGAAGUAAGGGAAAAUAUA	241	UAUAUUUUUCCCUUACUUAUG	1111	555-575
AD04331.um	CAAGUAAAGGGAUUUAUUGCA	242	UGCAAUUUUUUCCCUUACUUAUG	1112	558-578
AD04332.um	CUAAGGGAAAAUAUUGCUCGA	243	UCGAGCAUAUUUUUCCCUUAG	1113	561-581
AD04333.um	GAAGGGAUUUAUUGCUCGUA	244	UACGAGCAUAUUUUUCCCUUC	1114	562-582
AD04334.um	CGGAAAAUAUUGCUGUGGAA	245	UUCACGAGCAUAUUUUUCCG	1115	565-585
AD04335.um	GAAUAUUGCUCGUGGAAUGA	246	UCAUCCACGAGCAUAUUUUC	1116	568-588
AD04336.um	GAUAUUGCUCGUGGAAUGGCA	247	UGCCAUUCCACGAGCAUAUUC	1117	570-590
AD04337.um	GUCGUGGAAUGGCAUUUUUA	248	UUAAAAUUUGCAUUCACGAC	1118	577-597
AD04338.um	GCGUGGAUUGGCAUUUUAGA	249	UCUAAAAUUUGCAUUCACGC	1119	578-598
AD04339.um	GGUGGAAUGGCAUUUUAGGA	250	UCCUAAAAUUUGCAUUCACC	1120	579-599
AD04340.um	CUGGAUUGGCAUUUUAGGUA	251	UACCUAAAAUUUGCAUUCAG	1121	580-600
AD04341.um	GGGAUUGGCAUUUUAGGUCA	252	UGACCUAAAAUUUGCAUUCCC	1122	581-601
AD04342.um	GUUACCCUCGAUGCUCUUGUA	253	UACAAGAGCAUCGAGGGUAAC	1123	606-626
AD04343.um	GUACCCUCGAUGCUCUUGUA	254	UAACAAGAGCAUCGAGGGUAC	1124	607-627
AD04344.um	GCUCGAUGCUCUUGUUGAAUA	255	UAUUCACAAAGAGCAUCGAGC	1125	611-631
AD04345.um	GGUAGCUCUUGUUGAAUUGUA	256	UGACAUUCAAACAAGAGCAUCC	1126	614-634
AD04346.um	GGCUCUUGUUGAAUUGUCUUGA	257	UCAAGACAUUUCAACAAGAGCC	1127	617-637
AD04347.um	CCUCUUGUUGAAUUGUCUUGUA	258	UACAAGACAUUUCAACAAGAGG	1128	618-638
AD04348.um	GGUUGAAUGUCUUGUGAUUGA	259	UCAAUCACAAGACAUAUCAACC	1129	623-643
AD04349.um	GUGAAUGUCUUGUGAUUGGAA	260	UUCCAAUCACAAGACAUAUCAC	1130	625-645
AD04350.um	GAUGUCUUGUGAUUGGAGUUA	261	UAACUCCAUAUCAACAAGACAUC	1131	628-648
AD04351.um	GUGUCUUGUGAUUGGAGUUGA	262	UCAACUCCAUAUCAACAAGACAC	1132	629-649
AD04352.um	CUGAUUGGAGUUGGUACCAUA	263	UAUGGUACCAACUCCAUAUCAG	1133	636-656
AD04353.um	GUUGGAGUUGGUACCAUGUA	264	UGACAUGGUACCAACUCCAAC	1134	639-659
AD04354.um	CGUACGUCAGCUUGAAAAUUA	265	UUAAUUUCAAAGCUGACGUACG	1135	662-682
AD04355.um	CUACGUCAGCUUGAAAAUUAUA	266	UAUAAUUUCAAAGCUGACGUAG	1136	663-683
AD04356.um	GACGUCAGCUUGAAAAUUAUGA	267	UCAUAAUUUCAAAGCUGACGUC	1137	664-684
AD04357.um	GUUGAAAAUUUUGUGCUGCUUA	268	UAAGCAGCACAUAAUUUCAAAC	1138	672-692
AD04358.um	GAAUUAUGUGCUGCUUUUGGCA	269	UGCCAAAGCAGCACAUAAUUC	1139	676-696
AD04359.um	GUGUGCUCUUGGCUGGCAUA	270	UAUGCAGCCAAAGCAGCACAC	1140	681-701

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AD04360.µm	GUUUGGCUCAUGUCAGUUA	271	UGAACUGACAU	689-709
AD04361.µm	GUGCAUGUCAGUUCUUGCCAA	272	UUGGCAAGAAACUGACAU	695-715
AD04362.µm	CCAUGUCAGUUCUUGCCAA	273	UGUUGGCAAGAAACUGACAU	697-717
AD04363.µm	GUGUCAGUUCUUGCCAA	274	UUAUUGGCAAGAAACUGACAU	699-719
AD04364.µm	GUUGCCAAACUACUUCGUGUA	275	UAAACAGAAAGUAGUUGGCAAC	708-728
AD04365.µm	CCCAACUACUUCGUGUUA	276	UAUGAACACGAAGUAGUUGG	711-731
AD04366.µm	GAGCUUGUGUGUCCUUGUA	277	UUAACCAAGGACACAAAGCUC	742-762
AD04367.µm	GCUUGUAUUAAGAGCUUUA	278	UAGAAAGCUCUAAUACCAAGC	754-774
AD04368.µm	GUUGCCGAGUUUAAGAA	279	UUCUUCUAAACUCGGGCAAC	816-836
AD04369.µm	CAGGUCAAAGAUUAUGUA	280	UACAUAAUCAUCUUGACCCUG	866-886
AD04370.µm	GGGUCAAAGAUUAUGUA	281	UGACAUAAUCAUCUUGACCCC	867-887
AD04371.µm	CUCAAGUAUUAUGUCUA	282	UAGAGACAUAAUCAUCUUGAG	870-890
AD04372.µm	CUCUCAAGCUUGGUUCUA	283	UCAAGAACCAAGCCUAGAGAG	884-904
AD04373.µm	GCUAGGCUUGGUUCUUGUA	284	UGAACAAAGAACCAAGCCUAGC	887-907
AD04374.µm	GUGGUUCUUGUUAUGUCUA	285	UUGAGCAUGAACAAAGAACCCAC	894-914
AD04375.µm	CCUGAUCCUUCUCCUCUAAAA	286	UUUUUGAGGAGAAAGGAUCAGG	927-947
AD04376.µm	GUUCUCCUCAAAACAGUACAA	287	UUGUACUGUUUUGAGGAGAAC	934-954
AD04377.µm	GCAAAACAGUACAGCAGUAA	288	UUUACUGCUGUACUGUUUUGC	941-961
AD04378.µm	GAAACAGUACAGCAGUACUUA	289	UAGUAUCUGCUGUACUGUUC	944-964
AD04379.µm	CUACAGCAGUAUCUUCUAGA	290	UCUUAGAAGUAUCUGCUGUAG	949-969
AD04380.µm	GUCAUUAAGGACUGGAGUAAAA	291	UUUUCAUCCAGUCCUAAUUGAC	971-991
AD04381.µm	GAUUAAGGACUGGAGUAAAAU	292	UAUUUUCAUCCAGUCCUAAUUC	973-993
AD04382.µm	GAAAUGAUCAGCAUGGAUAA	293	UUUACCAUGCUGUACUAAUUC	1043-1063
AD04383.µm	GAAAUGAUCAGCAUGGAUUA	294	UUAUCCUUGCUGUACUAAUUC	1044-1064
AD04384.µm	GAGCAUGGAUUAUUGAACAA	295	UCUUUUCUAAUUAUCCUAGCUC	1052-1072
AD04385.µm	GUGAACAAAGUUAUUUACCCUAA	296	UUAGGGUAAUAAACUUGUUCAC	1063-1083
AD04386.µm	GUUAACCCUAAAGUUUAGCUCUA	297	UAGAGCUAAACUUAAGGGUAAAC	1074-1094
AD04387.µm	GUCCUUCUGGCGUGUCAAGUA	298	UUACUUGACAGCCAGAAAGGAC	1092-1112
AD04388.µm	GCUCUGGCGUGUCAAGUACAA	299	UUUUAUCUUGACAGCCAGAAAGC	1094-1114
AD04389.µm	GGUCAAGUACUUCUUAUGA	300	UCAAAGAAGAUUAUCUUGACC	1103-1123

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AD04390.um	GAGUACAUCUUCUUUGAACAA	301	UUGUCAAAGAAAGUACUC	1171	1107-1127
AD04391.um	GUAAAAAACCUAUCACAUCA	302	UGAUGUAUAGGGUUUUUAC	1172	1152-1172
AD04392.um	GCUGUAGUGACACAAAAAGAA	303	UUUCUUUUGUGACACUACAGC	1173	1173-1193
AD04393.um	GGUAGUGACACAAAAAGAAAG	304	UCUUUCUUUUGUGACUACC	1174	1175-1195
AD04394.um	GAGUGACACAAAAAGAAAGUCA	305	UGACUUUCUUUUGUGACUC	1175	1177-1197
AD04395.um	GGUAGUGGUCAGAAAUAA	306	UUUAUUUCUGACCAGCAUAGC	1176	1221-1241
AD04396.um	CCUGGUCAGAAAUAAACCAGAA	307	UUCUGGUUAUUUCUGACCAGG	1177	1226-1246
AD04397.um	GUGGUCAGAAAUAAACCAGAA	308	UUUCUGGUUAUUUCUGACCAC	1178	1227-1247
AD04398.um	CACAGGGAUAAACCGAGAAAA	309	UUUCUCGGUUUAUCCCUGUG	1179	1268-1288
AD04399.um	CGGAUAAACCGAGAAAGAAAA	310	UUUCUUUCUCGGUUUAUCCG	1180	1272-1292
AD04400.um	GGAAAGAAAGUUGAGGUAA	311	UUAACCUCAACUUUCUUUCC	1181	1283-1303
AD04401.um	GGGUUAUAAAAACCUUAGUGA	312	UCACUAAGGGUUUAUAAACC	1182	1297-1317
AD04402.um	GCCUUAGUGGCUGAAACAGAA	313	UUCUGUUUCAGCCACUAAAGC	1183	1308-1328
AD04403.um	CCUACAUUUGUGGUUGGUA	314	UUUACCAACCACAAAUUAGG	1184	1341-1361
AD04404.um	GUCCUCCUUAUCUGAUACUUA	315	UAAGUAUCGAGUAAAGGAGC	1185	1361-1381
AD04405.um	GCACAGGAACCUGAAAUUGAA	316	UUCAAUUUCAGGUUCCUGUGC	1186	1395-1415
AD04406.um	GAGAGAAAGGUGCAAAAUUCA	317	UGAAUUUUGCACCUUUCUCUC	1187	1468-1488
AD04407.um	GAGGUGCAAAAUUCCUUAUGA	318	UACUAAAGGAUUUUUGCACCC	1188	1474-1494
AD04408.um	GGGUGCAAAAUUCCUUAUGA	319	UCACUAAAGGAUUUUUGCACCC	1189	1475-1495
AD04409.um	CGUGCAAAAUUCCUUAUGAA	320	UUCACUAAAGGAUUUUUGCACG	1190	1476-1496
AD04410.um	GGCAAAAUUCCUUAUGAUGA	321	UCAUCACUAAAGGAUUUUUGCC	1191	1478-1498
AD04411.um	GUUAGUGAUGCUGAGAUCAUA	322	UAUGAUCUCAGCAUCACUAAC	1192	1488-1508
AD04412.um	GGCUGAGAUCAUCCAGUUAGA	323	UCUAAACUGGAUGAUCUCAGCC	1193	1496-1516
AD04413.um	CAGAUCAUCCAGUUAGUCAAA	324	UUUGACUAAACUGGAUGAUCUG	1194	1500-1520
AD04414.um	GGAUCAUCCAGUUAGUCAUA	325	UAUUGACUAAACUGGAUGAUCC	1195	1501-1521
AD04415.um	CAUCAUCCAGUUAGUCAUAGA	326	UCAUUGACUAAACUGGAUGAUG	1196	1502-1522
AD04416.um	GAUCCAGUUAGUCAAUUGCUAA	327	UUAGCAUUUGACUAAACUGGAUC	1197	1505-1525
AD04417.um	GAGUUAGUCAAUUGCUAAAGCAA	328	UUGCUUAGCAUUUGACUAAACUC	1198	1509-1529
AD04418.um	CUUAGUCAAUUGCUAAAGCAUAA	329	UUUAGCUUAGCAUUUGACUAAAG	1199	1511-1531
AD04419.um	GUAGUCAAUUGCUAAAGCAUUA	330	UAUAUGCUUAGCAUUUGACUAC	1200	1512-1532

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AD04420.um	GAGCCUACAAGUUGGAAACUA	331	UAGUUCCAACUUGUAGGCUC	1201	1534-1554
AD04421.um	GGCCUACAAAGUUGGAAACUCA	332	UGAGUUUCCAACUUGUAGGCC	1202	1535-1555
AD04422.um	GAGUUGGAAACUCUGAUGGAA	333	UCCCAUCAGAGUUUCCAACUC	1203	1542-1562
AD04423.um	CUUGGAAACUCUGAUGGAAA	334	UUUCCAUCAGAGUUUCCAAG	1204	1544-1564
AD04424.um	CGAAACUCUGAUGGAAACUCA	335	UGAGUUUCCAUCAGAGUUUCG	1205	1547-1567
AD04425.um	GCUCUGAGCGUGGUGUAUCA	336	UGAUCACCCAGCUCUAGAGC	1206	1563-1583
AD04426.um	CAAGCUUUCAGAACCUUUCUUA	337	UAAGAAAGGUUCUGAAAAGCUUG	1207	1607-1627
AD04427.um	GUUCAGAACCUUUCUUCUCUCA	338	UGAGAGAAAGAGGUUCUGAAC	1208	1612-1632
AD04428.um	CAACCUUUCUUCUCCAGUAA	339	UUACUGGAGAGAAAGGUUG	1209	1617-1637
AD04429.um	GUUACAGGGAUUAUAAUUA	340	UUAAUUUAAAUCCUGUAAGC	1210	1641-1661
AD04430.um	GUUACAGGGAUUAUAAUUA	341	UGUAAUUUAAAUCCUGUAAC	1211	1642-1662
AD04431.um	GACAGGAUUUAUAAUUAUCA	342	UGAGUAAUUUAAAUCCUGUC	1212	1644-1664
AD04432.um	CCUUGUGACUCUGCAGAAUA	343	UACUUCUGCAGAGUCACAAAG	1213	1899-1919
AD04433.um	GUUGACAGCACUAGCAGAUUA	344	UAUCUCGUAAGUCUGUCAAAC	1214	1968-1988
AD04434.um	GUAGCAGAUUUGCAGCUCUAA	345	UUAGACGUGCAAAUUCUGCUAC	1215	1978-1998
AD04435.um	GUUUGCACGUCUACAGAAACA	346	UGUUUCUGUAGACGUGCAAAC	1216	1985-2005
AD04436.um	GACGUCUACAGAAACUUAUA	347	UAUGAAGUUUCUGUAGACGUC	1217	1990-2010
AD04437.um	GGUCUACAGAAACUUAUAUA	348	UGUAUGAAGUUUCUGUAGACC	1218	1992-2012
AD04438.um	GAGAAACUUAUAUAUAUAUA	349	UAUACUUGUAUGAAGUUUCUC	1219	1998-2018
AD04439.um	GACUUAUAUAUAUAUAUAUA	350	UGCUUAACUUGUAUGAAGUUC	1220	2001-2021
AD04440.um	CGACGCAACCUUAUAUCCGA	351	UCGGAUUAUAAAGGUUGCGUCG	1221	2022-2042
AD04441.um	CACGCAACCUUAUAUCCGUA	352	UACGGAUUAUAAAGGUUGCGUG	1222	2023-2043
AD04442.um	CGUACAGAGAAAGCACUUUA	353	UGAAAGUGCUUUCUCUGUACG	1223	2091-2111
AD04443.um	GGAAAGCACUUAUAUAUAUA	354	UAAGUUUUUGAAAGUUCUUC	1224	2098-2118
AD04444.um	GUUUCCUGAAUUGCAGAUUA	355	UAUCUGCAUUUCAGGGAAC	1225	2125-2145
AD04445.um	GUUCCUGAAUUGCAGAUUA	356	UGAAUCUGCAUUUCAGGGAAC	1226	2126-2146
AD04446.um	GUAGUGGUAACUUAUUGUAUA	357	UAGUACAAUAGUUACCAUAC	1227	2152-2172
AD04447.um	GAGUGGUAACUUAUUGUAUA	358	UCAGUACAAUAGUUACCAUAC	1228	2153-2173
AD04448.um	GGGUAACUUAUUGUAUAUA	359	UUGUCAGUACAAUAGUUACCC	1229	2156-2176
AD04449.um	CGUAAACUUAUUGUAUAUA	360	UUUGUCAGUACAAUAGUUACG	1230	2157-2177

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AD04450.um	GCUAUUGUACUGACAAGAAAA	361	UUUUUUUGUCAGUACAAUAGC	1231	2161-2181
AD04451.um	GUUUUUGUACUGACAAGAAAA	362	UGUUUUUUUGUCAGUACAAUAC	1232	2162-2182
AD04452.um	CACAAGAAAACCGUCGUAUA	363	UAUAGCAGCAGGUUUUUUGUG	1233	2172-2192
AD04453.um	GAGAAACCGUCGUAUAUAAA	364	UUUUUAAGCAGCAGGUUUUCUC	1234	2175-2195
AD04454.um	GAUCUUGUUUGUAGAGCUA	365	UAGCUUCACAAAACAACAGAU	1235	2215-2235
AD04455.um	GCUGUUUUUGUAGAGCUGUA	366	UACAGCUUCACAAAACAACAGC	1236	2217-2237
AD04456.um	GUGUUUGUAGAGCUGUAUUA	367	UAUAGACAGCUUCACAAAACAC	1237	2221-2241
AD04457.um	GGUCAGAGAAGUAUUAAAAGAA	368	UUCUUUAUACUUCUCUGACC	1238	2252-2272
AD04458.um	GCAGAGAAGUAUUAAAAGACUA	369	UAGUCUUUAUACUUCUCUGC	1239	2254-2274
AD04459.um	GGAGAAGUAUUAAAAGACUACA	370	UGUAGUCUUUAUACUUCUCC	1240	2256-2276
AD04460.um	GGAGUAUUAAAAGACUACCAA	371	UUGGUAGUCUUUAUACUUC	1241	2258-2278
AD04461.um	CAGGCUAUGAUUGAGGGUCAA	372	UUUGACCUCAAUCAUAGCCUG	1242	2280-2300
AD04462.um	GAUGAUUGAGGUCAACAUUAA	373	UUAAUGUUUGACCUCAAUCAUC	1243	2285-2305
AD04463.um	GUGAUUGAGGUCAACAUUAAA	374	UUUAAUGUUUGACCUCAAUAC	1244	2286-2306
AD04464.um	GGAGGUCAACAUUAAACAAGAA	375	UUCUUGUUAAUGUUGACCUCC	1245	2291-2311
AD04465.um	GACAUUACAAGAAUUUAGUA	376	UACUAAAUUCUUGUUAAUUGUC	1246	2298-2318
AD04466.um	CCAGCACAGAAUGUUGGUAGA	377	UCUACCAACAUUUCUGUCUGG	1247	2406-2426
AD04467.um	CCACAGAAUGUUGGUAGUUA	378	UGAAUACCAACAUAUUCUGUGG	1248	2409-2429
AD04468.um	GAGAAUGUUGGUAGUUAUAAA	379	UUUUGAACUACCAACAUAUCUC	1249	2412-2432
AD04469.um	GGAAUGUUGGUAGUUAACA	380	UGUUUGAACUACCAACAUAUCC	1250	2413-2433
AD04470.um	CAUUGUUGGUAGUUAACAUA	381	UAGUUUGAACUACCAACAUAUG	1251	2414-2434
AD04471.um	GUGUUGGUAGUUAACAACUGUA	382	UACAGUUUGAACUACCAACAC	1252	2416-2436
AD04472.um	CUAGUUAACAACUGUAUUACUA	383	UAGUAAUACAGUUUUUAAUAG	1253	2422-2442
AD04473.um	GACUGUAUUACUUUAAUUGGAA	384	UUCCAUUAAAGUAAUACAGUC	1254	2430-2450
AD04474.um	GUGUAUUACUUUAAUUGGAA	385	UCUCCAUUAAAGUAAUACAC	1255	2432-2452
AD04475.um	GUACUUUAAUUGGAAGCAAGUA	386	UACUUGCUUCCAUUAAAGUAC	1256	2437-2457
AD04476.um	CGUCCCACAAAUAGAAUUA	387	UAAAUCUUCAUUUUGUGGAGC	1257	2457-2477
AD04477.um	GAGCUGCACCAUGCCAUUUA	388	UUAGAUUGGAUUGGUAGAGCUC	1258	2483-2503
AD04478.um	CCACCAUGCCAUUUAUAGAGA	389	UCUCUAUAGAUUGGAUUGGUGG	1259	2488-2508
AD04479.um	GCAUGCCAUUUAUAGAGUA	390	UUUUCUCUAUAGAUUGGAUUGC	1260	2491-2511

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AD04480.um	GAUGCCAUUUAUAGAGUAUA	391	UCUAUCUCUAUAGAUGGCAUC	1261	2492-2512
AD04481.um	GUCAAGGAGCAUGCAAAAGUA	392	UAUCUUUGCAUGCUCCUUGAC	1262	2572-2592
AD04482.um	GAAGAUAAUCCUGGGGAAAAA	393	UUUUUCCCCAGGAUUUAUCUUC	1263	2586-2606
AD04483.um	GUGGGAAUUGUCACUUAUGA	394	UCAUAAAGUGACAAUUCUCCAC	1264	2647-2667
AD04484.um	CCAGGACAUUCUUGUCAAAAGA	395	UCUUUUGACAAGAUGUCCUGG	1265	2679-2699
AD04485.um	GGGACAUUCUUGUCAAAAGUCA	396	UGACUUUUGACAAGAUUGUCC	1266	2681-2701
AD04486.um	GAGGUCGAAAGAUCAAUUUACA	397	UGUAAAUUUGAUUUUGGACCCUC	1267	2714-2734
AD04487.um	GCGAAGAUCAAUUUACAAAGAA	398	UUCUUGUAAAUUUGAUUUUCGC	1268	2718-2738
AD04488.um	GAGAUCAAUUUACAAAGACCUA	399	UAGGUCUUUGUAAAUUUGAUCUC	1269	2721-2741
AD04489.um	GUCUAAAGGACUAAACAUAAAA	400	UUUUUUGUUAGUCCUUUAGAC	1270	2810-2830
AD04490.um	CGACUAAACAUAAAAUCUGUGA	401	UCACAGAUUUUUAUGUUUAGUCG	1271	2817-2837
AD04491.um	GUAAACAUAAAAUCUGUGAAUA	402	UAUUCACAGAUUUUUAUGUUAC	1272	2820-2840
AD04492.um	GACAUAAAAUCUGUGAAUUAA	403	UUAAUUCACAGAUUUUUAUGUC	1273	2822-2842
AD04493.um	GAAUCUGUGAAUUAAAAAGA	404	UCUUUUUUAAUUCACAGAUUC	1274	2828-2848
AD04494.um	GGUUUAGUGCUUUACAUUCUA	405	UAGCAUGUAAAAGCUCUAAACC	1275	2966-2986
AD04495.um	CCUUUACAUGCUGUGCUCUUA	406	UAAGAGCACAGCAUGUAAAAGG	1276	2974-2994
AD04496.um	GUUACAUGCUGUGCUCUUUGA	407	UCAAAAGAGCACAGCAUGUAAAC	1277	2976-2996
AD04497.um	GGAGUUGGUAAUUCUACAGCUA	408	UAGCUGUAGAUUACCAUCUCC	1278	3033-3053
AD04498.um	GAAAGUUUUUGAUGAAAUUCUA	409	UAGAAUUUUAUCAAACUUUC	1279	3082-3102
AD04499.um	GUUGAUGAAAUUCUUUGAAGUA	410	UACUCAAAGAAUUUCAUCAAC	1280	3088-3108
AD04500.um	GUGAUGAAAUUCUUUGAAGUUA	411	UAACUUCAAAGAAUUUCAUCAC	1281	3089-3109
AD04501.um	GGAUGAAAUUCUUUGAAGUUCA	412	UGAAAUUCAAAGAAUUUCAUCC	1282	3090-3110
AD04502.um	GUCUUGAAGUUCAUGGUGAUUA	413	UAUCACCAUGAAACUUCAAAGAC	1283	3098-3118
AD04503.um	GUUGAAGUUCAUGGUGAUCAA	414	UUGAUCACCAUGAAACUUCAAC	1284	3100-3120
AD04504.um	CAAGUUC AUGGUGAUCAGUGA	415	UCACUGAUCACCAUGAACUUUG	1285	3103-3123
AD04505.um	CUUCAUGGUGAUCAGUGCAAA	416	UUUGCACUGAUCACCAUGAAG	1286	3106-3126
AD04506.um	GAUGGUGAUCAGUGCAAUUUGA	417	UCAAUUUGCACUGAUCACCAUC	1287	3109-3129
AD04507.um	GUGGUGAUCAGUGCAAUUUGAA	418	UUCAAUUGCACUGAUCACCCAC	1288	3110-3130
AD04508.um	CAUGAAACUCCUGAUUUUGUA	419	UACAAAACUACAGGAGUUUCAUG	1289	3184-3204
AD04509.um	CAAACUCCUGAUUUUGUAGUA	420	UACUACAAAACUACAGGAGUUUG	1290	3187-3207

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AD04510.um	GACUCCUGAUUUUGUAGUAA	421	UUAAUACAAAAUACAGGAGUC	1291	3189-3209
AD04511.um	GCUCCUGAUUUUGUAGUAAA	422	UUUAAUACAAAAUACAGGAGC	1292	3190-3210
AD04512.um	GGUAGUUAUUUAUUAAAGUCA	423	UGACUUAAUAAAUAAACUACC	1293	3201-3221
AD04513.um	GUUAUUAAAGUCUGGGAUGUAA	424	UUACAUCCAGACUUAAUAAAC	1294	3210-3230
AD04514.um	CAUGUAGAACUUCAAAGAAAGUA	425	UACUUCUUGAAGUUCUACAUG	1295	3224-3244
AD04515.um	GCUUCAAAGAAAGUAAAGAGCUAA	426	UUAGCUCUUACUUCUUGAAAGC	1296	3232-3252
AD04516.um	GUUCAAGAAAGUAAAGAGCUAAA	427	UUUAGCUCUUACUUCUUGAAC	1297	3233-3253
AD04517.um	GUCAAAGAAAGUAAAGAGCUAAGA	428	UCUUAGCUCUUACUUCUUGAC	1298	3234-3254
AD04518.um	GAAGAAGUAAAGAGCUAAGUUA	429	UACUUAGCUCUUACUUCUUC	1299	3236-3256
AD04519.um	GAUCAGCAUUUAUUCUUCAGAA	430	UUCUGAAGAAUAAUGCUGAUC	1300	3318-3338
AD04520.um	GGAAAGGGACCUGUUUUCUUA	431	UAAGAAAAACAGGUCCCCUCC	1301	3335-3355
AD04521.um	GUUCUUCAAAGGGAAGAAACAA	432	UUUUUCUUCUCCUUGAAGAAC	1302	3349-3369
AD04522.um	GCAACUACAGAAUAAUGUGA	433	UCACAUUAUUCUGUAGUUUGC	1303	3378-3398
AD04523.um	GAACUACAGAAUAAUGUGUUA	434	UACACAUUAUUCUGUAGUUUC	1304	3380-3400
AD04524.um	GCUCGCAGGCUAUUUUGUUA	435	UGAACAAAUAGCCUGCGGAGC	1305	3445-3465
AD04525.um	GCGCAGGCUAUUUUGUUCAGAA	436	UUCUGAACAAAUAGCCUGCGC	1306	3448-3468
AD04526.um	GUUGUUCAGAGAGGCCUUAUA	437	UAAAAGGCCUCUCUGAACAAAC	1307	3458-3478
AD04527.um	GUCAGAGAGGCCUUAUUGUUUA	438	UAAACAAAAGGCCUCUCUGAC	1308	3462-3482
AD04528.um	GCAGAGAGGCCUUAUUGUUUAA	439	UUAAACAAAAGGCCUCUCUGC	1309	3463-3483
AD04529.um	GAGAGAGGCCUUAUUGUUUAAA	440	UUUAAACAAAAGGCCUCUCUC	1310	3464-3484
AD04530.um	GGAGAGGCCUUAUUGUUUAAAA	441	UUUUAAACAAAAGGCCUCUC	1311	3465-3485
AD00810-19-1.um	UGUCAAGACUUAUUCGAAA	442	UUUCGAAAAAGUCUUGACA	1312	109-127
AD00811-19-1.um	UCAAGACUUAUUCGAAUGA	443	UCAUUCGAAAAAGUCUUGA	1313	111-129
AD00812-19-1.um	UCUGCAUGAUGUCCAUGAA	444	UUCAUGGACAUCAUGCAGA	1314	190-208
AD00813-19-1.um	UGUCCAUGAACAUUGUUUAA	445	UUAAACAUGUUCAUGGACA	1315	199-217
AD00814-19-1.um	AUGAAACAUGUUUACUGGUA	446	UACCAGUAAACAUGUUCAU	1316	204-222
AD00815-19-1.um	UGAACAUUGUUUACUGGUA	447	UUACCAGUAAACAUGUUCA	1317	205-223
AD00816-19-1.um	GAACAUGUUUACUGGUA	448	UUUACCAGUAAACAUGUUC	1318	206-224
AD00817-19-1.um	CAUGUUUACUGGUAACAAA	449	UUUGUUACCAUGUAAACAUG	1319	209-227
AD00818-19-1.um	AGAUUCUGGUGGAAUUA	450	UAAUCCAAACCACAGAUCU	1320	229-247

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AD00819-19-1.um	AUCUGUGGUUGGAAUUAUA	451	UAUAAUCCAACCACAGAU	1321	231-249
AD00820-19-1.um	AUCUGUGGUUGGAAUUAUA	452	UAUAAUCCAACCACAGAU	1322	231-249
AD00821-19-1.um	UUAUGAAUGUCCAAAGUUA	453	UAACUUUGGACAUUCAUAA	1323	245-263
AD00822-19-1.um	AGUUUGAAGAGGAUGUUUA	454	UAAACAUCCUCUCUCAAACU	1324	259-277
AD00823-19-1.um	UUUGAGCAGUGACAUUAUA	455	UAUAAUGUCACUCGUCAAA	1325	275-293
AD00824-19-1.um	GUGACAUUAUAAUUCUGAA	456	UUCAGAAUUAAUUGUCAC	1326	283-301
AD00825-19-1.um	CAUUAUAAUUCUGACAAUA	457	UAUUGUCAGAAUUAAUAAUG	1327	287-305
AD00826-19-1.um	UUCUGACAAUAACACGAUA	458	UAUCGUGUUAUUGUCAGAA	1328	295-313
AD00827-19-1.um	UCCUGUAUUAUUACUCCA	459	UGGAAGUAAAUUACAGGA	1329	322-340
AD00828-19-1.um	GUUCCAGAAUUUACGUCAA	460	UUGACGUAAAUUUCUGAAC	1330	341-359
AD00829-19-1.um	UUCAGAAUUUACGUCAAA	461	UUUGACGUAAAUUUCUGAA	1331	342-360
AD00830-19-1.um	UCCAGAAUUUACGUCAACA	462	UGUUGACGUAAAUUUCUGGA	1332	343-361
AD00831-19-1.um	UACGUCAAAUUGGUAUCAA	463	UUUGAUCCAAGUUGACGUA	1333	352-370
AD00832-19-1.um	ACGUCAAAUUGGUAUCAA	464	UUUGAUCCAAGUUGACGU	1334	353-371
AD00833-19-1.um	UGUAUUCAGUACAGUUGUA	465	UACAAUGUACUGAAUACA	1335	416-434
AD00834-19-1.um	UCAGUACAGUUGUUAUUA	466	UGAAUGACAAACUGUACUGA	1336	421-439
AD00835-19-1.um	CAGUACAGUUGUUAUUA	467	UUGAAUGACAAACUGUACUG	1337	422-440
AD00836-19-1.um	CAGUUGUCAUUCACUUCUA	468	UAGAAGUGAAUUGACAAACUG	1338	427-445
AD00837-19-1.um	AGUUGUCAUUCACUUCUA	469	UAGAAGUGAAUUGACAAACU	1339	428-446
AD00838-19-1.um	GUCAUUCACUUCUUAAGACA	470	UGUCUAAAGAAUGUAAUGAC	1340	432-450
AD00839-19-1.um	UCAUUCACUUCUUAAGACA	471	UUGUCUAAAGAAUGUAAUGA	1341	433-451
AD00840-19-1.um	CUUAGACAAAGAAUUGACA	472	UGUCAAUUCUUUUGUCUAAAG	1342	443-461
AD00841-19-1.um	AUGAAGCUUUUGCCUUUUA	473	UAAAAGGGCAAAAGCUUCAU	1343	469-487
AD00842-19-1.um	AGUCCCAACUCACAGGAUA	474	UAUCCUGUGAGUUGGAACU	1344	540-558
AD00843-19-1.um	AAUUAUUGCUCGUGGAAUA	475	UAUCCACGAGCAAAUUAUU	1345	569-587
AD00844-19-1.um	CUCGUGGAAUGGCAAUUA	476	UAAAUUGCCAUUCCACGAG	1346	577-595
AD00845-19-1.um	CGAUGCUCUUGUUGAAUGA	477	UCAUUCACAAAGAGCAUCG	1347	614-632
AD00846-19-1.um	UGCUCUUUGUUGAAUGUCUA	478	UAGACAUUCAACAAAGAGCA	1348	617-635
AD00847-19-1.um	UGUUGAAUGUCUUGUGUA	479	UAUCACAAAGCAUUAACA	1349	623-641
AD00848-19-1.um	UGAAUGUCUUGUUAUUGGA	480	UCCAUAUCAAGACAUUCA	1350	626-644

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AD00849-19-1.um	UUUGAUUGGAGUUGGUAA	481	UUACCAACUCCAUAUCACAA	1351	634-652
AD00850-19-1.um	AGCUUGAAAAUUUAUGUGCUA	482	UAGCACAUAAUUUCAAGCU	1352	670-688
AD00851-19-1.um	UGGCGCAUGUCAGUUCUA	483	UAGAACUGACAUGCAGCCA	1353	692-710
AD00852-19-1.um	UACUUCGUGUUCAGACUA	484	UAGUCAUGAACACGAAGUA	1354	717-735
AD00853-19-1.um	UCGUGUUCAGACUUUCUA	485	UAGAAAAGUCAUGAACACGA	1355	721-739
AD00854-19-1.um	GUGUGUCCUUGGUUUUAGA	486	UCUAAUACCAAGGACACAC	1356	748-766
AD00855-19-1.um	AGGCUUGGUUCUUGUUCAA	487	UUGAACAAAGAACCAAGCCU	1357	890-908
AD00856-19-1.um	UCCUUCUCCUCAAACACAGA	488	UCUGUUUUUGAGGAGAAAGGA	1358	932-950
AD00857-19-1.um	AACAGUACAGCAGAUACUA	489	UAGUAUCUGCUGUACUGUU	1359	945-963
AD00858-19-1.um	UACAGCAGAUACUUCUAAA	490	UUUAGAAGUAUCUGCUGUA	1360	950-968
AD00859-19-1.um	AGCAGAUACUUCUAAAGGUA	491	UACCUUAGAAGUAUCUGCU	1361	953-971
AD00860-19-1.um	GCAGUAACUUCUAAAGGUUA	492	UAACCUUAGAAGUAUCUGC	1362	954-972
AD00861-19-1.um	AGAUACUUCUUAAGGUUUA	493	UGAAACCUUAGAAGUAUCU	1363	956-974
AD00862-19-1.um	AGGACUGGAUAAAAUGUA	494	UACAUUUUCAUCCAGUCCU	1364	977-995
AD00863-19-1.um	CAGCAUGGAUUUUGAACAA	495	UUGUCAAUAUCCAUGCUG	1365	1052-1070
AD00864-19-1.um	ACAAGUUUUUACCCUAAAGA	496	UCUUAGGGUAAUAAUCUUGU	1366	1067-1085
AD00865-19-1.um	UUUUUACCCUAAAGUUUAGA	497	UCUAAACUUAGGGUAAUAA	1367	1072-1090
AD00866-19-1.um	ACCCUAAAGUUUAGCUCUCA	498	UGAGAGCUAAACUUAGGGU	1368	1077-1095
AD00867-19-1.um	AGUACAUUCUUCUUUGAACAA	499	UGUCAAAGAAAGAUUACU	1369	1108-1126
AD00868-19-1.um	UAUCACAUCUCCUGUAGUA	500	UACUACAGGAGAUUGUGUA	1370	1163-1181
AD00869-19-1.um	GAGGAAGAGACAGGGAUAA	501	UUUCCUUGUCUUCUCCUC	1371	1260-1278
AD00870-19-1.um	AACCGAGAAAAGAAAAGUUA	502	UAACUUUUUUUUUUCUGGUU	1372	1278-1296
AD00871-19-1.um	AGUUGAGGUUUUAAAAACCA	503	UGGUUUUUUAAACCUCAACU	1373	1292-1310
AD00872-19-1.um	GAGCUACAUUUUGUGGUUGA	504	UCAAACCAAAUUGUAGCUC	1374	1339-1357
AD00873-19-1.um	CUACAUUUUGUGGUUGGUAA	505	UUACCAACCACAAAUGUAG	1375	1342-1360
AD00874-19-1.um	CCUGCUUACUCGAUACUUA	506	UAAGUUCGAGUAAAGGAGG	1376	1363-1381
AD00875-19-1.um	ACAGGAACCCUGAAAUUUGAA	507	UUCAAUUUCAGGUUCCUGU	1377	1397-1415
AD00876-19-1.um	GGUGCAAAAUUCCUUUAGUA	508	UACUAAAGGAUUUUUGCACC	1378	1476-1494
AD00877-19-1.um	GUGCAAAAUUCCUUUAGUGA	509	UCACUAAAGGAUUUUUGCAC	1379	1477-1495
AD00878-19-1.um	UAGUGAUGCUGAGAUCAUA	510	UAUGAUCUCAGCAUCACUA	1380	1490-1508

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AD00879-19-1.um	AUCAUCCAGUUAGUCAAAUA	511	UAUUGACUAAACUGGAUGAU	1381	1503-1521
AD00880-19-1.um	UCAUCCAGUUAGUCAAAUGA	512	UCAUUGACUAAACUGGAUGA	1382	1504-1522
AD00881-19-1.um	UCCAGUUAGUCAAAUGCUAA	513	UUAGCAUUGACUAAACUGGA	1383	1507-1525
AD00882-19-1.um	GUUAGUCAAAUGCUAAGCAA	514	UUGCUUAGCAUUGACUAAAC	1384	1511-1529
AD00883-19-1.um	AGUCAAUUGCUAAGCAUAUA	515	UAUAUGCUUAGCAUUGACU	1385	1514-1532
AD00884-19-1.um	CCUACAAGUUGGAAACUCA	516	UGAGUUUCCAACUUGUAGG	1386	1537-1555
AD00885-19-1.um	UGGAAACUCUGAUGGAAAAA	517	UUUUCCAUCAGAGAUUUCCA	1387	1546-1564
AD00886-19-1.um	UCAUGAGCGUGGUGUAUCA	518	UGAUACACCCACGCUCAUGA	1388	1565-1583
AD00887-19-1.um	UCAGAACCUCUCUCUCUCA	519	UGAGAGAAAGAGGUUCUGA	1389	1614-1632
AD00888-19-1.um	CAGGGAUUAUAAUUCUCA	520	UGAGUAAUUAUAAUCCUUG	1390	1646-1664
AD00889-19-1.um	UUGUGACUCUGCAGAAGUA	521	UACUUCUGCAGAGUCACAA	1391	1901-1919
AD00890-19-1.um	UGACAGCACUAGCAGAUUA	522	UAUUCUGCUAGUGCUGUCA	1392	1970-1988
AD00891-19-1.um	UUGCACGUCUACAGAAACA	523	UGUUUCUGUAGACGUGCAA	1393	1987-2005
AD00892-19-1.um	GAAACUUCAUACAAGUAUA	524	UAUACUUGUAUGAAAUUUC	1394	2000-2018
AD00893-19-1.um	ACGCAACCUUUAUUAUCCGA	525	UCGGAUUAAAGGUUGCGU	1395	2024-2042
AD00894-19-1.um	UCCUGAAAUGCAGAUUCA	526	UGAAUCUGCAUUAUCAGGGA	1396	2128-2146
AD00895-19-1.um	AGUGGUAACUAAUUGUACUA	527	UAGUACAAUAGUUUACCAU	1397	2154-2172
AD00896-19-1.um	UAACUAAUUGUACUGACAAA	528	UUUGUCAGUACAAUAGUUA	1398	2159-2177
AD00897-19-1.um	GAAACCUUGCUGCUAAUAAA	529	UUUUUAGCAGCAGGUUUC	1399	2177-2195
AD00898-19-1.um	UCUGUUGUUUGUGAAGCUA	530	UAGCUUCACAAACAACAGA	1400	2217-2235
AD00899-19-1.um	UGUUGUUUGUGAAGCUGUA	531	UACAGCUUCACAAACAACA	1401	2219-2237
AD00900-19-1.um	AGAGAAGUAUUAAAAGACUA	532	UAGUCUUUAAUACUUCUCU	1402	2256-2274
AD00901-19-1.um	AGGUCAAACAUUAAACAAGAA	533	UUCUUGUUAAUGUUUGACCU	1403	2293-2311
AD00902-19-1.um	CAUGCAGCAAAACAUUGUCA	534	UGACAAUGUUUGCUGCAUG	1404	2358-2376
AD00903-19-1.um	CAAGGAGCAUGCAAAAGUA	535	UAUCUUUGCAGUCCUUG	1405	2574-2592
AD00904-19-1.um	GGGGAAUUGUCACUUAUGA	536	UCAUAAUGAGCAAAUUCCCC	1406	2649-2667
AD00905-19-1.um	GACAUCUUGUCAAAAAGUCA	537	UGACUUUUUGACAAGAUGUC	1407	2683-2701
AD00906-19-1.um	GGUCGAAAGAUCAAUUUACA	538	UGUAAAUUUGAUUUUCGACC	1408	2716-2734
AD00907-19-1.um	GAAGAUCAAUUUACAAGAA	539	UUCUUGUAAAUUUGAUUUUC	1409	2720-2738
AD00908-19-1.um	ACUAAACUAAAAUUCUGUGA	540	UCACAGAUUUUUUGUUUAGU	1410	2819-2837

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AD00909-19-1.um	AGAGAGGUCUCAGGUUCUA	541	UAGAACCUGAGACCUCUCU	1411	2919-2937
AD00910-19-1.um	UUUACAUGCTUGUCUCUUA	542	UAAGAGCACAGCAUGUAAA	1412	2976-2994
AD00911-19-1.um	AUGGUAAUCUACAGCUCAA	543	UUGAGCUGUAGAUUACCAU	1413	3037-3055
AD00912-19-1.um	UGAUGAAAUUCUUGAAGUA	544	UACUUCAAAGAAUUUCAUA	1414	3090-3108
AD00913-19-1.um	GGUGAUCAGUGCAAUUGAA	545	UUCAAUUGCACUGAUCACC	1415	3112-3130
AD01321-19-1.um	AGCUACAAGUUGUCAAGA	546	UCUUGACAACAUGUAGCU	1416	98-116
AD01322-19-1.um	UGUUGUCAAGACUUUUUCA	547	UGAAAAAGUCUUGACAACA	1417	106-124
AD01323-19-1.um	GUUGUCAAGACUUUUUCGA	548	UCGAAAAAGUCUUGACAAC	1418	107-125
AD01324-19-1.um	UUGUCAAGACUUUUUCGAA	549	UUCGAAAAAGUCUUGACAA	1419	108-126
AD01325-19-1.um	GUCAAGACUUUUUCGAAUA	550	UAUUCGAAAAAGUCUUGAC	1420	110-128
AD01326-19-1.um	GACUUUUCGAAUGCAUGA	551	UCAUGCAUUCGAAAAAGUC	1421	115-133
AD01327-19-1.um	UCCUGGGAAGUCAUAGUA	552	UACUAUGACUUCGCCAGGGA	1422	152-170
AD01328-19-1.um	CUGACCAUCUGCAUGAUGA	553	UCAUCAUGCAGAUUGGUCAG	1423	183-201
AD01329-19-1.um	CAUCUGCAUGAUGUCCAU	554	UAUGGACAUCAU'GCAGAU'G	1424	188-206
AD01330-19-1.um	CUGCAUGAUGUCCAUUGAAA	555	UUUCAUGGACAUCAU'GCAG	1425	191-209
AD01331-19-1.um	GCAUGAUGUCCAUUGAACAA	556	UUGUUCAUGGACAUCAU'GC	1426	193-211
AD01332-19-1.um	AUGAUGUCCAUUGAACAU'GA	557	UCAUGUUCAUGGACAUCAU	1427	195-213
AD01333-19-1.um	AUGUCCAU'GAACAU'GUUUA	558	UAAACAUGUUCAUGGACAUC	1428	198-216
AD01334-19-1.um	UCCAUGAACAU'GUUUA'CUA	559	UAGUAAACAUGUUCAUGGA	1429	201-219
AD01335-19-1.um	AACAUGUUUACUGGUAAACA	560	UGUUACCAAGUAAACAUGUU	1430	207-225
AD01336-19-1.um	ACAUGUUUA'CUGGUAA'CAA	561	UUGUUA'CCAGUAAACAUGU	1431	208-226
AD01337-19-1.um	AUGUUUACUGGUAAACAAUA	562	UAUUGUUACCAAGUAAACAUC	1432	210-228
AD01338-19-1.um	GUUUACUGGUAAACAAUAAA	563	UUUAUUGUUACCAAGUAAAC	1433	212-230
AD01339-19-1.um	UUUACUGGUAAACAAU'AGA	564	UCUUAUUGUUACCAAGUAAA	1434	213-231
AD01340-19-1.um	UUACUGGUAAACAAU'AGAA	565	UUCUUAUUGUUACCAAGUAA	1435	214-232
AD01341-19-1.um	ACUGGUAAACAAU'AGAU'CA	566	UGAUCUUAUUGUUACCAAGU	1436	216-234
AD01342-19-1.um	GUAACAAU'AGAU'CUUGUGA	567	UCACAGAU'CUUUAUUGUUAC	1437	220-238
AD01343-19-1.um	UAAGAU'CUUGUGGUUGGAAA	568	UUUCCA'ACCACAGAU'CUUA	1438	227-245
AD01344-19-1.um	AAGAU'CUUGUGGUUGGAAUA	569	UAUCCA'ACCACAGAU'CUU	1439	228-246
AD01345-19-1.um	GAUCUGUGGUUGGAAUUA	570	UUAAU'UCCA'ACCACAGAU'C	1440	230-248

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AD01346-19-1.um	UCUGUGGUUGGAAUUUAUGA	571	UCAUAAUUCCAACCACAGA	1441	232-250
AD01347-19-1.um	UAUUUACUUCACAGUUCCAA	572	UUGGAACUGGAAAGUAAAAUA	1442	329-347
AD01348-19-1.um	UUACUUCACAGUUCGAGAAA	573	UUUCUGGAACUGGAAGUAA	1443	332-350
AD01349-19-1.um	UCCAGUUCGAGAAUUUAA	574	UUAAAUUCUGGAACUGGAA	1444	336-354
AD01350-19-1.um	UCCAGUUCGAGAAUUUACA	575	UGUAAAUUCUGGAACUGGA	1445	337-355
AD01351-19-1.um	CCAGUUCGAGAAUUUACGA	576	UCGUAAAUUCUGGAACUGG	1446	338-356
AD01352-19-1.um	CAGUUCGAGAAUUUACGUA	577	UACGUAAAUUCUGGAACUG	1447	339-357
AD01353-19-1.um	AGUUCGAGAAUUUACGUCA	578	UGACGUAAAUUCUGGAACU	1448	340-358
AD01354-19-1.um	CCAGAAUUUACGUCAACUA	579	UAGUUGACGUAAAUUCUGG	1449	344-362
AD01355-19-1.um	AGAAUUUACGUCAACUUGA	580	UCAAGUUGACGUAAAUUCU	1450	346-364
AD01356-19-1.um	AUUUACGUCAACUUGGAA	581	UUCCAAAGUUGACGUAAAUU	1451	348-366
AD01357-19-1.um	AUUACGUCAACUUGGUAU	582	UAUCCAAGUUGACGUAAAU	1452	349-367
AD01358-19-1.um	UUUACGUCAACUUGGAUCA	583	UGAUCCAAGUUGACGUAAA	1453	350-368
AD01359-19-1.um	CGUCAACUUGGAUCAAAAA	584	UUUUUGAUCCAAGUUGACG	1454	354-372
AD01360-19-1.um	GUCAACUUGGAUCAAAAAUA	585	UAUUUGAUCCAAGUUGAC	1455	355-373
AD01361-19-1.um	UCAACUUGGAUCAAAAAUA	586	UUUUUUGAUCCAAGUUGA	1456	356-374
AD01362-19-1.um	UUUCACAAUUUUUCUCAAGA	587	UCUUUGAGAAAAUUUGUAAA	1457	395-413
AD04242-19-1.um	GCUACAAUGUUUGUCAAGAA	588	UUCUUGACAAACAUUGUAGC	1458	99-117
AD04243-19-1.um	CAAUGUUGUCAAGACUUUA	589	UAAAGUCUUGACAAACAUUG	1459	103-121
AD04244-19-1.um	AUGUUGUCAAGACUUUUUA	590	UAAAAAGUCUUGACAAACAU	1460	105-123
AD04245-19-1.um	CAAGACUUUUUCGAAUGCA	591	UGCAUUCGAAAAAAGUCUUG	1461	112-130
AD04246-19-1.um	UCGAAUGCAUGGCCUCUUA	592	UAAGAGGCCAUGCAUUCGA	1462	122-140
AD04247-19-1.um	CCAUCUGCAUGAUGUCCAA	593	UUGGACAUCAUGCAGAUUG	1463	187-205
AD04248-19-1.um	CUGGUAACAAUAAAGAUUA	594	UAGAUCUUUUUUUACCAG	1464	217-235
AD04249-19-1.um	UGGUAAACAAUAAAGAUUGA	595	UCAGAUCUUUUUUUACCA	1465	218-236
AD04250-19-1.um	GGUAAACAAUAAAGAUUGUA	596	UACAGAUCUUUUUUUUAACC	1466	219-237
AD04251-19-1.um	ACAAUAAAGAUUCUGUGGUUA	597	UAACCACAGAUUUUUUUUUG	1467	223-241
AD04252-19-1.um	CAAUAAAGAUUCUGUGGUUGA	598	UCAACCACAGAUUUUUUUUG	1468	224-242
AD04253-19-1.um	AAUAAAGAUUCUGUGGUUGGA	599	UCCAACCACAGAUUUUUUUU	1469	225-243
AD04254-19-1.um	AUAAGAUUCUGUGGUUGGAA	600	UUCCAACCACAGAUUUUUU	1470	226-244

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AD04255-19-1.um	UGGUUGGAAUUAUGAAUGA	601	UCAUUCAUAAUCCAAACCA	1471	236-254
AD04256-19-1.um	GUUGGAAUUAUGAAUGUCA	602	UGACAUUCAUAAUUCCAAC	1472	238-256
AD04257-19-1.um	UUGGAAUUAUGAAUGUCCA	603	UGGACAUUCAUAAUUCCAA	1473	239-257
AD04258-19-1.um	UGGAAUUAUGAAUGUCCAA	604	UUGGACAUUCAUAAUUCCA	1474	240-258
AD04259-19-1.um	GAAUUAUGAAUGUCCAAA	605	UUUUGGACAUUCAUAAUUC	1475	242-260
AD04260-19-1.um	UAUGAAUGUCCAAAGUUUA	606	UAAACUUUGGACAUUCAUA	1476	246-264
AD04261-19-1.um	UGAAUGUCCAAAGUUUGAA	607	UUCAAAACUUUGGACAUUCA	1477	248-266
AD04262-19-1.um	GAAUGUCCAAAGUUUGAAA	608	UUUCAAAACUUUGGACAUUC	1478	249-267
AD04263-19-1.um	AUGUCCAAAGUUUGAAGAA	609	UUCUUCAAACUUUGGACAU	1479	251-269
AD04264-19-1.um	CCAAAGUUUGAAGAGGAUA	610	UAUCCUUCUCAAACUUUGG	1480	255-273
AD04265-19-1.um	AAGAGGAUGUUUUGAGCAA	611	UUGCUCAAAACAUCUCUUU	1481	265-283
AD04266-19-1.um	GAGGAUGUUUUGAGCAGUA	612	UACUGCUCAAAACAUCUCUC	1482	267-285
AD04267-19-1.um	AUGUUUUGAGCAGUGACAA	613	UUGUCACUGCUCAAAACAUC	1483	271-289
AD04268-19-1.um	UGUUUUGAGCAGUGACAU	614	UAUGUCACUGCUCAAAACA	1484	272-290
AD04269-19-1.um	GUUUUGAGCAGUGACAUUA	615	UAAUGUCACUGCUCAAAAC	1485	273-291
AD04270-19-1.um	UUUUGAGCAGUGACAUUAA	616	UUAAUGUCACUGCUCAAAA	1486	274-292
AD04271-19-1.um	UGAGCAGUGACAUUUAUAAA	617	UUUAUAAUGUCACUGCUC	1487	277-295
AD04272-19-1.um	GCAUGGACAUUUAUAAUUA	618	UGAAUUAUAAUUGUCACUGC	1488	280-298
AD04273-19-1.um	CAGUGACAUUUAUAAUUCUA	619	UAGAAUUAUAAUUGUCACUG	1489	281-299
AD04274-19-1.um	AGUGACAUUUAUAAUUCUGA	620	UCAGAAUUAUAAUUGUCACU	1490	282-300
AD04275-19-1.um	UGACAUUUAUAAUUCUGACA	621	UGUCAGAAUUAUAAUUGUCA	1491	284-302
AD04276-19-1.um	GACAUUAUAAUUCUGACAA	622	UUGUCAGAAUUAUAAUUGUC	1492	285-303
AD04277-19-1.um	ACAUUAUAAUUCUGACAAA	623	UUUGUCAGAAUUAUAAUUGU	1493	286-304
AD04278-19-1.um	UUUAUAAUUCUGACAAUAAA	624	UUUAUUGUCAGAAUUAUAA	1494	289-307
AD04279-19-1.um	UCUGACAAUAAACACGAUGA	625	UCAUCGUGUUAUUGUCAGA	1495	296-314
AD04280-19-1.um	CUGACAAUAAACACGAUGCA	626	UGCAUCGUGUUAUUGUCAG	1496	297-315
AD04281-19-1.um	UGACAAUAAACACGAUGCAA	627	UUGCAUCGUGUUAUUGUCA	1497	298-316
AD04282-19-1.um	ACAAUAAACACGAUGCAUAA	628	UU AUGCAUCGUGUUAUUGU	1498	300-318
AD04283-19-1.um	CAAUAAACACGAUGCAUAGA	629	UCUAUGCAUCGUGUUAUUG	1499	301-319
AD04284-19-1.um	GUUAUUUAUCUCCAGUUA	630	UAAUGGAAGUAAAUAUAC	1500	326-344

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AD04285-19-1.um	UAUAUUUACUUCAGUUA	631	UGAACUGGAAGUAAAUA	1501	327-345
AD04286-19-1.um	AUAUUUACUUCAGUCCA	632	UGGAACUGGAAGUAAAUAU	1502	328-346
AD04287-19-1.um	UACUUCAGUUCAGAAUA	633	UAUUCUGGAACUGGAAGUA	1503	333-351
AD04288-19-1.um	ACUUCAGUUCAGAAUA	634	UAUUCUGGAACUGGAAGU	1504	334-352
AD04289-19-1.um	GAAUUACGUCACUUGGA	635	UCCAAGUUGACGUAAAUUC	1505	347-365
AD04290-19-1.um	UACGUCACUUGGAUCAA	636	UUGAUCCAAGUUGACGUAA	1506	351-369
AD04291-19-1.um	UUUACACAAUUUUCUCAA	637	UUUGAGAAAUUUGUAAAA	1507	394-412
AD04292-19-1.um	UUUGUAUUCAGUACAGUA	638	UAACUGUACUGAAUACAAA	1508	414-432
AD04293-19-1.um	UUUGUAUUCAGUACAGUA	639	UCAAACUGUACUGAAUACAA	1509	415-433
AD04294-19-1.um	GUUUUCAGUACAGUUA	640	UGACAAACUGUACUGAAUAC	1510	417-435
AD04295-19-1.um	UAUUCAGUACAGUUA	641	UUGACAAACUGUACUGAAUA	1511	418-436
AD04296-19-1.um	UUCAGUACAGUUGUCAUA	642	UAUUGACAAACUGUACUGAA	1512	420-438
AD04297-19-1.um	GUACAGUUGUCAUUCACUA	643	UAGUGAAUGACAAACUGUAC	1513	424-442
AD04298-19-1.um	UACAGUUGUCAUUCACUA	644	UAAGUGAAUGACAAACUGUA	1514	425-443
AD04299-19-1.um	ACAGUUGUCAUUCACUUA	645	UGAAGUGAAUGACAAACUGU	1515	426-444
AD04300-19-1.um	GUUGUCAUUCACUUCUUA	646	UUAAGAAGUGAAUGACAAAC	1516	429-447
AD04301-19-1.um	UUGUCAUUCACUUCUUA	647	UCUAAGAAGUGAAUGACAA	1517	430-448
AD04302-19-1.um	UGUCAUUCACUUCUUA	648	UUCUAAGAAGUGAAUGACA	1518	431-449
AD04303-19-1.um	CAUUCACUUCUUAAGACAAA	649	UUUGUCUAGAAGUGAAUG	1519	434-452
AD04304-19-1.um	AUUCACUUCUUAAGACAAA	650	UUUUGUCUAGAAGUGAAU	1520	435-453
AD04305-19-1.um	UUCACUUCUUAAGACAAA	651	UCUUUGUCUAGAAGUGAA	1521	436-454
AD04306-19-1.um	UCACUUCUUAAGACAAA	652	UUCUUUGUCUAGAAGUGA	1522	437-455
AD04307-19-1.um	CACUUCUUAAGACAAA	653	UUUCUUUGUCUAGAAGUG	1523	438-456
AD04308-19-1.um	ACUUCUUAAGACAAA	654	UAUUCUUUGUCUAGAAGU	1524	439-457
AD04309-19-1.um	CUUCUUAAGACAAA	655	UAAUUCUUUGUCUAGAAG	1525	440-458
AD04310-19-1.um	UUCUUUAAGACAAA	656	UCAAUUCUUUGUCUAGA	1526	441-459
AD04311-19-1.um	UCUUUAAGACAAA	657	UUCAAUUCUUUGUCUAGA	1527	442-460
AD04312-19-1.um	UUAGACAAAAGAAUUGACAA	658	UUGUCAAUUCUUUGUCUAA	1528	444-462
AD04313-19-1.um	AGAAUUGACAGGCUUGAAA	659	UUUCAAGCCUGUCAAUUCU	1529	452-470
AD04314-19-1.um	GAAUUGACAGGCUUGAAUA	660	UAUUCAAGCCUGUCAAUUC	1530	453-471

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AD04315-19-1.um	AAUUGACAGGCUUGAAUGA	661	UCAUUCAAAGCCUGUCAAUU	1531	454-472
AD04316-19-1.um	UUGACAGGCUUGAAUGAAA	662	UUUCAUUCAAAGCCUGUCA	1532	456-474
AD04317-19-1.um	UGACAGGCUUGAAUGAAGA	663	UCUUCAUUCAAAGCCUGUCA	1533	457-475
AD04318-19-1.um	CAGGCUUGAAUGAAGCUUA	664	UAAGCUCUUCUCAAAGCCUG	1534	460-478
AD04319-19-1.um	GCUUGAAUGAAGCUUUGCA	665	UGCAAAGCUUCAUUUAAGC	1535	463-481
AD04320-19-1.um	GAGCUUUGCCCUUUUUUCA	666	UGAAAAGGGCAAAAGCUUC	1536	471-489
AD04321-19-1.um	UUUGCCCUUUUUUCCUACUA	667	UAGUAGGAAAAAAGGGCAA	1537	476-494
AD04322-19-1.um	UUGCCCUUUUUUCCUACUUA	668	UAAGUAGGAAAAAAGGGCAA	1538	477-495
AD04323-19-1.um	CAAGUUTUGCCCTUCAGUUA	669	UAACUGAGGGCAAAACUUG	1539	526-544
AD04324-19-1.um	AGUUGCCCTUCAGUCCAA	670	UUGGAACUGAGGGCAAAACU	1540	529-547
AD04325-19-1.um	GCCUCAGUUCCAACUCA	671	UUGAGUUGGAAACUGAGGGC	1541	534-552
AD04326-19-1.um	UCCAAACUCACAGGAUGAA	672	UUCAUCCUGUGAGUUGGAA	1542	542-560
AD04327-19-1.um	UCCAAACUCACAGGAUGAAA	673	UUUCAUCCUGUGAGUUGGA	1543	543-561
AD04328-19-1.um	ACUCACAGGAUGAAGUAAA	674	UUUACUUCAUCCUGUGAGU	1544	547-565
AD04329-19-1.um	GGAUGAAGUAAAGGAAAAA	675	UUUUUCCCUUACUUAUCC	1545	554-572
AD04330-19-1.um	UGAAGUAAAGGAAAAAUUA	676	UAUAUUUUUCCCUUACUUA	1546	557-575
AD04331-19-1.um	AGUAAAGGAAAAAUUUGCA	677	UGCAAUAUUUUUCCCUUACU	1547	560-578
AD04332-19-1.um	AAGGAAAAAUUUGCUCGA	678	UCGAGCAAUAUUUUUCCCUU	1548	563-581
AD04333-19-1.um	AGGAAAAAUUUGCUCGUA	679	UACGAGCAAUAUUUUUCCCU	1549	564-582
AD04334-19-1.um	GAAAAUUAUUGCUCGUGGA	680	UCCACGAGCAAUAUUUUUC	1550	567-585
AD04335-19-1.um	AUAUUGCUCGUGGAAUGA	681	UCAUUCACGAGCAAUAUU	1551	570-588
AD04336-19-1.um	UAUUGCUCGUGGAAUGGCA	682	UGCCAUUCCACGAGCAAUA	1552	572-590
AD04337-19-1.um	CGUGGAAUGGCAAUUUUAA	683	UUAAAAUUGCCAUUCCACG	1553	579-597
AD04338-19-1.um	GUUGAAUGGCAAUUUUAGA	684	UCUAAAAUUGCCAUUCCAC	1554	580-598
AD04339-19-1.um	UGGAAUGGCAAUUUUAGGA	685	UCCUAAAAUUGCCAUUCCA	1555	581-599
AD04340-19-1.um	GGAAUGGCAAUUUUAGGUA	686	UACCUAAAAUUGCCAUUCC	1556	582-600
AD04341-19-1.um	GAAUGGCAAUUUUAGGUA	687	UGACCUAAAAUUGCCAUUCC	1557	583-601
AD04342-19-1.um	UACCCUCGAUGCUCUUGUA	688	UACAAGAGCAUCGAGGGUA	1558	608-626
AD04343-19-1.um	ACCCUCGAUGCUCUUGUA	689	UAACAAGAGCAUCGAGGGU	1559	609-627
AD04344-19-1.um	UCGAUGCUCUUGUUGAAUA	690	UAUUCAAACAAGAGCAUCGA	1560	613-631

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AD04345-19-1.um	AUGCUUUGUUGAAUGUCA	691	UGACAUUCAACAAGAGCAU	1561	616-634
AD04346-19-1.um	CUCUUGUUGAAUGUCUUGA	692	UCAAGACAUUCAACAAGAG	1562	619-637
AD04347-19-1.um	UCUUGUTUGAAUGUCUUGUA	693	UACAAGACAUUCAACAAGA	1563	620-638
AD04348-19-1.um	UUGAAUGUCUUGUGAUUGA	694	UCAUUCACAAGACAUUCA	1564	625-643
AD04349-19-1.um	GAAUGUCUUGUGAUUGGAA	695	UUCCAAUUCACAAGACAUUC	1565	627-645
AD04350-19-1.um	UGUCUUGUGAUUGGAGUUA	696	UAACUCCAUAUCAACAAGACA	1566	630-648
AD04351-19-1.um	GUCUUGUGAUUGGAGUUUA	697	UCAACUCCAUAUCAACAAGAC	1567	631-649
AD04352-19-1.um	GAUUGGAGUUGGUACCAUA	698	UAUGGUACCAACUCCAUAUC	1568	638-656
AD04353-19-1.um	UGGAGUUGGUACCAUGUCA	699	UGACAUUGGUACCAACUCCA	1569	641-659
AD04354-19-1.um	UACGUCAGCUUGAAAUAUA	700	UUAUUUCAAGCUGACGUA	1570	664-682
AD04355-19-1.um	ACGUCAGCUUGAAAUAUA	701	UAUAUUUCAAGCUGACGU	1571	665-683
AD04356-19-1.um	CGUCAGCUUGAAAUAUAUA	702	UCAUAAUUUCAAGCUGACG	1572	666-684
AD04357-19-1.um	UGAAAUUAUGUGCUGCUUA	703	UAAGCAGCACAUAAUUUCA	1573	674-692
AD04358-19-1.um	AUUAUGUGCUGCUUUGGCA	704	UGCCAAAGCAGCACAUAAU	1574	678-696
AD04359-19-1.um	GUGCUGCUUUGGCUGCAUA	705	UAUGCAGCCAAAGCAGCAC	1575	683-701
AD04360-19-1.um	UUGGUGCAUGUCAGUUUA	706	UGAACTUGACAUUGCAGCCAA	1576	691-709
AD04361-19-1.um	GCAUGUCAGUUCUUGCCAA	707	UUGGCAAGAAACUGACAUUC	1577	697-715
AD04362-19-1.um	AUGUCAGUUCUUGCCAAACA	708	UGUUGGCAAGAAACUGACAU	1578	699-717
AD04363-19-1.um	GUCAGUUCUUGCCAAACUAA	709	UUAGUUGGCAAGAAACUGAC	1579	701-719
AD04364-19-1.um	UGCCAAACUACUUCGUGUUA	710	UAACACGAAGUAGUUGGCA	1580	710-728
AD04365-19-1.um	CAACUACUUCGUGUUCAUUA	711	UAUGAAACACGAAGUAGUUG	1581	713-731
AD04366-19-1.um	GCUUGUGUGUCCUUGGUAA	712	UUACCAAGGACACACAAGC	1582	744-762
AD04367-19-1.um	UUGGUAAUAGAGCUUUCUA	713	UAGAAAGCUCUAAUAACCAA	1583	756-774
AD04368-19-1.um	UGCCCGAGUUUUAAGAGAA	714	UUCUUCUAAAACUCGGGCA	1584	818-836
AD04369-19-1.um	GGGUCAGAUGAUUAUGUA	715	UACAUAAUACUUCUUGACCC	1585	868-886
AD04370-19-1.um	GGUCAAGAUGAUUAUGUCA	716	UGACAUAAUACUUCUUGACC	1586	869-887
AD04371-19-1.um	CAAGAUGAUUAUGUCUCUA	717	UAGAGACAUAAUACUUCUUG	1587	872-890
AD04372-19-1.um	CUCUAGGCUUGGUUCUUGA	718	UCAAGAACCAGCCUAGAG	1588	886-904
AD04373-19-1.um	UAGGCUUGGUUCUUGUUA	719	UGAACAAAGAACCAAGCCUA	1589	889-907
AD04374-19-1.um	GGUUCUUGUUCUUGUCUAA	720	UUGAGCAUGAACCAAGAACCC	1590	896-914

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AD04375-19-1.um	UGAUCCUUCUCCUAAAAA	721	UUUUUGAGGAGAAGGAUCA	1591	929-947
AD04376-19-1.um	UCUCCUCAAACACAGUACAA	722	UUGUACUGUUUUGAGGAGA	1592	936-954
AD04377-19-1.um	AAAACAGUACAGCAGAUAA	723	UUACUCGUGUACUGUUUU	1593	943-961
AD04378-19-1.um	ACAGUACAGCAGAUACUUA	724	UAAAGUACUGCUGUACUGU	1594	946-964
AD04379-19-1.um	ACAGCAGAUACUUCUAAAG	725	UCUUAGAAAGUACUCGUGU	1595	951-969
AD04380-19-1.um	CAUUAGGACUGGAUGAAAA	726	UUUUCAUCCAGUCCUAAUG	1596	973-991
AD04381-19-1.um	UUAGGACUGGAUGAAAAUA	727	UAUUUUAUCCAGUCCUAA	1597	975-993
AD04382-19-1.um	AAUUGAUCAGCAUGGAUAA	728	UUAUCCAUUGCUGAUCAUUU	1598	1045-1063
AD04383-19-1.um	AAUGAUCAGCAUGGAUUA	729	UAUAUCCAUGCUGAUCAUU	1599	1046-1064
AD04384-19-1.um	GCAUGGAUAUUGAACAAAG	730	UCUUGUCAAUAUCCAUGC	1600	1054-1072
AD04385-19-1.um	GAACAAGUUAUUACCCUAA	731	UUAGGGUAAUAACUUGUUC	1601	1065-1083
AD04386-19-1.um	UACCCUAAAGUUUAGCUCUA	732	UAGAGCUAAAACUUAAGGUA	1602	1076-1094
AD04387-19-1.um	CCUUCUGGCUGUCAAGUAA	733	UUACUUGACAGCCAGAAGG	1603	1094-1112
AD04388-19-1.um	UUCUGGCUGUCAAGUACAA	734	UUGUACUUGACAGCCAGAA	1604	1096-1114
AD04389-19-1.um	UCAAGUACAUCUUCUUUGA	735	UCAAAGAAAGUUAUCUUGA	1605	1105-1123
AD04390-19-1.um	GUACAUUCUUCUUUGAACAA	736	UUGUCAAAGAAAGAUUAC	1606	1109-1127
AD04391-19-1.um	AAAAAACCCUAUCACAUCA	737	UGAUGUAUAGGGUUUUUU	1607	1154-1172
AD04392-19-1.um	UGUAGUGACACAAAAAGAAA	738	UUUCUUUUUGUGUCACUACA	1608	1175-1193
AD04393-19-1.um	UAGUGACACAAAAAGAAAG	739	UCUUUCUUUUUGUGUCACUA	1609	1177-1195
AD04394-19-1.um	GUGACACAAAAAGAAAGUCA	740	UGACUUUCUUUUUGUGUCAC	1610	1179-1197
AD04395-19-1.um	UUGCUGGUCAGAAAAUAAA	741	UUUAUUUCUGACCAGCAUA	1611	1223-1241
AD04396-19-1.um	UGGUCAGAAAAUAACCAGAA	742	UUCUGGUUAUUUCUGACCA	1612	1228-1246
AD04397-19-1.um	GGUCAGAAAAUAACCAGAAA	743	UUUCUGGUUAUUUCUGACC	1613	1229-1247
AD04398-19-1.um	CAGGGAUAAACCCGAGAAAA	744	UUUUCUGGUUUUAUCCUG	1614	1270-1288
AD04399-19-1.um	GAUAAACCGAGAAAGAAAA	745	UUUUCUUUCUGGUUUUAUC	1615	1274-1292
AD04400-19-1.um	AAAGAAAAGUUGAGGUUUA	746	UUAACCUCAACUUUUCUUU	1616	1285-1303
AD04401-19-1.um	GUUAUAAAAACCCUUUAGUGA	747	UCACUAAGGGUUUUUAUAAAC	1617	1299-1317
AD04402-19-1.um	CUUAGUGGCUGAAACAGAA	748	UUCUGUUUCAGCCACUAAAG	1618	1310-1328
AD04403-19-1.um	UACAUUUGUGGUUGGUAAA	749	UUUACCAACCCACAAUUGUA	1619	1343-1361
AD04404-19-1.um	CCUCCUUAUCUCGAUACUUA	750	UAAGUAUCGAGUAAAGGAGG	1620	1363-1381

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AD04405-19-1.um	ACAGGAACCGUGAAAUUGAA	751	UUCAAUUUCAGGUUCCUGU	1621	1397-1415
AD04406-19-1.um	GAGAAAGGUGCAAAAAUUA	752	UGAAUUUUGCACCUUUCUC	1622	1470-1488
AD04407-19-1.um	GGUGCAAAAUUCCUUAGUA	753	UACUAAAGGAUUUUUGCAC	1623	1476-1494
AD04408-19-1.um	GUGCAAAAUUCCUUAGUGA	754	UCACUAAAGGAUUUUUGCAC	1624	1477-1495
AD04409-19-1.um	UGCAAAAUUCCUUAGUGAA	755	UUCACUAAAGGAUUUUUGCA	1625	1478-1496
AD04410-19-1.um	CAAAAUCCUUAGUGAUGA	756	UCAUCACUAAAGGAUUUUUG	1626	1480-1498
AD04411-19-1.um	UAGUGAUGCUGAGAUCAUA	757	UAUGAUCUCAGCAUCACUA	1627	1490-1508
AD04412-19-1.um	CUGAGAUCAUCCAGUUAGA	758	UCUAAACUGGAUGAUCUCAG	1628	1498-1516
AD04413-19-1.um	GAUCAUCCAGUUAGUCAA	759	UUUGACUAAACUGGAUGAUC	1629	1502-1520
AD04414-19-1.um	AUCAUCCAGUUAGUCAAUA	760	UAUUGACUAAACUGGAUGAU	1630	1503-1521
AD04415-19-1.um	UCAUCCAGUUAGUCAAUGA	761	UCAUUGACUAAACUGGAUGA	1631	1504-1522
AD04416-19-1.um	UCCAGUUAGUCAAUUGCUAA	762	UUAGCAUUUGACUAAACUGGA	1632	1507-1525
AD04417-19-1.um	GUUAGUCAAUUGCUAAGCAA	763	UUGCUUAGCAUUUGACUAAAC	1633	1511-1529
AD04418-19-1.um	UAGUCAAUUGCUAAGCAUAA	764	UUUUGCUUAGCAUUUGACUA	1634	1513-1531
AD04419-19-1.um	AGUCAAUUGCUAAGCAUAUA	765	UAUAUGCUUAGCAUUUGACU	1635	1514-1532
AD04420-19-1.um	GCCUACAAGUUUGGAAACUA	766	UAGUUUCCAACUUGUAGGC	1636	1536-1554
AD04421-19-1.um	CCUACAAGUUUGGAAACUCA	767	UGAGUUUCCAACUUGUAGG	1637	1537-1555
AD04422-19-1.um	GUUGGAAACUCUGAUGGAA	768	UCCCAUCAGAGUUUCCAAC	1638	1544-1562
AD04423-19-1.um	UGGAAACUCUGAUGGAAAA	769	UUUCCAUCAGAGUUUCCA	1639	1546-1564
AD04424-19-1.um	AAACUCUGAUGGAAACUCA	770	UGAGUUUCCAUCAGAGUUU	1640	1549-1567
AD04425-19-1.um	UCAUGAGCGUGGUGUAUCA	771	UGAUACACCCAGCUCUAUGA	1641	1565-1583
AD04426-19-1.um	AGCUUUCAGAAACCUUCUUA	772	UAAGAAGGUUUCUGAAAAAGCU	1642	1609-1627
AD04427-19-1.um	UCAGAACCUUCUUCUCUCA	773	UGAGAGAAAGAAAGGUUCUGA	1643	1614-1632
AD04428-19-1.um	ACCUUCUUCUCUCCAGUAA	774	UUACUGGAGAGAAAGAGGU	1644	1619-1637
AD04429-19-1.um	UUACAGGGAUUUAUUUAUA	775	UUAAUUUAUUUUCCUGUAA	1645	1643-1661
AD04430-19-1.um	UACAGGGAUUUAUUUAUACA	776	UGUAAUUUAUUUUCCUGUA	1646	1644-1662
AD04431-19-1.um	CAGGGAUUUAUUUAUACUCA	777	UGAGUAAUUUAUUUUCCUG	1647	1646-1664
AD04432-19-1.um	UUUGACUCUCGAGAAAGUA	778	UACUUCUGCAGAGUCACAA	1648	1901-1919
AD04433-19-1.um	UGACAGCACUAGCAGAUUA	779	UAUUCUGCUAGUCUGUCA	1649	1970-1988
AD04434-19-1.um	AGCAGAUUUGCAGCUCUAA	780	UUAGACGUGCAAAUUCUGCU	1650	1980-1998

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AD04435-19-1.um	UUGCACGUCUACAGAAACA	781	UGUUUCUGUAGACGUGCAA	1651	1987-2005
AD04436-19-1.um	CGUCUACAGAAACUUCAUUA	782	UAUGAAGUUUCUGUAGACG	1652	1992-2010
AD04437-19-1.um	UCUACAGAAACUUCAUACA	783	UGUAUGAAGUUUCUGUAGA	1653	1994-2012
AD04438-19-1.um	GAAACUUCAUACAAGUAUA	784	UAUACUUGUAUGAAGUUUC	1654	2000-2018
AD04439-19-1.um	ACUUCAUACAAGUAUAGCA	785	UGCUAUACUUGUAUGAAGU	1655	2003-2021
AD04440-19-1.um	ACGCAACCUUUAUUAUCCGA	786	UCGGAUAUAAAGGUUGCGU	1656	2024-2042
AD04441-19-1.um	CGCAACCUUUAUUAUCCGUA	787	UACGGAUAUAAAGGUUGCG	1657	2025-2043
AD04442-19-1.um	UACAGAGAAAGCACUUUCA	788	UGAAAGUGCUUUCUCUGUA	1658	2093-2111
AD04443-19-1.um	AAAGCACUUUCAAAACUUA	789	UAAGUUUUUGAAAAGUCUUU	1659	2100-2118
AD04444-19-1.um	UUCCUGAAAUUGCAGAUUA	790	UAUCUGCAUUUCAGGGAA	1660	2127-2145
AD04445-19-1.um	UCCUGAAAUUGCAGAUUCA	791	UGAAUCUGCAUUUCAGGGA	1661	2128-2146
AD04446-19-1.um	AGUGGUAACUAUUGUACUA	792	UAGUACAAUAGUUACCACU	1662	2154-2172
AD04447-19-1.um	GUGGUAACUAUUGUACUGA	793	UCAGUACAAUAGUUACCAC	1663	2155-2173
AD04448-19-1.um	GUAAACUAUUGUACUGACAA	794	UUGUCAGUACAAUAGUUAC	1664	2158-2176
AD04449-19-1.um	UAACUAUUGUACUGACAAA	795	UUUGUCAGUACAAUAGUUA	1665	2159-2177
AD04450-19-1.um	UAUUGUACUGACAAAGAAA	796	UUUUCUUGUCAGUACAAUA	1666	2163-2181
AD04451-19-1.um	AUUGUACUGACAAAGAAA	797	UGUUUCUUGUCAGUACAAU	1667	2164-2182
AD04452-19-1.um	CAAGAAACCUGCUGCUAUA	798	UAUAGCAGCAGGUUUCUUG	1668	2174-2192
AD04453-19-1.um	GAAACCUGCUGCUAUAUAAA	799	UUUUUAAGCAGCAGGUUUC	1669	2177-2195
AD04454-19-1.um	UCUGUUGUUUGUGAAGCUA	800	UAGCUUCACAAACAAACAGA	1670	2217-2235
AD04455-19-1.um	UGUUGUUUGUGAAGCUGUA	801	UACAGCUUCACAAACAAACA	1671	2219-2237
AD04456-19-1.um	GUUUGUGAAGCUGUCAUUA	802	UAAUGACAGCUUCACAAAC	1672	2223-2241
AD04457-19-1.um	UCAGAGAAGUAUUAAAAGAA	803	UUCUUUAAUACUUUCUCUGA	1673	2254-2272
AD04458-19-1.um	AGAGAAGUAUUAAAAGACUA	804	UAGUCUUUAAUACUUUCU	1674	2256-2274
AD04459-19-1.um	AGAAGUAUUAAAAGACUACA	805	UGUAGUCUUUAAUACUUUCU	1675	2258-2276
AD04460-19-1.um	AAGUAUUAAAAGACUACCAA	806	UUGGUAGUCUUUAAUACUU	1676	2260-2278
AD04461-19-1.um	GGCUAUGAUUUGAGGUCAAA	807	UUUGACCUCAAUUCAUAGCC	1677	2282-2300
AD04462-19-1.um	UGAUUGAGGUCACAAUUA	808	UUAAUGUUUGACCUCAAUUA	1678	2287-2305
AD04463-19-1.um	GAUUGAGGUCACAAUUA	809	UUUAAUGUUUGACCUCAAUUC	1679	2288-2306
AD04464-19-1.um	AGGUCAACAUAUAAACAGAA	810	UUUUGUUAAUUGUUUGACCU	1680	2293-2311

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AD04465-19-1.um	CAUUAACAAAGAAUUUAGUA	811	UACUAAAUCUUGUUAAUG	1681	2300-2318
AD04466-19-1.um	AGCACAGAAUGUUGGUAGA	812	UCUACCAACAUCUCUGGCU	1682	2408-2426
AD04467-19-1.um	ACAGAAUGUUGGUAGUUA	813	UGAACUACCAACAUCUCUGU	1683	2411-2429
AD04468-19-1.um	GAUGUUGGUAGUUCAAAA	814	UUUUGAACUACCAACAUC	1684	2414-2432
AD04469-19-1.um	AUGUUGGUAGUUCAAAA	815	UGUUUGAACUACCAACAUC	1685	2415-2433
AD04470-19-1.um	AUGUUGGUAGUUCAAACUA	816	UAGUUUGAACUACCAACAUC	1686	2416-2434
AD04471-19-1.um	GUUGGUAGUUCAAAAUCUGUA	817	UACAGUUUGAACUACCAAC	1687	2418-2436
AD04472-19-1.um	AGUUCAAACUGUAUUACUA	818	UAGUAAUACAGUUUGAACU	1688	2424-2442
AD04473-19-1.um	CUGUAUUACUUUAAUGGAA	819	UUCCAUUAAAGUAAUACAG	1689	2432-2450
AD04474-19-1.um	GUUUUACUUUAAUGGAA	820	UCUUCCAUUAAAGUAAUAC	1690	2434-2452
AD04475-19-1.um	ACUUUAAUGGAAGCAAGUA	821	UACUUGCUUCCAUAUAAAGU	1691	2439-2457
AD04476-19-1.um	UCCACAAAAUGAAGAUUUA	822	UAAAUCUUAUUUGUGGGA	1692	2459-2477
AD04477-19-1.um	GCUGCACCAUGCCAUUCUA	823	UUAGAUUGCAUGGUGCAGC	1693	2485-2503
AD04478-19-1.um	ACCAUGCCAUUAUAGAGA	824	UCUCUAUAGAUUGCAUGGU	1694	2490-2508
AD04479-19-1.um	AUGCCAUCUAUAGAGAUAA	825	UUUUCUUAUAGAUUGGCAU	1695	2493-2511
AD04480-19-1.um	UGCCAUCUAUAGAGAUAGA	826	UCUUCUCUAUAGAUUGGCA	1696	2494-2512
AD04481-19-1.um	CAAGGAGCAUGCAAAAGUA	827	UAUCUUUGCAUGCUCUUG	1697	2574-2592
AD04482-19-1.um	AGAUAAUCCUGGGGAAAAA	828	UUUUUUUUUUUUUUUUUUUU	1698	2588-2606
AD04483-19-1.um	GGGAAUUGUCACUUAUGA	829	UCAUAAUGAGACAAUUCUCC	1699	2649-2667
AD04484-19-1.um	AGGACAUCUUGUCAAAAA	830	UCUUUUGACAAAGAUUGUCCU	1700	2681-2699
AD04485-19-1.um	GACAUUCUUGUCAAAAAGUA	831	UGACUUUUGACAAAGAUUGC	1701	2683-2701
AD04486-19-1.um	GGUCGAAGAUCAAUUUACA	832	UGUAAAUUUGAUUUUUGGACC	1702	2716-2734
AD04487-19-1.um	GAAGAUCAAUUUACAAGAA	833	UUUUUUUUUUUUUUUUUUUU	1703	2720-2738
AD04488-19-1.um	GAUCAAUUUACAAGACCUA	834	UAGGUCUUUGUAAAUUGAUC	1704	2723-2741
AD04489-19-1.um	CUAAAGGACUAACAUAUAAA	835	UUUUUUGUUUAGUCCUUUAG	1705	2812-2830
AD04490-19-1.um	ACUAAACUAUAAAUUCUGUGA	836	UCACAGAUUUUUUUGUUUAGU	1706	2819-2837
AD04491-19-1.um	AACAUAAAAUUCUGUGAAUA	837	UAUUCACAGAUUUUUUUGUU	1707	2822-2840
AD04492-19-1.um	CAUAAAAUUCUGUGAAUUA	838	UUAAUUUACAGAUUUUUUAG	1708	2824-2842
AD04493-19-1.um	AUCUGAGAAUUUAAAAAGA	839	UCUUUUUUUUUUUUCACAGAU	1709	2830-2848
AD04494-19-1.um	UUUAGUGCUUUUACAUGCUA	840	UAGCAUGUAAAGCACUAAA	1710	2968-2986

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AD04495-19-1.um	UUUACAUGCUGUCUCUUA	841	UAAGAGCACAGCAUGUAAA	1711	2976-2994
AD04496-19-1.um	UACAUGCUGUCUCUUUGA	842	UCAAAGAGCACAGCAUGUA	1712	2978-2996
AD04497-19-1.um	AGAUGGUAAUUCUACAGCUA	843	UAGCUGUAGAUUACCAUCU	1713	3035-3053
AD04498-19-1.um	AAGUUUUGAUGAAAUUCUA	844	UAGA AUUUCAUCAAAAACUU	1714	3084-3102
AD04499-19-1.um	UGAUGAAAUUCUUGAAGUA	845	UACUCAAAGAAUUUCAUCA	1715	3090-3108
AD04500-19-1.um	GAUGAAAUUCUUGAAGUUA	846	UAACUCAAAGAAUUUCAUC	1716	3091-3109
AD04501-19-1.um	AUGAAAUUCUUGAAGUUA	847	UGAACUUAAGAAUUUCAU	1717	3092-3110
AD04502-19-1.um	CUUGAAGUUCAUUGGUGAUA	848	UAUCACCAUGAACUUAAG	1718	3100-3118
AD04503-19-1.um	UGAAGUUCAUUGGUGAUCA	849	UUGAUCACCAUGAACUUA	1719	3102-3120
AD04504-19-1.um	AGUUCAUUGGUGAUCAGUA	850	UCACUGAUCACCAUGAACU	1720	3105-3123
AD04505-19-1.um	UCAUGGUGAUCAGUGCAA	851	UUUGCACUGAUCACCAUGA	1721	3108-3126
AD04506-19-1.um	UGGUGAUCAGUGCAAUUGA	852	UCAAUUGCACUGAUCACCA	1722	3111-3129
AD04507-19-1.um	GGUGAUCAGUGCAAUUGAA	853	UUCAAUUGCACUGAUCACC	1723	3112-3130
AD04508-19-1.um	UGAAACUCCUGAUUUUGUA	854	UACAAAUCAGGAGUUUCA	1724	3186-3204
AD04509-19-1.um	AACUCCUGAUUUUGUAGUA	855	UACUACAAAUCAGGAGUU	1725	3189-3207
AD04510-19-1.um	CUCUGAUUUUGUAGUUAA	856	UUAAUACAAAUCAGGAG	1726	3191-3209
AD04511-19-1.um	UCCUGAUUUUGUAGUUAAA	857	UUUAAUACAAAUCAGGA	1727	3192-3210
AD04512-19-1.um	UAGUUAUUUUUUAAAGUCA	858	UGACUUAUUAAAUUAAACUA	1728	3203-3221
AD04513-19-1.um	UAUUAAAGUCUGGGAGUUA	859	UUACAUCCCAGACUUAUA	1729	3212-3230
AD04514-19-1.um	UGUAGAACUUCAGAAAGUA	860	UACUUCUUGAAGUUCUACA	1730	3226-3244
AD04515-19-1.um	UUCAGAGAGUAAAGAGCUAA	861	UUAGCUCUUACUUCUUGAA	1731	3234-3252
AD04516-19-1.um	UCAAGAGAGUAAAGAGCUAAA	862	UUUAGCUCUUACUUCUUGA	1732	3235-3253
AD04517-19-1.um	CAAGAAGUAAAGAGCUAAGA	863	UCUUAGCUCUUACUUCUUG	1733	3236-3254
AD04518-19-1.um	AGAAGUAAGAGCUAAGUUA	864	UAACUUAAGCUCUUAACUUCU	1734	3238-3256
AD04519-19-1.um	UCAGCAUUAUUCUUCAGAA	865	UUCUGAAGAAUAAUGCUGA	1735	3320-3338
AD04520-19-1.um	AAGGGGACCUUUUUUCUUA	866	UAAGAAAACAGGUCCCCUU	1736	3337-3355
AD04521-19-1.um	UCUUCAGGGAAGAAACAA	867	UUGUUUCUCCCCUUGAAGA	1737	3351-3369
AD04522-19-1.um	AAACUACAGAAUAAUGUGA	868	UCACAUUAUUCUGUAGUUU	1738	3380-3398
AD04523-19-1.um	ACUACAGAAUAAUGUGUUA	869	UAACACAUUAUUCUGUAGU	1739	3382-3400
AD04524-19-1.um	UCCGCAGGCUAUUUGUUA	870	UGAACAAAUAAGCCUGCGGA	1740	3447-3465

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AD04525-19-1.um	GCAGGCUAUUUGUUCAGAA	871	UUCUGAACAAAUAGCCUGC	1741	3450-3468
AD04526-19-1.um	UGUUCAGAGAGGCCUUUUA	872	UAAAAGGCCUCUCUGAACA	1742	3460-3478
AD04527-19-1.um	CAGAGAGGCCUUUUGUUUA	873	UAAACAAAAGGCCUCUCUG	1743	3464-3482
AD04528-19-1.um	AGAGAGGCCUUUUGUUUA	874	UUAAACAAAAGGCCUCUCU	1744	3465-3483
AD04529-19-1.um	GAGAGGCCUUUUGUUUAAA	875	UUUAAACAAAAGGCCUCUC	1745	3466-3484
AD04530-19-1.um	AGAGGCCUUUUGUUUAAA	876	UUUAAACAAAAGGCCUCU	1746	3467-3485
AD06321.um	GACCAUCUGCAUGAUGUCCAA	3157	UUGGACAUC AUGCAGAU GGUC	3165	185-206
AD06322.um	UACUGGUACAUAAGAUCUA	3158	UAGAUCUU AUUGUU ACCAGUA	3166	215-236
AD06323.um	GUCCAGUUC CAGAAUUUACGA	3159	UCGUAAA UUUCUGGAAACUGGAC	3167	336-357
AD06324.um	UGUAUUCAGUACAGUUGUCA	3160	UUGACAACUGUACUGAAUACA	3168	416-437
AD06321-19-1.um	CCAUCUGCAUGAUGUCCAA	3161	UUGGACAUC AUGCAGAU GG	3169	187-206
AD06322-19-1.um	CUGGUACAUAAGAUCUA	3162	UAGAUCUU AUUGUU ACCAG	3170	217-236
AD06323-19-1.um	CCAGUUC CAGAAUUUACGA	3163	UCGUAAA UUUCUGGAAACUGG	3171	338-357
AD06324-19-1.um	UAUUCAGUACAGUUGUCA	3164	UUGACAACUGUACUGAAUA	3172	418-437
AD06076.um	GCTACAAATGTTGTCAAGACTA	3181	TAGTCTTGACAACATTTGTAGC	3389	100-120
AD06152.um	CATGATGTCCATGAACATGTA	3182	TACATGTTTCATGGACATCATG	3390	195-215
AD06612.um	TCCAAGAGAATTGAACCAAGA	3183	TCTGGTTCAATTCTCTTGA	3391	997-1017
AD06613.um	AAGAGAATTGAACCAAGTGT	3184	TACACTTGGTTCAATTCTCTT	3392	1000-1020
AD06614.um	AAAAAGTTGAGGTTATAAAAACA	3185	TGTTTATAAACCTCAACTTTT	3393	1290-1310
AD06617.um	CTTTATATCCGTTTCCAGTCA	3186	TGACTGGAAAACGGATATAAAG	3394	2032-2052
AD06618.um	AACTGTATTACTTTAATGGAA	3187	TTCCATTAAAGTAATACAGTT	3395	2431-2451
AD06619.um	GACATGTTTACTGGTAACAAA	3188	TTTGTACCAGTAAACATGTC	3396	208-228
AD06624.um	GGTTATTACCCTAAGTTTAGA	3189	TCTAAACTTAGGGTAATAACC	3397	1071-1091
AD06629.um	CAGAAATGTTGGTAGTTCAAAA	3190	TTTGAACACTACCAACATTCGT	3398	2413-2433
AD06632.um	GATGTAGAACTTCAAGAAGTA	3191	TACTTCTTGAAGTTCTACATC	3399	3225-3245
AD06325.um	TTGAATGAAGCTTTGCCCTTA	3192	TAAGGGCAAAAGCTTCATTCAA	3400	466-486
AD01021.um	GGTTGTCAAGACTTTTTCGAA	3193	TTCGAAAAAGCTTTGACAACC	3401	107-127
AD01022.um	GTGTCAAGACTTTTTCGAATA	3194	TATTCGAAAAAGCTTTGACAC	3402	109-129
AD01023.um	GTGCATGATGTCCATGAACAA	3195	TTGTTTCATGGACATCATGCAC	3403	192-212
AD01024.um	GTGTTTACTGGTAACAATAAA	3196	TTTATTGTTACCAGTAAACAC	3404	211-231

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AD01025.um	GATAAGATCTGTGGTTGGAAA	3197	TTTCCAACCACAGATCTTATC	3405	226-246
AD02039.um	TTTCGAATGCATGGCCTCTTA	3198	TAAGAGGCCATGCATTCGAAA	3406	121-141
AD02042.um	ACTGGTAACAATAAGATCTGA	3199	TCAGATCTTATTGTTACCAGT	3407	217-237
AD02043.um	TAAACAATAAGATCTGTGGTTA	3200	TAACCACAGATCTTATTGTTA	3408	222-242
AD02044.um	TGTGGTTGGAATTATGAATGA	3201	TCATTCAATAATTCCAACCACA	3409	235-255
AD02045.um	ATTATGAATGTCCAAAAGTTA	3202	TAAACTTTGGACATTCATAAT	3410	245-265
AD02046.um	GTCCAAAAGTTTGAAGAGGATA	3203	TATCCTCTTCAAACTTTGGAC	3411	254-274
AD02047.um	TGAAGAGGATGTTTGGAGCAA	3204	TTGCTCAAAAACATCCTCTTCA	3412	264-284
AD02048.um	AAGAGGATGTTTTGAGCAGTA	3205	TACTGCTCAAAAACATCCTCTT	3413	266-286
AD02049.um	TGTTTTGAGCAGTGACATTAA	3206	TTAATGTCACTGCTCAAAAACA	3414	273-293
AD02050.um	TTTGAGCAGTGACATTATAAA	3207	TTTATAATGTCACTGCTCAAA	3415	276-296
AD02051.um	CATTATAATTCTGACAATAAA	3208	TTTATTGTCAGAAATTATAATG	3416	288-308
AD02052.um	TGACAAATAACACGATGCATAA	3209	TTATGCATCGTGTATTGTCA	3417	299-319
AD02053.um	CTGTATATTTACTTCCAGTTA	3210	TAACTGGAAGTAAATATACAG	3418	325-345
AD02054.um	TGTATATTTACTTCCAGTTCA	3211	TGAACTGGAAGTAAATATACA	3419	326-346
AD02055.um	GTATATTTACTTCCAGTTCCA	3212	TGGAACCTGGAAGTAAATATAC	3420	327-347
AD02056.um	TTACTTCCAGTTCAGAAATTA	3213	TAAITCTGGAACTGGAAAGTAA	3421	333-353
AD02057.um	CAGAAATTTACGTCAACTTGGA	3214	TCCAAAGTTGACGTAAATTTCTG	3422	346-366
AD02058.um	CCTTTTCACAAATTTTCTCAAA	3215	TTTGAGAAAAATTTGAAAAAGG	3423	393-413
AD02060.um	CAGTACAGTTGTCAATTCACTA	3216	TAGTGAATGACAACTGTACTG	3424	423-443
AD02061.um	AGTACAGTTGTCAATTCACTTA	3217	TAAGTGAATGACAACTGTACT	3425	424-444
AD02062.um	GACAGGCTTGAATGAAGCTTA	3218	TAAGCTTCATTCAAGCCTGTC	3426	459-479
AD02063.um	CCTCGATGCTCTTGTGAATA	3219	TATTCAACAAGAGCATCGAGG	3427	612-632
AD02064.um	TTGAACAAGTTATTAACCCCTAA	3220	TTAGGGTAATAAAGTTGTTCAA	3428	1064-1084
AD02067.um	TTGATGAAAATCTTGAAGTTA	3221	TAACTTCAAGAATTTTCATCAA	3429	3090-3110
AD02068.um	CTTGAAAGTTTCATGGTGATCAA	3222	TTGATCACCATGAACCTTCAAG	3430	3101-3121
AD02069.um	AACCTCTGATTTGTAGTTAA	3223	TTAACTACAAAAATCAGGAGTT	3431	3190-3210
AD02070.um	TGTAGTTAAATTTATTAAGTCA	3224	TGACTTAAATAAATTAAGTACA	3432	3202-3222
AD02071.um	AATCAGCATTATTTCTTCAGAA	3225	TTCTGAAGAATAAATGCTGATT	3433	3319-3339
AD02072.um	TTTGTTCAAGAGAGGCCTTTTA	3226	TAAAAGGCCTCTCTGAAACAAA	3434	3459-3479

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AD02073.um	TTCAGAGAGGCCTTTTGT	3227	TAAACAAAAGGCCTCTCTGAA	3435	3463-3483
AD02074.um	AGAGAGGCCTTTTGTAAAA	3228	TTTAAACAAAAGGCCTCTCT	3436	3466-3486
AD02302.um	CATTCACTTCTTAGACAAAGA	3229	TCCTTGTCTAAGAAGTGAATG	3437	435-455
AD02303.um	AATTGACAGGCTTGAATGAAA	3230	TTTCATTCAAGCCTGTCAATT	3438	455-475
AD02304.um	TGTCAAGTACATCTTCTTTGA	3231	TCAAAAGAAAGATGACTTGACA	3439	1104-1124
AD02305.um	AGAAAAGAAAAGTTGAGGTTAA	3232	TTAACCTCAACTTTTCTTTCT	3440	1284-1304
AD02311.um	CAGAAATGTTGGTAGTTCAAAA	3233	TTTGAACCTACCAACATCTG	3441	2413-2433
AD02313.um	TGATGAAATTTCTTGAAGTTCA	3234	TGAACCTTCAAGAAATTTTCATCA	3442	3091-3111
AD02314.um	GATGTAGAACTTCAAGAAAGTA	3235	TACTTCTTGAAGTTCTACATC	3443	3225-3245
AD02610.um	GTATATTTACTTCCAGTTCCA	3236	TGGAACCTGGAAGTAAATATAC	3444	327-347
AD02613.um	CAGTACAGTTGTCAATCACTA	3237	TAGTGAATGACAACTGTACTG	3445	423-443
AD02614.um	CCTTTCACAATTTTCTCAAA	3238	TTTGAGAAAATTTGTGAAAAGG	3446	393-413
AD02615.um	CATTCACTTCTTAGACAAAGA	3239	TCCTTGTCTAAGAAGTGAATG	3447	435-455
AD06077.um	CTACAAATGTTGTCAAGACTTA	3240	TAAGTCTTGACAAACATTGTAG	3448	101-121
AD06078.um	ACAAATGTTGTCAAGACTTTTA	3241	TAAAAGTCTTGACAAACATTGT	3449	103-123
AD06079.um	TCAAGACTTTTTCGAATGCAA	3242	TTGCATTGAAAAAGTCTTGA	3450	112-132
AD06080.um	CAAGACTTTTTCGAATGCATA	3243	TATGCATTGAAAAAGTCTTG	3451	113-133
AD06081.um	AGACTTTTTCGAATGCATGGA	3244	TCCATGGATTGAAAAAAGTCT	3452	115-135
AD06082.um	GACTTTTTCGAATGCATGGCA	3245	TGCCATGCATTGAAAAAAGTC	3453	116-136
AD06083.um	ACTTTTTCGAATGCATGGCCA	3246	TGGCCATGCATTGAAAAAAGT	3454	117-137
AD06084.um	CTTTTTCGAATGCATGGCCTA	3247	TAGGCCATGCATTGAAAAAAG	3455	118-138
AD06085.um	TTTTTCGAATGCATGGCCTCA	3248	TGAGGCCATGCATTGAAAAAA	3456	119-139
AD06086.um	TTTTTCGAATGCATGGCCTCTA	3249	TAGAGGCCATGCATTGAAAAA	3457	120-140
AD06087.um	TTCGAATGCATGGCCTCTTTA	3250	TAAAGAGGCCATGCATTGCGAA	3458	122-142
AD06088.um	TCGAATGCATGGCCTCTTTGA	3251	TCAAAAGAGGCCATGCATTGCA	3459	123-143
AD06089.um	CGAATGCATGGCCTCTTTGTA	3252	TACAAAAGAGGCCATGCATTGCG	3460	124-144
AD06090.um	GAATGCATGGCCTCTTTGTGA	3253	TCACAAAAGAGGCCATGCATTTC	3461	125-145
AD06091.um	AATGCATGGCCTCTTTGTGGA	3254	TCCACAAAAGAGGCCATGCATT	3462	126-146
AD06092.um	ATGCATGGCCTCTTTGTGGCA	3255	TGCCACAAAAGAGGCCATGCAT	3463	127-147
AD06093.um	TGCATGGCCTCTTTGTGGCCA	3256	TGGCCACAAAAGAGGCCATGCA	3464	128-148

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AD06094.um	GCAATGGCCCTCTTTGTGGCCTA	3257	TAGGCCACAAAGAGGCCATGC	3465	129-149
AD06095.um	CATGGCCCTCTTTGTGGCCTCA	3258	TGAGGCCACAAAGAGGCCATG	3466	130-150
AD06096.um	ATGGCCCTCTTTGTGGCCTCCA	3259	TGGAGGCCACAAAGAGGCCAT	3467	131-151
AD06097.um	TGGCCCTCTTTGTGGCCTCCCA	3260	TGGAGGCCACAAAGAGGCCA	3468	132-152
AD06098.um	GGCCCTCTTTGTGGCCTCCCAA	3261	TTGGGAGGCCACAAAGAGGCC	3469	133-153
AD06099.um	GCCTCTTTGTGGCCTCCCAT	3262	TATGGGAGGCCACAAAGAGGC	3470	134-154
AD06100.um	CCCTCTTTGTGGCCTCCCATCA	3263	TGATGGGAGGCCACAAAGAGG	3471	135-155
AD06101.um	CTCTTTGTGGCCTCCCATCCA	3264	TGGATGGGAGGCCACAAAGAG	3472	136-156
AD06102.um	TCTTTGTGGCCTCCCATCCCA	3265	TGGATGGGAGGCCACAAAGA	3473	137-157
AD06103.um	CTTTGTGGCCTCCCATCCCTA	3266	TAGGGATGGGAGGCCACAAAG	3474	138-158
AD06104.um	TTTGTGGCCTCCCATCCCTGA	3267	TCAGGGATGGGAGGCCACAAA	3475	139-159
AD06105.um	TTGTGGCCTCCCATCCCTGGA	3268	TCCAGGGATGGGAGGCCACAA	3476	140-160
AD06106.um	TGTGGCCTCCCATCCCTGGGA	3269	TCCAGGGATGGGAGGCCACA	3477	141-161
AD06107.um	GTGGCCTCCCATCCCTGGGAA	3270	TTCCAGGGATGGGAGGCCAC	3478	142-162
AD06108.um	TGGCCTCCCATCCCTGGGAAA	3271	TTTCCAGGGATGGGAGGCCA	3479	143-163
AD06109.um	GGCCTCCCATCCCTGGGAAGA	3272	CTTCCAGGGATGGGAGGCC	3480	144-164
AD06110.um	GCCTCCCATCCCTGGGAAGTA	3273	TACTTCCAGGGATGGGAGGC	3481	145-165
AD06111.um	CCTCCCATCCCTGGGAAGTCA	3274	TGACTTCCAGGGATGGGAGG	3482	146-166
AD06112.um	CTCCCATCCCTGGGAAGTCAA	3275	TTGACTTCCAGGGATGGGAG	3483	147-167
AD06113.um	TCCCATCCCTGGGAAGTCATA	3276	TATGACTTCCAGGGATGGGA	3484	148-168
AD06114.um	CCCATCCCTGGGAAGTCATAA	3277	TTATGACTTCCAGGGATGGG	3485	149-169
AD06115.um	CCATCCCTGGGAAGTCATAGA	3278	TCATGACTTCCAGGGATGG	3486	150-170
AD06116.um	ATCCCTGGGAAGTCATAGTGA	3279	TCACTATGACTTCCAGGGAT	3487	152-172
AD06117.um	TCCCTGGGAAGTCATAGTGA	3280	TCCACTATGACTTCCAGGGA	3488	153-173
AD06118.um	CCCTGGGAAGTCATAGTGGGA	3281	TCCCACTATGACTTCCAGGG	3489	154-174
AD06119.um	CCTGGGAAGTCATAGTGGGGA	3282	TCCCACTATGACTTCCAGG	3490	155-175
AD06120.um	CTGGGAAGTCATAGTGGGGAA	3283	TCCCACTATGACTTCCAG	3491	156-176
AD06121.um	TGGGAAGTCATAGTGGGGACA	3284	TGTCCCACTATGACTTCCCA	3492	157-177
AD06122.um	GGGAAGTCATAGTGGGGACAA	3285	TTGTCCCACTATGACTTCCC	3493	158-178
AD06123.um	GGAAAGTCATAGTGGGGACAGA	3286	TCTGTCCCACTATGACTTCC	3494	159-179

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AD06124.um	GAAGTCATAGTGGGACAGTA	3287	TACTGTCCCACATATGACTTC	3495	160-180
AD06125.um	AAGTCATAGTGGGACAGTGA	3288	TCACGTGTCCCACATATGACTT	3496	161-181
AD06126.um	AGTCATAGTGGGACAGTGAA	3289	TTCACGTGTCCCACATATGACT	3497	162-182
AD06127.um	GTCATAGTGGGACAGTGACA	3290	TGTCACGTGTCCCACATATGAC	3498	163-183
AD06128.um	TCATAGTGGGACAGTGACAA	3291	TTGTCACGTGTCCCACATATGA	3499	164-184
AD06129.um	CATAGTGGGACAGTGACACA	3292	TGTCACGTGTCCCACATATG	3500	165-185
AD06130.um	ATAGTGGGACAGTGACACTA	3293	TAGTGTCACTGTCCCCACTAT	3501	166-186
AD06131.um	TAGTGGGACAGTGACACTGA	3294	TCAGTGTCACTGTCCCCACTA	3502	167-187
AD06132.um	AGTGGGACAGTGACACTGAA	3295	TTCAGTGTCACTGTCCCCACT	3503	168-188
AD06133.um	GTGGGACAGTGACACTGACA	3296	TGTCAGTGTCACTGTCCCCAC	3504	169-189
AD06134.um	TGGGACAGTGACACTGACCA	3297	TGGTCAGTGTCACTGTCCCCA	3505	170-190
AD06135.um	GGGGACAGTGACACTGACCAA	3298	TTGGTCAGTGTCACTGTCCCC	3506	171-191
AD06136.um	GGGACAGTGACACTGACCATA	3299	TATGGTCAGTGTCACTGTCCCC	3507	172-192
AD06137.um	GGACAGTGACACTGACCATCA	3300	TGATGGTCAGTGTCACTGTCCC	3508	173-193
AD06138.um	GACAGTGACACTGACCATCTA	3301	TAGATGGTCAGTGTCACTGTCC	3509	174-194
AD06139.um	ACAGTGACACTGACCATCTGA	3302	TCAGATGGTCAGTGTCACTGT	3510	175-195
AD06140.um	CAGTGACACTGACCATCTGCA	3303	TGCAGATGGTCAGTGTCACTG	3511	176-196
AD06141.um	AGTGACACTGACCATCTGCAA	3304	TTGCAGATGGTCAGTGTCACT	3512	177-197
AD06142.um	GTGACACTGACCATCTGCGATA	3305	TATGCAGATGGTCAGTGTCCAC	3513	178-198
AD06143.um	TGACACTGACCATCTGCGATGA	3306	TCATGCAGATGGTCAGTGTCA	3514	179-199
AD06144.um	GACACTGACCATCTGCGATGAA	3307	TTCATGCAGATGGTCAGTGTCC	3515	180-200
AD06145.um	ACACTGACCATCTGCGATGATA	3308	TATCATGCAGATGGTCAGTGT	3516	181-201
AD06146.um	ACTGACCATCTGCGATGATGA	3309	TACATCATGCAGATGGTCACT	3517	183-203
AD06147.um	CTGACCATCTGCGATGATGTCA	3310	TGACATCATGCAGATGGTCCAG	3518	184-204
AD06148.um	TGACCATCTGCGATGATGTCCA	3311	TGGACATCATGCAGATGGTCA	3519	185-205
AD06149.um	CCATCTGCGATGATGTCCATGA	3312	TCATGGACATCATGCAGATGG	3520	188-208
AD06150.um	TCTGCGATGATGTCCATGAACA	3313	TGTCATGGACATCATGCAGAGA	3521	191-211
AD06151.um	TGCGATGATGTCCATGAACATA	3314	TATGTTTATGGACATCATGCA	3522	193-213
AD06153.um	ATGATGTCCATGAACATGTTA	3315	TAACATGTTTATGGACATCAT	3523	196-216
AD06154.um	ATGTCCATGAACATGTTTACA	3316	TGTAACATGTTTATGGACAT	3524	199-219

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AD06155.um	GTCCATGAACATGTTTACTGA	3317	TCAGTAAACATGTTTCATGGAC	3525	201-221
AD06156.um	TCCATGAACATGTTTACTGGA	3318	TCCAGTAAACATGTTTCATGGA	3526	202-222
AD06157.um	CATGTTTACTGGTAACAATAA	3319	TTATTGTTACCAGTAAACATG	3527	210-230
AD06158.um	TTTACTGGTAACAATAAGATA	3320	TATCTTATTGTTACCAGTAAA	3528	214-234
AD06159.um	GGTAACAATAAAGATCTGTGGA	3321	TCCACAGATCTTATTGTTACC	3529	220-240
AD06160.um	GTAACAATAAAGATCTGTGGTA	3322	TACCACAGATCTTATTGTTAC	3530	221-241
AD06161.um	ATCTGTGGTTGGAATTATGAA	3323	TTCATAATTCCAAACCACAGAT	3531	232-252
AD06162.um	TCTGTGGTTGGAATTATGAAA	3324	TTTCATAATTCCAAACCACAGA	3532	233-253
AD06163.um	CTGTGGTTGGAATTATGAATA	3325	TATTCATAATTCCAAACCACAG	3533	234-254
AD06164.um	GTGGTTGGAATTATGAATGTA	3326	TACATTTCATAAATCCAAACCAC	3534	236-256
AD06165.um	TTGGAATTATGAATGTCCAAA	3327	TTTGACATTCATAAATCCAA	3535	240-260
AD06166.um	GGAATTATGAATGTCCAAAGA	3328	TCITTTGGACATTCATAAATCC	3536	242-262
AD06167.um	GAATTATGAATGTCCAAAGTA	3329	TACTTTGGACATTCATAAATTC	3537	243-263
AD06168.um	TTATGAATGTCCAAAGTTTGA	3330	TCAAACTTTGGACATTCATAA	3538	246-266
AD06169.um	TGAATGTCCAAAGTTTGAAGA	3331	TCITCAAACTTTGGACATTCA	3539	249-269
AD06170.um	AATGTCCAAAGTTTGAAGAGA	3332	TCCTTCAAACTTTGGACATT	3540	251-271
AD06171.um	ATGTCCAAAGTTTGAAGAGGA	3333	TCCTTCAAACTTTGGACAT	3541	252-272
AD06172.um	TGTCCAAAGTTTGAAGAGGAA	3334	TTCTCTTCAAACTTTGGACA	3542	253-273
AD06173.um	TCCAAAGTTTGAAGAGGATGA	3335	TCATCTCTTCAAACTTTGGGA	3543	255-275
AD06174.um	CCAAAGTTTGAAGAGGATGTA	3336	TACATCTCTTCAAACTTTGG	3544	256-276
AD06175.um	CAAAGTTTGAAGAGGATGTTA	3337	TAACATCTCTTCAAACTTTG	3545	257-277
AD06176.um	AAGTTTGAAGAGGATGTTTA	3338	TAAACATCTCTTCAAACTT	3546	259-279
AD06177.um	AGTTTGAAGAGGATGTTTGA	3339	TCAAACATCTCTTCAAACT	3547	260-280
AD06178.um	GTTTGAAGAGGATGTTTGA	3340	TTCAAAACATCTCTTCAAAAC	3548	261-281
AD06179.um	TTTGAAGAGGATGTTTGA	3341	TCCTCAAAACATCTCTTCAAA	3549	262-282
AD06180.um	TTGAAGAGGATGTTTGA	3342	TGCTCAAAACATCTCTTCA	3550	263-283
AD06181.um	GAAGAGGATGTTTGA	3343	TCCTCAAAACATCTCTTCTC	3551	265-285
AD06182.um	AGAGGATGTTTGA	3344	TCACTGCTCAAAACATCTCT	3552	267-287
AD06183.um	GAGGATGTTTGA	3345	TTCACTGCTCAAAACATCTCTC	3553	268-288
AD06184.um	AGGATGTTTGA	3346	TGTCACCTGCTCAAAACATCTCT	3554	269-289

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AD06185.um	TTTGTGAGCAGTGACATTATAA	3347	TTATAATGTCACTGCTCAAAA	3555	275-295
AD06186.um	TTGAGCAGTGACATTATAATA	3348	TATTATAATGTCACTGCTCAA	3556	277-297
AD06187.um	TGAGCAGTGACATTATAATTA	3349	TAATTATAATGTCACTGCTCA	3557	278-298
AD06188.um	ACATTATAAATTCTGACAAATAA	3350	TTATTGTCAAGAAATTATAATGT	3558	287-307
AD06189.um	ATTATAAATTCTGACAAATAACA	3351	TGTTATTGTCAAGAAATTATAAT	3559	289-309
AD06190.um	TTATAAATTCTGACAAATAACAA	3352	TTGTTATTGTCAAGAAATTATAA	3560	290-310
AD06191.um	TATAAATTCTGACAAATAACACA	3353	TGTTATTGTCAAGAAATTATA	3561	291-311
AD06192.um	ATAATTCTGACAAATAACACGA	3354	TCGTGTTATTGTCAAGAAATTAT	3562	292-312
AD06193.um	TAATTCTGACAAATAACACGAA	3355	TTCGTGTTATTGTCAAGAAATTA	3563	293-313
AD06194.um	CTGACAAATAACACGATGCATA	3356	TATGCATCGTGTATTATTGTCAG	3564	298-318
AD06195.um	ACAATAACACGATGCATAGCA	3357	TGCTATGCATCGTGTATTGT	3565	301-321
AD06196.um	CAATAACACGATGCATAGCCA	3358	TGGCTATGCATCGTGTATTG	3566	302-322
AD06197.um	AATAACACGATGCATAGCCAA	3359	TTGGCTATGCATCGTGTATT	3567	303-323
AD06198.um	ATAACACGATGCATAGCCATA	3360	TATGGCTATGCATCGTGTATT	3568	304-324
AD06199.um	TAAACGATGCATAGCCATCA	3361	TGATGGCTATGCATCGTGTTA	3569	305-325
AD06200.um	AACACGATGCATAGCCATCCA	3362	TGGATGGCTATGCATCGTGT	3570	306-326
AD06201.um	ACACGATGCATAGCCATCCTA	3363	TAGGATGGCTATGCATCGTGT	3571	307-327
AD06202.um	CACGATGCATAGCCATCCTGA	3364	TCAGGATGGCTATGCATCGTG	3572	308-328
AD06203.um	ACGATGCATAGCCATCCTGTA	3365	TACAGGATGGCTATGCATCGT	3573	309-329
AD06204.um	CGATGCATAGCCATCCTGTAA	3366	TTACAGGATGGCTATGCATCG	3574	310-330
AD06205.um	GATGCATAGCCATCCTGTATA	3367	TATACAGGATGGCTATGCATC	3575	311-331
AD06206.um	ATGCATAGCCATCCTGTATAA	3368	TTATACAGGATGGCTATGCAT	3576	312-332
AD06207.um	TGCATAGCCATCCTGTATATA	3369	TATATACAGGATGGCTATGCA	3577	313-333
AD06208.um	GCATAGCCATCCTGTATATTA	3370	TAATATACAGGATGGCTATGC	3578	314-334
AD06209.um	CATAGCCATCCTGTATATTTA	3371	TAAATATACAGGATGGCTATG	3579	315-335
AD06210.um	ATAGCCATCCTGTATATTTAA	3372	TTAAATATACAGGATGGCTAT	3580	316-336
AD06211.um	TAGCCATCCTGTATATTTACA	3373	TGTAATATACAGGATGGCTA	3581	317-337
AD06212.um	AGCCATCCTGTATATTTACTA	3374	TAGTAAATATACAGGATGGCT	3582	318-338
AD06213.um	GCCATCCTGTATATTTACTTA	3375	TAAAGTAAATATACAGGATGGC	3583	319-339
AD06214.um	CCATCCTGTATATTTACTTCA	3376	TGAAAGTAAATATACAGGATGG	3584	320-340

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AD06215.um	ATCCTGTATATTTACTTCCAA	3377	TTGGAAAGTAAATATACAGGAT	3585	322-342
AD06216.um	TCCTGTATATTTACTTCCAGA	3378	TCCTGGAAAGTAAATATACAGGA	3586	323-343
AD06217.um	CCTGTATATTTACTTCCAGTA	3379	TACTGGAAAGTAAATATACAGG	3587	324-344
AD06218.um	ATATTTACTTCCAGTTCCAGA	3380	TCTGGAACTGGGAAGTAAATAT	3588	329-349
AD06219.um	TATTTACTTCCAGTTCCAGAA	3381	TTCTGGAACTGGGAAGTAAATA	3589	330-350
AD06220.um	TACTTCCAGTTCCAGAAATTA	3382	TAAATTTCTGGAACTGGGAAGTA	3590	334-354
AD06221.um	TCCAGAAATTTACGTCAACTTA	3383	TAAGTTGACGTAAATTTCTGGA	3591	344-364
AD06222.um	GTCAAACCTTGGATCAAAATATA	3384	TATATTTTGGATCCCAAGTTGAC	3592	356-376
AD06223.um	TCAAACCTTGGATCAAAAATATAA	3385	TTATATTTTGGATCCCAAGTTGA	3593	357-377
AD06224.um	CAAACTTGGATCAAAAATATATA	3386	TATATATTTTGGATCCCAAGTTG	3594	358-378
AD06225.um	AACTTGGATCAAAAATATATTA	3387	TAATATATTTTGGATCCCAAGTT	3595	359-379
AD06226.um	ACTTGGATCAAAAATATATTA	3388	TAAATATATTTTGGATCCCAAGT	3596	360-380

Table 2 shows certain chemically modified HMGCR RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, an RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex identified in a row in Table 2, column one and includes the sequence modifications show in the sense and antisense strand sequences in the same row in Table 2, columns three and six, respectively. In some embodiments of methods of the invention, a sequence shown in Table 2 may be attached to (also referred to herein as “conjugated to”) a compound capable of delivering the RNAi agent to a cell and/or tissue in a subject. A non-limiting example of a delivery compound that may be used in certain embodiments of the invention is a GalNAc-containing compound or a GLS-15*-containing compound. In Table 2, the first column indicates the Duplex AV# of the base sequences as shown in Table 1. Table 2 discloses Duplex AV# and also shows chemical modifications included in sense and antisense sequence of the duplexes. For example, Table 1 shows base single-strand sequences SEQ ID NO: 7 (sense) and SEQ ID NO: 877 (antisense), which together are the double-stranded duplex identified as: Duplex AD# AD00810.um and Table 2 lists Duplex AV# AV00810, which indicates that the duplex of SEQ ID NO: 1747 and SEQ ID NO: 2182 includes base sequences of SEQ ID NO: 7 and SEQ ID NO: 877, respectively, but with the chemical modifications shown in the sense and antisense sequences shown in columns three and six, respectively. The “Sense strand SS#” in Table 2 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 2 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six.

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Table 2: provides chemically modified HMGCR RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. These sequences were used in certain *in vitro* testing studies described herein.

Duplex AV#	Sense strand SS#	Sense Sequence	SEQ ID NO.	Antisense strand AS#	Antisense Sequence	SEQ ID NO.
AV00810	AV00810-SS	g*u*ugucacGfcaGfuUfuucgaa*a	1747	AV00810-AS	u*U*f*ucgaAfaagUfcUfuGfaca*a*c	2182
AV00811	AV00811-SS	u*g*ucaagaCfuUfuUfucgaug*a	1748	AV00811-AS	u*C*f*auucGfaaaaAfgUfcUfuga*c*a	2183
AV00812	AV00812-SS	c*a*ucugcaUfgAfuGfuccauga*a	1749	AV00812-AS	u*U*f*caugGfacaCfaUfgCfaga*u*g	2184
AV00813	AV00813-SS	g*a*uguccaUfgAfaCfauguuu*a	1750	AV00813-AS	u*U*f*aaacAfuguuCfaUfgGfaca*u*c	2185
AV00814	AV00814-SS	c*c*augaacAfuGfuUfuacuggu*a	1751	AV00814-AS	u*A*f*ccagUfaaacAfuGfuUfcau*g*g	2186
AV00815	AV00815-SS	c*a*ugaacaUfgUfuUfucugua*a	1752	AV00815-AS	u*U*f*accaGfuuaaCfaUfgUfuca*u*g	2187
AV00816	AV00816-SS	a*u*gaacauGfuUfuAfcugguu*a	1753	AV00816-AS	u*U*f*uaccAfguaaAfcAfuGfuuc*a*u	2188
AV00817	AV00817-SS	a*a*cauguUfaCfuGfguaacaa*a	1754	AV00817-AS	u*U*f*uguuAfcagUfaAfaCfaug*u*u	2189
AV00818	AV00818-SS	u*a*agaucuGfuGfgUfugaaau*a	1755	AV00818-AS	u*A*f*auucCfaacAfcAfgAfuca*u*a	2190
AV00819	AV00819-SS	a*g*aucuguGfgUfuGfgaauuau*a	1756	AV00819-AS	u*A*f*uaauUfecaacCfaAfcAfgau*c*u	2191
AV00820	AV00820-SS	a*g*aucuguGfgUfuGfgaauuau*a	1757	AV00820-AS	u*A*f*uaauUfecaacCfaAfcAfgau*c*u	2192
AV00821	AV00821-SS	a*a*uaugaAfuGfuCfcaaguu*a	1758	AV00821-AS	u*A*f*acuuUfggacAfuUfcAfuuaa*u*u	2193
AV00822	AV00822-SS	a*a*aguugAfaGfaGfgauguuu*a	1759	AV00822-AS	u*A*f*aacaUfcauUfuCfaAfaa*u*u	2194
AV00823	AV00823-SS	g*u*uuugagCfaGfuGfacaauuau*a	1760	AV00823-AS	u*A*f*uaauGfucacUfgCfuCfaaa*a*c	2195
AV00824	AV00824-SS	c*a*guagacUfuAfuAfaucuga*a	1761	AV00824-AS	u*U*f*cagaAfuuaaAfaUfgUfcau*u*g	2196
AV00825	AV00825-SS	g*a*cauuauAfaUfuCfugacaau*a	1762	AV00825-AS	u*A*f*uuugCfagaaUfuAfuAfaug*u*c	2197
AV00826	AV00826-SS	a*a*uuucugaCfaAfuAfaacagau*a	1763	AV00826-AS	u*A*f*ucguGfuuaUfgUfcAfgaa*u*u	2198
AV00827	AV00827-SS	c*a*uccuguAfuAfuUfuacuucc*a	1764	AV00827-AS	u*G*f*gaagUfaaaAfuAfaAfgga*u*g	2199
AV00828	AV00828-SS	c*a*guuccaGfaAfuUfuacuga*a	1765	AV00828-AS	u*U*f*gaagUfaaaUfcUfgGfaac*u*g	2200
AV00829	AV00829-SS	a*g*uuccagAfaUfuUfagucuaa*a	1766	AV00829-AS	u*U*f*ugacGfuuaaUfuCfuGfgaa*c*u	2201
AV00830	AV00830-SS	g*u*uccagaAfuUfuAfcuguaac*a	1767	AV00830-AS	u*G*f*uuGfa(cUNA)guaaAfuUfcUfgga*a*c	2202
AV00831	AV00831-SS	u*u*uaagucAfaCfuUfggaacaa*a	1768	AV00831-AS	u*U*f*ugauCfcaagUfuGfaCfguaa*a	2203
AV00832	AV00832-SS	u*u*acgucAfcUfuCfugaacaa*a	1769	AV00832-AS	u*U*f*uuugaUfcaacGfuUfgAfcgu*a*a	2204
AV00833	AV00833-SS	u*u*uguauuAfaGfuAfcaguuu*a	1770	AV00833-AS	u*A*f*caacUfguaaCfaUfcafaa*a	2205
AV00834	AV00834-SS	a*u*ucaguaCfaGfuUfgucauuc*a	1771	AV00834-AS	u*G*f*aaugAfaacUfgUfaCfugaa*a*u	2206

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AV00835	AV00835-SS	u*u*caguacAfgUfuGfcauua*a	1772	AV00835-AS	u*Uf*gaauGfcaacCfuGfuAfcug*a*a	2207
AV00836	AV00836-SS	u*a*caguugUfcAfuUfcauucua*a	1773	AV00836-AS	u*Af*gaagUfgaauGfaCfaAfcug*u*a	2208
AV00837	AV00837-SS	a*c*aguuguCfaUfuCfcauucuu*a	1774	AV00837-AS	u*Af*agaaGfugaafUfgAfcAfacu*g*u	2209
AV00838	AV00838-SS	u*u*gucauuCfaCfuUfcauagac*a	1775	AV00838-AS	u*Gf*ucuaAfgaagUfgAfaUfgac*a*a	2210
AV00839	AV00839-SS	u*g*ucauucAfcUfuCfuagaca*a	1776	AV00839-AS	u*Uf*gucaAfgaagGfuGfaAfuca*c*a	2211
AV00840	AV00840-SS	u*u*cuuagaCfaAfaGfaauugac*a	1777	AV00840-AS	u*Gf*ucuaUfuuuUfgUfcUfaag*a*a	2212
AV00841	AV00841-SS	g*a*augaagCfuUfuGfcauucuu*a	1778	AV00841-AS	u*Af*aaagGfgcaafUfgCfuUfcau*u*c	2213
AV00842	AV00842-SS	u*c*aguuccAfaCfuCfcaagau*a	1779	AV00842-AS	u*Af*uccuGfugagUfuGfgAfacu*g*a	2214
AV00843	AV00843-SS	g*a*aaauuUfgCfuCfugugau*a	1780	AV00843-AS	u*Af*uuccAfcgagCfaAfuAfuuu*u*c	2215
AV00844	AV00844-SS	u*g*euugugGfaAfuGfgcauua*a	1781	AV00844-AS	u*Af*auuGfcauUfcCfaCfagag*c*a	2216
AV00845	AV00845-SS	c*u*cgaugCfuUfuGfuaagau*a	1782	AV00845-AS	u*CT*auucAfaaaGfaGfcAfcug*a*g	2217
AV00846	AV00846-SS	g*a*ugcuuUfgUfuGfaugucu*a	1783	AV00846-AS	u*Af*gacaUfuaaCfaAfgAfgca*u*c	2218
AV00847	AV00847-SS	c*u*uguugaAfuGfuCfuugau*a	1784	AV00847-AS	u*Af*ucacAfgacAfuUfcAfaa*a*g	2219
AV00848	AV00848-SS	g*u*ugaugUfcUfuGfuauggg*a	1785	AV00848-AS	u*CT*cauGfcaaaGfaCfaUfuca*a*c	2220
AV00849	AV00849-SS	u*c*unguaUfuGfgAfguugua*a	1786	AV00849-AS	u*Uf*accaAfcuccAfaUfcAfaaa*g*a	2221
AV00850	AV00850-SS	u*c*ageuugAfaAfuUfaugucu*a	1787	AV00850-AS	u*Af*geacAfuaauUfuCfaAfgcu*g*a	2222
AV00851	AV00851-SS	u*u*uggeugCfaUfgUfcauucua*a	1788	AV00851-AS	u*Af*gaacUfgacaUfgCfaGfcca*a*a	2223
AV00852	AV00852-SS	a*c*uacuuCfuGfuUfcaugacu*a	1789	AV00852-AS	u*Af*gucaUfgaagAfcGfaAfgua*g*u	2224
AV00853	AV00853-SS	c*u*ucguuUfcAfuGfcauucua*a	1790	AV00853-AS	u*Af*gaagGfuaaGfaAfcAfga*a*g	2225
AV00854	AV00854-SS	u*u*guugugCfcUfuGfguaauag*a	1791	AV00854-AS	u*CT*uaauAfcacaaGfgAfcAfcac*a*a	2226
AV00855	AV00855-SS	c*u*aggeuuGfgUfuCfuaugua*a	1792	AV00855-AS	u*Uf*gaacAfgaagCfcAfaGfcau*a*g	2227
AV00856	AV00856-SS	g*a*uccuucUfcCfuCfaaagac*a	1793	AV00856-AS	u*CT*uguuUfugagGfaGfaAfgga*u*c	2228
AV00857	AV00857-SS	a*a*aaacguAfcAfgCfagaucua*a	1794	AV00857-AS	u*Af*guauCfugeuGfuAfcUfguu*u*u	2229
AV00858	AV00858-SS	a*g*uaagacAfgAfuAfcuucuaa*a	1795	AV00858-AS	u*Uf*uaagaAfguaaCfuGfcUfgua*c*u	2230
AV00859	AV00859-SS	a*c*agcagaUfaCfuUfcauaggu*a	1796	AV00859-AS	u*Af*ccuuAfgaagUfaUfcUfgcu*g*u	2231
AV00860	AV00860-SS	c*a*gcagauAfcUfuCfuaaguu*a	1797	AV00860-AS	u*Af*accuUfagaagGfaAfuCfugc*u*g	2232
AV00861	AV00861-SS	g*c*agauacUfuCfuAfaagguuc*a	1798	AV00861-AS	u*Gf*aaacCfuuaagAfaGfuAfcu*c*c	2233
AV00862	AV00862-SS	u*u*aggacuGfgAfuGfaaauu*a	1799	AV00862-AS	u*Af*cauuUfuaaCfcAfgUfcau*a*a	2234
AV00863	AV00863-SS	a*u*cagcauGfgAfuAfuagaaca*a	1800	AV00863-AS	u*Uf*guucAfuaaCfcAfuGfcug*a*u	2235

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AV00864	AV00864-SS	g*a*acaaguUfaUfuAfcuuaa*a	1801	AV00864-AS	u*CI*uuAfg(gUNA)guaaUfaAfcUfugu*u*c	2236
AV00865	AV00865-SS	a*g*uuuuCfcCfuAfguuuag*a	1802	AV00865-AS	u*CI*uaaaCfuuagGfgUfaAfuua*c*u	2237
AV00866	AV00866-SS	u*u*acceuaAfgUfuUfagcucuc*a	1803	AV00866-AS	u*Gf*agAfg(cUNA)uaaaCfuUfaGfggu*a*a	2238
AV00867	AV00867-SS	c*a*aguacaUfcUfuCfuuuagaa*a	1804	AV00867-AS	u*Gf*uucaAfgaaGfaUfgUfacu*u*g	2239
AV00868	AV00868-SS	c*c*uaucacAfuCfuCfcuguaa*u	1805	AV00868-AS	u*AI*cuacAfgagAfuGfuGfaa*g*g	2240
AV00869	AV00869-SS	u*a*gaggaaGfaGfaCfaggguu*a	1806	AV00869-AS	u*Uf*auccCfugucUfcUfuCfcuc*u*a	2241
AV00870	AV00870-SS	u*a*aaecgaGfaAfaGfaaagu*u	1807	AV00870-AS	u*AI*acuuUfuuUfcUfcGfguu*u*a	2242
AV00871	AV00871-SS	a*a*aguugaGfgUfuAfuuaa*c*a	1808	AV00871-AS	u*Gf*guuuUfaaaCfcUfcAfacu*u*u	2243
AV00872	AV00872-SS	c*a*gagcuaCfaUfuUfgugguu*a	1809	AV00872-AS	u*CI*aaCfc(aUNA)caaaUfgUfaGfeuc*u*g	2244
AV00873	AV00873-SS	a*g*cuacauUfuGfuGfgugguu*a	1810	AV00873-AS	u*Uf*accaAfcacAfaAfuGfuag*c*u	2245
AV00874	AV00874-SS	c*u*ccuccUfaCfuCfauacu*u	1811	AV00874-AS	u*AI*aguaUfcgagUfaAfgGfagg*a*g	2246
AV00875	AV00875-SS	a*c*acaggaaCfcCfuGfaaauu*a	1812	AV00875-AS	u*Uf*caauUfucagGfuUfcCfugu*g*u	2247
AV00876	AV00876-SS	a*a*ggugcaAfaAfuUfcuuagu*a	1813	AV00876-AS	u*AI*cuuaGfgaaUfuUfgCfacc*u*u	2248
AV00877	AV00877-SS	a*g*gugcaaaAfaUfuCfcuuagu*a	1814	AV00877-AS	u*CI*acuaAfgaaUfuUfuGfcac*c*u	2249
AV00878	AV00878-SS	c*u*uaugaUfgCfuGfaucau*a	1815	AV00878-AS	u*AI*ugauCfucagCfaUfcAfcua*a*g	2250
AV00879	AV00879-SS	a*g*aucaucCfaGfuUfagucau*a	1816	AV00879-AS	u*AI*ungaCfuacUfgGfaUfgau*c*u	2251
AV00880	AV00880-SS	g*a*ucauccAfgUfuAfgucaau*a	1817	AV00880-AS	u*CI*auugAfcuaaCfuGfgAfuga*u*c	2252
AV00881	AV00881-SS	c*a*uccaguUfaGfuCfaugcuu*a	1818	AV00881-AS	u*Uf*agcaUfugacUfaAfcUfgga*u*g	2253
AV00882	AV00882-SS	c*a*guuaguCfaAfuGfauagca*a	1819	AV00882-AS	u*Uf*gcuuAfgcauUfgAfcUfaac*u*g	2254
AV00883	AV00883-SS	u*u*agucaUfgCfuAfgcauau*a	1820	AV00883-AS	u*AI*uaugCfuuagCfaUfuGfau*a*a	2255
AV00884	AV00884-SS	a*g*ccuacaAfgUfuGfgaaacuc*a	1821	AV00884-AS	u*Gf*aguuUfccaaCfuUfgUfagg*c*u	2256
AV00885	AV00885-SS	g*u*uggaaaCfuCfuGfauggaaa*a	1822	AV00885-AS	u*Uf*uuccAfcuagAfgUfuUfcc*a*c	2257
AV00886	AV00886-SS	a*c*ucaugaGfcGfuGfgugauuc*a	1823	AV00886-AS	u*Gf*auacAfcacGfcUfcAfuga*g*u	2258
AV00887	AV00887-SS	u*u*ucagaaCfcUfuCfuucucuc*a	1824	AV00887-AS	u*Gf*agagAfgaaGfgUfuCfuga*a*a	2259
AV00888	AV00888-SS	u*a*cagggaUfuAfuAfuuaucuc*a	1825	AV00888-AS	u*Gf*aguaAfuuaAfaUfcCfcug*u*a	2260
AV00889	AV00889-SS	g*c*ungugaCfuCfuGfagaagu*a	1826	AV00889-AS	u*AI*cuucUfgcagAfgUfcAfcua*g*c	2261
AV00890	AV00890-SS	u*u*ugacagCfaCfuAfgcaguu*a	1827	AV00890-AS	u*AI*aucuGfcuagUfgCfuGfua*a*a	2262
AV00891	AV00891-SS	a*u*uugcacGfuCfuAfcagaaac*a	1828	AV00891-AS	u*Gf*uuucUfguagAfcGfuGfcaa*a*u	2263
AV00892	AV00892-SS	c*a*gaacuUfcAfuAfcagauu*a	1829	AV00892-AS	u*AI*uaauUfguauGfaAfgUfuuc*u*g	2264

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AV00893	AV00893-SS	g*g*acgcaaCfcUfuUfaauccg*a	1830	AV00893-AS	u*CI*ggauAfuuaaGfgUfuGfgcu*c*c	2265
AV00894	AV00894-SS	u*u*ucccuAfaAfuGfcauuc*a	1831	AV00894-AS	u*GI*auuUfgcauUfuCfaGfgga*a*a	2266
AV00895	AV00895-SS	u*u*agugguAfaCfuAfuugauu*a	1832	AV00895-AS	u*A*f*guacAfaugUfuAfcCfacu*a*a	2267
AV00896	AV00896-SS	g*g*uaacuaUfuGfuAfcugaca*a	1833	AV00896-AS	u*U*f*ugucAfguacAfaUfaGfuua*c*c	2268
AV00897	AV00897-SS	a*a*gaaccUfgCfuGfcauaaa*a	1834	AV00897-AS	u*U*f*uuauAfgcagCfaGfgUfuuc*u*u	2269
AV00898	AV00898-SS	a*a*ucuguuGfuUfuGfugagaagcu*a	1835	AV00898-AS	u*A*f*guuGfcaaaAfaCfaga*u*u	2270
AV00899	AV00899-SS	u*c*uguuuUfuGfuGfcaugcu*a	1836	AV00899-AS	u*A*f*cagcUfucacAfaAfcAfaca*g*a	2271
AV00900	AV00900-SS	u*c*agagaaGfuAfuUfaagacu*a	1837	AV00900-AS	u*A*f*guuUfuuaaUfcUfuCfucul*g*a	2272
AV00901	AV00901-SS	u*g*aggucaAfcAfuUfaacaaga*a	1838	AV00901-AS	u*U*f*cuugUfuuaaGfuUfgAfccu*c*a	2273
AV00902	AV00902-SS	c*c*caugcaGfcAfaAfcuugcu*a	1839	AV00902-AS	u*GI*acaaUfguuuGfcUfgCfaug*g*g	2274
AV00903	AV00903-SS	u*u*caaggaGfcAfuGfcaagau*a	1840	AV00903-AS	u*A*f*ucuuUfgcauGfcUfcCfuug*a*a	2275
AV00904	AV00904-SS	c*u*gggaaUfuGfuCfcauugcu*a	1841	AV00904-AS	u*CI*auaaGfugacAfaUfuCfccc*a*g	2276
AV00905	AV00905-SS	a*g*gaacuUfuGfuCfcaagcu*a	1842	AV00905-AS	u*GI*acuuUfugacAfaGfaUfguc*c*u	2277
AV00906	AV00906-SS	c*a*ggugcaAfgAfuCfcauuuac*a	1843	AV00906-AS	u*GI*uaaaUfugauCfuUfcGfacc*u*g	2278
AV00907	AV00907-SS	u*c*gaagauCfaAfuUfuacaaga*a	1844	AV00907-AS	u*U*f*cuugUfaaaUfgAfuCfuuc*g*a	2279
AV00908	AV00908-SS	g*g*acuacAfuAfaAfaucugcu*a	1845	AV00908-AS	u*CI*acagAfuuuAfuGfuUfagu*c*c	2280
AV00909	AV00909-SS	u*c*agagagGfuCfuCfagguuac*a	1846	AV00909-AS	u*A*f*gaacCfugagAfcCfuCfucv*g*a	2281
AV00910	AV00910-SS	g*c*uuuacaUfgCfuGfugcuu*a	1847	AV00910-AS	u*A*f*agagCfagagCfaUfgUfaaa*g*c	2282
AV00911	AV00911-SS	a*g*auuguaAfuCfuAfcagcuca*a	1848	AV00911-AS	u*U*f*gaGfc(uUNA)guagAfuUfaCfcau*c*u	2283
AV00912	AV00912-SS	u*u*lgauagaAfaUfuCfugaagcu*a	1849	AV00912-AS	u*A*f*cuucAfaagaaUfuUfcAfuca*a*a	2284
AV00913	AV00913-SS	a*u*ggugauCfaGfuGfcauuuga*a	1850	AV00913-AS	u*U*f*caauUfgcacUfgAfuCfacc*a*u	2285
AV01321	AV01321-SS	g*u*agcuacAfaUfgUfugcaaa*g*a	1851	AV01321-AS	u*CI*uuugaCfaacaUfuGfuAfgcu*a*c	2286
AV01322	AV01322-SS	a*a*lguuuguCfaAfgAfcuuuuu*c*a	1852	AV01322-AS	u*GI*aaaaAfgucUfgAfcAfaca*u*u	2287
AV01323	AV01323-SS	a*u*guugcuAfaGfaCfuuuuu*c*g*a	1853	AV01323-AS	u*CI*gaaaaAfgucUfuGfaCfaac*a*u	2288
AV01324	AV01324-SS	u*g*uuugcaAfgAfcUfuuuuugcu*a	1854	AV01324-AS	u*U*f*cgaaAfaaguCfuUfgAfcaaa*c*a	2289
AV01325	AV01325-SS	u*u*gucaagAfcUfuUfucgaa*u*a	1855	AV01325-AS	u*A*f*uuugAfaaaaGfuCfuUfgac*a*a	2290
AV01326	AV01326-SS	a*a*gaacuuUfuCfGfaugcuu*g*a	1856	AV01326-AS	u*CI*augcAfuugAfaAfaAfguc*u*u	2291
AV01327	AV01327-SS	c*a*ucccuGfgAfaGfcauagcu*a	1857	AV01327-AS	u*A*f*cuauGfcauuCfcCfaGfgga*u*g	2292
AV01328	AV01328-SS	c*a*cugaccAfuCfuGfcaugcuu*g*a	1858	AV01328-AS	u*CI*aucaUfgcagAfuGfgUfcaug*u*g	2293

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AV01329	AV01329-SS	a*c*caucugCfaUfgAfuugucca*u*a	1859	AV01329-AS	u*Af*uggaCfaucaUfgCfaGfang*g*u	2294
AV01330	AV01330-SS	a*u*ueauGfgaUfgUfcauga*a*a	1860	AV01330-AS	u*Uf*ueauGfgaUfgAfuGfcag*a*u	2295
AV01331	AV01331-SS	c*u*gcaugaUfgUfcfaugaac*a*a	1861	AV01331-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2296
AV01332	AV01332-SS	g*c*augaugUfcCfaUfgaauu*g*a	1862	AV01332-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2297
AV01333	AV01333-SS	u*g*auguccAfuGfAfcAugu*u*a	1863	AV01333-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2298
AV01334	AV01334-SS	u*g*uccaugAfaCfaUfguuuac*u*a	1864	AV01334-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2299
AV01335	AV01335-SS	u*g*aacaugUfuUfaCfugguuac*c*a	1865	AV01335-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2300
AV01336	AV01336-SS	g*a*acaugUfuUfaCfugguuac*c*a	1866	AV01336-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2301
AV01337	AV01337-SS	a*c*auguuuAfcUfgGfuuaac*a*u	1867	AV01337-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2302
AV01338	AV01338-SS	a*u*guuuuacUfgGfuUfaCfugguuac*c*a	1868	AV01338-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2303
AV01339	AV01339-SS	u*g*uuuacuGfgUfaAfcuuuac*g*a	1869	AV01339-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2304
AV01340	AV01340-SS	g*u*uuuacuGfgUfaAfcuuuac*g*a	1870	AV01340-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2305
AV01341	AV01341-SS	u*u*acugguAfaCfaUfguuuac*c*a	1871	AV01341-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2306
AV01342	AV01342-SS	u*g*guuacAfaUfaCfugguuac*c*a	1872	AV01342-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2307
AV01343	AV01343-SS	a*a*uaagauCfuGfuGfuuuac*c*a	1873	AV01343-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2308
AV01344	AV01344-SS	a*u*aagauCfuGfuGfuuuac*c*a	1874	AV01344-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2309
AV01345	AV01345-SS	a*a*gaucugUfgGfuUfaCfugguuac*c*a	1875	AV01345-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2310
AV01346	AV01346-SS	g*a*ucugugGfuUfgGfuuuac*c*a	1876	AV01346-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2311
AV01347	AV01347-SS	u*a*uaauuacCfuUfaCfugguuac*c*a	1877	AV01347-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2312
AV01348	AV01348-SS	a*u*uaucuuCfuUfaCfugguuac*c*a	1878	AV01348-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2313
AV01349	AV01349-SS	a*c*uaucuuCfuUfaCfugguuac*c*a	1879	AV01349-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2314
AV01350	AV01350-SS	c*u*uccaguUfcCfaGfuuuac*c*a	1880	AV01350-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2315
AV01351	AV01351-SS	u*u*ccaguuCfuUfaCfugguuac*c*a	1881	AV01351-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2316
AV01352	AV01352-SS	u*c*caguuCfuUfaCfugguuac*c*a	1882	AV01352-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2317
AV01353	AV01353-SS	c*c*aguuuacCfuUfaCfugguuac*c*a	1883	AV01353-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2318
AV01354	AV01354-SS	u*u*ccaguuCfuUfaCfugguuac*c*a	1884	AV01354-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2319
AV01355	AV01355-SS	c*c*aguuuacCfuUfaCfugguuac*c*a	1885	AV01355-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2320
AV01356	AV01356-SS	a*g*aaauuacCfuUfaCfugguuac*c*a	1886	AV01356-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2321
AV01357	AV01357-SS	g*a*aaauuacCfuUfaCfugguuac*c*a	1887	AV01357-AS	u*Uf*guucAfuggaCfaUfcAfugc*a*g	2322

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AV01358	AV01358-SS	a*a*uuuacgUfcAfaCfuungau*c*a	1888	AV01358-AS	u*Gf*auccAfauuGfaCfGfUfaaa*u*u	2323
AV01359	AV01359-SS	u*a*egueaaCfuUfgGfaucaaa*a*a	1889	AV01359-AS	u*Uf*uuuGfuaaAfgUfuGfaag*u*a	2324
AV01360	AV01360-SS	a*c*gucaacUfuGfgAfucaaaa*u*a	1890	AV01360-AS	u*Af*uuuGfaucaAfaGfuUfgac*g*u	2325
AV01361	AV01361-SS	c*g*ucaacuUfgGfaUfcaaaa*a*a	1891	AV01361-AS	u*Uf*auuuUfgaucCfaAfgUfuga*c*g	2326
AV01362	AV01362-SS	c*u*uuuacAfaUfuUfucuaa*g*a	1892	AV01362-AS	u*Cl*ungaGfaaaaUfuGfuGfaaa*a*g	2327
AV04242	AV04242-SS	g*a*gucaaaAfuGfuUfgucaag*a*a	1893	AV04242-AS	u*Uf*cuugAfaaaAfuUfgUfagc*u*c	2328
AV04243	AV04243-SS	g*a*caaugUfgUfcAfaaguuu*u*a	1894	AV04243-AS	u*Af*aaGuCfuugaCfaAfcAfuug*u*c	2329
AV04244	AV04244-SS	g*a*auguugUfcAfaGfaucuuu*u*a	1895	AV04244-AS	u*Af*aaaaGfuuuGfaCfaAfaa*u*c	2330
AV04245	AV04245-SS	c*u*caagacUfuUfuUfegaag*c*a	1896	AV04245-AS	u*Gf*caUfu(cUNA)gaaaAfaGfuCfuug*a*g	2331
AV04246	AV04246-SS	g*u*ucgaauGfcAfuGfgccuuu*u*a	1897	AV04246-AS	u*Af*agAfg(gUNA)ccauGfcAfuUfega*a*c	2332
AV04247	AV04247-SS	c*a*ccauuGfcAfuGfaugucc*a*a	1898	AV04247-AS	u*Uf*ggacAfucauGfcAfgAfuug*u*g	2333
AV04248	AV04248-SS	g*a*cugguAfaAfaUfagauc*u*a	1899	AV04248-AS	u*Af*gaucUfuuuGfuUfaCfcau*u*c	2334
AV04249	AV04249-SS	g*c*ugguaaCfaAfuAfaaguuu*g*a	1900	AV04249-AS	u*Cl*agauCfuuaUfgUfuAfaa*g*c	2335
AV04250	AV04250-SS	g*u*gguaaAfaUfaAfaaguuu*u*a	1901	AV04250-AS	u*Af*cagaUfcuuuUfuGfuUfacc*a*c	2336
AV04251	AV04251-SS	g*a*acaauaAfgAfuCfuuguuu*u*a	1902	AV04251-AS	u*Af*accaCfagauCfuUfaUfuug*u*c	2337
AV04252	AV04252-SS	g*a*caauaAfaUfuUfguguuu*g*a	1903	AV04252-AS	u*Cl*aaCfc(aUNA)cagaUfcUfuAfuug*u*c	2338
AV04253	AV04253-SS	g*c*auuaagAfuCfuGfguguuu*g*a	1904	AV04253-AS	u*Cl*caAfc(cUNA)acagAfuCfuUfaauu*g*c	2339
AV04254	AV04254-SS	g*a*auaagaUfcUfgUfguguuu*a*a	1905	AV04254-AS	u*Uf*ccAfa(cUNA)cacaGfaUfcUfuauu*u*c	2340
AV04255	AV04255-SS	g*g*ugguugGfaAfuUfauguuu*g*a	1906	AV04255-AS	u*Cl*auucAfuauUfcCfaAfaa*c*c	2341
AV04256	AV04256-SS	g*g*guuuggaAfuUfaUfgaauu*c*a	1907	AV04256-AS	u*Gf*acauUfcauaAfuUfcCfaa*c*c	2342
AV04257	AV04257-SS	c*g*uuuggaUfuAfuGfauguu*c*a	1908	AV04257-AS	u*Gf*gacaUfcauaAfuUfcCfaa*c*g	2343
AV04258	AV04258-SS	c*u*uggaauUfaUfgAfaugucc*a*a	1909	AV04258-AS	u*Uf*ggacAfucaUfaAfuUfcca*a*g	2344
AV04259	AV04259-SS	g*g*gaauuaUfgAfaUfguccaa*a*a	1910	AV04259-AS	u*Uf*unggaAfaauCfaUfaAfuuc*c*c	2345
AV04260	AV04260-SS	g*u*uaugaaUfgUfcCfaaauu*u*a	1911	AV04260-AS	u*Af*acauUfuggaCfaUfuCfaaa*a*c	2346
AV04261	AV04261-SS	g*a*ugaugUfcCfaAfauguuu*a*a	1912	AV04261-AS	u*Uf*caaaCfuugGfaCfaUfucau*u*c	2347
AV04262	AV04262-SS	g*u*gauguCfcAfaAfguuuua*a*a	1913	AV04262-AS	u*Uf*ucaaAfcuuuGfgAfaAfuuc*a*c	2348
AV04263	AV04263-SS	c*a*auguccAfaAfgUfuugaaag*a*a	1914	AV04263-AS	u*Uf*cuucAfaacuUfuGfgAfaa*u*g	2349
AV04264	AV04264-SS	c*u*ccaaagUfuUfgAfaagaga*u*a	1915	AV04264-AS	u*Af*uccuCfucaAfaCfuUfugg*a*g	2350
AV04265	AV04265-SS	g*g*aaaggaAfuGfuUfugagc*a*a	1916	AV04265-AS	u*Uf*gcucAfaaacAfuCfcUfcuu*c*c	2351

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AV04266	AV04266-SS	g*a*gaagauGfuUfuUfgagcag*u*a	1917	AV04266-AS	u*A*f*cuGfc(uUNA)caaaAfcAfuCfcuc*u*c	2352
AV04267	AV04267-SS	c*g*anguuuUfgAfgCfagugac*a*a	1918	AV04267-AS	u*U*f*gucaCfugcuCfaAfaAfcu*c*g	2353
AV04268	AV04268-SS	c*a*uguuuuGfaGfcAfgugac*a*u*a	1919	AV04268-AS	u*A*f*ugucAfcugeUfcAfaAfaa*u*g	2354
AV04269	AV04269-SS	g*u*guuuugAfgCfaGfugacau*u*a	1920	AV04269-AS	u*A*f*auguCfacugCfuCfaAfaa*c*c	2355
AV04270	AV04270-SS	g*g*uuuugaGfcAfgUfgacauu*a*a	1921	AV04270-AS	u*U*f*auugUfcacuGfcUfcAfaaa*c*c	2356
AV04271	AV04271-SS	g*u*ugagcaGfuGfaCfaauuaa*a*a	1922	AV04271-AS	u*U*f*uaauAfgucAfcUfgCfuca*a*c	2357
AV04272	AV04272-SS	c*a*gcagugAfcAfuUfaauuu*c*a	1923	AV04272-AS	u*G*f*auuAfuauuGfuCfaCfuge*u*g	2358
AV04273	AV04273-SS	g*g*cagugaCfaUfuAfuauu*c*a	1924	AV04273-AS	u*A*f*gaauUfaauUfgUfcAfcug*c*c	2359
AV04274	AV04274-SS	c*c*agugacAfuUfaUfaauu*c*a	1925	AV04274-AS	u*U*f*agaaUfuuaaAfuGfuCfacu*g*g	2360
AV04275	AV04275-SS	g*g*ugacauUfaUfaAfuucuga*c*a	1926	AV04275-AS	u*G*f*ucagAfaauaUfaAfuGfuca*c*c	2361
AV04276	AV04276-SS	c*u*gacauuAfuAfaUfucugac*a*a	1927	AV04276-AS	u*U*f*gucaGfaauAfuAfaUfguc*a*g	2362
AV04277	AV04277-SS	g*g*acauuaUfaAfuUfugac*a*a	1928	AV04277-AS	u*U*f*ugucAfgaaUfaUfaAfuug*c*c	2363
AV04278	AV04278-SS	g*a*uuuaaUfuCfuGfacaaua*a*a	1929	AV04278-AS	u*U*f*uaauGfucagAfaUfuAfuuaa*u*c	2364
AV04279	AV04279-SS	g*u*ucugacAfaUfaAfcacgau*g*a	1930	AV04279-AS	u*U*f*auCfc(uUNA)guuaUfuGfuCfaga*a*c	2365
AV04280	AV04280-SS	g*u*ucugacAfaUfaAfcacgau*g*a	1931	AV04280-AS	u*G*f*caUfc(uUNA)guuuAfuUfgUfcag*a*c	2366
AV04281	AV04281-SS	g*c*ugacaaUfaAfaAfcaguc*c*a	1932	AV04281-AS	u*U*f*gcAfu(cUNA)guguUfaUfuGfuca*g*c	2367
AV04282	AV04282-SS	g*g*acaauaAfcAfcGfaugcau*a*a	1933	AV04282-AS	u*U*f*augcAfcugcuGfuUfaUfuug*c*c	2368
AV04283	AV04283-SS	c*a*caauaaCfaCfGfaugcau*a*a	1934	AV04283-AS	u*U*f*auugCfaugUfgUfuAfuug*u*g	2369
AV04284	AV04284-SS	g*u*guauuuUfaAfaUfuccagui*u*a	1935	AV04284-AS	u*A*f*acugGfaagUfaAfuAfuac*a*c	2370
AV04285	AV04285-SS	g*g*uaauuuUfaCfuUfcccaguu*c*a	1936	AV04285-AS	u*G*f*aaCfu(gUNA)gaagUfaAfaUfaua*c*c	2371
AV04286	AV04286-SS	c*u*auauuuAfcUfuCfcaguu*c*a	1937	AV04286-AS	u*G*f*gaAfc(uUNA)ggaaGfuAfaAfuau*a*g	2372
AV04287	AV04287-SS	g*u*uaucuuCfaGfuUfcccagaa*u*a	1938	AV04287-AS	u*A*f*uuuuGfgaacUfgGfaAfgua*a*c	2373
AV04288	AV04288-SS	g*u*acuuccAfgUfuCfcagaa*u*a	1939	AV04288-AS	u*A*f*auucUfggaaCfuGfgAfgu*a*c	2374
AV04289	AV04289-SS	g*a*gaauuuAfcGfuCfaacug*g*a	1940	AV04289-AS	u*U*f*caagUfugacGfuAfaAfuuc*u*c	2375
AV04290	AV04290-SS	g*u*uuacguCfaAfcUfugauc*a*a	1941	AV04290-AS	u*U*f*gaucCfaagUfgAfcGfuuaa*a*c	2376
AV04291	AV04291-SS	g*c*uuuuccAfaAfuUfucucua*a*a	1942	AV04291-AS	u*U*f*ugagAfaauUfgUfgAfaaa*g*c	2377
AV04292	AV04292-SS	c*u*uuuguaUfuCfaGfuacagui*u*a	1943	AV04292-AS	u*A*f*acugUfacugAfaUfaCfaaa*a*g	2378
AV04293	AV04293-SS	g*u*uuuguaUfcAfgUfacagui*g*a	1944	AV04293-AS	u*U*f*acugUfacugAfaUfaCfaaa*a*g	2379
AV04294	AV04294-SS	g*u*guauuuAfgUfaCfaguuu*c*a	1945	AV04294-AS	u*G*f*acaaCfuguaCfuGfaAfuac*a*c	2380

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AV04295	AV04295-SS	g*g*uaaucaGfuAfcAfguugc*a*a	1946	AV04295-AS	u*Uf*gacaAfcuGfuAfcUfgAfaa*c*c	2381
AV04296	AV04296-SS	g*a*uucaguAfcAfgUfugucuu*u*a	1947	AV04296-AS	u*Af*augaCfaacuGfuAfcUfgaa*u*c	2382
AV04297	AV04297-SS	g*a*guacagUfuGfuCfaucac*u*a	1948	AV04297-AS	u*Af*gugaAfuGacAfaCfuGfuac*u*c	2383
AV04298	AV04298-SS	g*g*uaacaguUfgUfcAfuacac*u*a	1949	AV04298-AS	u*Af*agugAfaugaCfaAfcUfgua*c*c	2384
AV04299	AV04299-SS	c*u*acaguGfuCfaUfucacuu*c*a	1950	AV04299-AS	u*Gf*aaguGfaaagAfcAfaCfugu*a*g	2385
AV04300	AV04300-SS	g*a*guugucAfuUfcAfeucuu*a*a	1951	AV04300-AS	u*Uf*aagaAfgugAfuGfaCfaac*u*c	2386
AV04301	AV04301-SS	g*g*ungucaUfuCfaCfuucuu*a*g	1952	AV04301-AS	u*CT*uaagAfaugAfaUfgAfaa*c*c	2387
AV04302	AV04302-SS	c*u*ugucuuUfcAfcUfucuuag*a*a	1953	AV04302-AS	u*Uf*cuuaGfaaagGfaAfuGfaa*a*g	2388
AV04303	AV04303-SS	c*u*cauucacUfuUfcUfuagaca*a*a	1954	AV04303-AS	u*Uf*ugucUfaaagAfgUfgAfaug*a*g	2389
AV04304	AV04304-SS	g*c*auucacUfuCfuUfagacaa*a*a	1955	AV04304-AS	u*Uf*uuugUfuaagAfaGfuGfaa*u*g	2390
AV04305	AV04305-SS	g*a*uucacuUfcUfuAfgacaa*a*a	1956	AV04305-AS	u*CT*uuugUfuaagAfgUfgaa*u*c	2391
AV04306	AV04306-SS	g*u*ucacuuCfuUfaGfaacaa*a*a	1957	AV04306-AS	u*Uf*cuuuGfucuaAfgAfaGfuga*a*c	2392
AV04307	AV04307-SS	g*u*cauucUfuAfgAfaaaga*a*a	1958	AV04307-AS	u*Uf*ucuuUfugucUfaGfaAfgug*a*c	2393
AV04308	AV04308-SS	g*c*acuucUfaGfaCfaaagaa*u*a	1959	AV04308-AS	u*Af*uuucUfugucUfaAfgAfaug*a*g	2394
AV04309	AV04309-SS	g*a*cuucuuAfgAfcAfaagaa*u*a	1960	AV04309-AS	u*Af*auucUfuuugCfuAfaGfaag*u*c	2395
AV04310	AV04310-SS	g*c*ucuuuaGfaCfaAfaagaa*u*a	1961	AV04310-AS	u*CT*auucUfuuugUfaAfaAfgaa*g*c	2396
AV04311	AV04311-SS	g*u*ucuuagAfcAfaAfgaaug*a*a	1962	AV04311-AS	u*Uf*caauUfuuugGfuCfuAfaa*a*c	2397
AV04312	AV04312-SS	g*c*uuagacAfaAfgAfaaagac*a*a	1963	AV04312-AS	u*Uf*gucaAfuucUfuGfuCfuuaa*g*c	2398
AV04313	AV04313-SS	g*a*agaauGfaCfaGfgcuuga*a*a	1964	AV04313-AS	u*Uf*ucaGfgcuugUfaAfaUfuuu*u*c	2399
AV04314	AV04314-SS	g*a*gaauugAfcAfgGfcuugaa*u*a	1965	AV04314-AS	u*Af*uucaAfgcuGfuCfaAfuuc*u*c	2400
AV04315	AV04315-SS	g*g*aaungacAfaGfgCfuugaa*u*a	1966	AV04315-AS	u*CT*auucAfgcuUfgUfaAfaa*c*c	2401
AV04316	AV04316-SS	g*a*ungacaGfgCfuUfgaauga*a*a	1967	AV04316-AS	u*Uf*ucauUfcaagCfcUfgUfcaaa*u*c	2402
AV04317	AV04317-SS	g*u*ugacagGfcUfuGfaaagaa*a*a	1968	AV04317-AS	u*CT*uucaUfuaagGfcCfuGfuca*a*c	2403
AV04318	AV04318-SS	c*a*caggcuUfgAfaUfgaaagcu*a*a	1969	AV04318-AS	u*Af*agcuUfcauUfaAfgCfcug*u*g	2404
AV04319	AV04319-SS	g*g*gcuaagAfuGfaAfgcuuug*c*a	1970	AV04319-AS	u*Gf*caAfa(gUNA)cuucAfuUfaAfaa*c*c	2405
AV04320	AV04320-SS	g*u*gaagcuUfuGfcCfuuuuu*c*a	1971	AV04320-AS	u*Gf*aaaaAfggcAfaAfgCfuuc*a*c	2406
AV04321	AV04321-SS	c*c*uuugccCfuUfuUfucuuac*a*a	1972	AV04321-AS	u*Af*guagGfaaaaAfgGfgCfaaa*g	2407
AV04322	AV04322-SS	g*u*uuugccUfuUfuUfucuuac*a*a	1973	AV04322-AS	u*Af*aguaGfgaaaAfaGfgGfaaa*a*c	2408
AV04323	AV04323-SS	g*g*caagcuUfuGfcCfuucagcu*a*a	1974	AV04323-AS	u*Af*acugAfggcAfaAfcUfuug*c*c	2409

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AV04324	AV04324-SS	g*a*aguuugCfcCfuCfaguucc*a*a	1975	AV04324-AS	u*Uf*ggaaCfugagGfgCfaAfaeu*u*c	2410
AV04325	AV04325-SS	g*u*geccucAfgUfuCfcauc*a*a	1976	AV04325-AS	u*Uf*gaguUfggaaCfuGfaGfggc*a*c	2411
AV04326	AV04326-SS	g*g*uucauAfuCfaCfaggag*a*a	1977	AV04326-AS	u*Uf*caucCfugagAfgUfuGfgaa*c*c	2412
AV04327	AV04327-SS	c*u*uccaacUfcAfcAfggaug*a*a	1978	AV04327-AS	u*Uf*ucauCfugagGfgGfuUfgga*a*g	2413
AV04328	AV04328-SS	g*a*acucacAfgGfaUfgaagua*a*a	1979	AV04328-AS	u*Uf*uaeuUfcaucCfuGfuGfagu*u*c	2414
AV04329	AV04329-SS	g*a*gggaugAfgUfaAfgggaa*a*a	1980	AV04329-AS	u*Uf*uuucCfcauAfuUfcAfuuc*u*c	2415
AV04330	AV04330-SS	c*a*ugaaguAfaGfgGfaaaua*u*a	1981	AV04330-AS	u*Af*uaauUfuuccCfuUfuca*u*g	2416
AV04331	AV04331-SS	c*a*aguagGfgAfaAfaauug*c*a	1982	AV04331-AS	u*Gf*caauAfuuuCfcCfuUfaeu*u*g	2417
AV04332	AV04332-SS	c*u*aagggaAfaAfuAfuugcuc*a	1983	AV04332-AS	u*CF*gaGfc(aUNA)auauUfuUfcCfcuu*a*g	2418
AV04333	AV04333-SS	g*a*agggaaAfaUfaUfugcucg*u*a	1984	AV04333-AS	u*Af*cgAfg(cUNA)auauUfuUfuCfcu*u*c	2419
AV04334	AV04334-SS	c*g*gaauuAfuUfgCfugcugg*a*a	1985	AV04334-AS	u*Uf*ccAfc(gUNA)agcaAfuAfuUfuuc*c*g	2420
AV04335	AV04335-SS	g*a*auuuuGfcUfcGfuggaau*g*a	1986	AV04335-AS	u*CF*auucCfaagGfcAfaUfaau*u*c	2421
AV04336	AV04336-SS	g*a*uaugcUfcGfuGfgaugg*c*a	1987	AV04336-AS	u*Gf*ccAfu(uUNA)ccacGfaGfcAfaau*u*c	2422
AV04337	AV04337-SS	g*u*cguggaAfuGfgCfaauuuu*a*a	1988	AV04337-AS	u*Uf*aaaaUfugccAfuUfcCfagc*a*c	2423
AV04338	AV04338-SS	g*c*guggaaUfgGfcAfaauuuu*a*a	1989	AV04338-AS	u*CF*uaaaAfuugCfaUfuCfcau*c*c	2424
AV04339	AV04339-SS	g*g*uggaauGfgCfaAfuuuugg*a	1990	AV04339-AS	u*CF*cuuaAfaugCfaAfuUfcca*c*c	2425
AV04340	AV04340-SS	c*u*gggaugGfcAfaUfuuuagg*u*a	1991	AV04340-AS	u*Af*ccuaAfaauGfcCfaUfuuc*a*g	2426
AV04341	AV04341-SS	g*g*gauggCfaAfuUfuaggc*c*a	1992	AV04341-AS	u*Gf*accuAfaauUfgCfcAfuuc*c*c	2427
AV04342	AV04342-SS	g*u*uaaccuCfgAfuGfcauug*u*a	1993	AV04342-AS	u*Af*caagAfgcaUfgAfgGfgua*a*c	2428
AV04343	AV04343-SS	g*u*accucGfaUfgCfucuuu*u*a	1994	AV04343-AS	u*Af*acaaGfagcaUfcGfaGfggu*a*c	2429
AV04344	AV04344-SS	g*c*ucgaugCfuCfuUfguugaa*u*a	1995	AV04344-AS	u*Af*uucaAfaagAfgCfaUfcau*c*c	2430
AV04345	AV04345-SS	g*g*augcucUfuGfuUfgaauu*c*a	1996	AV04345-AS	u*Gf*acauUfcauAfaGfaGfcau*c*c	2431
AV04346	AV04346-SS	g*g*cuuugUfuGfaAfuugcuu*g*a	1997	AV04346-AS	u*CF*aagaCfaucAfaCfaAfgag*c*c	2432
AV04347	AV04347-SS	c*c*cuuugUfgAfaUfgcuug*u*a	1998	AV04347-AS	u*Af*caagAfaauCfaAfaAfgaag*c*g	2433
AV04348	AV04348-SS	g*g*uuuauuGfuCfuUfguauu*g*a	1999	AV04348-AS	u*CF*auucAfaagAfuUfcau*c*c	2434
AV04349	AV04349-SS	g*u*gauguCfuUfgUfgaauug*a*a	2000	AV04349-AS	u*Uf*ccaaUfcauAfgAfaAfuuc*a*c	2435
AV04350	AV04350-SS	g*a*ugucuuGfuGfaUfggaguu*u*a	2001	AV04350-AS	u*Af*acucCfaucAfaAfaGfaca*u*c	2436
AV04351	AV04351-SS	g*u*gucuuGfuGfaUfggaguu*g*a	2002	AV04351-AS	u*CF*aaCfu(cUNA)caauCfaAfgac*a*c	2437
AV04352	AV04352-SS	c*u*gauggAfgUfuGfuagaa*u*a	2003	AV04352-AS	u*Af*ugguAfcacCfuCfcAfauc*a*g	2438

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AV04353	AV04353-SS	g*u*uggaguUfgGfuAfcgaug*c*a	2004	AV04353-AS	u*Gf*acAfuf(gUNA)guacCfaAfcUfcca*a*c	2439
AV04354	AV04354-SS	c*g*ucgucAfgCfuUfgaaau*a	2005	AV04354-AS	u*Uf*auuUfcaagCfuGfaCfigua*c*g	2440
AV04355	AV04355-SS	c*u*acgucaGfcUfuGfaaaua*u*a	2006	AV04355-AS	u*Af*uaauUfucaagGfcUfgAfcgu*a*g	2441
AV04356	AV04356-SS	g*a*cgucagCfuUfgAfaauau*g*a	2007	AV04356-AS	u*CT*auaaUfuucaAfgCfuGfiag*u*c	2442
AV04357	AV04357-SS	g*u*ugaaauUfaUfgUfgucgu*u*a	2008	AV04357-AS	u*Af*agCfa(gUNA)caaaUfaAfuUfucca*a*c	2443
AV04358	AV04358-SS	g*a*auuaugUfgCfuGfcauugg*c*a	2009	AV04358-AS	u*Gf*ccAfa(aUNA)gcagCfaCfaUfaau*u*c	2444
AV04359	AV04359-SS	g*u*ugucguCfuUfuGfcaugca*u*a	2010	AV04359-AS	u*Af*ugCfa(gUNA)ccaaAfgCfaGfcaac*a*c	2445
AV04360	AV04360-SS	g*u*ugucguCfuAfuGfcaugul*c*a	2011	AV04360-AS	u*Gf*aaauGfcauGfcaAfgCfcaaa*a*c	2446
AV04361	AV04361-SS	g*u*gcaugCfaGfuUfcaugcc*a	2012	AV04361-AS	u*Uf*ggCfa(aUNA)gaacUfgAfcAfuugc*a*c	2447
AV04362	AV04362-SS	c*c*augucaGfuUfuUfugccaa*c*a	2013	AV04362-AS	u*Gf*uuGfg(cUNA)aagaAfcUfgAfcuu*g*g	2448
AV04363	AV04363-SS	g*u*ugucguUfcUfuGfcaacu*a	2014	AV04363-AS	u*Uf*aguuGfgcaagGfaAfcUfgac*a*c	2449
AV04364	AV04364-SS	g*u*ugccaaCfuAfcUfucguu*u*a	2015	AV04364-AS	u*Af*acacGfaagUfgUfuGfcca*a*c	2450
AV04365	AV04365-SS	c*c*caacuaCfuUfcGfuguuca*u*a	2016	AV04365-AS	u*Af*ugaaCfacgaAfgUfaGfugng*g	2451
AV04366	AV04366-SS	g*a*gcuuguGfuGfuCfcuuggu*a	2017	AV04366-AS	u*Uf*accaAfggacAfcAfcAfcagc*u*c	2452
AV04367	AV04367-SS	g*c*ungguaUfuAfgAfgcuuc*u*a	2018	AV04367-AS	u*Af*gaaaGfcuucUfaUfaCfcaaa*g*c	2453
AV04368	AV04368-SS	g*u*ugcccgAfgUfuUfuaagaa*a	2019	AV04368-AS	u*Uf*cuucUfaaaaCfuCfugGfcca*a*c	2454
AV04369	AV04369-SS	c*a*gggucaAfgAfuGfaauug*u*a	2020	AV04369-AS	u*Af*cauaAfcuaCfuUfgAfccecu*g	2455
AV04370	AV04370-SS	g*g*ggucaaGfaUfgAfuauugl*c*a	2021	AV04370-AS	u*Gf*acauAfaucUfcUfuGfacc*c*c	2456
AV04371	AV04371-SS	c*u*caagauGfaUfuAfuuguc*u*a	2022	AV04371-AS	u*Af*gagaCfaaaUfcAfuCfugng*a*g	2457
AV04372	AV04372-SS	c*u*cuuagGfcUfuGfguucuu*g*a	2023	AV04372-AS	u*CT*aaagaAfcuaGfcCfuAfgag*a*g	2458
AV04373	AV04373-SS	g*c*uaugcuUfgGfuUfcauguu*c*a	2024	AV04373-AS	u*Gf*aaacAfgaacCfaAfgCfuaa*g*c	2459
AV04374	AV04374-SS	g*u*ggucuuUfgUfuCfauugcu*a	2025	AV04374-AS	u*Uf*ggagCfuaagAfcAfgAfcacc*a*c	2460
AV04375	AV04375-SS	c*c*ugaucUfuCfuCfcauaa*a	2026	AV04375-AS	u*Uf*uuugAfggagAfaGfGfAfuca*g*g	2461
AV04376	AV04376-SS	g*u*ucucuuCfaAfaAfcaguu*c*a	2027	AV04376-AS	u*Uf*guacUfguuUfgAfgGfaga*a*c	2462
AV04377	AV04377-SS	g*c*aaaaaGfuAfcAfgcaguu*a	2028	AV04377-AS	u*Uf*aucuGfcuuAfcUfgUfuuu*g*c	2463
AV04378	AV04378-SS	g*a*acagaaCfaGfcAfgaauu*u*a	2029	AV04378-AS	u*Af*agaaUfcuugUfgUfaCfuguu*u*c	2464
AV04379	AV04379-SS	c*u*acagaaGfaUfaCfcauuaa*g*a	2030	AV04379-AS	u*CT*uuagAfaaaUfcUfgCfuguu*a*g	2465
AV04380	AV04380-SS	g*u*cauugGfaCfuGfcaugaa*a	2031	AV04380-AS	u*Uf*uucaUfccaagUfcCfuAfaug*a*c	2466
AV04381	AV04381-SS	g*a*uaaggaCfuGfgAfuagaaa*u*a	2032	AV04381-AS	u*Af*uuuuCfauccAfgUfcCfuuaa*u*c	2467

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AV04382	AV04382-SS	g*a*aaauaUfcAfgCfaugau*a*a	2033	AV04382-AS	u*Uf*auccAfuuguGfaUfcAfuuu*u*c	2468
AV04383	AV04383-SS	g*a*aaugauCfaGfcAfuugaua*u*a	2034	AV04383-AS	u*Af*uaucCfaugcUfgAfuCfauu*u*c	2469
AV04384	AV04384-SS	g*a*gauggaAfuAfuUfgaaca*a	2035	AV04384-AS	u*CI*unguUfcauAfuCfcAfugc*a*c	2470
AV04385	AV04385-SS	g*u*gaacaAfuUfaUfuaccu*a*a	2036	AV04385-AS	u*Uf*agggUfaauAfcUfuGfuuc*a*c	2471
AV04386	AV04386-SS	g*u*uaaccuAfaGfuUfuugc*u*a	2037	AV04386-AS	u*Af*gaacUfaaacUfuAfgGfgua*a*c	2472
AV04387	AV04387-SS	g*u*ccuucuGfgCfuGfucaau*a*a	2038	AV04387-AS	u*Uf*acuuGfaccGfcAfgAfagg*a*c	2473
AV04388	AV04388-SS	g*c*uuugcCfuGfuCfaaguac*a*a	2039	AV04388-AS	u*Uf*guacUfugacAfgCfcAfgaa*g*c	2474
AV04389	AV04389-SS	g*g*ucaaguAfcAfuCfuucuu*g*a	2040	AV04389-AS	u*CI*aaagAfaagAfuAfcUfuga*c*c	2475
AV04390	AV04390-SS	g*a*guacauCfuUfcUfuugaac*a*a	2041	AV04390-AS	u*Uf*guucAfaagaAfgAfuGfuac*u*c	2476
AV04391	AV04391-SS	g*u*aaaaaCfcCfuAfuacau*c*a	2042	AV04391-AS	u*GI*anguGfaugGfgUfuUfuuu*a*c	2477
AV04392	AV04392-SS	g*c*uguaguGfaCfaCfaaaga*a*a	2043	AV04392-AS	u*Uf*ucuuUfugugUfcAfcUfaca*g*c	2478
AV04393	AV04393-SS	g*g*uauguaCfaCfaAfaagaa*g*a	2044	AV04393-AS	u*CI*uuucUfuuuUfgUfcAfcua*c*c	2479
AV04394	AV04394-SS	g*a*guagcaCfaAfaAfgaaau*c*a	2045	AV04394-AS	u*GI*acuuUfeuuUfgUfgUfcac*u*c	2480
AV04395	AV04395-SS	g*c*uaugcuGfgUfcAfgaaau*a*a	2046	AV04395-AS	u*Uf*uaauUfcugacCfcAfgCfaaa*g*c	2481
AV04396	AV04396-SS	c*c*uggucaGfaAfaUfaaccag*a*a	2047	AV04396-AS	u*Uf*cugguUfuuuUfcUfgAfcga*g*g	2482
AV04397	AV04397-SS	g*u*ggucagAfaAfaUfaaccag*a*a	2048	AV04397-AS	u*Uf*ueugGfuuuUfuCfuGfacc*a*c	2483
AV04398	AV04398-SS	c*a*cagggaUfaAfaCfcgagaa*a*a	2049	AV04398-AS	u*Uf*uuuuCfugguUfaUfcCfcug*u*g	2484
AV04399	AV04399-SS	c*g*gaauaaCfcGfaGfaagaa*a*a	2050	AV04399-AS	u*Uf*uuuuUfucucGfgUfuUfauc*c*g	2485
AV04400	AV04400-SS	g*g*aaagaaAfaGfuUfgagguu*a*a	2051	AV04400-AS	u*Uf*aaccUfcaacUfuUfuCfuuu*c*c	2486
AV04401	AV04401-SS	g*g*guuuuaAfaAfcCfcuuagu*u*a	2052	AV04401-AS	u*CI*acuaAfgggUfuUfaUfaac*c*c	2487
AV04402	AV04402-SS	g*c*cuuaguGfgCfuGfaaacag*a*a	2053	AV04402-AS	u*Uf*cuguUfucagCfcAfcUfaag*g*c	2488
AV04403	AV04403-SS	c*c*uaauuUfgUfgGfuugguu*a*a	2054	AV04403-AS	u*Uf*uaacAfaacaCfaAfaUfgua*g*g	2489
AV04404	AV04404-SS	g*u*ccuucuUfaCfuCfauacu*u*a	2055	AV04404-AS	u*Af*aguaUfcggagUfaAfgGfagg*a*c	2490
AV04405	AV04405-SS	g*c*acaggaaAfcCfuGfaaaauu*g*a	2056	AV04405-AS	u*Uf*cauuUfucagGfuUfcCfugu*g*c	2491
AV04406	AV04406-SS	g*a*gaagaaGfgUfgCfaaaauu*c*a	2057	AV04406-AS	u*GI*aaauUfugcaCfcUfuUfcuc*u*c	2492
AV04407	AV04407-SS	g*a*ggugcaAfaAfuUfcuuag*u*a	2058	AV04407-AS	u*Af*cuuaGfgaaUfuUfgCfacc*u*c	2493
AV04408	AV04408-SS	g*g*guagcaAfaUfuCfcuuagu*g*a	2059	AV04408-AS	u*CI*acuaAfggaaUfuUfuGfcac*c*c	2494
AV04409	AV04409-SS	c*g*ugcaaaAfuUfcCfuugag*a*a	2060	AV04409-AS	u*Uf*cacuAfaagAfuUfuUfgca*c*g	2495
AV04410	AV04410-SS	g*g*caauuUfcCfuUfagugau*g*a	2061	AV04410-AS	u*CI*aucaCfuagGfaAfuUfuug*c*c	2496

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AV04411	AV04411-SS	g*u*uagugaUfgCfuGfagaucua*u*a	2062	AV04411-AS	u*Af*uugauCfucagCfaUfcAfcaua*a*c	2497
AV04412	AV04412-SS	g*g*cugagaUfcAfuCfegaucua*g*a	2063	AV04412-AS	u*Cl*uaacUfggaUfgaUfcUfcag*c*c	2498
AV04413	AV04413-SS	c*a*gaucauCfcAfgUfugaucua*a*a	2064	AV04413-AS	u*Uf*uugacUfaaucUfgaUfgaUfcuau*u*g	2499
AV04414	AV04414-SS	g*g*aucaucCfaGfuUfugaucua*u*a	2065	AV04414-AS	u*Af*uugaCfuaucUfgGfaUfgau*c*c	2500
AV04415	AV04415-SS	c*a*ucauccAfgUfuAfgucau*g*a	2066	AV04415-AS	u*Cl*auugAfcauaCfuGfgAfuga*u*g	2501
AV04416	AV04416-SS	g*a*uccaguUfaGfuCfaaugcu*a*a	2067	AV04416-AS	u*Uf*ageaUfugaUfaAfcUfgga*u*c	2502
AV04417	AV04417-SS	g*a*guaguCfaAfuGfcaagc*a*a	2068	AV04417-AS	u*Uf*guuAfgaucUfgAfcUfaac*u*c	2503
AV04418	AV04418-SS	c*u*uaucuaAfuGfcUfaagcau*a*a	2069	AV04418-AS	u*Uf*auagCfuagcAfuUfgAfcau*a*g	2504
AV04419	AV04419-SS	g*u*agucuaUfgCfuAfgcauua*u*a	2070	AV04419-AS	u*Af*auugCfuagCfaUfuGfaua*a*c	2505
AV04420	AV04420-SS	g*a*gccuacAfaGfuUfggaucua*a*a	2071	AV04420-AS	u*Af*guuuCfcaucUfuGfuAfggc*u*c	2506
AV04421	AV04421-SS	g*g*ccuacaAfgUfuGfgaauu*c*a	2072	AV04421-AS	u*Gf*aguuUfcaucUfuUfgUfagg*c*c	2507
AV04422	AV04422-SS	g*a*guuggaAfaCfuCfugaugc*a*a	2073	AV04422-AS	u*Uf*ccauCfagagUfuUfcCfaac*u*c	2508
AV04423	AV04423-SS	c*u*uggaaaCfuCfuGfauugaa*a*a	2074	AV04423-AS	u*Uf*uuccAfucagAfgUfuUfcca*a*g	2509
AV04424	AV04424-SS	c*g*aaucUfgAfuGfgaauu*c*a	2075	AV04424-AS	u*Gf*aguuUfcaucUfaGfaGfuuu*c*g	2510
AV04425	AV04425-SS	g*c*ucaugaGfcGfuGfgugauu*c*a	2076	AV04425-AS	u*Gf*auacAfccagGfcUfcAfuga*g*c	2511
AV04426	AV04426-SS	c*a*ageuuuCfaGfaAfcuucua*u*a	2077	AV04426-AS	u*Af*agaaGfguucUfgAfaAfgeu*u*g	2512
AV04427	AV04427-SS	g*u*ucagaaCfcUfuCfuucucu*c*a	2078	AV04427-AS	u*Gf*agagAfagaagGfgUfuCfuga*a*c	2513
AV04428	AV04428-SS	c*a*accuucUfuCfuCfuccagu*a*a	2079	AV04428-AS	u*Uf*acugGfagagAfaGfaAfggu*u*g	2514
AV04429	AV04429-SS	g*c*unacagGfgAfuUfaucuu*a*a	2080	AV04429-AS	u*Uf*auuAfuaucUfcCfuGfuua*g*c	2515
AV04430	AV04430-SS	g*u*uaucagGfaUfuAfuauuaa*c*a	2081	AV04430-AS	u*Gf*uaauUfauaaUfcCfcUfguaa*a*c	2516
AV04431	AV04431-SS	g*a*cagggaUfuAfuAfaucua*c*a	2082	AV04431-AS	u*Gf*agaaAfuaaAfaUfcCfcug*u*c	2517
AV04432	AV04432-SS	c*c*unuggaCfuCfuCfcaagc*a*a	2083	AV04432-AS	u*Af*cuucUfcaagAfgUfcAfcaa*g*g	2518
AV04433	AV04433-SS	g*u*ugacagCfaCfuAfgcauua*u*a	2084	AV04433-AS	u*Af*auucUfcaagUfgCfuGfuaa*a*c	2519
AV04434	AV04434-SS	g*u*agcagaUfuUfgCfagcuu*a*a	2085	AV04434-AS	u*Uf*agacGfugaAfaUfcUfgcu*a*c	2520
AV04435	AV04435-SS	g*u*unucacGfuCfuAfcagaa*c*a	2086	AV04435-AS	u*Gf*uuucUfguagAfcGfuGfcaa*a*c	2521
AV04436	AV04436-SS	g*a*cguucaCfaGfaAfaucua*u*a	2087	AV04436-AS	u*Af*ugaaGfuucUfgUfaGfagc*u*c	2522
AV04437	AV04437-SS	g*g*ucuaaGfaAfaCfuucuaa*c*a	2088	AV04437-AS	u*Gf*uaugAfaguuUfcUfgUfaga*c*c	2523
AV04438	AV04438-SS	g*a*gaauuUfcAfuAfaagaa*u*a	2089	AV04438-AS	u*Af*uaucUfguauGfaAfgUfuuc*u*c	2524
AV04439	AV04439-SS	g*a*acuuaUfaCfaAfguauag*c*a	2090	AV04439-AS	u*Gf*cuauAfcuugUfaUfgAfagu*u*c	2525

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AV04440	AV04440-SS	c*g*acgcaacCfcUfuUfaauacc*g*a	2091	AV04440-AS	u*CI*ggauAfuuaaGfgUfuGfcgu*c*g	2526
AV04441	AV04441-SS	c*a*cgcgaacCfuUfuAfuauccg*u*a	2092	AV04441-AS	u*Af*cgggaUfauaaAfgGfuUfgeg*u*g	2527
AV04442	AV04442-SS	c*g*uaacagaGfaAfaGfcacuuu*c*a	2093	AV04442-AS	u*Gf*aaagUfgcuUfCfuUfgua*c*c	2528
AV04443	AV04443-SS	g*g*aaagcaCfuUfuCfaaacu*u*a	2094	AV04443-AS	u*Af*aguuUfugaAfgUfgCfuuu*c*c	2529
AV04444	AV04444-SS	g*u*uucccuGfaAfaUfGfcagau*u*a	2095	AV04444-AS	u*Af*aucuGfcauuUfCfaGfgaa*a*c	2530
AV04445	AV04445-SS	g*u*ucccuGfaAfaUfGfcagau*c*a	2096	AV04445-AS	u*Gf*auucUfgcaUfuCfaGfgga*a*c	2531
AV04446	AV04446-SS	g*u*agugguAfaCfuAfuugau*c*a	2097	AV04446-AS	u*Af*guacAfaugUfuAfcCfcac*a*c	2532
AV04447	AV04447-SS	g*a*guuguaAfcUfaUfugau*c*a	2098	AV04447-AS	u*CI*aguaCfaauaGfuUfaCfcac*u*c	2533
AV04448	AV04448-SS	g*g*guacuAfuUfgUfagucac*a*a	2099	AV04448-AS	u*Uf*gucaGfuacaAfuAfgUfuac*c*c	2534
AV04449	AV04449-SS	c*g*uaacuaUfuGfuAfcugaca*a*a	2100	AV04449-AS	u*Uf*ugucAfguacAfaUfaGfuua*c*g	2535
AV04450	AV04450-SS	g*c*uauguaAfcUfgAfaagaa*a*a	2101	AV04450-AS	u*Uf*uuuuUfgucaGfuAfcAfaaa*g*c	2536
AV04451	AV04451-SS	g*u*auuguaCfuGfaCfaagaa*c*c	2102	AV04451-AS	u*Gf*uuucUfugucAfgUfaCfaaa*a*c	2537
AV04452	AV04452-SS	c*a*caagaaAfcCfuGfcugua*u*a	2103	AV04452-AS	u*Af*uaacAfgcagGfuUfuCfuug*u*g	2538
AV04453	AV04453-SS	g*a*gaacccUfgCfuGfcuaaua*a*a	2104	AV04453-AS	u*Uf*uuauAfgcagCfaGfgUfuuc*u*c	2539
AV04454	AV04454-SS	g*a*ucuguuGfuUfuGfugagc*u*a	2105	AV04454-AS	u*Af*gcuuCfaaaaAfcAfaCfaga*u*c	2540
AV04455	AV04455-SS	g*c*uguuugUfuGfuGfagcug*u*a	2106	AV04455-AS	u*Af*cagcUfuacAfaAfcAfaa*g*c	2541
AV04456	AV04456-SS	g*u*guuugUfuGfaAfgCfugucuu*u*a	2107	AV04456-AS	u*Af*augaCfagcuUfCfaAfaa*c*c	2542
AV04457	AV04457-SS	g*g*ucagagAfaGfuAfuuaag*a*a	2108	AV04457-AS	u*Uf*cuuuAfaaacUfuCfuCfuga*c*c	2543
AV04458	AV04458-SS	g*c*agagaaGfuAfuUfaagac*u*a	2109	AV04458-AS	u*Af*guuuUfuuaaAfcUfuCfuuc*u*c	2544
AV04459	AV04459-SS	g*g*agaguuAfuUfaAfaagaa*c*a	2110	AV04459-AS	u*Gf*uaagUfuuaaAfuAfcUfuuc*c*c	2545
AV04460	AV04460-SS	g*g*aguuuuUfaAfaGfauuac*a*a	2111	AV04460-AS	u*Uf*gguaGfuuuUfaAfuAfcuu*c*c	2546
AV04461	AV04461-SS	c*a*ggcuuuGfaUfuGfagguca*a*a	2112	AV04461-AS	u*Uf*ugacCfuaaUfCfaAfuAfgcc*u*g	2547
AV04462	AV04462-SS	g*a*ugauugAfgGfuCfaaauu*a*a	2113	AV04462-AS	u*Uf*auugUfugacCfuCfaAfuca*u*c	2548
AV04463	AV04463-SS	g*u*gaauugaGfgUfCfaaauu*a*a	2114	AV04463-AS	u*Uf*uaauGfuugaCfcUfCfaaau*a*c	2549
AV04464	AV04464-SS	g*g*aggucaAfcAfuUfaaagaa*a*a	2115	AV04464-AS	u*Uf*cuugUfuuaaGfuUfgAfcuu*c*c	2550
AV04465	AV04465-SS	g*a*cauuaaCfaAfgAfaauuag*u*a	2116	AV04465-AS	u*Af*cuuaaAfuucUfGfuAfaug*u*c	2551
AV04466	AV04466-SS	c*c*agcacaGfaAfuGfuuguaa*g*a	2117	AV04466-AS	u*CI*uaaccAfaaaUfCfuUfgUfgcu*g*g	2552
AV04467	AV04467-SS	c*c*acagaaUfgUfuGfugauu*c*a	2118	AV04467-AS	u*Gf*acuAfcacaCfaUfuCfuga*g*g	2553
AV04468	AV04468-SS	g*a*gauguuUfgCfuAfguucaaa*a*a	2119	AV04468-AS	u*Uf*uuugaAfcuacCfaAfcAfuuc*u*c	2554

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AV04469	AV04469-SS	g*g*aauguuGfgUfaGfuuaa*c*a	2120	AV04469-AS	u*Gf*uuugAfacuaCfcAfaCfauu*c*c	2555
AV04470	AV04470-SS	c*a*auguugGfuAfgUfuaaac*u*a	2121	AV04470-AS	u*Af*guuuGfaacuAfeCfaAfaau*u*g	2556
AV04471	AV04471-SS	g*u*guugguAfgUfuCfaaacug*u*a	2122	AV04471-AS	u*Af*caguUfugaaCfuAfcCfaac*a*c	2557
AV04472	AV04472-SS	c*u*aguuaaAfaCfuGfuuauc*u*a	2123	AV04472-AS	u*Af*guuaUfacagUfuUfgAfauc*a*g	2558
AV04473	AV04473-SS	g*a*cuguuUfaCfuUfaaugg*a*a	2124	AV04473-AS	u*Uf*ccauUfaaagUfaAfuAfcag*u*c	2559
AV04474	AV04474-SS	g*u*guuuuAfaCfuUfaauggaa*g*a	2125	AV04474-AS	u*CF*uuccAfuuaaAfgUfaAfuac*a*c	2560
AV04475	AV04475-SS	g*u*acuuaAfuGfgAfaagaa*g*a	2126	AV04475-AS	u*Af*cuugCfuuccAfuUfaAfaa*a*c	2561
AV04476	AV04476-SS	c*g*uccacAfaAfuGfaaguu*u*a	2127	AV04476-AS	u*Af*aaucUfucuuUfuGfuGfgga*c*g	2562
AV04477	AV04477-SS	g*a*gcugcaCfcAfuGfcaucuu*a*a	2128	AV04477-AS	u*Uf*agauGfgcauGfgUfgCfagc*u*c	2563
AV04478	AV04478-SS	c*c*aceaugCfcAfuCfuuaaga*g*a	2129	AV04478-AS	u*CF*ucuaUfagauGfgCfaUfggu*g*g	2564
AV04479	AV04479-SS	g*c*augccaUfcUfaUfagagau*a*a	2130	AV04479-AS	u*Uf*auccAfuuaaGfaUfgGfcau*g*c	2565
AV04480	AV04480-SS	g*a*ugccauCfuAfuAfgagaua*g*a	2131	AV04480-AS	u*CF*uaucUfcuaaAfgAfuGfgca*u*c	2566
AV04481	AV04481-SS	g*u*caaggaGfcAfuGfcaagaa*u*a	2132	AV04481-AS	u*Af*ucuuUfgcauGfcUfcCfuug*a*c	2567
AV04482	AV04482-SS	g*a*agauaaUfcCfuGfggga*a*a	2133	AV04482-AS	u*Uf*uuucCfccagGfaUfuAfuau*u*c	2568
AV04483	AV04483-SS	g*u*gggaaUfuGfuCfauuau*g*a	2134	AV04483-AS	u*CF*auaaGfugacAfaUfuCfcc*a*c	2569
AV04484	AV04484-SS	c*c*aggacaUfcUfuGfuaaaa*g*a	2135	AV04484-AS	u*CF*uuuuGfacaGfaUfgUfcu*g*g	2570
AV04485	AV04485-SS	g*g*gacaucUfuGfuCfaaaguu*c*a	2136	AV04485-AS	u*Gf*acuuUfugacAfaGfaUfguc*c*c	2571
AV04486	AV04486-SS	g*a*ggucgaAfgAfuCfaauua*c*a	2137	AV04486-AS	u*Gf*uaaaUfugauCfuUfcGfacc*u*c	2572
AV04487	AV04487-SS	g*c*gaagauCfaAfuUfaacag*a*a	2138	AV04487-AS	u*Uf*cuugUfaaaUfgAfuCfuuc*g*c	2573
AV04488	AV04488-SS	g*a*gaucuaUfuUfaCfaagacc*u*a	2139	AV04488-AS	u*Af*ggucUfuguaAfaUfuGfauc*u*c	2574
AV04489	AV04489-SS	g*u*cuuaagGfaCfuAfaaaua*a*a	2140	AV04489-AS	u*Uf*uuauGfuuaagUfcCfuUfuag*a*c	2575
AV04490	AV04490-SS	c*g*acuacAfuAfaAfaucuu*g*a	2141	AV04490-AS	u*CF*acagAfuuuuAfuGfuUfagu*c*g	2576
AV04491	AV04491-SS	g*u*acauaAfaAfuCfugugaa*u*a	2142	AV04491-AS	u*Af*uucaCfagauUfuUfaUfguu*a*c	2577
AV04492	AV04492-SS	g*a*cauaaaAfuCfuGfugaauu*a*a	2143	AV04492-AS	u*Uf*aaauCfacagAfuUfuUfaug*u*c	2578
AV04493	AV04493-SS	g*a*aucuguGfaAfuUfaaaaa*g*a	2144	AV04493-AS	u*CF*uuuuUfuauUfcAfaAfgau*u*c	2579
AV04494	AV04494-SS	g*g*uuuaguGfcUfuUfaacugc*u*a	2145	AV04494-AS	u*Af*geauGfuuaaGfcAfaUfaaa*c*c	2580
AV04495	AV04495-SS	c*c*uuuacaUfgCfuGfgucuuu*u*a	2146	AV04495-AS	u*Af*agagCfacagCfaUfgUfaaa*g*g	2581
AV04496	AV04496-SS	g*u*uacaugCfuGfuGfucuuu*g*a	2147	AV04496-AS	u*CF*aaagAfgcacAfgCfaUfgua*a*c	2582
AV04497	AV04497-SS	g*g*agauugUfaAfuCfuacagc*u*a	2148	AV04497-AS	u*Af*gcugUfagauUfaCfaAfuuc*c*c	2583

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AV04498	AV04498-SS	g*a*aaguuuUfgAfuGfaauu*c*u*a	2149	AV04498-AS	u*Af*gaauUfucAuCfaAfaAfcuu*u*c	2584
AV04499	AV04499-SS	g*u*ugaugaAfaUfuCfugaag*u*a	2150	AV04499-AS	u*Af*cuucAfagaaUfuUfcAfuca*a*c	2585
AV04500	AV04500-SS	g*u*gaugaaAfuUfcUfugaagu*u*a	2151	AV04500-AS	u*Af*acuuCfaagaAfuUfuCfauc*a*c	2586
AV04501	AV04501-SS	g*g*augaaaUfuCfuUfgaagu*c*a	2152	AV04501-AS	u*Gf*aaUfcaagAfaUfuUfcuu*c*c	2587
AV04502	AV04502-SS	g*u*cuugaaGfuUfcAfuguga*u*a	2153	AV04502-AS	u*Af*ucacCfaugaAfcUfuCfaag*a*c	2588
AV04503	AV04503-SS	g*u*ugaaguUfcAfuGfugauc*a*a	2154	AV04503-AS	u*Uf*gaucAfecauGfaAfcUfuca*a*c	2589
AV04504	AV04504-SS	c*a*aguucaUfgGfuGfaucagu*g*a	2155	AV04504-AS	u*CT*acugAfucacCfaUfgAfacu*u*g	2590
AV04505	AV04505-SS	c*u*ucauggUfgAfuCfagugca*a*a	2156	AV04505-AS	u*Uf*ugcaCfugaCfaCfcAfuga*a*g	2591
AV04506	AV04506-SS	g*a*uggugaUfcAfgUfgcauu*g*a	2157	AV04506-AS	u*CT*aaUgfcacuGfaUfcAfcca*u*c	2592
AV04507	AV04507-SS	g*u*ggugauCfaGfuGfcauug*a*a	2158	AV04507-AS	u*Uf*cauUfgcacUfgAfuCfacc*a*c	2593
AV04508	AV04508-SS	c*a*ugaaacUfcCfuGfaauug*u*a	2159	AV04508-AS	u*Af*caaaAfucagGfaGfuUfuca*u*g	2594
AV04509	AV04509-SS	c*a*aacuccUfgAfuUfugaug*u*a	2160	AV04509-AS	u*Af*cuacAfaaaCfaGfgAfguu*u*g	2595
AV04510	AV04510-SS	g*a*cuccugAfuUfuUfguaguu*a*a	2161	AV04510-AS	u*Uf*aaUfcaaaAfuCfaGfgag*u*c	2596
AV04511	AV04511-SS	g*c*uccugaUfuUfuGfugaaua*a*a	2162	AV04511-AS	u*Uf*uaacUfacaaAfaUfcAfgga*g*c	2597
AV04512	AV04512-SS	g*g*uauguuaAfuUfuAfuuaagu*c*a	2163	AV04512-AS	u*Gf*acuuAfaaaAfuUfaAfcua*c*c	2598
AV04513	AV04513-SS	g*u*uaauaaGfuCfuGfugaug*u*a	2164	AV04513-AS	u*Uf*acuuCfcaagAfcUfuAfaaa*a*c	2599
AV04514	AV04514-SS	c*a*uguugaAfcUfuCfaagaag*u*a	2165	AV04514-AS	u*Af*cuucUfugaAGfuUfcUfaca*u*g	2600
AV04515	AV04515-SS	g*c*uucaagAfaGfuAfaagcu*a*a	2166	AV04515-AS	u*Uf*agcuCfuuaCfuCfuUfgaa*g*c	2601
AV04516	AV04516-SS	g*u*ucaagaAfgUfaAfgagcu*a*a	2167	AV04516-AS	u*Uf*uaagCfuuaCfuUfcUfuga*a*c	2602
AV04517	AV04517-SS	g*u*caagaaGfuAfaGfagcuua*g*a	2168	AV04517-AS	u*CT*uaagCfuuuAfcUfuCfuug*a*c	2603
AV04518	AV04518-SS	g*a*agaaguAfaGfaGfcauagu*u*a	2169	AV04518-AS	u*Af*acuuAfgcuCfuAfcUfuu*u*c	2604
AV04519	AV04519-SS	g*a*ucagcaUfuAfuUfcuucag*a*a	2170	AV04519-AS	u*Uf*cugaAfgaaAfaUfgCfuga*u*c	2605
AV04520	AV04520-SS	g*g*aagggaGfcCfuGfuuuu*u*a	2171	AV04520-AS	u*Af*agaaAfacagGfuCfcCfeuu*c*c	2606
AV04521	AV04521-SS	g*u*ucuucaAfgGfgAfaagaac*a*a	2172	AV04521-AS	u*Uf*guuuCfuuccCfuUfgAfaa*a*c	2607
AV04522	AV04522-SS	g*c*aaacuaCfaGfaAfuuaugu*g*a	2173	AV04522-AS	u*CT*acauUfaauCfuUfgAfaa*u*g*c	2608
AV04523	AV04523-SS	g*a*acuacaGfaAfuAfaugug*u*a	2174	AV04523-AS	u*Af*acacAfuuaUfcUfgUfagu*u*c	2609
AV04524	AV04524-SS	g*c*uccgcaGfgCfuAfuuaugu*c*a	2175	AV04524-AS	u*Gf*aaAfaagCfcUfgCfuga*g*c	2610
AV04525	AV04525-SS	g*c*gcagcUfaUfuUfguucag*a*a	2176	AV04525-AS	u*Uf*cugaAfaaaUfaGfcCfugc*g*c	2611
AV04526	AV04526-SS	g*u*uguucaGfaGfaGfgcuuu*u*a	2177	AV04526-AS	u*Af*aaagGfcucUfcUfgAfaa*a*c	2612

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AV06101	AV06101-SS	c*u*cuuuguGfgCfcUfcccac*c*a	2748	AV06101-AS	u*Gf*gaugGfgaggCfcAfcAfaag*a*g	2899
AV06102	AV06102-SS	u*c*uuugugGfgCfcUfcccac*c*a	2749	AV06102-AS	u*Gf*ggauGfgaggGfgCfcAfaaa*g*a	2900
AV06103	AV06103-SS	c*u*uuugugGfgCfcUfcccac*c*a	2750	AV06103-AS	u*Af*gggaUfggggGfgCfcAfaa*a*g	2901
AV06104	AV06104-SS	u*u*uguggcCfuCfcCfauccu*g*a	2751	AV06104-AS	u*Cl*aggGafuggGfgCfcAfaa*a*a	2902
AV06105	AV06105-SS	u*u*uguggcUfCfcAfuuccu*g*a	2752	AV06105-AS	u*Cl*caggGfaugGfgGfgCfcac*a*a	2903
AV06106	AV06106-SS	u*g*ugggcuCfcCfuUfcccugg*g*a	2753	AV06106-AS	u*Cl*ccagGfgauGfgAfgGfcca*c*a	2904
AV06107	AV06107-SS	g*u*ggccucCfcAfuCfcuccggg*a*a	2754	AV06107-AS	u*Uf*cccaGfggaUfgGfgGfcc*a*c	2905
AV06108	AV06108-SS	u*g*ggccuccCfuUfCfcuccggg*a*a	2755	AV06108-AS	u*Uf*ucccAfggggaUfgGfgAfggc*c*a	2906
AV06109	AV06109-SS	g*g*ccuccAfuCfcCfuccggg*a*a	2756	AV06109-AS	u*Cl*uccCfaggGfaUfgGfgGfagg*c*c	2907
AV06110	AV06110-SS	g*c*cuuccAfuCfcUfugggag*u*a	2757	AV06110-AS	u*Af*cuucCfcaggGfaUfgGfgagg*g*c	2908
AV06111	AV06111-SS	c*c*ucccauCfcCfuGfggaagu*c*a	2758	AV06111-AS	u*Gf*acuuCfccagGfgAfuGfgga*g*g	2909
AV06112	AV06112-SS	c*u*cccauGfgUfgGfggaug*c*a	2759	AV06112-AS	u*Uf*gaucUfcccGfgGfaUfggg*a*g	2910
AV06113	AV06113-SS	u*c*ccaucCfuGfgGfggauga*u*a	2760	AV06113-AS	u*Af*ugacUfuuccAfgGfgAfuugg*g*a	2911
AV06114	AV06114-SS	c*c*cauccUfgGfgAfaugau*c*a	2761	AV06114-AS	u*Uf*angaCfuuccCfaGfgGfaug*g*g	2912
AV06115	AV06115-SS	c*c*auccuGfgGfaAfaugau*c*a	2762	AV06115-AS	u*Cl*uangAfcuucCfcAfgGfgau*g*g	2913
AV06116	AV06116-SS	a*u*ccugGfaAfgUfaugau*c*a	2763	AV06116-AS	u*Cl*acuUfgauUfCfcAfggg*a*u	2914
AV06117	AV06117-SS	u*c*ccugGfaGfuCfaugau*c*a	2764	AV06117-AS	u*Cl*cauAfaugacUfuCfcCfagg*g*a	2915
AV06118	AV06118-SS	c*c*cuuggaAfgUfCfaugau*c*a	2765	AV06118-AS	u*Cl*ccacUfaugaCfuUfCfcag*g*g	2916
AV06119	AV06119-SS	c*c*ugggaaGfuCfaUfaguggg*g*a	2766	AV06119-AS	u*Cl*cccaCfuangAfcUfuCfcca*g*g	2917
AV06120	AV06120-SS	c*u*gggaagUfCfaUfaguggg*g*a	2767	AV06120-AS	u*Uf*ccccAfcuauGfaCfuUfccc*a*g	2918
AV06121	AV06121-SS	u*g*gggaugCfaUfagugggg*a*c	2768	AV06121-AS	u*Gf*uccCfaucUfgAfcUfuucc*c*a	2919
AV06122	AV06122-SS	g*g*gaagucAfuAfgUfagggg*a*a	2769	AV06122-AS	u*Uf*guccCfcacuAfuGfaCfuuc*c*c	2920
AV06123	AV06123-SS	g*g*gauguaUfaGfuGfggggac*a*a	2770	AV06123-AS	u*Cl*ugucCfccacUfaUfgAfcuu*c*c	2921
AV06124	AV06124-SS	g*a*gaucuaAfgUfgGfggagac*u*a	2771	AV06124-AS	u*Af*cuugCfcccaCfuAfuGfauc*u*c	2922
AV06125	AV06125-SS	a*a*gaucuaGfuGfgGfgagac*u*a	2772	AV06125-AS	u*Cl*acugUfccccAfcUfaUfgac*u*u	2923
AV06126	AV06126-SS	a*g*ucauagUfgGfgGfgagac*u*a	2773	AV06126-AS	u*Uf*cauGfuuccCfaCfuAfuaga*c*u	2924
AV06127	AV06127-SS	g*u*cauagUfgGfgAfcagac*c*a	2774	AV06127-AS	u*Gf*ueacUfguuccCfcAfeUfaug*a*c	2925
AV06128	AV06128-SS	u*c*auagugGfgGfaCfaugac*a*a	2775	AV06128-AS	u*Uf*gucaCfugucCfcCfaCfuau*g*a	2926
AV06129	AV06129-SS	c*a*uaugugGfgAfcAfgagac*c*a	2776	AV06129-AS	u*Gf*ugucAfcuugCfcCfcAfcua*u*g	2927

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AV06130	AV06130-SS	a*u*aguggGfaCfaGfugacac*u*a	2777	AV06130-AS	u*Af*guGuCfagucUfcCfcCfacu*a*u	2928
AV06131	AV06131-SS	u*a*guggGfaCfaGfugacac*u*a	2778	AV06131-AS	u*Cl*agugUfcacUGfuCfcCfcau*a	2929
AV06132	AV06132-SS	a*g*ugggGfaCfaGfugacac*u*a	2779	AV06132-AS	u*Uf*caguGfucacUfgUfcCfcau*c*u	2930
AV06133	AV06133-SS	g*u*ggggGfaCfaGfugacac*u*a	2780	AV06133-AS	u*Gf*ucagUfgucaCfuGfuCfccc*a*c	2931
AV06134	AV06134-SS	u*g*ggGfaCfaGfugacac*u*a	2781	AV06134-AS	u*Gf*gucaGfugacAfcUfgUfccc*c*a	2932
AV06135	AV06135-SS	g*g*ggGfaCfaGfugacac*u*a	2782	AV06135-AS	u*Uf*ggucAfgugucCfaCfuGfucc*c*c	2933
AV06136	AV06136-SS	g*g*ggGfaCfaGfugacac*u*a	2783	AV06136-AS	u*Af*ugguCfagugUfcAfcUfguc*c*c	2934
AV06137	AV06137-SS	g*g*ggGfaCfaGfugacac*u*a	2784	AV06137-AS	u*Gf*auggUfcagugGfuCfaCfuguc*c*c	2935
AV06138	AV06138-SS	g*a*cagugGfaCfaGfugacac*u*a	2785	AV06138-AS	u*Af*gaugGfucagUfgUfcAfcug*u*c	2936
AV06139	AV06139-SS	a*c*agugGfaCfaGfugacac*u*a	2786	AV06139-AS	u*Cl*agauGfugacGfuGfuCfacu*g*u	2937
AV06140	AV06140-SS	c*a*gugGfaCfaGfugacac*u*a	2787	AV06140-AS	u*Gf*cagaUfgugacAfgUfgUfcac*u*g	2938
AV06141	AV06141-SS	a*g*ugGfaCfaGfugacac*u*a	2788	AV06141-AS	u*Uf*gcagAfgugGfuCfaGfuGfuc*c*u	2939
AV06142	AV06142-SS	g*u*ggGfaCfaGfugacac*u*a	2789	AV06142-AS	u*Af*ugcaGfugGfuCfaGfuGfuc*c*c	2940
AV06143	AV06143-SS	u*g*acagGfaCfaGfugacac*u*a	2790	AV06143-AS	u*Cl*augcAfgaugGfuCfaGfuguc*c*a	2941
AV06144	AV06144-SS	g*a*cacGfaCfaGfugacac*u*a	2791	AV06144-AS	u*Uf*cagCfagugGfuCfaGfuguc*u*c	2942
AV06145	AV06145-SS	a*c*acugGfaCfaGfugacac*u*a	2792	AV06145-AS	u*Af*ueauGfagugUfgGfuCfagu*g*u	2943
AV06146	AV06146-SS	a*c*ugGfaCfaGfugacac*u*a	2793	AV06146-AS	u*Af*caucAfgucGfaUfgGfucac*g*u	2944
AV06147	AV06147-SS	c*u*gacGfaCfaGfugacac*u*a	2794	AV06147-AS	u*Gf*acauCfagucAfgAfuGfucac*g	2945
AV06148	AV06148-SS	u*g*accGfaCfaGfugacac*u*a	2795	AV06148-AS	u*Gf*gacaUfcagGfaGfaUfguc*c*a	2946
AV06149	AV06149-SS	c*c*aucGfaCfaGfugacac*u*a	2796	AV06149-AS	u*Cl*augGfagucAfuGfuCfaguc*g	2947
AV06150	AV06150-SS	u*c*ugGfaCfaGfugacac*u*a	2797	AV06150-AS	u*Gf*ucaUfggacAfuCfaUfgca*g*a	2948
AV06151	AV06151-SS	u*g*caugGfaCfaGfugacac*u*a	2798	AV06151-AS	u*Af*uguuCfagucAfcAfuCfaguc*c*a	2949
AV06152	AV06152-SS	c*a*ugGfaCfaGfugacac*u*a	2799	AV06152-AS	u*Af*caugUfcuagGfuCfaUfgca*u*g	2950
AV06153	AV06153-SS	a*u*gaugGfaCfaGfugacac*u*a	2800	AV06153-AS	u*Af*acauGfucacUfgGfaCfauca*a	2951
AV06154	AV06154-SS	a*u*guccGfaCfaGfugacac*u*a	2801	AV06154-AS	u*Gf*uaaaCfagugUfcAfuGfagac*a	2952
AV06155	AV06155-SS	g*u*ccagGfaCfaGfugacac*u*a	2802	AV06155-AS	u*Cl*aguaAfcuagGfuUfcAfguc*c*c	2953
AV06156	AV06156-SS	u*c*caugGfaCfaGfugacac*u*a	2803	AV06156-AS	u*Cl*caguAfaaaUfgUfuCfaguc*g	2954
AV06157	AV06157-SS	c*a*uguuGfaCfaGfugacac*u*a	2804	AV06157-AS	u*Uf*auugUfuaccAfgUfaAfaa*u*g	2955
AV06158	AV06158-SS	u*u*ucugGfaCfaGfugacac*u*a	2805	AV06158-AS	u*Af*ucuuAfuugUfaCfaAfgua*a	2956

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AV06159	AV06159-SS	g*g*uaacaaUfaAfgAfucugug*g*a	2806	AV06159-AS	u*CI*cacaGfaucuUfaUfuGfuaa*c*c	2957
AV06160	AV06160-SS	g*u*aacaaUfaGfaUfugugg*u*a	2807	AV06160-AS	u*A*f*ceacAfgaucUfuAfuUfguu*a*c	2958
AV06161	AV06161-SS	a*u*cugugguUfuGfgAfauuug*a*a	2808	AV06161-AS	u*U*f*cauaAfuuccAfaCfcAfcag*a*u	2959
AV06162	AV06162-SS	u*c*ugugguUfgGfaAfuauga*a*a	2809	AV06162-AS	u*U*f*ucauAfaucCfaAfcCfaca*g*a	2960
AV06163	AV06163-SS	c*u*gugguGfgAfaUfuuga*u*a	2810	AV06163-AS	u*A*f*uucaUfaauuCfcAfaCfcac*a*g	2961
AV06164	AV06164-SS	g*u*gguugAfaUfuAfgaau*g*a	2811	AV06164-AS	u*A*f*cauuCfaaaUfuCfcAfac*c*c	2962
AV06165	AV06165-SS	u*u*ggauuAfuGfaAfgucca*a*a	2812	AV06165-AS	u*U*f*uggaCfaucAfuAfaUfucc*a*a	2963
AV06166	AV06166-SS	g*g*aaauuGfaAfuGfuccaa*g*a	2813	AV06166-AS	u*CI*uuugGfacauUfcAfuAfaui*c*c	2964
AV06167	AV06167-SS	g*a*auuugAfaUfgUfccaaug*u*a	2814	AV06167-AS	u*A*f*cuuuGfgacaUfuCfaUfaau*u*c	2965
AV06168	AV06168-SS	u*u*augaaUGfuCfcAfaaguuu*g*a	2815	AV06168-AS	u*CI*aaacUfuuggAfcAfuUfcau*a*a	2966
AV06169	AV06169-SS	u*g*aaugucCfaAfaGfuugaa*g*a	2816	AV06169-AS	u*CI*uucaAfacuuUfgGfaCfaui*c*a	2967
AV06170	AV06170-SS	a*a*uguccaAfaGfuUfugaaga*g*a	2817	AV06170-AS	u*CI*ucuuCfaaacUfuUfgGfaca*u*u	2968
AV06171	AV06171-SS	a*u*guccaaAfgUfuUfgaagag*g*a	2818	AV06171-AS	u*CI*cucuUfcaaaCfuUfuGfgac*a*u	2969
AV06172	AV06172-SS	u*g*uccaaaGfuUfuGfaagagg*a*a	2819	AV06172-AS	u*U*f*ccucUfuccaaAfaUfuUfgga*c*a	2970
AV06173	AV06173-SS	u*c*caaguUfuGfaAfgaggau*g*a	2820	AV06173-AS	u*CI*auccUfcuucAfaAfcUfugg*g*a	2971
AV06174	AV06174-SS	c*c*aaaguuUfgAfaGfaggau*g*a	2821	AV06174-AS	u*A*f*caucCfucuuCfaAfaCfuui*g*g	2972
AV06175	AV06175-SS	c*a*aguuuGfaAfgAfggaugu*u*a	2822	AV06175-AS	u*A*f*acauCfcucuUfcAfaAfcuu*u*g	2973
AV06176	AV06176-SS	a*a*guungaAfgAfgGfauguu*u*a	2823	AV06176-AS	u*A*f*aaacAfuucuCfuUfcAfaac*u*u	2974
AV06177	AV06177-SS	a*g*uuugaGfaGfgAfguuuu*g*a	2824	AV06177-AS	u*CI*aaaaCfauccUfcUfuCfaaa*c*u	2975
AV06178	AV06178-SS	g*u*uuugaAfgGfaUfguuuu*g*a	2825	AV06178-AS	u*U*f*caaaAfaucCfuCfuUfcaaa*g*c	2976
AV06179	AV06179-SS	u*u*ugaagaGfgAfuGfuuuuga*g*a	2826	AV06179-AS	u*CI*ucaaAfaacuCfcUfcUfuca*a*a	2977
AV06180	AV06180-SS	u*u*gaagagGfaUfgUfuugaug*c*a	2827	AV06180-AS	u*G*f*cucaAfaacaUfcCfuCfuuc*a*a	2978
AV06181	AV06181-SS	g*a*agaggaUfgUfuUfgagaca*g*a	2828	AV06181-AS	u*CI*ugcuCfaaaaCfaUfcCfucu*u*c	2979
AV06182	AV06182-SS	a*g*aggauUfuUfuGfagcagu*g*a	2829	AV06182-AS	u*CI*acugCfucaaAfaCfaUfcucu*c*u	2980
AV06183	AV06183-SS	g*a*ggauuUfuUfgAfgcagu*a*a	2830	AV06183-AS	u*U*f*cacuGfucuaAfaAfcAfucc*u*c	2981
AV06184	AV06184-SS	a*g*gauguUfuGfaGfaguga*c*a	2831	AV06184-AS	u*G*f*ucacUfgucAfaAfaCfauc*c*u	2982
AV06185	AV06185-SS	u*u*uuagcAfgUfgAfcAuauu*a*a	2832	AV06185-AS	u*U*f*auaaUfgucaCfuGfcUfcaaa*a*a	2983
AV06186	AV06186-SS	u*u*gagcagUfgAfaAfuuaaa*u*a	2833	AV06186-AS	u*A*f*uuauAfauguCfaCfuGfcuc*a*a	2984
AV06187	AV06187-SS	u*g*agcaguGfaCfaUfuuaaa*u*a	2834	AV06187-AS	u*A*f*auuaUfaaugUfcAfcUfgcu*c*a	2985

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AV06188	AV06188-SS	a*c*auuauAfuUfcUfgcaau*a*a	2835	AV06188-AS	u*U*f*auugUfcagaAfuUfaUfaau*g*u	2986
AV06189	AV06189-SS	a*u*u*uuauUfcUfgAfeauaa*c*a	2836	AV06189-AS	u*G*f*uuauUfgucaGfaAfuUfaua*a*u	2987
AV06190	AV06190-SS	u*u*auauuUfcUfgCfaauaac*a*a	2837	AV06190-AS	u*U*f*guuaUfgucAfgAfaUfuau*a*a	2988
AV06191	AV06191-SS	u*a*u*auuUfcUfgAfcAfaauaac*c*a	2838	AV06191-AS	u*G*f*uguuAfuugCfaGfaAfuua*u*a	2989
AV06192	AV06192-SS	a*u*a*auuUfcUfgCfaAfaauaac*g*a	2839	AV06192-AS	u*U*f*guuUfaauUfcAfgAfaau*a*u	2990
AV06193	AV06193-SS	u*a*a*auueugAfcAfaUfaaacg*a*a	2840	AV06193-AS	u*U*f*cgugUfuauUfcCfaGfaau*u*a	2991
AV06194	AV06194-SS	c*u*g*auuAfaCfaCfcauagc*a*a	2841	AV06194-AS	u*A*f*ugcaUfcgugUfuAfuUfguc*a*g	2992
AV06195	AV06195-SS	a*c*a*auaacAfcGfaUfgcauag*c*a	2842	AV06195-AS	u*G*f*cuauGfcaucGfuGfuUfaau*g*u	2993
AV06196	AV06196-SS	c*a*a*auaacCfcaUfgAfuGfcauagc*c*a	2843	AV06196-AS	u*G*f*geuaUfgcauUfgUfgUfuau*u*g	2994
AV06197	AV06197-SS	a*a*u*auaacGfaUfgCfcauagc*a*a	2844	AV06197-AS	u*U*f*ggcuAfuugcaUfcGfuGfuua*u*u	2995
AV06198	AV06198-SS	a*u*a*acacgAfuGfcAfuagcca*u*a	2845	AV06198-AS	u*A*f*uggcUfaugcAfuCfcUfguu*a*u	2996
AV06199	AV06199-SS	u*a*a*acacgaUfgCfaUfgcauagc*c*a	2846	AV06199-AS	u*G*f*auugCfuugCfaUfcGfugu*u*a	2997
AV06200	AV06200-SS	a*a*a*caugauGfcAfuAfgcauagc*c*a	2847	AV06200-AS	u*G*f*gaugGfcauGfcAfuCfugc*u*u	2998
AV06201	AV06201-SS	a*c*a*acgaugCfaUfaGfcauagc*c*a	2848	AV06201-AS	u*A*f*ggauGfgcuUfgCfaUfcgug*g*u	2999
AV06202	AV06202-SS	c*a*a*cgauagAfuAfgCfcauagc*c*a	2849	AV06202-AS	u*U*f*aggaUfggcuAfuGfcAfuagc*u*g	3000
AV06203	AV06203-SS	a*c*a*gaugcaUfaGfcCfcauagc*c*a	2850	AV06203-AS	u*A*f*caggAfuagcUfaUfgCfcauagc*g*u	3001
AV06204	AV06204-SS	c*g*a*ugcauAfgCfcAfuagcugc*c*a	2851	AV06204-AS	u*U*f*acagGfaugcGfuAfuGfcau*c*g	3002
AV06205	AV06205-SS	g*a*a*ugcauGfcCfaUfgcugua*u*a	2852	AV06205-AS	u*A*f*uaacGfcaugGfcUfaUfgcau*u*c	3003
AV06206	AV06206-SS	a*u*a*gaugcaUfaGfcCfcauagc*c*a	2853	AV06206-AS	u*U*f*auacAfggcuGfgCfuAfuagc*a*u	3004
AV06207	AV06207-SS	u*g*a*cauagCfaUfcCfcauagc*c*a	2854	AV06207-AS	u*A*f*uaacCfcaugGfgGfcUfaugc*c*a	3005
AV06208	AV06208-SS	g*c*a*auagcaUfaCfcUfgcauagc*c*a	2855	AV06208-AS	u*A*f*auauAfcaggAfuGfgCfuau*g*c	3006
AV06209	AV06209-SS	c*a*a*uaagcaUfcCfuGfcauagc*c*a	2856	AV06209-AS	u*A*f*auauUfaagGfgAfuGfgCfuau*g*c	3007
AV06210	AV06210-SS	a*u*a*agcauGfcCfuGfcauagc*c*a	2857	AV06210-AS	u*U*f*auauAfuagGfgAfuGfgCfuau*g*c	3008
AV06211	AV06211-SS	u*a*a*gaugcaUfaGfcCfcauagc*c*a	2858	AV06211-AS	u*G*f*uaaaUfaaacAfgGfgUfggcau*u*a	3009
AV06212	AV06212-SS	a*g*a*cauagCfuGfgAfuauagc*c*a	2859	AV06212-AS	u*A*f*guuaAfuuaCfaGfgAfuagc*c*u	3010
AV06213	AV06213-SS	g*c*a*cauagCfuGfgAfuauagc*c*a	2860	AV06213-AS	u*A*f*guuaAfuuaCfaGfgAfuagc*c*u	3011
AV06214	AV06214-SS	c*c*a*cauagCfuGfgAfuauagc*c*a	2861	AV06214-AS	u*G*f*aggaAfuuaAfuuaCfaGfgAfuagc*c*u	3012
AV06215	AV06215-SS	a*u*a*cauagCfuGfgAfuauagc*c*a	2862	AV06215-AS	u*U*f*ggaaGfuuaAfuuaCfaGfgAfuagc*c*u	3013
AV06216	AV06216-SS	u*c*a*cauagCfuGfgAfuauagc*c*a	2863	AV06216-AS	u*U*f*ggaaGfuuaAfuuaCfaGfgAfuagc*c*u	3014

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AV06217	AV06217-SS	c*c*uguauaUfuUfaCfuuccag*u*a	2864	AV06217-AS	u*Af*cuggAfaguaAfaUfaUfaca*g*g	3015
AV06218	AV06218-SS	a*u*aauuacUfuCfcAfguuca*g*a	2865	AV06218-AS	u*Cl*fuggAfucgAfaGfuAfaau*a*u	3016
AV06219	AV06219-SS	u*a*uuuacuUfcCfaGfuuccag*a*a	2866	AV06219-AS	u*Uf*cuggAfacugGfaAfgUfaaa*u*a	3017
AV06220	AV06220-SS	u*a*cuuccaGfuUfcCfagaauu*u*a	2867	AV06220-AS	u*Af*aaauCfuggAfcUfgGfaag*u*a	3018
AV06221	AV06221-SS	u*c*cagauUfuAfcGfucaacu*u*a	2868	AV06221-AS	u*Af*aguuGfacguAfaAfuUfcug*g*a	3019
AV06222	AV06222-SS	g*u*caacuGfgAfuCfaaaaua*u*a	2869	AV06222-AS	u*Af*uauUfugauCfcAfaGfuug*a*c	3020
AV06223	AV06223-SS	u*c*aacuugGfaUfcAfaaaaua*u*a	2870	AV06223-AS	u*Uf*auauUfuugaUfcCfaAfguu*g*a	3021
AV06224	AV06224-SS	c*a*acuuggAfuCfaAfaauaaua*u*a	2871	AV06224-AS	u*Af*uauUfuugAfuCfcAfaUfu*g	3022
AV06225	AV06225-SS	a*a*cuuggAfuCfaAfaauaaua*u*a	2872	AV06225-AS	u*Af*auauAfuuuGfaUfcCfaag*u*u	3023
AV06226	AV06226-SS	a*c*uuggauCfaAfaAfaauaaua*u*a	2873	AV06226-AS	u*Af*auaUfauuUfgAfuCfaa*g*u	3024
AV06321	AV06321-SS	g*a*ccaucuGfcAfuGfaugucc*a*a	3173	AV06321-SS	u*Uf*ggacAfucauGfcAfgAfgg*u*c	3177
AV06322	AV06322-SS	u*a*cugguaAfcAfaUfagauc*u*a	3174	AV06322-SS	u*Af*gaucUfauuGfuUfaCfcag*u*a	3178
AV06323	AV06323-SS	g*u*ccaguuCfcAfgAfaauuac*g*a	3175	AV06323-SS	u*Cl*f*guaaAfuucGfgAfaCfugg*a*c	3179
AV06324	AV06324-SS	u*g*uaaucaGfuAfcAfguuguc*a*a	3176	AV06324-SS	u*Uf*gacaAfcuguAfcUfgAfaa*c*a	3180

Table 3 shows certain chemically modified HMGCR RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, RNAi agents shown in Table 3 are administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex identified in a row in Table 3, column one and includes the sequence modifications and/or delivery compound shown in the sense and antisense strand sequences in the same row in Table 3, columns three and six, respectively. The sequences were used in certain *in vivo* testing studies described elsewhere herein. In some embodiments of methods of the invention, a sequence shown in Table 3 may be attached to (also referred to herein as “conjugated to”) a compound for delivery, a non-limiting example of which is a GalNAc-containing compound, with a delivery compound identified in Table 3 as “GLX-n” on sense strands in column three. As used herein, “GLX-n” is used to represent either a “GLS-n*” or a “GLO-n” delivery compound (“X” can be either “S” or “O”) and GLX-0 can be any of the “GLS-n*” and “GLO-n” delivery compounds that can be attached to 3'-end of oligonucleotide during synthesis. As used herein and shown in Table 3, “GLX-n” is used to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is provided elsewhere herein. One skilled in the art will be able to prepare and use a dsRNA compound of the invention in which the attached delivery compound is one of GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16. Column one of Table 3 provides a Duplex AD# assigned to the duplex of the sense and antisense sequences in that row of the table. For example, Duplex AD# AD00842 is the duplex of sense strand SEQ ID NO: 2642 and antisense strand SEQ ID NO: 2695. Each line in Table 3 provides a sense strand and an antisense strand, and discloses the duplex of the sense and antisense strands shown. The “Sense strand SS#” in Table 3 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 3 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six. An identifier for certain attached GalNAc-containing “GLO-n” or “GLS-n*” compounds is shown as GLS-5*, GLS-15* or GLX-0, and it will be understood that another of the “GLO-n” or “GLS-n*” compounds may be substituted for the compound shown as GLO-0, with the resulting compound included in an embodiment of a method and/or a composition of the invention.

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Table 3 provides chemically modified HMGCR RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. The sequences were used in certain *in vivo* testing studies described elsewhere herein. A delivery molecule used in the *in vivo* studies is indicated as “GLO-n” or “GLS-n*” at the 3'-end or 5'-end of each sense strand.

Duplex AD#	Sense strand SS#	Sense Sequence	SEQ ID NO	Antisense strand AS#	Antisense Sequence	SEQ ID NO
AD00608	AD00608-SS	(GLS-15*)(invab*)guagcuacAfaUfgUfugucaaga*(invab)	2617	AD00608-AS	u*Ci ^{1*} uugaCfaacaUfuGfuAfgcu*a*c	2670
AD00609	AD00609-SS	(GLS-15*)(invab*)gcuacaauGfuUfgUfcaagacua*(invab)	2618	AD00609-AS	u*A ^{1*} guuUfgacaAfcAfuUfgua*g*c	2671
AD00610	AD00610-SS	(GLS-15*)(invab*)caugauguCfcAfuGfaacaugua*(invab)	2619	AD00610-AS	u*A ^{1*} caugUfucauGfgAfcAfuca*u*g	2672
AD00611	AD00611-SS	(GLS-15*)(invab*)gaagaagCfuUfuGfcccuuua*(invab)	2620	AD00611-AS	u*A ^{1*} aaagGfgcaaAfgCfuUfcau*u*c	2673
AD00612	AD00612-SS	(GLS-15*)(invab*)juccaagagAfaUfuGfaaccaaga*(invab)	2621	AD00612-AS	u*Ci ^{1*} uuggUfucaaUfuCfuCfuug*g*a	2674
AD00613	AD00613-SS	(GLS-15*)(invab*)jaagagauUfgAfaCfaagugua*(invab)	2622	AD00613-AS	u*A ^{1*} cacuUfgguuCfaAfuUfcuc*u*u	2675
AD00614	AD00614-SS	(GLS-15*)(invab*)jaaauguuAfgGfuUfauaaaca*(invab)	2623	AD00614-AS	u*Gi ^{1*} uuuAfuacCfuCfaAfcuu*u*u	2676
AD00615	AD00615-SS	(GLS-15*)(invab*)jaaguugaGfgUfuAfuuaaaca*(invab)	2624	AD00615-AS	u*Gi ^{1*} guuUfauaaCfcUfcAfacu*u*u	2677
AD00616	AD00616-SS	(GLS-15*)(invab*)gcuugugaCfuCfuGfcaagaa*(invab)	2625	AD00616-AS	u*A ^{1*} cuucUfgcagAfgUfcAfcua*g*c	2678
AD00617	AD00617-SS	(GLS-15*)(invab*)juuuaauCfcGfuUfucaagaa*(invab)	2626	AD00617-AS	u*Gi ^{1*} acugGfaaacGfgAfuAfuua*a*g	2679
AD00618	AD00618-SS	(GLS-15*)(invab*)aacuguauUfaCfuUfuuaugaa*(invab)	2627	AD00618-AS	u*Uj ^{1*} ccauUfaaagUfaAfuAfcag*u*u	2680
AD00619	AD00619-SS	(GLS-15*)(invab*)gacauguUfaCfuGfguaacaa*(invab)	2628	AD00619-AS	u*Uj ^{1*} uguuAfcagUfaAfaCfaug*u*c	2681
AD00620	AD00620-SS	(GLS-15*)(invab*)cauccguAfuAfuUfuacua*(invab)	2629	AD00620-AS	u*Gi ^{1*} gaagUfaaaUfuAfcAfcga*u*g	2682
AD00621	AD00621-SS	(GLS-15*)(invab*)juuacgucaAfcUfuGfgaucaaaa*(invab)	2630	AD00621-AS	u*Uj ^{1*} uugaUfcaaaGfuUfgAfcgu*a*a	2683
AD00622	AD00622-SS	(GLS-15*)(invab*)gauugacaGfgCfuUfgaungaaa*(invab)	2631	AD00622-AS	u*Uj ^{1*} ucauUfcaagCfcUfgUfcau*u*c	2684
AD00623	AD00623-SS	(GLS-15*)(invab*)cuugugaAfuGfuCfuugugua*(invab)	2632	AD00623-AS	u*A ^{1*} ucacAfcagAfuUfcAfcua*a*g	2685
AD00624	AD00624-SS	(GLS-15*)(invab*)gguaauaCfcCfuAfgauuaga*(invab)	2633	AD00624-AS	u*Ci ^{1*} uaaaCfuugGfgUfaAfuua*c*c	2686
AD00625	AD00625-SS	(GLS-15*)(invab*)ggaaagaaAfaGfuUfgagguua*(invab)	2634	AD00625-AS	u*Uj ^{1*} aacUfcaacUfuUfuCfuuu*c*c	2687
AD00626	AD00626-SS	(GLS-15*)(invab*)jaagugcaAfaAfuUfcauua*(invab)	2635	AD00626-AS	u*A ^{1*} cuuaGfgaaUfuUfgCfacc*u*u	2688
AD00627	AD00627-SS	(GLS-15*)(invab*)cuuagugaUfgCfuGfgaucaua*(invab)	2636	AD00627-AS	u*A ^{1*} ugauCfucagCfaUfcAfcua*a*g	2689
AD00628	AD00628-SS	(GLS-15*)(invab*)gguaaauUfuGfuAfcugacaaa*(invab)	2637	AD00628-AS	u*Uj ^{1*} ugucAfguacAfaUfaGfuua*c*c	2690
AD00629	AD00629-SS	(GLS-15*)(invab*)caagauguUfgGfuAfguuaaaa*(invab)	2638	AD00629-AS	u*Uj ^{1*} uugaAfcuacCfaAfcAfuuc*u*g	2691
AD00630	AD00630-SS	(GLS-15*)(invab*)caggugcaAfgAfuCfaauuaa*(invab)	2639	AD00630-AS	u*Gi ^{1*} uaaaUfugaUfuUfcGfacc*u*g	2692

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AD00631	AD00631-SS	(GLS-15*)(invab*)ggauaaaUfuCfuUfgaaguca*(invab)	2640	AD00631-AS	u*Gf ^u *aacUfcaagAfaUfuUfcau*c*c	2693
AD00632	AD00632-SS	(GLS-15*)(invab*)gauguaaAfcUfuCfaagaau*(invab)	2641	AD00632-AS	u*Af ^u *cuucUfugaaGfuUfuUfaca*u*c	2694
AD00842	AD00842-SS	(GLS-15*)(imann*)guuguaaGfaCfuUfuucgaa*a*(imann)	2642	AD00842-AS	u*Uf ^u *ucgaAfaaagUfcUfuGfaca*a*c	2695
AD00843	AD00843-SS	(GLS-15*)(imann*)juguaaGfaCfuUfuUfucgaa*a*(imann)	2643	AD00843-AS	u*Cf ^u *auucGfaaaAfgUfcUfuga*c*a	2696
AD00844	AD00844-SS	(GLS-15*)(imann*)caucugaUfgAfuGfucca*a*(imann)	2644	AD00844-AS	u*Uf ^u *caugGfacaCfaUfgCfaga*u*g	2697
AD00845	AD00845-SS	(GLS-15*)(imann*)gauguaaUfgAfaCfauguua*a*(imann)	2645	AD00845-AS	u*Uf ^u *aaacAfuuguCfaUfgGfaca*u*c	2698
AD00846	AD00846-SS	(GLS-15*)(imann*)caugaaAfuGfuUfuacugua*a*(imann)	2646	AD00846-AS	u*Af ^u *ccagUfaaacAfuGfuUfcau*g*g	2699
AD00847	AD00847-SS	(GLS-15*)(imann*)caugaaUfgUfuUfuacugua*a*(imann)	2647	AD00847-AS	u*Uf ^u *accaGfuuaaCfaUfgUfuca*u*g	2700
AD00848	AD00848-SS	(GLS-15*)(imann*)augaaGfuUfuAfcuguaa*a*(imann)	2648	AD00848-AS	u*Uf ^u *uaccAfguaaAfcAfuGfuuc*a*u	2701
AD00849	AD00849-SS	(GLS-15*)(imann*)cagugaaUfuAfuAfaucuga*a*(imann)	2649	AD00849-AS	u*Uf ^u *cagaAfuuaAfaUfgUfcac*u*g	2702
AD00850	AD00850-SS	(GLS-15*)(imann*)aaucugaCfaAfuAfacagau*a*(imann)	2650	AD00850-AS	u*Af ^u *ucguGfuuaUfgUfcAfgaa*u*u	2703
AD00851	AD00851-SS	(GLS-15*)(imann*)caguuaGfaAfuUfuacuga*a*(imann)	2651	AD00851-AS	u*Uf ^u *gagUfaaaUfcUfgGfaac*u*g	2704
AD00852	AD00852-SS	(GLS-15*)(imann*)aguucagAfaUfuUfuacuga*a*(imann)	2652	AD00852-AS	u*Uf ^u *ugacGfuuaaUfuCfuGfgaa*c*u	2705
AD00853	AD00853-SS	(GLS-15*)(imann*)guucagaAfuUfuAfcugaa*a*(imann)	2653	AD00853-AS	u*Gf ^u *uuGfa(cUNA)guaaAfuUfcUfgga*a*c	2706
AD00854	AD00854-SS	(GLS-15*)(imann*)uuacgacAfaCfuUfggaac*a*(imann)	2654	AD00854-AS	u*Uf ^u *ugauCfaagUfuGfaCfgua*a*a	2707
AD00855	AD00855-SS	(GLS-15*)(imann*)auucaguaCfaGfuUfgcauuc*a*(imann)	2655	AD00855-AS	u*Gf ^u *aagAfaaacUfgUfaCfuga*a*u	2708
AD00856	AD00856-SS	(GLS-15*)(imann*)uacaguUfcAfuUfcauuc*a*(imann)	2656	AD00856-AS	u*Af ^u *gaagUfgaaGfaCfaAfcug*u*a	2709
AD00857	AD00857-SS	(GLS-15*)(imann*)uugcauUfcAfuUfcauagac*a*(imann)	2657	AD00857-AS	u*Gf ^u *uuaAfgaagUfgAfaUfgac*a*a	2710
AD00858	AD00858-SS	(GLS-15*)(imann*)uucuaaCfaAfaGfaauugac*a*(imann)	2658	AD00858-AS	u*Gf ^u *ucaaUfucuuUfgUfcUfaag*a*a	2711
AD00859	AD00859-SS	(GLS-15*)(imann*)uuuaaAfaGfuUfugccuu*a*(imann)	2659	AD00859-AS	u*Af ^u *agGfg(cUNA)aaagCfuUfcAfuuc*a*a	2712
AD00860	AD00860-SS	(GLS-15*)(imann*)gaauuUfcCfuCfuggaau*a*(imann)	2660	AD00860-AS	u*Af ^u *uuccAfcagCfaAfuAfuuu*u*c	2713
AD00861	AD00861-SS	(GLS-15*)(imann*)gaugcuUfgUfuGfaugcu*a*(imann)	2661	AD00861-AS	u*Af ^u *gacUfucaaCfaAfgAfgca*u*c	2714
AD00862	AD00862-SS	(GLS-15*)(imann*)agauguaAfuCfuAfcagcuca*a*(imann)	2662	AD00862-AS	u*Uf ^u *gaGfc(uUNA)guagAfuUfaCfcau*c*c	2715
AD00863	AD00863-SS	(GLS-15*)(imann*)uuugaAfaUfuCfugaau*a*(imann)	2663	AD00863-AS	u*Af ^u *cuucAfaaAfuUfcAfuca*a*a	2716
AD01021	AD01021-SS	(GLS-15*)(imann*)jguuguaAfgAfcUfuuuuca*a*(imann)	2664	AD01021-AS	u*Uf ^u *cgaaAfaaguCfuUfgAfaa*c*c	2717
AD01022	AD01022-SS	(GLS-15*)(imann*)guucaagAfcUfuUfuucgaau*a*(imann)	2665	AD01022-AS	u*Af ^u *uucAfaaaaGfuCfuUfgac*a*c	2718

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AD01023	AD01023-SS	(GLS-15*)(imann*)gugcaugUfgUfcCfaugaaca*a*(imann)	2666	AD01023-AS	u*Uf*guucAfuuggaCfaUfcAfuugc*a*c	2719
AD01024	AD01024-SS	(GLS-15*)(imann*)guguuacUfgGfuAfaaaua*a*(imann)	2667	AD01024-AS	u*Uf*uuuGfuacCfaGfuAfaa*a*c	2720
AD01025	AD01025-SS	(GLS-15*)(imann*)gaaagauCfuGfuGfguuggaa*a*(imann)	2668	AD01025-AS	u*Uf*uccaAfaaCfaGfuCfuua*a*c	2721
AD01026	AD01026-SS	(GLS-15*)(imann*)guccaguCfaAfaAfauuag*a*(imann)	2669	AD01026-AS	u*Uf*guuaAfuucGfgAfaCfuugg*a*c	2722
AD02039	AD02039-SS	(GLS-15*)(imann*)uuuagauGfcAfuGfgcucu*a*(imann)	3025	AD02039-AS	u*Uf*agAfg(gUNA)ccauGfcAfuUfuga*a*a	3091
AD02040	AD02040-SS	(GLS-15*)(imann*)gaccauGfcAfuGfaugucca*a*(imann)	3026	AD02040-AS	u*Uf*ggacAfuauGfcAfaAfuugg*a*c	3092
AD02041	AD02041-SS	(GLS-15*)(imann*)uacuguaAfaUfaagaua*a*(imann)	3027	AD02041-AS	u*Uf*gaucUfuauuGfuUfaCfag*a*a	3093
AD02042	AD02042-SS	(GLS-15*)(imann*)acuguaCfaAfuAfaugc*a*(imann)	3028	AD02042-AS	u*Uf*agauCfuauUfgUfuAfaa*a*c	3094
AD02043	AD02043-SS	(GLS-15*)(imann*)uaacaauAfaUfaCfugguu*a*(imann)	3029	AD02043-AS	u*Uf*accaCfagauCfuUfaUfugu*a*a	3095
AD02044	AD02044-SS	(GLS-15*)(imann*)jugguugGfaAfuUfaugaau*a*(imann)	3030	AD02044-AS	u*Uf*auucAfuauUfcCfaAfaa*a*c	3096
AD02045	AD02045-SS	(GLS-15*)(imann*)auuagauUfgUfcCfaaguuu*a*(imann)	3031	AD02045-AS	u*Uf*auucUfuggaCfaUfuCfaa*a*a	3097
AD02046	AD02046-SS	(GLS-15*)(imann*)guccaagUfuUfgAfaagga*a*(imann)	3032	AD02046-AS	u*Uf*auucCfuuaAfaCfuUfugg*a*c	3098
AD02047	AD02047-SS	(GLS-15*)(imann*)jugagagAfuGfuUfuugagca*a*(imann)	3033	AD02047-AS	u*Uf*gucaAfaaCfaCfuCfuua*a*c	3099
AD02048	AD02048-SS	(GLS-15*)(imann*)aagagauGfuUfuUfgagcu*a*(imann)	3034	AD02048-AS	u*Uf*cuGfc(uUNA)caaaAfaCfuCfuua*a*c	3100
AD02049	AD02049-SS	(GLS-15*)(imann*)juguuuugaGfcAfaUfgacaaua*a*(imann)	3035	AD02049-AS	u*Uf*auugUfcacuGfcUfcAfaa*a*c	3101
AD02050	AD02050-SS	(GLS-15*)(imann*)uuugagcaGfuGfaCfaauuaa*a*(imann)	3036	AD02050-AS	u*Uf*auuaAfuugcAfaUfgCfuca*a*a	3102
AD02051	AD02051-SS	(GLS-15*)(imann*)cauuuaUfuCfuGfaaaua*a*(imann)	3037	AD02051-AS	u*Uf*auuuGfucagAfaUfuAfaa*a*g	3103
AD02052	AD02052-SS	(GLS-15*)(imann*)jugacaauAfaAfaGfaugcau*a*(imann)	3038	AD02052-AS	u*Uf*augAfuagcuGfuUfaUfugu*a*c	3104
AD02053	AD02053-SS	(GLS-15*)(imann*)cuguauUfuAfaUfuccagu*a*(imann)	3039	AD02053-AS	u*Uf*acugGfaaguAfaAfaAfaa*a*g	3105
AD02054	AD02054-SS	(GLS-15*)(imann*)jugauuuUfaCfuUfcaguuu*a*(imann)	3040	AD02054-AS	u*Uf*aaCfu(gUNA)gaagUfaAfaUfaa*a*c	3106
AD02055	AD02055-SS	(GLS-15*)(imann*)guauuuuAfaUfuCfaguuu*a*(imann)	3041	AD02055-AS	u*Uf*gaAfa(uUNA)ggaaGfuAfaAfaa*a*c	3107
AD02056	AD02056-SS	(GLS-15*)(imann*)uuuuccAfaUfuCfaaguuu*a*(imann)	3042	AD02056-AS	u*Uf*auucUfuggaCfuGfgAfaa*a*a	3108
AD02057	AD02057-SS	(GLS-15*)(imann*)cagaauuAfaCfuCfaaugg*a*(imann)	3043	AD02057-AS	u*Uf*caagUfugagCfuAfaAfaa*a*g	3109
AD02058	AD02058-SS	(GLS-15*)(imann*)ccuuucaCfaAfuUfuucuaa*a*(imann)	3044	AD02058-AS	u*Uf*ugagAfaaauUfgUfgAfaa*a*g	3110

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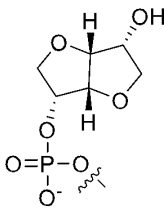
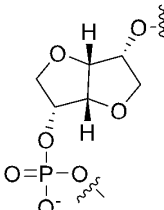
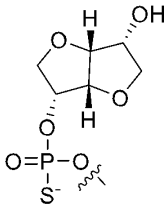
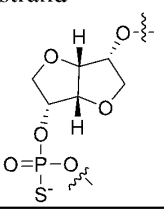
AD02059	AD02059-SS	(GLS-15*)(imann*)juguauucaGfuAfcAfguuguca*a*(imann)	3045	AD02059-AS	u*Uf*gacaAfcugcuAfcUfgAfaua*c*a	3111
AD02060	AD02060-SS	(GLS-15*)(imann*)jaguuaagUfuGfuCfauucau*a*(imann)	3046	AD02060-AS	u*Af*gugaAfuagacAfaCfuGfuac*u*g	3112
AD02061	AD02061-SS	(GLS-15*)(imann*)jaguacaguUfgUfcAfuaacuu*a*(imann)	3047	AD02061-AS	u*Af*agugAfaugaCfaAfcUfgua*c*u	3113
AD02062	AD02062-SS	(GLS-15*)(imann*)jagacagcuUfgAfaUfgaaguu*a*(imann)	3048	AD02062-AS	u*Af*agcuUfcauuCfaAfcGfcug*u*c	3114
AD02063	AD02063-SS	(GLS-15*)(imann*)jccucagcuCfuUfguugaau*a*(imann)	3049	AD02063-AS	u*Af*uucaAfcagAfcGfafaUfcga*g*g	3115
AD02064	AD02064-SS	(GLS-15*)(imann*)juugaaacaGfuUfaUfuacccua*a*(imann)	3050	AD02064-AS	u*Uf*aggUfaauaAfcUfuGfuuc*a*a	3116
AD02065	AD02065-SS	(GLS-15*)(imann*)jcauccaguUfaGfuCfaagcuu*a*(imann)	3051	AD02065-AS	u*Uf*agcaUfugacUfaAfcUfgga*u*g	3117
AD02066	AD02066-SS	(GLS-15*)(imann*)juuugaagaAfaUfuCfuugaagu*a*(imann)	3052	AD02066-AS	u*Af*cuucAfcagaaUfuUfcAfua*a*a	3118
AD02067	AD02067-SS	(GLS-15*)(imann*)juugaagaAfuUfcUfugaagu*a*(imann)	3053	AD02067-AS	u*Af*acuuCfaagaAfuUfuCfauc*a*a	3119
AD02068	AD02068-SS	(GLS-15*)(imann*)juugaaguUfcAfuGfgugaucua*a*(imann)	3054	AD02068-AS	u*Uf*gaucAfcacauGfaAfcUfua*a*g	3120
AD02069	AD02069-SS	(GLS-15*)(imann*)jaaccucagAfuUfuUfguaguu*a*(imann)	3055	AD02069-AS	u*Uf*aacuAfcacaaAfuCfaGfgag*u*u	3121
AD02070	AD02070-SS	(GLS-15*)(imann*)juguaguuAfuUfuAfuuaaguc*a*(imann)	3056	AD02070-AS	u*Gf*acuuAfauaaAfuUfaAfcua*c*a	3122
AD02071	AD02071-SS	(GLS-15*)(imann*)jaucagcaUfuAfuUfuaucaga*a*(imann)	3057	AD02071-AS	u*Uf*cugaAfgaauAfaUfcGfuga*u*u	3123
AD02072	AD02072-SS	(GLS-15*)(imann*)juuuguucaGfaGfaGfgccuuu*a*(imann)	3058	AD02072-AS	u*Af*aaagGfcccUfcUfgAfaca*a*a	3124
AD02073	AD02073-SS	(GLS-15*)(imann*)juucagagaGfgCfuUfuuguuuu*a*(imann)	3059	AD02073-AS	u*Af*aacaAfaagGfcUfcUfcug*a*a	3125
AD02074	AD02074-SS	(GLS-15*)(imann*)jagagagcCfuUfuUfguuuaa*a*(imann)	3060	AD02074-AS	u*Uf*uaaaAfcacaaAfcGfcCfuuc*c*u	3126
AD02302	AD02302-SS	(GLS-15*)(invab*)cauucacuUfcUfuAfgacaaa*a*(invab)	3061	AD02302-AS	u*Cf*uuugUfcuaaGfaAfgUfgaa*u*g	3127
AD02303	AD02303-SS	(GLS-15*)(invab*)jaauagcaGfgCfuUfgaagaa*a*(invab)	3062	AD02303-AS	u*Uf*ucauUfcaagCfcUfgUfcaa*u*u	3128
AD02304	AD02304-SS	(GLS-15*)(invab*)juguaaguAfcAfuCfuucuuu*a*(invab)	3063	AD02304-AS	u*Cf*aaagAfaagUfuAfcUfuga*c*a	3129
AD02305	AD02305-SS	(GLS-15*)(invab*)jagaagaaAfaGfuUfgaguuu*a*(invab)	3064	AD02305-AS	u*Uf*aacUfcaacUfuUfuCfuuu*c*u	3130
AD02306	AD02306-SS	(GLS-15*)(invab*)jacacaggaAfcCfuGfaauuua*a*(invab)	3065	AD02306-AS	u*Uf*caauUfucagGfuUfcCfugu*g*u	3131
AD02307	AD02307-SS	(GLS-15*)(invab*)jaaggugcaAfaAfuUfcccuaa*a*(invab)	3066	AD02307-AS	u*Af*cuuaGfgaaUfuUfgCfacc*u*u	3132
AD02308	AD02308-SS	(GLS-15*)(invab*)juuagagaUfgCfuGfagaucuu*a*(invab)	3067	AD02308-AS	u*Af*ugauCfuacagCfaUfcAfcua*a*g	3133
AD02309	AD02309-SS	(GLS-15*)(invab*)guugggaaaCfuCfuGfagggaaa*a*(invab)	3068	AD02309-AS	u*Uf*uucaAfuacagAfgUfuUfcca*a*c	3134
AD02310	AD02310-SS	(GLS-15*)(invab*)jguuacuaUfuGfuAfcugacaa*a*(invab)	3069	AD02310-AS	u*Uf*ugucAfguacAfaUfaGfuua*c*c	3135
AD02311	AD02311-SS	(GLS-15*)(invab*)jcaagauguUfgGfuAfguucaaa*a*(invab)	3070	AD02311-AS	u*Uf*uuugaAfcuaecCfaAfcAfuuc*u*g	3136
AD02312	AD02312-SS	(GLS-15*)(invab*)jcaagguegaAfgAfuCfaauuuc*a*(invab)	3071	AD02312-AS	u*Gf*uaaaUfugauCfuUfcGface*u*g	3137
AD02313	AD02313-SS	(GLS-15*)(invab*)jugaugaaaUfuCfuUfgaaguuc*a*(invab)	3072	AD02313-AS	u*Gf*aacuUfcaagAfaUfuUfcau*c*a	3138
AD02314	AD02314-SS	(GLS-15*)(invab*)janguagaAfcUfuCfaagaa*a*(invab)	3073	AD02314-AS	u*Af*cuucUfugaaGfuUfcUfaca*u*c	3139

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AD00850-1	AD00850-1-SS	(GLS-15*)(invab*)jaauucugaCfaAfuAfacacgau*a*(invab)	3074	AD00850-1-AS	u*Af*ucguGfuauuUfgUfcAfgaa*u*u	3140
AD00851-1	AD00851-1-SS	(GLS-15*)(invab*)caguuccaGfaAfuUfuacguca*a*(invab)	3075	AD00851-1-AS	u*Uf*gaagUfaaaUfcUfgGfaac*u*g	3141
AD02602	AD02602-SS	(GLS-15*)guccaguuCfcAfgAfauuuag*a*(invab)	3076	AD02602-AS	u*Ci*guaaAfuucuGfgAfaCfugg*a*c	3142
AD02603	AD02603-SS	(GLS-15*)aguuccagAfaUfuUfacgucaa*a*(invab)	3077	AD02603-AS	u*Uf*ugacGfuuaaUfuCfuGfgaa*c*u	3143
AD02604	AD02604-SS	(GLS-15*)gaccuucuGfcAfuGfaugucca*a*(invab)	3078	AD02604-AS	u*Uf*ggacAfucauGfcAfgAfuagg*u*c	3144
AD02605	AD02605-SS	(GLS-15*)caguuccaGfaAfuUfuacguca*a*(invab)	3079	AD02605-AS	u*Uf*gaagUfaaaUfcUfgGfaac*u*g	3145
AD02606	AD02606-SS	(GLS-15*)juacgucaAfcUfuGfgaucaaaa*(invab)	3080	AD02606-AS	u*Uf*uugaUfcaaaGfuUfgAfcgu*a*a	3146
AD02607	AD02607-SS	(GLS-15*)uacuguaAfcAfaUfaagauu*a*(invab)	3081	AD02607-AS	u*Af*gaucUfuauuGfuUfaCfcag*u*a	3147
AD02608	AD02608-SS	(GLS-15*)juucuugaCfaAfaGfaauugac*a*(invab)	3082	AD02608-AS	u*Gf*ucaaUfuuuUfgUfcUfaag*a*a	3148
AD02609	AD02609-SS	(GLS-15*)cauccuguAfuAfuUfuacucca*a*(invab)	3083	AD02609-AS	u*Gf*gaagUfaaaUfuAfcAfgga*u*g	3149
AD02610	AD02610-SS	(GLS-15*)guauuuuAfcUfuCfcaguucc*a*(invab)	3084	AD02610-AS	u*Gf*gaAfc(uNA)ggaaGfuAfaAfuau*a*c	3150
AD02611	AD02611-SS	(GLS-15*)juguaaucaGfuAfcAfguuguca*a*(invab)	3085	AD02611-AS	u*Uf*gacaAfcuguAfcUfgAfaaa*c*a	3151
AD02612	AD02612-SS	(GLS-15*)jugucaagaCfuUfuUfucgaug*a*(invab)	3086	AD02612-AS	u*Ci*auucGfaaaaAfgUfcUfuga*c*a	3152
AD02613	AD02613-SS	(GLS-15*)caguacagUfuGfuCfaaucau*a*(invab)	3087	AD02613-AS	u*Af*guagaAfgacAfaCfuGfuac*u*g	3153
AD02614	AD02614-SS	(GLS-15*)ccuuuicaCfaAfuUfuucuaa*a*(invab)	3088	AD02614-AS	u*Uf*ugagAfaaaUfgUfgAfaaa*g*g	3154
AD02615	AD02615-SS	(GLS-15*)cauucacuUfcUfuAfgacaag*a*(invab)	3089	AD02615-AS	u*Ci*uuugUfcuaaGfaAfgUfgaa*u*g	3155
AD02616	AD02616-SS	(GLS-15*)caucugcaUfgAfuGfuuccaag*a*(invab)	3090	AD02616-AS	u*Uf*caugGfacauCfaUfgCfaga*u*g	3156

Table 4: Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds, and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position of the parent nucleotide (i.e., it is a 2'-deoxy-2'- fluoronucleotide). It will also be understood that the abbreviations correspond to nucleotides which omit the 3'-phosphate when found at the 3'-terminal position (i.e., they are 3'-OH). A skilled artisan will understand that these abbreviations are just identification symbols and are able to determine the linking modes of the nucleotide sequences containing these abbreviations.

Abbreviations	Nucleotide(s)
A	adenosine-3'-phosphate
C	cytidine-3'-phosphate
G	guanosine-3'-phosphate
T	5-methyluridine-3'-phosphate
U	uridine-3'-phosphate
a	2'-O-methyladenosine-3'-phosphate
c	2'-O-methylcytidine-3'-phosphate
g	2'-O-methylguanosine-3'-phosphate
t	2'-O-methyl-5-methyluridine-3'-phosphate
u	2'-O-methyluridine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Gf	2'-fluoroguanosine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Af*	2'-fluoroadenosine-3'-phosphorothioate
Cf*	2'-fluorocytidine-3'-phosphorothioate
Gf*	2'-fluoroguanosine-3'-phosphorothioate
Tf*	2'-fluoro-5-methyluridine-3'-phosphorothioate
Uf*	2'-fluorouridine-3'-phosphorothioate
a*	2'-O-methyladenosine-3'-phosphorothioate
c*	2'-O-methylcytidine-3'-phosphorothioate
g*	2'-O-methylguanosine-3'-phosphorothioate
t*	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u*	2'-O-methyluridine-3'-phosphorothioate
aUNA	2', 3'-seco-adenosine-3'-phosphate
cUNA	2', 3'-seco-cytidine-3'-phosphate
gUNA	2', 3'-seco-guanosine-3'-phosphate
tUNA	2', 3'-seco-5-methyluridine-3'-phosphate
uUNA	2', 3'-seco- uridine-3'-phosphate
Vp	Vinyl-phosphate

invab	inverted abasic-5'-phosphate. Linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand; linked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand. It will also be understood that the abbreviations correspond to invab which omit the 5'-phosphate when found at the 3'-terminal position (i.e., they are 5'-OH)	
invab*	inverted abasic-5'-phosphorothioate. Linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strandlinked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand. It will also be understood that the abbreviations correspond to invab* which omit the 5'- phosphorothioate when found at the 3'-terminal position (i.e., they are 5'-OH);	
imann	imann when at the end of each strand 	imann when in the middle of each strand 
imann*	isomannide residue- phosphorothioate	
	imann* when at the end of each strand 	imann* when in the middle of each strand 

In certain embodiments of the invention a dsRNA (also referred to herein as a “duplex”) is one disclosed in one of Tables 1-3. Each row in Tables 1-3 discloses a duplex comprising the sequence of the sense strand and the sequence of the antisense strand in that table row. In addition to the duplexes disclosed in Tables 1-3, it will be understood that in some embodiments, a duplex of the invention may include sense and antisense sequences shown in Tables 1-3, that differ by zero, one, two, or three nucleotides shown in a sequence shown in Tables 1-3. Thus, as non-limiting examples, in some embodiments, an antisense strand in a duplex of the invention may be SEQ ID NO: 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677 or 2678 with zero, one, two, or three different nucleotides than those in SEQ ID NO: 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677 or 2678, respectively.

It will be understood that the sequence of the sense strand and the sequence of the antisense strand in a duplex of the invention may be independently selected. Thus, a dsRNA of the invention may comprise a sense strand and an antisense strand of a duplex disclosed in a row in Tables 1-3. Alternatively, in a dsRNA of the invention, one or both of the selected sense and antisense strand in the dsRNA may include sequences shown in Tables 1-3 but with one or both of the sense and antisense sequences including 1, 2, 3, or more nucleobase substitutions

from the parent sequence. The selected sequences may in some embodiments be longer or shorter than their parent sequence. Thus, dsRNA agents included in the invention can but need not include exact sequences of the sense and antisense pairs disclosed as duplexes in Tables 1-3.

5 In some embodiments, a dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to an HMGCR RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting
10 ligand. In some instances, the region of complementarity to the HMGCR RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3. In some embodiments of a dsRNA agent of the invention, the antisense strand of the dsRNA is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in
15 any one of Tables 1-3. In some embodiments, an antisense strand of a dsRNA agent of the invention is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments a dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In other
20 embodiments, a dsRNA agent of the invention comprises a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some instances, a dsRNA agent of the invention comprises an antisense strand sequence set forth in any one of Tables 1-3. Some embodiments of a dsRNA agent of the invention comprises the sense and antisense sequences disclosed as
25 duplex in any of Tables 1-3. As described herein, it will be understood that the sense and antisense strands in a duplex of the invention may be independently selected.

Mismatches

It is known to skilled in art, mismatches are tolerated for efficacy in dsRNA, especially
30 the mismatches are within terminal region of dsRNA. Certain mismatches tolerate better, for example mismatches with wobble base pairs G:U and A:C are tolerated better for efficacy (Du et al., A systematic analysis of the silencing effects of an active siRNA at all single-nucleotide mismatched target sites. Nucleic Acids Res. 2005 Mar 21;33(5):1671-7. Doi: 10.1093/nar/gki312. Nucleic Acids Res. 2005;33(11):3698). Some embodiments of methods
35 and compounds of the invention an HMGCR dsRNA agent may contain one or more mismatches to the HMGCR target sequence. In some embodiments, HMGCR dsRNA agent of the invention includes no mismatches. In certain embodiments, HMGCR dsRNA agent of the invention includes no more than 1 mismatch. In some embodiments, HMGCR dsRNA agent of the invention includes no more than 2 mismatches. In certain embodiments, HMGCR dsRNA

agent of the invention includes no more than 3 mismatches. In some embodiments of the invention, an antisense strand of an HMGCR dsRNA agent contains mismatches to an HMGCR target sequence that are not located in the center of the region of complementarity. In some embodiments, the antisense strand of the HMGCR dsRNA agent includes 1, 2, 3, 4, or more mismatches that are within the last 5, 4, 3, 2, or 1 nucleotide from one or both of the 5' or 3' end of the region of complementarity. Methods described herein and/or methods known in the art can be used to determine whether an HMGCR dsRNA agent containing a mismatch to an HMGCR target sequence is effective in inhibiting the expression of the HMGCR gene.

10 *Complementarity*

As used herein, unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence (e.g., HMGCR dsRNA agent sense strand or targeted HMGCR mRNA) in relation to a second nucleotide sequence (e.g., HMGCR dsRNA agent antisense strand or a single-stranded antisense polynucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize [form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions *in vitro*)] and form a duplex or double helical structure under certain conditions with an oligonucleotide or polynucleotide including the second nucleotide sequence. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. A skilled artisan will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification.

Complementary sequences, for example, within an HMGCR dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as “fully complementary” with respect to each other herein. It will be understood that in embodiments when two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs are not regarded herein as mismatches with regard to the determination of complementarity. For example, an HMGCR dsRNA agent comprising one oligonucleotide 19 nucleotides in length and another oligonucleotide 20 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 19 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein. Thus, as used herein, “fully complementary” means that all (100%) of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a

second polynucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

The term “substantially complementary” as used herein means that in a hybridized pair of nucleobase sequences, at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The term “substantially complementary” can be used in reference to a first sequence with respect to a second sequence if the two sequences include one or more, for example at least 1, 2, 3, 4, or 5 mismatched base pairs upon hybridization for a duplex up to 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs (bp), while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of HMGCRC gene expression via a RISC pathway.

The term, “partially complementary” may be used herein in reference to a hybridized pair of nucleobase sequences, in which at least 75%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. In some embodiments, “partially complementary” means at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide.

The terms “complementary,” “fully complementary,” “substantially complementary,” and “partially complimentary” are used herein in reference to the base matching between the sense strand and the antisense strand of an HMGCRC dsRNA agent, between the antisense strand of an HMGCRC dsRNA agent and a sequence of a target HMGCRC mRNA, or between a single-stranded antisense oligonucleotide and a sequence of a target HMGCRC mRNA. It will be understood that the term “antisense strand of an HMGCRC dsRNA agent” may refer to the same sequence of an “HMGCRC antisense polynucleotide agent”.

As used herein, the term “substantially identical” or “substantial identity” used in reference to a nucleic acid sequence means a nucleic acid sequence comprising a sequence with at least about 85% sequence identity or more, preferably at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the identical nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompasses nucleotide sequences substantially identical to those disclosed herein. e.g., in Tables 1-3. In some embodiments, the sequences disclosed herein are exactly

identical, or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to those disclosed herein, e.g., in Tables 1-3.

As used herein, the term “strand comprising a sequence” means an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature. The term “double-stranded RNA” or “dsRNA,” as used herein, refers to an RNAi that includes an RNA molecule or complex of molecules having a hybridized duplex region comprising two anti-parallel and substantially or fully complementary nucleic acid strands, which are referred to as having “sense” and “antisense” orientations with respect to a target HMGC RNA. The duplex region can be of any length that permits specific degradation of a desired target HMGC RNA through a RISC pathway but will typically range from 9 to 30 base pairs in length, e.g., 15-30 base pairs in length. Considering a duplex between 9 and 30 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. HMGC dsRNA agents generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of an HMGC dsDNA agent comprises a sequence that is substantially complementary to a region of a target HMGC RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a “hairpin loop”) between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. In some embodiments of the invention, a hairpin look comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more unpaired nucleotides. Where the two substantially complementary strands of an HMGC dsRNA agent are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than a hairpin loop, the connecting structure is referred to as a “linker.” The term “siRNA” is also used herein to refer to a dsRNA agent as described herein.

In some embodiments of the invention an HMGC dsRNA agent may include a sense and antisense sequence that have no-unpaired nucleotides or nucleotide analogs at one or both terminal ends of the dsRNA agent. An end with no unpaired nucleotides is referred to as a

“blunt end” and as having no nucleotide overhang. If both ends of a dsRNA agent are blunt, the dsRNA is referred to as “blunt ended.” In some embodiments of the invention, a first end of a dsRNA agent is blunt, in some embodiments a second end of a dsRNA agent is blunt, and in certain embodiments of the invention, both ends of an HMGCR dsRNA agent are blunt.

5 In some embodiments of dsRNA agents of the invention, the dsRNA does not have one or two blunt ends. In such instances there is at least one unpaired nucleotide at the end of a strand of a dsRNA agent. 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. A dsRNA can comprise an overhang of at least 1, 2, 3, 4, 5, 6, or more nucleotides. A nucleotide
10 overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. It will be understood that in some embodiments a nucleotide overhang is on a sense strand of a dsRNA agent, on an antisense strand of a dsRNA agent, or on both ends of a dsRNA agent and nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA. In certain embodiments
15 of the invention, one or more of the nucleotides in an overhang is replaced with a nucleoside thiophosphate.

As used herein, the term “antisense strand” or “guide strand” refers to the strand of an HMGCR dsRNA agent that includes a region that is substantially complementary to an HMGCR target sequence. As used herein the term “sense strand,” or “passenger strand” refers
20 to the strand of an HMGCR dsRNA agent that includes a region that is substantially complementary to a region of the antisense strand of the HMGCR dsRNA agent.

Modifications

In some embodiments of the invention the RNA of an HMGCR RNAi agent is
25 chemically modified to enhance stability and/or one or more other beneficial characteristics. Nucleic acids in certain embodiments of the invention may be synthesized and/or modified by methods well established in the art, for example, those described in “Current protocols in Nucleic Acid Chemistry,” Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is incorporated herein by reference. Modifications that can be present in
30 certain embodiments of HMGCR dsRNA agents of the invention include, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, conjugation, inverted linkages, etc.) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or
35 conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in certain embodiments of HMGCR dsRNA agents, HMGCR antisense polynucleotides, and HMGCR sense polynucleotides of the invention include, but are not limited to RNAs comprising

modified backbones or no natural internucleoside linkages. As a non-limiting example, an RNA having a modified backbone may not have a phosphorus atom in the backbone. RNAs that do not have a phosphorus atom in their internucleoside backbone may be referred to as oligonucleosides. In certain embodiments of the invention, a modified RNA has a phosphorus atom in its internucleoside backbone.

It will be understood that the term “RNA molecule” or “RNA” or “ribonucleic acid molecule” encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. The terms “ribonucleoside” and “ribonucleotide” may be used interchangeably herein. An RNA molecule can be modified in the nucleobase structure or in the ribose-phosphate backbone structure, e.g., as described herein below, and molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. In some embodiments of the invention, an RNA molecule comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or up to the full length of the HMGCR dsRNA agent molecule's ribonucleosides that are modified ribonucleosides. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule.

DsRNA agents, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides of the invention may, in some embodiments comprise one or more independently selected modified nucleotide and/or one or more independently selected non-phosphodiester linkage. As used herein, the terms “internucleotide linkage”, “internucleoside linkage”, “linkage”, and “linker” may be used interchangeably, and refer to the linking groups between unmodified or modified nucleosides, and/or between an unmodified or modified nucleoside and one or more targeting groups in an oligonucleotide strand. In some embodiments, the linkage may be independently selected from a phosphodiester (PO) linkage, a phosphorothioate (PS) linkage, and/or a phosphorodithioate (PS2) linkage of a dinucleotide at any position of single stranded or double stranded oligonucleotide. As used herein the term “independently selected” used in reference to a selected element, such as a modified nucleotide, non-phosphodiester linkage, etc., means that two or more selected elements can but need not be the same as each other.

As used herein, a “nucleotide base,” “nucleotide,” or “nucleobase” is a heterocyclic pyrimidine or purine compound, which is a standard constituent of all nucleic acids, and includes the bases that form the nucleotides adenine, guanine, cytosine, thymine, and uracil. A

nucleobase may further be modified to include, though not intended to be limiting: universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. The term “ribonucleotide” or “nucleotide” may be used herein to refer to an unmodified nucleotide, a modified nucleotide, or a surrogate replacement moiety. Those in the art will recognize that

5 guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety.

In one embodiment, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form

10 the required duplex structure and that permit or mediate the specific degradation of a target RNA via a RISC pathway. In certain embodiments of the invention, an HMGCR RNA interference agent includes a single stranded RNA that interacts with a target HMGCR RNA sequence to direct the cleavage of the target HMGCR RNA.

Modified RNA backbones can include, for example, phosphorothioates, chiral

15 phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked

20 analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included. Means of preparing phosphorus-containing linkages are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents, certain modified HMGCR antisense polynucleotides, and/or certain modified HMGCR sense

25 polynucleotides of the invention.

Modified RNA backbones 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

30 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. Means of

35 preparing modified RNA backbones that do not include a phosphorus atom are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents, certain modified HMGCR antisense polynucleotides, and/or certain modified HMGCR sense polynucleotides of the invention.

In certain embodiments of the invention, RNA mimetics are included in HMGCR dsRNAs, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides, such as, but not limited to: replacement of the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units with novel groups. In such embodiments, base units are maintained for hybridization with an appropriate HMGCR nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Means of preparing RNA mimetics are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents of the invention.

Some embodiments of the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular $-\text{CH}_2\text{-NH-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-O-CH}_2-$ [known as a methylene (methylimino) or MMI backbone], $-\text{CH}_2\text{-O-N(CH}_3\text{)-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-N(CH}_3\text{)-CH}_2-$ and $-\text{N(CH}_3\text{)-CH}_2-$ [wherein the native phosphodiester backbone is represented as $-\text{O-P-O-CH}_2-$]. Means of preparing RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents, certain HMGCR antisense polynucleotides, and/or certain HMGCR sense polynucleotides of the invention.

Modified RNAs can also contain one or more substituted sugar moieties. HMGCR dsRNAs, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides of the invention may comprise one of the following at the 2' position: 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 may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $\text{O}[(\text{CH}_2)_n\text{O}]_m\text{CH}_3$, $\text{O}(\text{CH}_2)_n\text{OCH}_3$, $\text{O}(\text{CH}_2)_n\text{NH}_2$, $\text{O}(\text{CH}_2)_n\text{CH}_3$, $\text{O}(\text{CH}_2)_n\text{ONH}_2$, and $\text{O}(\text{CH}_2)_n\text{ON}[(\text{CH}_2)_n\text{CH}_3]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3 , OCN, Cl, Br, CN, CF_3 , OCF_3 , SOCH_3 , SO_2CH_3 , ONO_2 , NO_2 , N_3 , NH_2 , heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an HMGCR dsRNA agent, or a group for improving the pharmacodynamic properties of an HMGCR dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O- $\text{CH}_2\text{CH}_2\text{OCH}_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78:486-504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, i.e., a $\text{O}(\text{CH}_2)$

2ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₂)₂. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents of the invention.

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an HMGCR dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide of the invention, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked HMGCR dsRNAs, HMGCR antisense polynucleotides, or HMGCR sense polynucleotides, and the 5' position of 5' terminal nucleotide. HMGCR dsRNA agents, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides of the invention.

A HMGCR dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide may, in some embodiments, include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine and guanine, and the pyrimidine bases thymine, cytosine and uracil. Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-Me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine.

Additional nucleobases that may be included in certain embodiments of HMGCR dsRNA agents of the invention are known in the art, see for example: Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. Ed. Wiley-VCH, 2008; The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L., Ed. John Wiley & Sons, 1990, English et al., Angewandte Chemie, International Edition, 1991, 30, 613, Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Means of preparing dsRNAs, HMGCR antisense strand polynucleotides and/or HMGCR sense strand polynucleotides that comprise nucleobase modifications and/or substitutions such as those described herein are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA

agents, HMGCR sense polynucleotides, and/or HMGCR antisense polynucleotides of the invention. Teachings regarding the synthesis of particular modified oligonucleotides may be found in the following U.S. patents: U.S. Pat. No. 5,218,105, drawn to polyamine conjugated oligonucleotides; U.S. Pat. No. 5,541,307, drawn to oligonucleotides having modified
 5 backbones; U.S. Pat. No. 5,521,302, drawn to processes for preparing oligonucleotides having chiral phosphorus linkages; U.S. Pat. No. 5,539,082, drawn to peptide nucleic acids; U.S. Pat. No. 5,554,746, drawn to oligonucleotides having (3-lactam backbones; U.S. Pat. No. 5,571,902, drawn to methods and materials for the synthesis of oligonucleotides; U.S. Pat. No. 5,578,718, drawn to nucleosides having alkylthio groups, wherein such groups may be used as
 10 linkers to other moieties attached at any of a variety of positions of the nucleoside; U.S. Pat. No. 5,587,361 drawn to oligonucleotides having phosphorothioate linkages of high chiral purity; U.S. Pat. No. 5,506,351, drawn to processes for the preparation of 2'-O-alkyl guanosine and related compounds, including 2,6-diaminopurine compounds; U.S. Pat. No. 5,587,469, drawn to oligonucleotides having N-2 substituted purines; U.S. Pat. No. 5,587,470, drawn to
 15 oligo- nucleotides having 3-deazapurines; U.S. Pat. No. 5,608,046, both drawn to conjugated 4'-desmethyl nucleoside analogs; U.S. Pat. No. 5,610,289, drawn to backbone-modified oligonucleotide analogs; U.S. Pat. No. 6,262,241 drawn to, inter alia, methods of synthesizing 2'-fluoro-oligonucleotides.

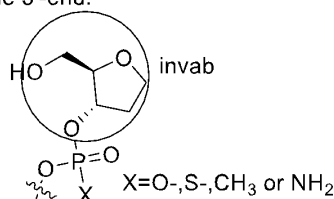
Certain embodiments of HMGCR dsRNA agents, HMGCR antisense polynucleotides,
 20 and/or HMGCR sense polynucleotides of the invention include RNA modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide with a modified ribose moiety comprising an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids in an HMGCR dsRNA agent, HMGCR antisense polynucleotides, and/or
 25 HMGCR sense polynucleotides of the invention may increase stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) Nucleic Acids Research 33(1):439-447; Mook, O R. et al., (2007) Mol Canc Ther 6(3):833-843; Grunweller, A. et al., (2003) Nucleic Acids Research 31(12):3185-3193). Means of preparing dsRNA agents, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides that comprise locked nucleic acid(s)
 30 are routinely practiced in the art and such methods can be used to prepare certain modified HMGCR dsRNA agents of the invention.

Certain embodiments of HMGCR dsRNA compounds, sense polynucleotides, and/or antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide,
 35 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine- glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S- Isomer,

a nucleotide comprising 2'-deoxythymidine-3'-phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, a nucleotide comprising 2'-deoxyadenosine-3'-phosphate, a nucleotide comprising 2'-deoxycytidine-3'-phosphate, a nucleotide comprising 2'-deoxyuridine-3'-phosphate, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide. In some embodiments, an HMGCR dsRNA compound includes an E-vinylphosphonate nucleotide at the 5'-end of the antisense strand, also referred to herein as the guide strand.

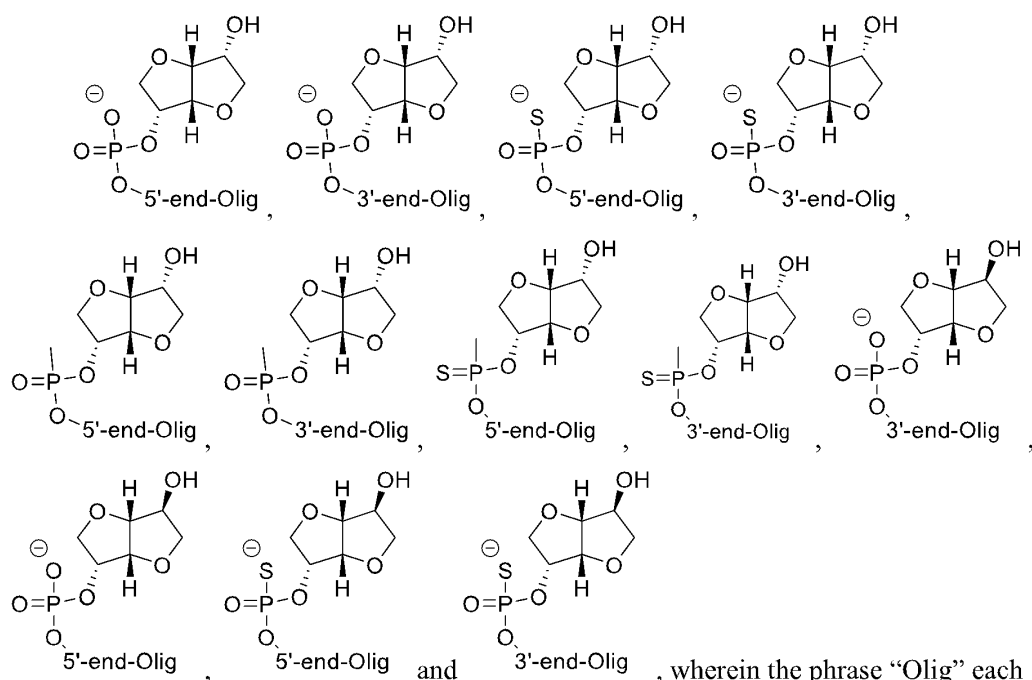
Certain embodiments of HMGCR dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide. It is known to skilled in art, including an abasic or inverted abasic nucleotide at the end of oligonucleotide enhances stability (Czauderna et al. Structural variations and stabilizing modifications of synthetic siRNAs in mammalian cells. Nucleic Acids Res. 2003;31(11):2705-2716. doi:10.1093/nar/gkg393). In some embodiments, an HMGCR dsRNA compound includes one or more inverted abasic residues (invab) at either 3'-end or 5'-end, or both 3'-end and 5'-end. Exemplified inverted abasic residues (invab) include, but are not limited to the following:

when at the 3'-end:

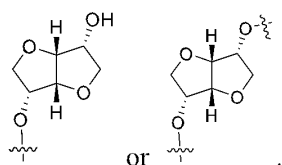


attached to 3'-end of oligonucleotide

Certain embodiments of HMGCR dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: isomannide nucleotide or stereoisomer of said isomannide nucleotide. Specific examples of isomannide nucleotides or stereoisomers of said isomannide nucleotides include, but are not limited to:



independently represents a polynucleotide moiety. Exemplified isomannide residues (imann) include, but are not limited to, the following:



In certain embodiments, the isomannide nucleotides may further conjugate to one or more targeting groups or delivery molecules, such as GalNAc moieties.

Certain embodiments of HMGCR dsRNA compounds, antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises unlocked nucleic acid nucleotide (UNA) or/and glycol nucleic acid nucleotide (GNA). It is known to skilled in art, UNA and GNA are thermally destabilizing chemical modifications, can significantly improves the off-target profile of a siRNA compound (Janas, et al., Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity. Nat Commun. 2018;9(1):723. doi:10.1038/s41467-018-02989-4; Laursen et al., Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo. Mol BioSyst. 2010;6:862–70).

Another modification that may be included in the RNA of certain embodiments of HMGCR dsRNA agents, HMGCR antisense polynucleotides, and/or HMGCR sense polynucleotides of the invention, comprises chemically linking to the RNA one or more ligands, moieties or conjugates that enhance one or more characteristics of the HMGCR dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide, respectively. Non-limiting examples of characteristics that may be enhanced are: HMGCR

dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide activity, cellular distribution, delivery of an HMGCR dsRNA agent, pharmacokinetic properties of an HMGCR dsRNA agent, and cellular uptake of the HMGCR dsRNA agent. In some embodiments of the invention, an HMGCR dsRNA agent comprises one or more

5 targeting groups or linking groups, which in certain embodiments of HMGCR dsRNA agents of the invention are conjugated to the sense strand. A non-limiting example of a targeting group is a compound comprising N-acetyl-galactosamine (GalNAc). The terms “targeting group”, “targeting agent”, “linking agent”, “targeting compound”, “delivery molecule”, “delivery compound” and “targeting ligand” may be used interchangeably herein. In certain

10 embodiments of the invention an HMGCR dsRNA agent comprises a targeting compound that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments of the invention an HMGCR dsRNA agent comprises a targeting compound that is conjugated to the 3'-terminal end of the sense strand. In some embodiments of the invention, an HMGCR dsRNA agent comprises a targeting group that comprises GalNAc. In certain embodiments of

15 the invention an HMGCR dsRNA agent does not include a targeting compound conjugated to one or both of the 3'-terminal end and the 5'-terminal end of the sense strand. In certain embodiments of the invention an HMGCR dsRNA agent does not include a GalNAc containing targeting compound conjugated to one or both of the 5'-terminal end and the 3'-terminal end of the sense strand.

20 Additional targeting and linking agents are well known in the art, for example, targeting and linking agents that may be used in certain embodiments of the invention include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86: 6553-6556), cholic acid (Manoharan et al., Biorg. Med. Chem. Let., 1994, 4:1053-1060), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad.

25 Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Let., 1993, 3:2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (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), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-

30 glycerol-3-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237), or an octadecylamine or hexylamino-

35 carbonyloxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937).

Certain embodiments of a composition comprising an HMGCR dsRNA agent, HMGCR antisense polynucleotide, and/or HMGCR sense polynucleotide may comprise a ligand that alters distribution, targeting, or etc. of the HMGCR dsRNA agent. In some embodiments of a composition comprising an HMGCR dsRNA agent of the invention, the

ligand increases affinity for a selected target, e.g., molecule, cell or cell type, compartment, e.g., a cellular or organ compartment, tissue, organ or region of the body, as, e.g., compared to a species absent such a ligand. A ligand useful in a composition and/or method of the invention may be a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA),
 5 low-density lipoprotein (LDL), or globulin); a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. A ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid or polyamine. Examples of polyamino acids are a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolid)
 10 copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine,
 15 amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

A ligand included in a composition and/or method of the invention may comprise a targeting group, non-limiting examples of which are a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody that binds to a specified cell type such as
 20 a kidney cell or a liver cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12,
 25 vitamin A, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g., cholesterol, cholic acid, adamantane acetic acid, 1-pyrene
 30 butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG, [MPEG]₂, polyamino,
 35 alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g., biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu³⁺ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

A ligand included in a composition and/or method of the invention may be a protein, e.g., glycoprotein, or peptide, for example a molecule with a specific affinity for a co-ligand, or an antibody, for example an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, cardiac cell, or bone cell. A ligand useful in an embodiment of a composition and/or method of the invention can be a hormone or hormone receptor. A ligand useful in an embodiment of a composition and/or method of the invention can be a lipid, lectin, carbohydrates, vitamin, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-galucosamine multivalent mannose, or multivalent fucose. A ligand useful in an embodiment of a composition and/or method of the invention can be a substance that can increase uptake of the HMGCR dsRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. Non-limiting examples of this type of agent are: taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, and myoservin.

In some embodiments, a ligand attached to an HMGCR dsRNA agent of the invention functions as a pharmacokinetic (PK) modulator. An example of a PK modulator that may be used in compositions and methods of the invention includes but is not limited to: a lipophiles, a bile acid, a steroid, a phospholipid analogue, a peptide, a protein binding agent, PEG, a vitamin, cholesterol, a fatty acid, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, a phospholipid, a sphingolipid, naproxen, ibuprofen, vitamin E, biotin, an aptamer that binds a serum protein, etc. Oligonucleotides comprising a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, e.g., oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone may also be used in compositions and/or methods of the invention as ligands.

HMGCR dsRNA agent compositions

In some embodiments of the invention, an HMGCR dsRNA agent is in a composition. A composition of the invention may include one or more HMGCR dsRNA agent and optionally one or more of a pharmaceutically acceptable carrier, a delivery agent, a targeting agent, detectable label, etc. A non-limiting example of a targeting agent that may be useful according to some embodiments of methods of the invention is an agent that directs an HMGCR dsRNA agent of the invention to and/or into a cell to be treated. A targeting agent of choice will depend upon such elements as: the nature of the HMGCR-associated disease or condition, and on the cell type being targeted. In a non-limiting example, in some embodiments of the invention it may be desirable to target an HMGCR dsRNA agent to and/or into a liver cell. It will be understood that in some embodiments of methods of the invention, a therapeutic agent comprises an HMGCR dsRNA agent with only a delivery agent, such as a delivery agent comprising N-Acetylgalactosamine (GalNAc), without any additional attached

elements. For example, in some aspects of the invention an HMGCR dsRNA agent may be attached to a delivery compound comprising GalNAc and included in a composition comprising a pharmaceutically acceptable carrier and administered to a cell or subject without any detectable labels, or targeting agents, etc. attached to the HMGCR dsRNA agent.

5 In cases where an HMGCR dsRNA agent of the invention is administered with and/or attached to one or more delivery agents, targeting agents, labeling agents, etc. a skilled artisan will be aware of and able to select and use suitable agents for use in methods of the invention. Labeling agents may be used in certain methods of the invention to determine the location of an HMGCR dsRNA agent in cells and tissues and may be used to determine a cell, tissue, or
10 organ location of a treatment composition comprising an HMGCR dsRNA agent that has been administered in methods of the invention. Procedures for attaching and utilizing labeling agents such as enzymatic labels, dyes, radiolabels, etc. are well known in the art. It will be understood that in some embodiments of compositions and methods of the invention, a labeling agent is attached to one or both of a sense polynucleotide and an antisense
15 polynucleotide included in an HMGCR dsRNA agent.

Delivery of HMGCR dsRNA agents and HMGCR antisense polynucleotide agents

Certain embodiments of methods of the invention, includes delivery of an HMGCR dsRNA agent into a cell. As used herein the term, “delivery” means facilitating or effecting
20 uptake or absorption into the cell. Absorption or uptake of an HMGCR dsRNA agent can occur through unaided diffusive or active cellular processes, or by use of delivery agents, targeting agents, etc. that may be associated with an HMGCR dsRNA agent of the invention. Delivery means that are suitable for use in methods of the invention include, but are not limited to: *in vivo* delivery, in which an HMGCR dsRNA agent is injected into a tissue site or
25 administered systemically. In some embodiments of the invention, an HMGCR dsRNA agent is attached to a delivery agent.

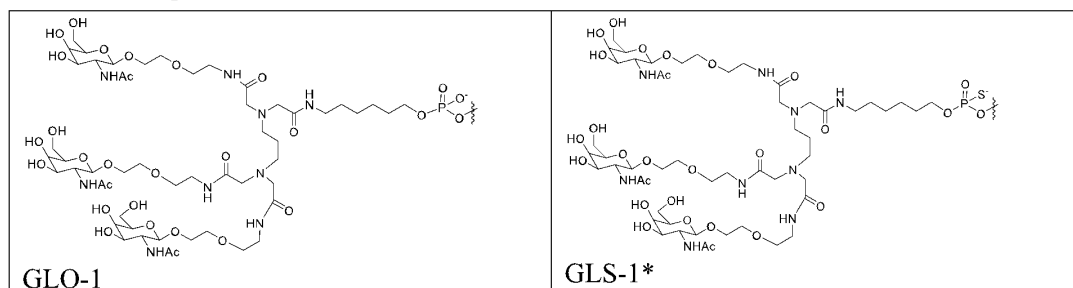
Non-limiting examples of methods that can be used to deliver HMGCR dsRNA agents to cells, tissues and/or subjects include: HMGCR dsRNA-GalNAc conjugates, SAMiRNA technology, LNP-based delivery methods, and naked RNA delivery. These and other delivery
30 methods have been used successfully in the art to deliver therapeutic RNAi agents for treatment of various diseases and conditions, such as but not limited to: liver diseases, acute intermittent porphyria (AIP), hemophilia, pulmonary fibrosis, etc. Details of various delivery means are found in publications such as: Nikam, R.R. & K. R. Gore (2018) *Nucleic Acid Ther.* 28 (4), 209-224 Aug 2018; Springer A.D. & S.F. Dowdy (2018) *Nucleic Acid Ther.* Jun 1;
35 28(3): 109–118; Lee, K. et al., (2018) *Arch Pharm Res*, 41(9), 867-874; and Nair, J.K. et al., (2014) *J. Am. Chem. Soc.* 136:16958-16961, the content each of which is incorporated by reference herein.

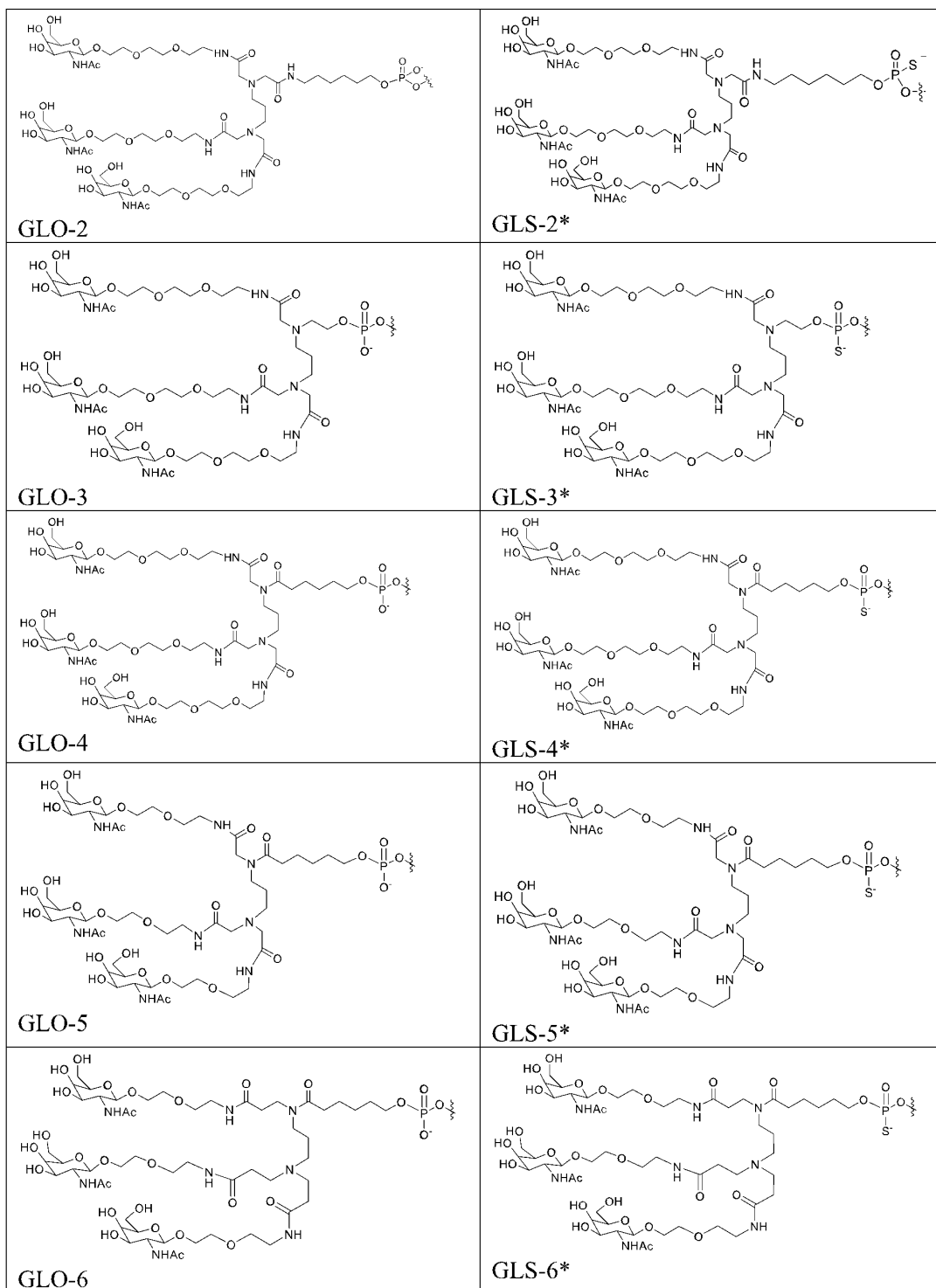
Some embodiments of the invention comprise use of lipid nanoparticles (LNPs) to deliver an HMGCR dsRNA agent of the invention to a cell, tissue, and/or subject. LNPs are

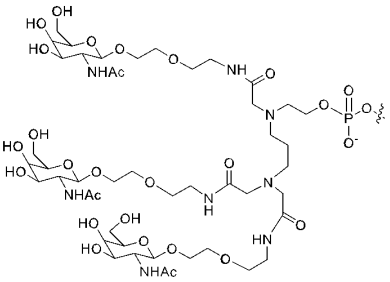
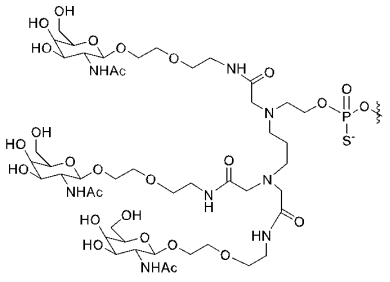
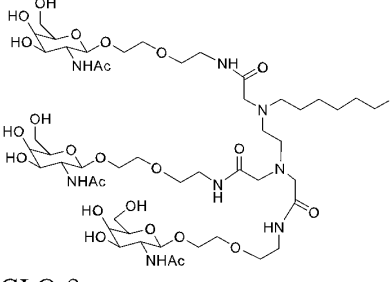
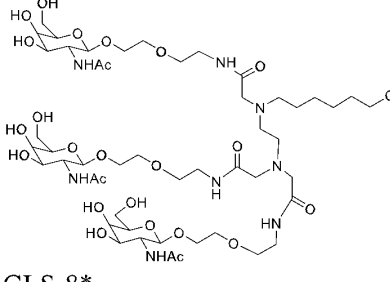
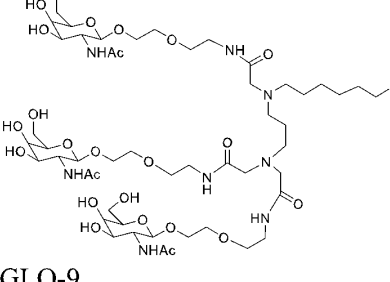
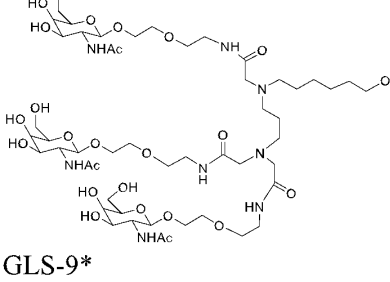
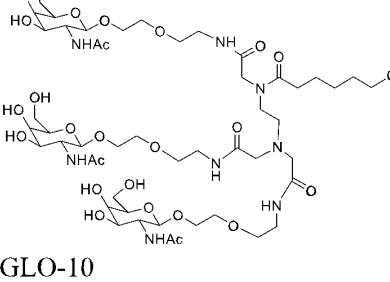
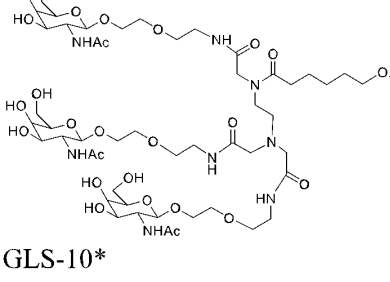
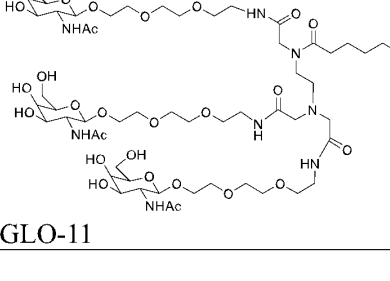
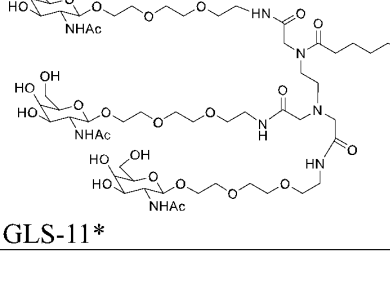
routinely used for *in vivo* delivery of HMGCR dsRNA agents, including therapeutic HMGCR dsRNA agents. One benefit of using an LNP or other delivery agent is an increased stability of the HMGCR RNA agent when it is delivered to a subject using the LNP or other delivery agent. In some embodiments of the invention an LNP comprises a cationic LNP that is loaded with one or more HMGCR RNAi molecules of the invention. The LNP comprising the HMGCR RNAi molecule(s) is administered to a subject, the LNPs and their attached HMGCR RNAi molecules are taken up by cells via endocytosis, their presence results in release of RNAi trigger molecules, which mediate RNAi.

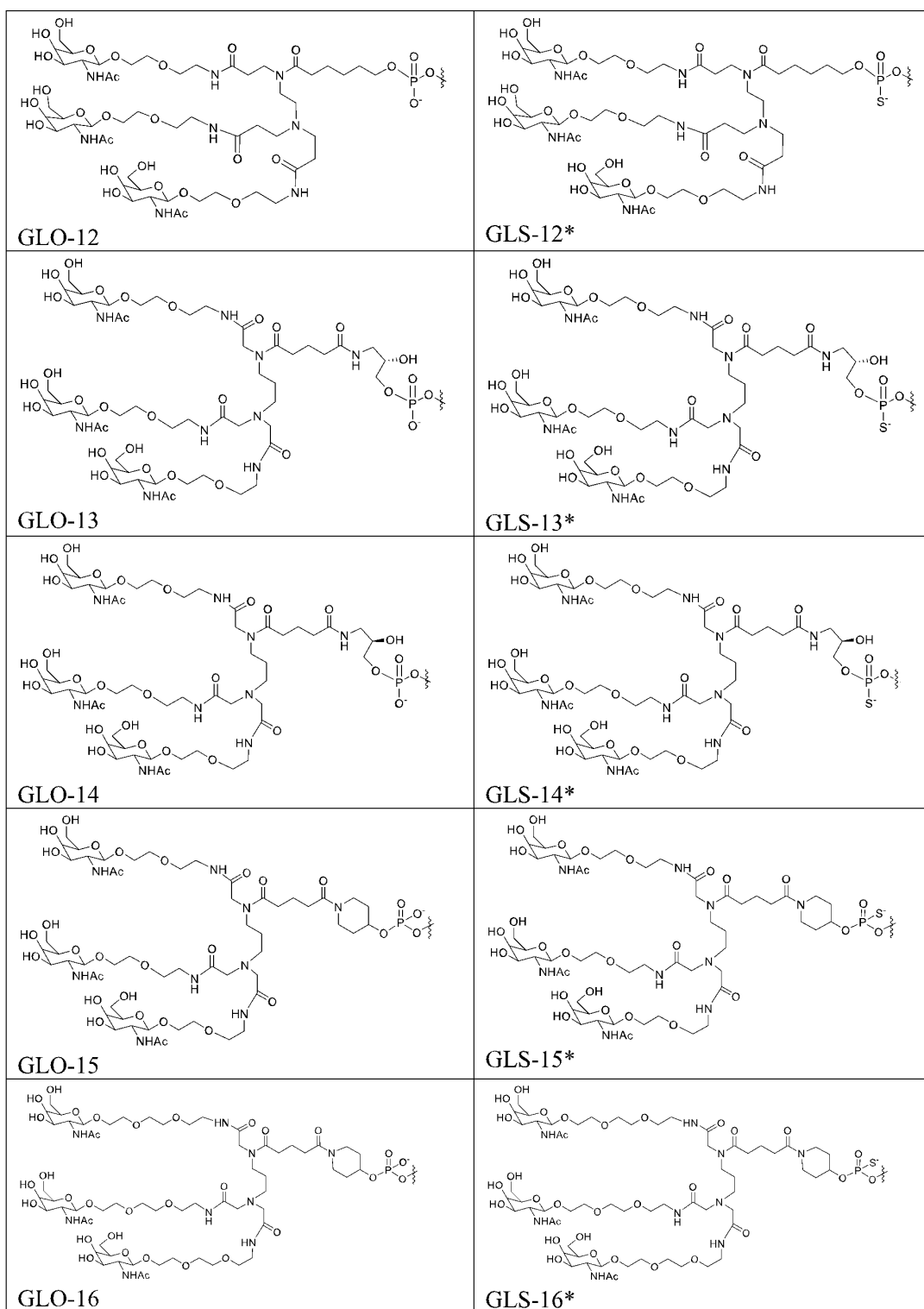
Another non-limiting example of a delivery agent that may be used in embodiments of the invention to delivery an HMGCR dsRNA agent of the invention to a cell, tissue and/or subject is an agent comprising GalNAc that is attached to an HMGCR dsRNA agent of the invention and delivers the HMGCR dsRNA agent to a cell, tissue, and/or subject. Examples of certain additional delivery agents comprising GalNAc that can be used in certain embodiments of methods and composition of the invention are disclosed in PCT Application:

WO2020191183A1 (incorporated herein in its entirety). A non-limiting example of a GalNAc targeting ligand that can be used in compositions and methods of the invention to deliver an HMGCR dsRNA agent to a cell is a targeting ligand cluster. Examples of targeting ligand clusters that are presented herein are referred to as: GalNAc Ligand with phosphodiester link (GLO) and GalNAc Ligand with phosphorothioate link (GLS). The term "GLX-n" may be used herein to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is shown below, with the below with location of attachment of the GalNAc-targeting ligand to an RNAi agent of the invention at far right of each (shown with "§"). It will be understood that any RNAi and dsRNA molecule of the invention can be attached to the GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, GLO-1 through GLO-16 and GLS-1* through GLS-16* structures are shown below.

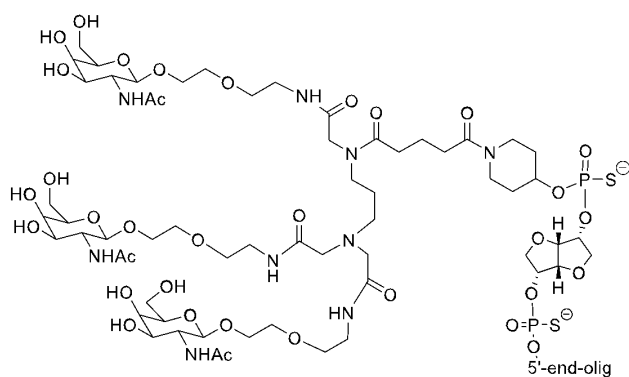
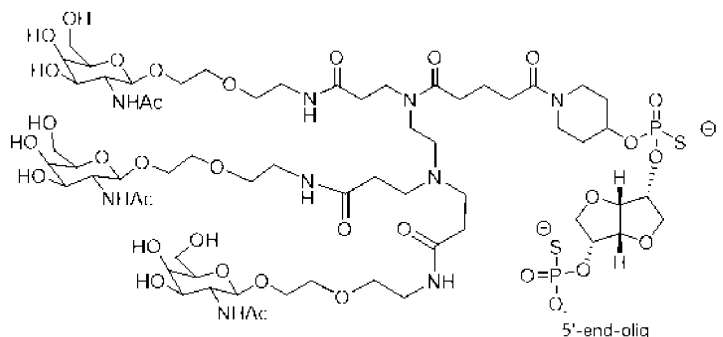




 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*



In certain embodiments, the aforesaid isomannide nucleotides may further conjugate to one or more GalNAc targeting ligands. Specific examples of isomannide nucleotides conjugated to a GalNAc targeting ligand include, but are not limited to:



5 , wherein the phrase "olig" each independently represents a polynucleotide moiety.

In some embodiments of the invention, *in vivo* delivery can also be by a beta-glucan delivery system, such as those described in U.S. Pat. Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. *In vitro* introduction of an HMGCR RNAi agent into a cell may also be done using art-known methods such as electroporation and lipofection. In certain embodiments of methods of the invention, an HMGCR dsRNA is delivered without a targeting agent. These RNAs may be delivered as "naked" RNA molecules. As a non-limiting example, an HMGCR dsRNA of the invention may be administered to a subject to treat an HMGCR-associated disease or condition in the subject, such as hyperlipidemia, in a pharmaceutical composition comprising the RNAi agent, but not including a targeting agent such as a GalNAc targeting compound.

In addition to certain delivery means described herein, it will be understood that RNAi delivery means, such as but not limited to those described herein and those used in the art, can be used in conjunction with embodiments of HMGCR RNAi agents and treatment methods described herein.

HMGCR dsRNA agents of the invention may be administered to a subject in an amount and manner effective to reduce a level and activity of HMGCR polypeptide in a cell and/or subject. In some embodiments of methods of the invention one or more HMGCR dsRNA

agents are administered to a cell and/or subject to treat a disease or condition associated with HMGCR expression and activity. Methods of the invention, in some embodiments, include administering one or more HMGCR dsRNA agents to a subject in need of such treatment to reduce a disease or condition associated with HMGCR expression in the subject. HMGCR dsRNA agents or HMGCR antisense polynucleotide agents of the invention can be administered to reduce HMGCR expression and/or activity in one more of *in vitro*, *ex vivo*, and *in vivo* cells.

In some embodiments of the invention, a level, and thus an activity, of HMGCR polypeptide in a cell is reduced by delivering (e.g. introducing) an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent into a cell. Targeting agents and methods may be used to aid in delivery of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to a specific cell type, cell subtype, organ, spatial region within a subject, and/or to a sub-cellular region within a cell. A HMGCR dsRNA agent can be administered in certain methods of the invention singly or in combination with one or more additional HMGCR dsRNA agents. In some embodiments, 2, 3, 4, or more independently selected HMGCR dsRNA agents are administered to a subject.

In certain embodiments of the invention, an HMGCR dsRNA agent is administered to a subject to treat an HMGCR-associated disease or condition in conjunction with one or more additional therapeutic regimens for treating the HMGCR-associated disease or condition. Non-limiting examples of additional therapeutic regimens are: administering one or more HMGCR antisense polynucleotides of the invention, administering a non-HMGCR dsRNA therapeutic agent, and a behavioral modification. An additional therapeutic regimen may be administered at a time that is one or more of: prior to, simultaneous with, and following administration of an HMGCR dsRNA agent of the invention. It will be understood that simultaneous with as used herein, within five minutes of time zero, within 10 minutes of time zero, within 30 minutes of time zero, within 45 minutes of time zero, and within 60 minutes of time zero, with "time zero" the time of administration of the HMGCR dsRNA agent of the invention to the subject. Non-limiting examples of non-HMGCR dsRNA therapeutic agents are: an HMG-CoA reductase inhibitor (e.g., a statin), a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist (e.g., losartan potassium, such as Merck & Co. 's Cozaar®), an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protectant (e.g., AGT 1067, from Atherogenics), a glycoprotein IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor (e.g., S-8921, from Shionogi), a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor, or a combination of any of the foregoing, wherein HMG-CoA reductase inhibitors include, but are not limited to, atorvastatin (Pfizer's

Lipitor®/Tahor/Sortis/Torvast/Cardyl), pravastatin (Bristol-Myers Squibb's Pravachol, Sankyo's Mevalotin/Sanaprav), simvastatin (Merck's Zocor®/Sinvacor, Boehringer Ingelheim's Denan, Banyu's Lipovas), lovastatin (Merck's Mevacor/Mevinacor, Bexal's Lovastatina, Cepa; Schwarz Pharma's Liposcler), fluvastatin (Novartis' Lescol®/Locol/Lochol, Fujisawa's Cranoc, Solvay's Digaril), cerivastatin (Bayer's Lipobay/GlaxoSmithKline's Baycol), rosuvastatin (AstraZeneca's Crestor®), and pitivastatin (itavastatin/risivastatin) (Nissan Chemical, Kowa Kogyo, Sankyo, and Novartis), wherein fibrates include, but are not limited to, bezafibrate (e.g., Roche's Befizal®/Cedur®/Bezalip®, Kissei's Bezatol), clofibrate (e.g., Wyeth's Atromid-S®), fenofibrate (e.g., Founder's Lipidil/Lipantil, Abbott's Tricor®, Takeda's Lipantil, generics), gemfibrozil (e.g., Pfizer's Lopid/Lipur) and ciprofibrate (Sanofi-Synthelabo's Modalim®), wherein bile acid sequestrants include, but are not limited to, cholestyramine (Bristol-Myers Squibb's Questran® and Questran Light™), colestipol (e.g., Pharmacia's Colestid), and colesevelam (Genzyme/Sankyo's WelChol™), wherein niacin therapies include, but are not limited to, immediate release formulations, such as Aventis' Nicobid, Upsher-Smith's Niacor, Aventis' Nicolar, and Sanwakagaku's Perycit, wherein Niacin extended release formulations include, e.g., Kos Pharmaceuticals' Niaspan and Upsher-Smith's SIO- Niacin, wherein antiplatelet agents include, but are not limited to, aspirin (e.g., Bayer's aspirin), clopidogrel (Sanofi-Synthelabo/Bristol-Myers Squibb's Plavix), and ticlopidine (e.g., Sanofi-Synthelabo's Ticlid and Daiichi's Panaldine), wherein aspirin-like compounds include, but are not limited to, Asacard (slow-release aspirin, by Pharmacia) and Pamicogrel (Kanebo/Angelini Ricerche/CEPA), wherein angiotensin-converting enzyme inhibitors include, but are not limited to, ramipril (e.g., Aventis' Altace) and enalapril (e.g., Merck & Co.'s Vasotec), wherein acyl CoA cholesterol acetyltransferase (AC AT) inhibitors include, but are not limited to, avasimibe (Pfizer), eflucimibe (BioMsrieux Pierre Fabre/Eli Lilly), CS-505 (Sankyo and Kyoto), and SMP-797 (Sumito), wherein cholesterol absorption inhibitors include, but are not limited to, ezetimibe (Merck/Schering-Plough Pharmaceuticals Zetia®) and Pamaqueside (Pfizer), wherein CETP inhibitors include, but are not limited to, Torcetrapib (also called CP-529414, Pfizer), JTT-705 (Japan Tobacco), and CETi-I (Avant Immunotherapeutics), wherein microsomal triglyceride transfer protein (MTTP) inhibitors include, but are not limited to, implitapide (Bayer), R-103757 (Janssen), and CP-346086 (Pfizer), wherein cholesterol modulators include, but are not limited to, NO-1886 (Otsuka/TAP Pharmaceutical), CT 1027 (Pfizer), and WAY- 135433 (Wyeth-Ayerst), wherein bile acid modulators include, but are not limited to, HBS-107 (Hisamitsu/Banyu), Btg-511 (British Technology Group), BARI- 1453 (Aventis), S-8921 (Shionogi), SD-5613 (Pfizer), and AZD-7806 (AstraZeneca), wherein peroxisome proliferation activated receptor (PPAR) agonists include, but are not limited to, tesaglitazar (AZ-242) (AstraZeneca), Netoglitazone (MCC-555) (Mitsubishi/Johnson & Johnson), GW-409544 (Ligand Pharmaceuticals/GlaxoSmithKline), GW-501516 (Ligand Pharmaceuticals/GlaxoSmithKline), LY-929 (Ligand Pharmaceuticals and Eli Lilly), LY-465608 (Ligand Pharmaceuticals and Eli

Lilly), LY-518674 (Ligand Pharmaceuticals and Eli Lilly), and MK-767 (Merck and Kyorin), wherein gene-based therapies include, but are not limited to, AdGWEGF 121.10 (GenVec), ApoA1 (UCB Pharma/Groupe Fournier), EG-004 (Trinam) (Ark Therapeutics), and ATP - binding cassette transporter- A1 (ABCA1) (CV Therapeutics/Incyte, Aventis, Xenon), wherein

5 Glycoprotein IIb/IIIa inhibitors include, but are not limited to, roxifiban (also called DMP754, Bristol-Myers Squibb), Gantofiban (Merck KGaA/Yamanouchi), and Cromafiban (Millennium Pharmaceuticals), wherein squalene synthase inhibitors include, but are not limited to, BMS-1884941 (Bristol-Myers Squibb), CP-210172 (Pfizer), CP-295697 (Pfizer), CP-294838 (Pfizer), and TAK-475 (Takeda), wherein MCP-I inhibitor include, but are not limited to, RS-

10 504393 (Roche Bioscience), wherein anti-atherosclerotic agent include, but are not limited to, BO- 653 (Chugai Pharmaceuticals), wherein the nicotinic acid derivative include, but are not limited to, Nyclin (Yamanouchi Pharmaceuticals). Exemplary combination therapies suitable for administration with a dsRNA targeting HMGCR include, but are not limited to, advicor (Niacin/lovastatin from Kos Pharmaceuticals), amlodipine/atorvastatin (Pfizer), and

15 ezetimibe/simvastatin (e.g., Vytarin® 10/10, 10/20, 10/40, and 10/80 tablets by Merck/Schering-Plough Pharmaceuticals). Non-limiting examples of behavioral modifications are: a dietary regimen, counseling, and an exercise regimen. These and other therapeutic agents and behavior modifications are known in the art and used to treat an HMGCR-associated disease or condition in a subject and may be administered to a subject in

20 combination with the administration of one or more HMGCR dsRNA agents of the invention to treat the HMGCR-associated disease or condition. A HMGCR dsRNA agent of the invention administered to a cell or subject to treat an HMGCR-associated disease or condition may act in a synergistic manner with one or more other therapeutic agents or activities and increase the effectiveness of the one or more therapeutic agents or activities and/or to increase

25 the effectiveness of the HMGCR dsRNA agent at treating the HMGCR-associated disease or condition.

Treatment methods of the invention that include administration of an HMGCR dsRNA agent can be used prior to the onset of an HMGCR-associated disease or condition and/or when an HMGCR-associated disease or condition is present, including at an early stage, mid-

30 stage, and late stage of the disease or condition and all times before and after any of these stages. Methods of the invention may also be to treat subjects who have previously been treated for an HMGCR-associated disease or condition with one or more other therapeutic agents and/or therapeutic activities that were not successful, were minimally successful, and/or are no longer successful at treating the HMGCR-associated disease or condition in the subject.

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Vector Encoded dsRNAs

In certain embodiments of the invention, an HMGCR dsRNA agent can be delivered into a cell using a vector. HMGCR dsRNA agent transcription units can be included in a DNA or RNA vector. Prepare and use of such vectors encoding transgenes for delivering sequences

into a cell and or subject are well known in the art. Vectors can be used in methods of the invention that result in transient expression of HMGCR dsRNA, for example for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more weeks. The length of the transient expression can be determined using routine methods based on elements such as, but not limited to the specific vector construct selected and the target cell and/or tissue. Such transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, et al., Proc. Natl. Acad. Sci. USA (1995) 92:1292).

An individual strand or strands of an HMGCR dsRNA agent can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced to a cell using means such as transfection or infection. In certain embodiments each individual strand of an HMGCR dsRNA agent of the invention can be transcribed by promoters that are both included on the same expression vector. In certain embodiments of the invention an HMGCR dsRNA agent is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the HMGCR dsRNA agent has a stem and loop structure.

Non-limiting examples of RNA expression vectors are DNA plasmids or viral vectors. Expression vectors useful in embodiments of the invention can be compatible with eukaryotic cells. Eukaryotic cell expression vectors are routinely used in the art and are available from a number of commercial sources. Delivery of HMGCR dsRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that allows for introduction into a desired target cell.

Viral vector systems that may be included in an embodiment of a method of the invention include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, etc.; (c) adeno-associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, e.g., vaccinia virus vectors or avipox, e.g. canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Constructs for the recombinant expression of an HMGCR dsRNA agent may include regulatory elements, such as promoters, enhancers, etc., which may be selected to provide constitutive or regulated/inducible expression. Viral vector systems, and the use of promoters and enhancers, etc. are routine in the art and can be used in conjunction with methods and compositions described herein.

Certain embodiments of the invention include use of viral vectors for delivery of HMGCR dsRNA agents into cells. Numerous adenovirus-based delivery systems are routinely used in the art for delivery to, for example, lung, liver, the central nervous system, endothelial cells, and muscle. Non-limiting examples of viral vectors that may be used in methods of the

invention are: AAV vectors, a pox virus such as a vaccinia virus, a Modified Virus Ankara (MVA), NYVAC, an avipox such as fowl pox or canary pox.

Certain embodiments of the invention include methods of delivering HMGCR dsRNA agents into cells using a vector and such vectors may be in a pharmaceutically acceptable carrier that may, but need not, include a slow release matrix in which the gene delivery vehicle is imbedded. In some embodiments, a vector for delivering an HMGCR dsRNA can be produced from a recombinant cell, and a pharmaceutical composition of the invention may include one or more cells that produced the HMGCR dsRNA delivery system.

10 *Pharmaceutical Compositions Containing HMGCR dsRNA or ssRNA agents*

Certain embodiments of the invention include use of pharmaceutical compositions containing an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent can be used in methods of the invention to reduce HMGCR gene expression and HMGCR activity in a cell and is useful to treat an HMGCR-associated disease or condition. Such pharmaceutical compositions can be formulated based on the mode of delivery. Non-limiting examples of formulations for modes of delivery are: a composition formulated for subcutaneous delivery, a composition formulated for systemic administration via parenteral delivery, a composition formulated for intravenous (IV) delivery, a composition formulated for intrathecal delivery, a composition formulated for direct delivery into brain, etc. Administration of a pharmaceutical composition of the invention to deliver an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent into a cell may be done using one or more means such as: topical (e.g., by a transdermal patch), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, e.g., via an implanted device; or intracranial, e.g., by intraparenchymal, intrathecal or intraventricular, administration. A HMGCR dsRNA agent or HMGCR antisense polynucleotide agent can also be delivered directly to a target tissue, for example directly into the liver, directly into a kidney, etc. It will be understood that “delivering an HMGCR dsRNA agent” or “delivering an HMGCR antisense polynucleotide agent” into a cell encompasses delivering an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent, respectively, directly as well as expressing an HMGCR dsRNA agent in a cell from an encoding vector that is delivered into a cell, or by any suitable means with which the HMGCR dsRNA or HMGCR antisense polynucleotide agent becomes present in a cell. Preparation and use of formulations and means for delivering inhibitory RNAs are well known and routinely used in the art.

As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of

the invention and a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs
5 administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating
10 agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein terms such as: “pharmacologically effective amount,” “therapeutically
15 effective amount” and “effective amount” refers to that amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the
20 treatment of that disease or disorder is the amount necessary to effect at least a 10% reduction in that parameter. For example, a therapeutically effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent can reduce HMGCR polypeptide levels by at least 10%.

25 *Effective amounts*

Methods of the invention, in some aspects comprise contacting a cell with an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent in an effective amount to reduce HMGCR gene expression in the contacted cell. Certain embodiments of methods of the invention comprise administering an HMGCR dsRNA agent or an HMGCR antisense
30 polynucleotide agent to a subject in an amount effective to reduce HMGCR gene expression and treat an HMGCR-associated disease or condition in the subject. An “effective amount” used in terms of reducing expression of HMGCR and/or for treating an HMGCR-associated disease or condition, is an amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of an HMGCR dsRNA agent or HMGCR antisense
35 polynucleotide agent to treat an HMGCR-associated disease or condition could be that amount necessary to (i) slow or halt progression of the disease or condition; or (ii) reverse, reduce, or eliminate one or more symptoms of the disease or condition. In some aspects of the invention, an effective amount is that amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent that when administered to a subject in need of a treatment of an

HMGCR-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. According to some aspects of the invention, an effective amount is that amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention that when combined or co-administered with another therapeutic treatment for an HMGCR-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. In some embodiments of the invention, a biologic effect of treating a subject with an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention may be the amelioration and or absolute elimination of symptoms resulting from the HMGCR-associated disease or condition. In some embodiments of the invention, a biologic effect is the complete abrogation of the HMGCR-associated disease or condition, as evidenced for example, by a diagnostic test that indicates the subject is free of the HMGCR-associated disease or condition. A non-limiting example of a physiological symptom that may be detected includes a reduction in HMGCR level in liver of a subject following administration of an agent of the invention. Additional art-known means of assessing the status of an HMGCR-associated disease or condition can be used to determine an effect of an agent and/or methods of the invention on an HMGCR-associated disease or condition.

Typically, an effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to decrease HMGCR polypeptide activity to a level to treat an HMGCR-associated disease or condition will be determined in clinical trials, establishing an effective dose for a test population versus a control population in a blind study. In some embodiments, an effective amount will be that results in a desired response, e.g., an amount that diminishes an HMGCR-associated disease or condition in cells, tissues, and/or subjects with the disease or condition. Thus, an effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to treat an HMGCR-associated disease or condition that can be treated by reducing HMGCR polypeptide activity may be the amount that when administered decreases the amount of HMGCR polypeptide activity in the subject to an amount that is less than the amount that would be present in the cell, tissue, and/or subject without the administration of the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent. In certain aspects of the invention the level of HMGCR polypeptide activity, and/or HMGCR gene expression present in a cell, tissue, and/or subject that has not been contacted with or administered an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention is referred to as a "control" amount. In some embodiments of methods of the invention a control amount for a subject is a pre-treatment amount for the subject, in other words, a level in a subject before administration of an HMGCR agent can be a control level for that subject and compared to a level of HMGCR polypeptide activity and/or HMGCR gene expression in the subject following siRNA administered to the subject. In the case of treating an HMGCR-associated disease or condition the desired response may be reducing or eliminating one or more symptoms of the disease or condition in the cell, tissue, and/or subject. The reduction or

elimination may be temporary or may be permanent. It will be understood that the status of an HMGCR-associated disease or condition can be monitored using methods of determining HMGCR polypeptide activity, HMGCR gene expression, symptom evaluation, clinical testing, etc. In some aspects of the invention, a desired response to treatment of an HMGCR-associated disease or condition is delaying the onset or even preventing the onset of the disease or condition.

An effective amount of a compound that decreases HMGCR polypeptide activity may also be determined by assessing physiological effects of administration of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent on a cell or subject, such as a decrease of an HMGCR-associated disease or condition following administration. Assays and/or symptomatic monitoring of a subject can be used to determine efficacy of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention, which may be administered in a pharmaceutical compound of the invention, and to determine the presence or absence of a response to the treatment. A non-limiting example, is that one or more art-known tests of serum cholesterol or triglyceride levels. Another non-limiting example, is that one or more art-known tests of liver function can be used to determine the status of the HMGCR-associated lipid imbalance in a subject before and after treatment of the subject with an HMGCR dsRNA agent of the invention.

Some embodiments of the invention include methods of determining an efficacy of an dsRNA agent or HMGCR antisense polynucleotide agent of the invention administered to a subject, to treat an HMGCR-associated disease or condition by assessing and/or monitoring one or more “physiological characteristics” of the HMGCR-associated disease or condition in the subject. Non-limiting examples of physiological characteristics of an HMGCR-associated disease or condition are the HMGCR mRNA level, the HMGCR protein level, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum, etc. Standard means of determining such physiological characteristic are known in the art and include, but are not limited to, blood tests, imaging studies, physical examination, etc.

It will be understood that the amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent administered to a subject can be modified based, at least in part, on such determinations of disease and/or condition status and/or physiological characteristics determined for a subject. The amount of a treatment may be varied for example by increasing or decreasing the amount of an HMGCR-dsRNA agent or HMGCR antisense polynucleotide agent, by changing the composition in which the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent, respectively, is administered, by changing the route of administration, by changing the dosage timing and so on. The effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent will vary with the particular condition being treated,

the age and physical condition of the subject being treated; the severity of the condition, the duration of the treatment, the nature of the concurrent therapy (if any), the specific route of administration, and additional factors within the knowledge and expertise of the health practitioner. For example, an effective amount may depend upon the desired level of HMGCR polypeptide activity and or HMGCR gene expression that is effective to treat the HMGCR-associated disease or condition. A skilled artisan can empirically determine an effective amount of a particular HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention for use in methods of the invention without necessitating undue experimentation. Combined with the teachings provided herein, by selecting from among various HMGCR dsRNA agents or HMGCR antisense polynucleotide agents of the invention, and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned that is effective to treat the particular subject. As used in embodiments of the invention, an effective amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention can be that amount that when contacted with a cell results in a desired biological effect in the cell.

It will be recognized that HMGCR gene silencing may be determined in any cell expressing HMGCR, either constitutively or by genomic engineering, and by any appropriate assay. In some embodiments of the invention, HMGCR gene expression is reduced by at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% by administration of an HMGCR dsRNA agent of the invention. In some embodiments of the invention, HMGCR gene expression is reduced by at between 5% and 10%, 5% and 25%, 10% and 50%, 10% and 75%, 25% and 75%, 25% and 100%, or 50% and 100% by administration of an HMGCR dsRNA agent of the invention.

Dosing

HMGCR dsRNA agents and HMGCR antisense polynucleotide agents are delivered in pharmaceutical compositions in dosages sufficient to inhibit expression of HMGCR genes. In certain embodiments of the invention, a dose of HMGCR dsRNA agent or HMGCR antisense polynucleotide agent is in a range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of 1 to 50 mg per kilogram body weight, 5 to 40 mg/kg body weight, 10 to 30 mg/kg body weight, 1 to 20 mg/kg body weight, 1 to 10 mg/kg body weight, 4 to 15 mg/kg body weight per day, inclusive. For example, the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent can be administered in an amount that is from about 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4 mg/kg, 4.1

mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg, 5.9 mg/kg, 6 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, through 50 mg/kg body per single dose.

Various factors may be considered in the determination of dosage and timing of delivery of an HMGCRC dsRNA agent of the invention. The absolute amount of an HMGCRC dsRNA agent or HMGCRC antisense polynucleotide agent delivered will depend upon a variety of factors including a concurrent treatment, the number of doses and the individual subject parameters including age, physical condition, size and weight. These are factors well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. In some embodiments, a maximum dose can be used, that is, the highest safe dose according to sound medical judgment.

Methods of the invention may in some embodiments include administering to a subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more doses of an HMGCRC dsRNA agent or HMGCRC antisense polynucleotide agent. In some instances, a pharmaceutical compound, (e.g., comprising an HMGCRC dsRNA agent or comprising an HMGCRC antisense polynucleotide agent) can be administered to a subject at least daily, every other day, weekly, every other week, monthly, etc. Doses may be administered once per day or more than once per day, for example, 2, 3, 4, 5, or more times in one 24 hour period. A pharmaceutical composition of the invention may be administered once daily, or the HMGCRC dsRNA agent or HMGCRC antisense polynucleotide agent may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In some embodiments of methods of the invention, a pharmaceutical composition of the invention is administered to a subject one or more times per day, one or more times per week, one or more times per month, or one or more times per year.

Methods of the invention, in some aspects, include administration of a pharmaceutical compound alone, in combination with one or more other HMGCRC dsRNA agents or HMGCRC antisense polynucleotide agents, and/or in combination with other drug therapies or treatment activities or regimens that are administered to subjects with an HMGCRC-associated disease or condition. Pharmaceutical compounds may be administered in pharmaceutical compositions.

Pharmaceutical compositions used in methods of the invention may be sterile and contain an amount of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent that will reduce activity of an HMGCR polypeptide to a level sufficient to produce the desired response in a unit of weight or volume suitable for administration to a subject. A dose administered to a
 5 subject of a pharmaceutical composition that includes an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to reduce HMGCR protein activity can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively
 10 higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

Treatment

As used herein, “HMGCR-associated disease”, “HMGCR-associated diseases and
 15 conditions” and “diseases and conditions caused and/or modulated by HMGCR”, “HMGCR-associated disorder” includes a disease, disorder or condition that would benefit from a decrease in HMGCR gene expression, replication, or protein activity. Exemplary HMGCR-associated diseases include acquired or inherited “disorders of lipid metabolism” which include any disorder associated with or caused by a disturbance in lipid metabolism. For example, this
 20 term includes any disorder, disease or condition characterized by abnormal elevation of levels of any or all lipids and/or lipoproteins in the blood or a condition that can lead to abnormal elevation of levels of any or all lipids and/or lipoproteins in the blood, such as a hyperlipidemia, and other forms of lipid imbalance such as hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, as well as the pathological conditions associated
 25 with these disorders, e.g., congestive heart disease (CHD) and atherosclerosis. Exemplary disorders of lipid metabolism include, but are not limited to, atherosclerosis, dyslipidemia, hypertriglyceridemia (including drug-induced hypertriglyceridemia, diuretic-induced hypertriglyceridemia, alcohol-induced hypertriglyceridemia, β -adrenergic blocking agent-induced hypertriglyceridemia, estrogen-induced hypertriglyceridemia, glucocorticoid-induced
 30 hypertriglyceridemia, retinoid-induced hypertriglyceridemia, and cimetidine-induced hypertriglyceridemia, and familial hypertriglyceridemia), acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, hyperlipidemia (including familial combined hyperlipidemia), familial partial lipodystrophy type 1 (FPLD1), hypercholesterolemia, mixed
 35 hyperlipidemia (or mixed hyperlipoproteinemia familial, gout associated with hypercholesterolemia, xanthomatosis (subcutaneous cholesterol deposits), hyperlipidemia with heterogeneous LPL deficiency, and hyperlipidemia with high LDL, heterogeneous LPL deficiency, and an induced or acquired disorder, such as a disorder induced or acquired as a result of a disease. As used herein, the term “serum lipid” refers to any major lipid present in

the blood. Serum lipids may be present in the blood either in free form or as a part of a protein complex, e.g., a lipoprotein complex. Non-limiting examples of serum lipids include triglycerides, cholesterol, such as total cholesterol, low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C). In some embodiments, the disorder of lipid metabolism is a hyperlipidemia. As used herein, the term “hyperlipidemia” refers to any any disorder, disease or condition characterized by abnormal elevation of levels of any or all lipids, such as cholesterol and triglycerides, and/or lipoproteins in the blood or a condition that can lead to abnormal elevation of levels of any or all lipids and/or lipoproteins in the blood. In one embodiment, the hyperlipidemia is hypertriglyceridemia. As used herein, the term “hypertriglyceridemia” refers to a condition in which triglyceride levels are elevated, often caused or exacerbated by uncontrolled hyperlipidemia mellitus, obesity, and sedentary habits. This condition is a risk factor for coronary artery disease. Hypertriglyceridemia is usually asymptomatic until triglycerides are greater than 1000-2000 mg/dL. Signs and symptoms may include the following: pain in the mid-epigastric, chest, or back regions; nausea, vomiting, dyspnea, xanthomas, corneal arcus, and/or xanthelasmas. In some embodiments, the hyperlipidemia is hypercholesterolemia. As used herein the term “hypercholesterolemia” refers to a form of hyperlipidemia (elevated levels of lipids in the blood) in which there are high levels of cholesterol in the serum of a subject, e.g., at least about 240 mg/dL of total cholesterol. In other embodiments, the hyperlipidemia is mixed hyperlipidemia. As used herein the term “mixed hyperlipidemia” also referred to as type 5 hyperlipidemia refers to a form of hyperlipidemia in which there are elevated levels of VLDL and chylomicrons found in plasma in the serum of a subject, e.g., at least about 240 mg/dL of total cholesterol. Cardiovascular diseases associated with disorders of lipid metabolism are also considered “disorders of lipid metabolism”, as defined herein. These diseases may include coronary artery disease (also called ischemic heart disease), atherosclerosis, inflammation associated with coronary artery disease, restenosis, peripheral vascular diseases, and stroke. Disorders related to body weight are also considered “disorders of lipid metabolism”, as defined herein. Such disorders may include obesity, metabolic syndrome including independent components of metabolic syndrome (e.g., central obesity, FBG/pre-hyperlipidemia/hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, and hypertension), hypothyroidism, uremia, and other conditions associated with weight gain (including rapid weight gain), weight loss, maintenance of weight loss, or risk of weight regain following weight loss. Blood sugar disorders are further considered “disorders of lipid metabolism”, as defined herein. Such disorders may include hyperlipidemia, hypertension, and polycystic ovarian syndrome related to insulin resistance. Other exemplary disorders of lipid metabolism may also include renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus, dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease.

In certain aspects of the invention, a subject may be administered an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention at a time that is one or more of before or after diagnosis of an HMGCR-associated disease or condition. In some aspects of the invention, a subject is at risk of having or developing an HMGCR-associated disease or condition. A subject at risk of developing an HMGCR-associated disease or condition is one who has an increased probability of developing the HMGCR-associated disease or condition, compared to a control risk of developing the HMGCR-associated disease or condition. In some embodiments of the invention, a level of risk may be statistically significant compared to a control level of risk. A subject at risk may include, for instance, a subject who is, or will be, a subject who has a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to an HMGCR-associated disease or condition than a control subject without the preexisting disease or genetic abnormality; a subject having a family and/or personal medical history of the HMGCR-associated disease or condition; and a subject who has previously been treated for an HMGCR-associated disease or condition. It will be understood that a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to an HMGCR-associated disease or condition, may be a disease or genetic abnormality that when present has been previously identified as having a correlative relation to a higher likelihood of developing an HMGCR-associated disease or condition.

It will be understood that an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be administered to a subject based on a medical status of the individual subject. For example, a health-care provider for a subject may assess an HMGCR level measured in a sample obtained from a subject and determine it is desirable to reduce the subject's HMGCR level, by administration of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention. In this example, the HMGCR level may be considered to be a physiological characteristic of an HMGCR-associated condition, even if the subject is not diagnosed as having an HMGCR-associated disease such as one disclosed herein. A healthcare provider may monitor changes in the subject's HMGCR level, as a measure of efficacy of the administered HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention. In a non-limiting example, a biological sample, such as a blood or serum sample may be obtained from a subject and an HMGCR level for the subject determined in the sample. A HMGCR dsRNA agent or HMGCR antisense polynucleotide agent is administered to the subject and a blood sample is obtained from the subject following the administration and the HMGCR level determined using the sample and the results compared to the results determined in the subject's pre-administration (prior) sample. A reduction in the subject's HMGCR level in the later sample compared to the pre-administration level indicates the administered HMGCR dsRNA agent or HMGCR antisense polynucleotide agent efficacy in reducing the lipid level in the subject.

Certain embodiments of methods of the invention include adjusting a treatment that includes administering a dsRNA agent or an HMGCR antisense polynucleotide agent of the

invention to a subject based at least in part on assessment of a change in one or more of the subject's physiological characteristics of an HMGCR-associated disease or condition resulting from the treatment. For example, in some embodiments of the invention, an effect of an administered dsRNA agent or HMGCR antisense polynucleotide agent of the invention may be determined for a subject and used to assist in adjusting an amount of a dsRNA agent or HMGCR antisense polynucleotide agent of the invention subsequently administered to the subject. In a non-limiting example, a subject is administered a dsRNA agent or HMGCR antisense polynucleotide agent of the invention, the subject's HMGCR level is determined after the administration, and based at least in part on the determined level, a greater amount of the dsRNA agent or HMGCR antisense polynucleotide agent is determined to be desirable in order to increase the physiological effect of the administered agent, for example to reduce or further reduce the subject's HMGCR level. In another non-limiting example, a subject is administered a dsRNA agent or HMGCR antisense polynucleotide agent of the invention, the subject's HMGCR level is determined after the administration and based at least in part on the determined level, a lower amount of the dsRNA agent or HMGCR antisense polynucleotide agent is desirable to administer to the subject.

Thus, some embodiments of the invention include assessing a change in one or more physiological characteristics of resulting from a subject's previous treatment to adjust an amount of a dsRNA agent or HMGCR antisense polynucleotide agent of the invention subsequently administered to the subject. Some embodiments of methods of the invention include 1, 2, 3, 4, 5, 6, or more determinations of a physiological characteristic of an HMGCR-associated disease or condition to assess and/or monitor the efficacy of an administered HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention, and optionally using the determinations to adjust one or more of: a dose, administration regimen, and or administration frequency of a dsRNA agent or HMGCR antisense polynucleotide agent of the invention to treat an HMGCR-associated disease or condition in a subject. In some embodiments of methods of the invention, a desired result of administering an effective amount of a dsRNA agent or HMGCR antisense polynucleotide agent of the invention to a subject is a reduction of the subject's the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum, etc., as compared to a prior level determined for the subject, or to a control level.

As used herein, the terms "treat", "treated", or "treating" when used with respect to an HMGCR-associated disease or condition may refer to a prophylactic treatment that decreases the likelihood of a subject developing the HMGCR-associated disease or condition, and also may refer to a treatment after the subject has developed an HMGCR-associated disease or condition in order to eliminate or reduce the level of the HMGCR-associated disease or

condition, prevent the HMGCR-associated disease or condition from becoming more advanced (e.g., more severe), and/or slow the progression of the HMGCR-associated disease or condition in a subject compared to the subject in the absence of the therapy to reduce activity in the subject of HMGCR polypeptide.

5 Certain embodiments of agents, compositions, and methods of the invention can be used to inhibit HMGCR gene expression. As used herein in reference to expression of an HMGCR gene, the terms “inhibit,” “silence,” “reduce,” “down-regulate,” and “knockdown” mean the expression of the HMGCR gene, as measured by one or more of: a level of RNA transcribed from the gene, a level of activity of HMGCR expressed, and a level of HMGCR
10 polypeptide, protein or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the HMGCR gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is contacted with (e.g., treated with) an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention, compared to a control level of RNA transcribed from the HMGCR gene, a level of activity of expressed
15 HMGCR, or a level of HMGCR translated from the MRNA, respectively. In some embodiments, a control level is a level in a cell, tissue, organ or subject that has not been contacted with (e.g., treated with) the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent.

20 Administration methods

A variety of administration routes for an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent are available for use in methods of the invention. The particular delivery mode selected will depend at least in part, upon the particular condition being treated and the dosage required for therapeutic efficacy. Methods of this invention, generally speaking, may
25 be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of treatment of an HMGCR-associated disease or condition without causing clinically unacceptable adverse effects. In some embodiments of the invention, an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be administered via an oral, enteral, mucosal, subcutaneous, and/or parenteral route. The term
30 “parenteral” includes subcutaneous, intravenous, intrathecal, intramuscular, intraperitoneal, and intrasternal injection, or infusion techniques. Other routes include but are not limited to nasal (e.g., via a gastro-nasal tube), dermal, vaginal, rectal, sublingual, and inhalation. Delivery routes of the invention may include intrathecal, intraventricular, or intracranial. In some embodiments of the invention, an HMGCR dsRNA agent or HMGCR antisense
35 polynucleotide agent may be placed within a slow-release matrix and administered by placement of the matrix in the subject. In some aspects of the invention, an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be delivered to a subject cell using nanoparticles coated with a delivery agent that targets a specific cell or organelle. Various delivery means, methods, agents are known in the art. Non-limiting examples of delivery

methods and delivery agents are additionally provided elsewhere herein. In some aspects of the invention, the term “delivering” in reference to an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may mean administration to a cell or subject of one or more “naked” HMGCR dsRNA agent or HMGCR antisense polynucleotide agent sequences and in certain aspects of the invention “delivering” means administration to a cell or subject via transfection means, delivering a cell comprising an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to a subject, delivering a vector encoding an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent into a cell and/or subject, etc. Delivery of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent using a transfection means may include administration of a vector to a cell and/or subject.

In some methods of the invention one or more HMGCR dsRNA agents or HMGCR antisense polynucleotide agents may be administered in formulations, which may be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients. In some embodiments of the invention an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be formulated with another therapeutic agent for simultaneous administration. According to methods of the invention, an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be administered in a pharmaceutical composition. In general, a pharmaceutical composition comprises an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent and optionally, a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those of ordinary skill in the art. As used herein, a pharmaceutically acceptable carrier means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients, e.g., the ability of the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent to inhibit HMGCR gene expression in a cell or subject. Numerous methods to administer and deliver dsRNA agents or HMGCR antisense polynucleotide agents for therapeutic use are known in the art and may be utilized in methods of the invention.

Pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers and other materials that are well-known in the art. Exemplary pharmaceutically acceptable carriers are described in U.S. Pat. No. 5,211,657 and others are known by those skilled in the art. Such preparations may routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic,

succinic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Some embodiments of methods of the invention include administering one or more HMGCR dsRNA agents or HMGCR antisense polynucleotide agents directly to a tissue. In some embodiments, the tissue to which the compound is administered is a tissue in which the HMGCR-associated disease or condition is present or is likely to arise, non-limiting examples of which are the heart. Direct tissue administration may be achieved by direct injection or other means. Many orally delivered compounds naturally travel to and through the liver and kidneys and some embodiments of treatment methods of the invention include oral administration of one or more HMGCR dsRNA agents to a subject. HMGCR dsRNA agents or HMGCR antisense polynucleotide agents, either alone or in conjunction with other therapeutic agents, may be administered once, or alternatively they may be administered in a plurality of administrations. If administered multiple times, the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be administered via different routes. For example, though not intended to be limiting, a first (or first several) administrations may be made via subcutaneous means and one or more additional administrations may be oral and/or systemic administrations.

For embodiments of the invention in which it is desirable to administer an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent systemically, the HMGCR dsRNA agent or HMGCR antisense polynucleotide agent may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with or without an added preservative. HMGCR dsRNA agent formulations (also referred to as pharmaceutical compositions) may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Lower doses will result from other forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day may be

used as needed to achieve appropriate systemic or local levels of one or more HMGCR dsRNA agents or HMGCR antisense polynucleotide agents and to achieve appropriate reduction in HMGCR protein activity.

5 In yet other embodiments, methods of the invention include use of a delivery vehicle such as biocompatible microparticle, nanoparticle, or implant suitable for implantation into a recipient, e.g., a subject. Exemplary bioerodible implants that may be useful in accordance with this method are described in PCT Publication No. WO 95/24929 (incorporated by reference herein), which describes a biocompatible, biodegradable polymeric matrix for containing a biological macromolecule.

10 Both non-biodegradable and biodegradable polymeric matrices can be used in methods of the invention to deliver one or more HMGCR dsRNA agents or HMGCR antisense polynucleotide agents to a subject. In some embodiments, a matrix may be biodegradable. Matrix polymers may be natural or synthetic polymers. A polymer can be selected based on the period of time over which release is desired, generally in the order of a few hours to a year
15 or longer. Typically, release over a period ranging from between a few hours and three to twelve months can be used. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multivalent ions or other polymers.

In general, HMGCR dsRNA agents or HMGCR antisense polynucleotide agents may
20 be delivered in some embodiments of the invention using the bioerodible implant by way of diffusion, or by degradation of the polymeric matrix. Exemplary synthetic polymers for such use are well known in the art. Biodegradable polymers and non-biodegradable polymers can be used for delivery of HMGCR dsRNA agents or HMGCR antisense polynucleotide agents using art-known methods. Bioadhesive polymers such as bioerodible hydrogels (see H. S.
25 Sawhney, C. P. Pathak and J. A. Hubell in *Macromolecules*, 1993, 26, 581-587, the teachings of which are incorporated by reference herein) may also be used to deliver HMGCR dsRNA agents or HMGCR antisense polynucleotide agents for treatment of an HMGCR-associated disease or condition. Additional suitable delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations
30 of an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent, increasing convenience to the subject and the medical care professional. Many types of release delivery systems are available and known to those of ordinary skill in the art. (See for example: U.S. Pat. Nos. 5,075,109; 4,452,775; 4,675,189; 5,736,152; 3,854,480; 5,133,974; and 5,407,686 (the teaching of each of which is incorporated herein by reference). In addition, pump-based
35 hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be suitable for prophylactic treatment of subjects and for subjects at risk of developing a recurrent HMGCR-associated disease or condition. Long-term release, as used herein, means that the implant is constructed and arranged to deliver a therapeutic level of an HMGCR dsRNA agent or HMGCR antisense

polynucleotide agent for at least up to 10 days, 20 days, 30 days, 60 days, 90 days, six months, a year, or longer. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

- Therapeutic formulations of HMGCR dsRNA agents or HMGCR antisense polynucleotide agents may be prepared for storage by mixing the molecule or compound having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [Remington's Pharmaceutical Sciences 21st edition, (2006)], in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and 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; and 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, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN[®], PLURONICS[®] or polyethylene glycol (PEG).

Cells, Subjects, and Controls

- Methods of the invention may be used in conjunction with cells, tissues, organs and/or subjects. In some aspects of the invention a subject is a human or vertebrate mammal including but not limited to a dog, cat, horse, cow, goat, mouse, rat, and primate, e.g., monkey. Thus, the invention can be used to treat HMGCR-associated diseases or conditions in human and non-human subjects. In some aspects of the invention a subject may be a farm animal, a zoo animal, a domesticated animal or non-domesticated animal and methods of the invention can be used in veterinary prevention and treatment regimens. In some embodiments of the invention, the subject is a human and methods of the invention can be used in human prevention and treatment regimens.

- Non-limiting examples of subjects to which the present invention can be applied are subjects who are diagnosed with, suspected of having, or at risk of having a disease or condition associated with a higher than desirable HMGCR expression and/or activity, also referred to as “elevated levels of HMGCR expression”. Non-limiting examples of diseases and conditions associated with a higher than desirable levels of HMGCR expression and/or activity are described elsewhere herein. Methods of the invention may be applied to a subject who, at the time of treatment, has been diagnosed as having the disease or condition associated with a

higher than desirable HMGCR expression and/or activity, or a subject who is considered to be at risk for having or developing a disease or condition associated with a higher than desirable HMGCR expression and/or activity. In some aspects of the invention a disease or condition associated with a higher than desirable HMGCR level of expression and/or activity is an acute disease or condition, and in certain aspects of the invention a disease or condition associated with a higher than desirable HMGCR level of expression and/or activity is a chronic disease or condition.

In a non-limiting example, an HMGCR dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, statin resistant hypercholesterolemia, which is a disease in which it is desirable to reduce HMGCR expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

In another non-limiting example, an HMGCR dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, hyperlipidemia, which is a disease in which it is desirable to reduce HMGCR expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

A cell to which methods of the invention may be applied include cells that are *in vitro*, *in vivo*, *ex vivo* cells. Cells may be in a subject, in culture, and/or in suspension, or in any other suitable state or condition. A cell to which a method of the invention may be applied can be a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, kidney cell or other type of vertebrate cell, including human and non-human mammalian cells. In certain aspects of the invention, a cell to which methods of the invention may be applied is a healthy, normal cell that is not known to be a disease cell. In certain embodiments of the invention a cell to which methods and compositions of the invention are applied to a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, and/or a kidney cell. In certain aspects of the invention, a control cell is a normal cell, but it will be understood that a cell having a disease or condition may also serve as a control cell in particular circumstances for example to compare results in a treated cell having a disease or condition versus an untreated cell having the disease or condition, etc.

A level of HMGCR polypeptide activity can be determined and compared to control level of HMGCR polypeptide activity, according to methods of the invention. A control may be a predetermined value, which can take a variety of forms. It can be a single cut-off value, such as a median or mean. It can be established based upon comparative groups, such as in groups having normal levels of HMGCR polypeptide and/or HMGCR polypeptide activity and groups having increased levels of HMGCR polypeptide and/or HMGCR polypeptide activity. Another non-limiting example of comparative groups may be groups having one or more

symptoms of or a diagnosis of an HMGCR-associated disease or condition; groups without having one or more symptoms of or a diagnosis of the disease or condition; groups of subjects to whom an siRNA treatment of the invention has been administered; groups of subjects to whom an siRNA treatment of the invention has not been administered. Typically, a control
5 may be based on apparently healthy normal individuals in an appropriate age bracket or apparently healthy cells. It will be understood that controls according to the invention may be, in addition to predetermined values, samples of materials tested in parallel with the experimental materials. Examples include samples from control populations or control samples generated through manufacture to be tested in parallel with the experimental samples. In some
10 embodiments of the invention, a control may include a cell or subject not contacted or treated with an HMGCR dsRNA agent of the invention and in such instances, a control level of HMGCR polypeptide and/or HMGCR polypeptide activity can be compared to a level of HMGCR polypeptide and/or HMGCR polypeptide activity in a cell or subject contacted with an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention.

15 In some embodiments of the invention a level of HMGCR polypeptide determined for a subject can be a control level against which a level of HMGCR polypeptide determined for the same subject at a different time is compared. In a non-limiting example, a level of HMGCR is determined in a biological sample obtained from a subject who has not been administered an HMGCR treatment of the invention. In some embodiments, the biological sample is a serum
20 sample. The level of HMGCR polypeptide determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of an HMGCR dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and the level of HMGCR polypeptide in the subsequent sample or samples can be compared to the control/baseline level
25 for the subject. Such comparisons can be used to assess onset, progression, or recession of an HMGCR associated disease or condition in the subject. For example, a level of HMGCR polypeptide in the baseline sample obtained from the subject that is higher than a level obtained from the same subject after the subject has been administered an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention indicates regression of the
30 HMGCR-associated disease or condition and indicates efficacy of the administered HMGCR dsRNA agent of the invention for treatment of the HMGCR-associated disease or condition.

In some aspects of the invention, values of one or more of a level of HMGCR polypeptide and/or HMGCR polypeptide activity determined for a subject may serve as control values for later comparison of levels of HMGCR polypeptide and/or HMGCR activity, in that
35 same subject, thus permitting assessment of changes from a "baseline" HMGCR polypeptide activity in a subject. Thus, an initial HMGCR polypeptide level and/or initial HMGCR polypeptide activity level may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of HMGCR polypeptide and/or

HMGCR polypeptide activity in the subject, with the initial level serving as a control level for that subject.

Using methods of the invention, HMGCR dsRNA agents and/or HMGCR antisense polynucleotide agents of the invention may be administered to a subject. Efficacy of the administration and treatment of the invention can be assessed when a level of HMGCR polypeptide in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration level of HMGCR polypeptide in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example a level of HMGCR polypeptide in a control serum sample. It will be understood that a level of HMGCR polypeptide and a level of HMGCR polypeptide activity both correlate with a level of HMGCR gene expression. Certain embodiments of methods of the invention comprise administering an HMGCR dsRNA and/or HMGCR antisense agent of the invention to a subject in an amount effective to inhibit HMGCR gene expression and thereby reduce a level of HMGCR polypeptide and reduce a level of HMGCR polypeptide activity in the subject.

Some embodiments of the invention, include determining presence, absence, and/or an amount (also referred to herein as a level) of HMGCR polypeptide in one or more biological samples obtained from one or more subjects. The determination can be used to assess efficacy of a treatment method of the invention. For example, methods and compositions of the invention can be used to determine a level of HMGCR polypeptide in a biological sample obtained from a subject previously treated with administration of an HMGCR dsRNA agent and/or an HMGCR antisense agent of the invention. A level of HMGCR polypeptide determined in a serum sample obtained from the treated subject that is lower by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pretreatment level of HMGCR polypeptide determined for the subject, or compared to a non-contacted control biological sample level, indicates a level of efficacy of the treatment administered to the subject.

In some embodiments of the invention a physiological characteristic of an HMGCR-associated disease or condition determined for a subject can be a control determination against which a determination of the physiological characteristic in the same subject at a different time is compared. In a non-limiting example, a physiological characteristic such as the HMGCR mRNA level, the HMGCR protein level in the subject, or the lipid level, the triglyceride, the cholesterol level in the plasma or the tissue sample is determined in a biological sample, such as a serum sample, obtained from a subject who has not been administered an HMGCR treatment of the invention. The HMGCR mRNA level (and/or other physiological characteristic of an HMGCR disease or condition) determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of an HMGCR dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and

HMGCR mRNA level and/or HMGCR protein level in the subsequent sample or samples are compared to the control/baseline level and/or ratio, respectively, for the subject. Such comparisons can be used to assess onset, progression, or recession of an HMGCR associated disease or condition in the subject. For example, HMGCR mRNA level in the baseline sample
5 obtained from the subject that is higher than HMGCR mRNA level determined in a sample obtained from the same subject after the subject has been administered an HMGCR dsRNA agent or HMGCR antisense polynucleotide agent of the invention indicates regression of the HMGCR-associated disease or condition and indicates efficacy of the administered HMGCR dsRNA agent of the invention for treatment of the HMGCR-associated disease or condition.

10 In some aspects of the invention, values of one or more of a physiological characteristic of an HMGCR-associated disease or condition determined for a subject may serve as control values for later comparison of the physiological characteristics in that same subject, thus permitting assessment of changes from a “baseline” physiological characteristic in a subject. Thus, an initial physiological characteristic may be present and/or determined in a subject and
15 methods and compounds of the invention may be used to decrease the level of HMGCR polypeptide and/or HMGCR polypeptide activity in the subject, with the initial physiological characteristic determination serving as a control for that subject.

Using methods of the invention, HMGCR dsRNA agents and/or HMGCR antisense polynucleotide agents of the invention may be administered to a subject in an effective amount
20 to treat an HMGCR disease or condition. Efficacy of the administration and treatment of the invention can be assessed by determining a change in one or more physiological characteristics of the HMGCR disease or condition. In a non-limiting example, an HMGCR mRNA level in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration lipid in a
25 serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example HMGCR mRNA level in a control serum sample. It will be understood that the HMGCR mRNA level, the HMGCR protein level in the subject, or the lipid level, the triglyceride, the cholesterol level in the plasma or the tissue sample each correlates with a level of HMGCR gene expression. Certain embodiments of methods of the
30 invention comprise administering an HMGCR dsRNA and/or HMGCR antisense agent of the invention to a subject in an amount effective to inhibit HMGCR gene expression and thereby reduce the HMGCR mRNA level, the HMGCR protein level in the subject, or otherwise positively impact a physiological characteristic of an HMGCR-associated disease or condition in the subject.

35 Some embodiments of the invention, include determining presence, absence, and/or a change in a physiological characteristic of an HMGCR-associated disease or condition using methods such as but not limited to: (1) assessing one or more biological samples obtained from one or more subjects for the physiological characteristic; (2) imaging a subject (for example

but not limited to obtaining a liver image); and (3) or physical examination of the subject. The determination can be used to assess efficacy of a treatment method of the invention.

Kits

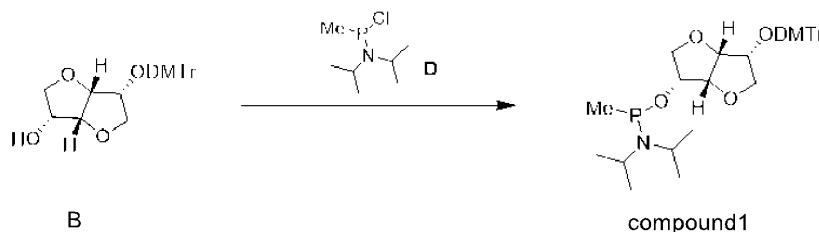
Also within the scope of the invention are kits that comprise one or more HMGCR dsRNA agents and/or HMGCR antisense polynucleotide agents and instructions for its use in methods of the invention. Kits of the invention may include one or more of an HMGCR dsRNA agent, HMGCR sense polynucleotide, and HMGCR antisense polynucleotide agent that may be used to treat an HMGCR-associated disease or condition. Kits containing one or more HMGCR dsRNA agents, HMGCR sense polynucleotides, and HMGCR antisense polynucleotide agents can be prepared for use in treatment methods of the invention. Components of kits of the invention may be packaged either in aqueous medium or in lyophilized form. A kit of the invention may comprise a carrier being compartmentalized to receive in close confinement therein one or more container means or series of container means such as test tubes, vials, flasks, bottles, syringes, or the like. A first container means or series of container means may contain one or more compounds such as an HMGCR dsRNA agent and/or HMGCR sense or antisense polynucleotide agent. A second container means or series of container means may contain a targeting agent, a labelling agent, a delivery agent, etc. that may be included as a portion of an HMGCR dsRNA agent and/or HMGCR antisense polynucleotide to be administered in an embodiment of a treatment method of the invention.

A kit of the invention may also include instructions. Instructions typically will be in written form and will provide guidance for carrying-out a treatment embodied by the kit and for making a determination based upon that treatment.

The following examples are provided to illustrate specific instances of the practice of the present invention and are not intended to limit the scope of the invention. As will be apparent to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

Examples

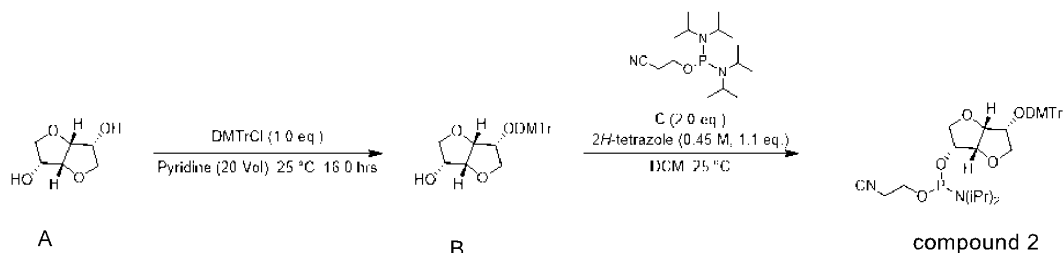
Example 1. Phosphoramidite Compound 1



To a solution of compound B (500 mg, 1.11 mmol, 1.0 eq) in DCM (5.0 mL) was added compound D (607 mg, 3.34 mmol, 3.0 eq) and DIEA (432 mg, 3.34 mmol, 582 μ L, 3.0 eq) under N₂ atmosphere at 0-5 °C, the mixture was stirred at 25 °C for 1.0 hrs. LC-MS showed Compound B was consumed completely, several new peaks were shown on LC-MS and ~70.9% of desired compound was detected. The resulting reaction mixture was cooled to -20 °C and poured into cold (0-5 °C) sat.NaHCO₃ (5.0 mL) solution, extracted with DCM (5.0 mL *2), the combined organic layers were washed with cold (0-5 °C) sat.NaHCO₃/brine =1:1 (5.0 mL/5.0 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue (~5 mL). The residue was purified by column chromatography (alkaline Al₂O₃, Petroleum ether/Ethyl acetate=10/1 to 5/1, 0.1% Et₃N) to give compound 1 (280 mg, 471 μ mol, 42.3% yield) was obtained as a white solid.

¹H NMR: EC10615-49-P1N (400 MHz, DMSO-d₆) δ ppm 7.44 (br d, J=7.63 Hz, 2 H), 7.31 (br t, J=7.94 Hz, 6 H), 7.18 - 7.26 (m, 1 H), 6.89 (brd, J=8.00 Hz, 4 H), 4.08 - 4.13 (m, 1 H), 3.95 - 4.03 (m, 1 H), 3.84 - 3.93 (m, 1 H), 3.77 - 3.83 (m, 1 H), 3.74 (s, 6 H), 3.43 - 3.53 (m, 3 H), 3.38 (br d, J=6.75 Hz, 1 H), 2.94 - 3.04 (m, 1 H), 2.70 - 2.85 (m, 1 H), 1.09 - 1.15 (m, 12 H), 1.07 (br s, 3 H).

Example 2. Phosphoramidite Compound 2



DMTrCl (232 g, 684 mmol, 1.0 eq) in pyridine (400 mL) was added to the solution of isomannide compound A (100 g, 684 mmol, 1.0 eq) in pyridine (600 mL), and the mixture was stirred at 25 °C for 12 hrs. LC-MS showed compound A was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was diluted with water (500 mL), extracted with DCM (500 mL *2), and the combined organic phases were washed with brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue. The residue was purified by column chromatography (DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound B (150 g, 48.9% yield) a yellow solid.

¹H NMR: EC4783-404-P1B1_C (400 MHz, DMSO-d₆) δ ppm 7.46 (br d, J=7.63 Hz, 2 H) 7.28 - 7.37 (m, 6 H) 7.19 - 7.25 (m, 1 H) 6.90 (br d, J=7.88 Hz, 4 H) 4.70 (d, J=6.50 Hz, 1 H) 3.99 - 4.09 (m, 6 H) 3.88 - 3.96 (m, 2 H) 3.83 (br dd, J=7.82, 6.94 Hz, 1 H) 3.74 (s, 6 H) 3.41 (br t, J=8.13 Hz, 1 H) 3.05 (t, J=8.44 Hz, 1 H) 2.85 (br t, J=7.50 Hz, 1 H).

To a solution of compound B (80.0 g, 178 mmol, 1.0 eq) in DCM (800 mL) at 25 °C under N₂ atmosphere was added dropwise 2H-tetrazole (0.45 M, 436 mL, 1.1 eq), then compound C (80.6 g, 267 mmol, 85.0 mL, 1.5 eq) in DCM (200 mL) was added dropwise to

the mixture. The reaction mixture was stirred at 25 °C under for 1.0 hr. LC-MS showed compound B was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was cooled to -20 °C and poured into ice cold sat. NaHCO₃ (500 mL), extracted with DCM (500 mL *3), the combined organic layers were washed with

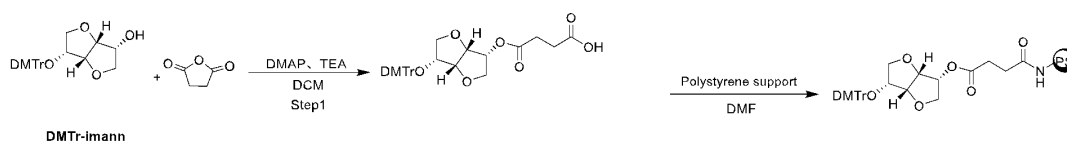
5 sat. NaHCO₃/brine=1:1 (3 00 mL/300 mL), dried over Na₂SO₄ and concentrated in vacuum (35 °C) to get the residue (100 mL). The residue was purified by column chromatography (Al₂O₃, DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound 2 (77 g, 119 mmol, 66.5% yield) as a white solid.

1H NMR: EC4783-423-P1B1_C (400 MHz, DMSO-d₆) δ ppm 7.22 (br d, J=7.50 Hz, 2
 10 H) 7.05 - 7.14 (m, 6 H) 6.96 - 7.02 (m, 1 H) 6.67 (br dd, J=8.82, 1.81 Hz, 4 H) 3.95 - 4.07 (m, 2 H) 3.73 - 3.83 (m, 1 H) 3.62 - 3.72 (m, 2 H) 3.48 - 3.53 (m, 6 H) 3.27 - 3.37 (m, 3 H) 3.11 (s, 6 H) 2.82 (td, J=8.54, 2.31 Hz, 1 H) 2.47 - 2.63 (m, 3 H) 2.28 (br d, J=1.63 Hz, 3 H) 0.82 - 1.00 (m, 13 H).

15 Other phosphoramidites may be prepared according to procedures described herein and/or prior arts such as, but are not limited to, US426,220 and WO02/36743.

Example 3. Preparation of a solid support comprising phosphoramidites monomers of the present invention

20



represents amine methyl polyethylene macroporous resin carrier part

Dichloromethane (19.50kg) was added to the 50 L glass kettle under the protection of nitrogen and started stirring. The temperature was controlled at 20~30 °C, and DMTr imann
 25 (1.47 kg), triethylamine (1.50 kg), 4-dimethylaminopyridine (0.164 kg) and succinic anhydride (1.34 kg) was added to the glass kettle. The system was kept at 20~30 °C for 18h, samples were taken and the reaction was ended. Saturated sodium bicarbonate solution (22.50 kg) was added into the reaction system, stirred for 10-20 min, and allowed to separate into layers. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane,
 30 and the organic phase was combined and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to get the residue forming a gray to off-white solid of 1.83 kg.

N, N-dimethylformamide (23.50 kg) was added into a 100L glass kettle and stirred. The temperature was controlled at 20~30 °C. Under the protection of nitrogen, the products of the previous step, O-benzotriazole tetramethylurea hexafluorophosphate (0.33 kg) and N, N-
 35 diisopropylethylamine (0.13 kg) were added into the aforesaid 100L glass kettle through the solid feeding funnel and stirred for 10~30 minutes and were discharged into a 50 L zinc barrel

for use. Macroporous amine methyl resin (3.25 kg) (purchased from Tianjin Nankai Hecheng Science and Technology Co., Ltd., batch number HA2X1209, load capacity 0.48 mmol/g) were added into the aforesaid 100 L solid phase synthesis reactor through the solid feeding funnel, the temperature was controlled at 20~30 °C, N, N-dimethylformamide (21.00 kg+21.00 kg) and the reaction solution in the zinc barrel of the previous step were add into the solid phase synthesis reactor. The system was subject to thermal insulation reaction, and the solid load was tracked to $\geq 250\mu\text{mol/g}$, and the load detection method was UV. The system was filtered under the pressure of nitrogen, the filter cake was washed with N, N-dimethylformamide for three times (26.00kg+26.10kg+26.00kg), and the filter cake was left in the kettle. CAP.A (50% acetonitrile and 50% acetic anhydride, 4.40kg+4.42kg+4.30kg) and CAP.B (20% pyridine and 30% N-methylimidazole and 50% acetonitrile, 4.40kg+4.40kg+4.47kg) were added into the 80L glass kettle, and stirred for 3~8min before use. This operation was repeated for three times to cap, and acetonitrile (18.00 kg+18.00 kg+18.00 kg+17.50 kg+17.50 kg) was added into the solid phase synthesis kettle. Filter-pressed after nitrogen bubbling for 10~30 min. This operation was repeated for four times, the filter cake was purged in the solid phase synthesis kettle with nitrogen for 2-4 h, and then was transferred to a 50 L filter press tank. The temperature was controlled at 15~30 °C, continued drying, and obtained yellow to white solid product after drying, weight: 3.516 kg.

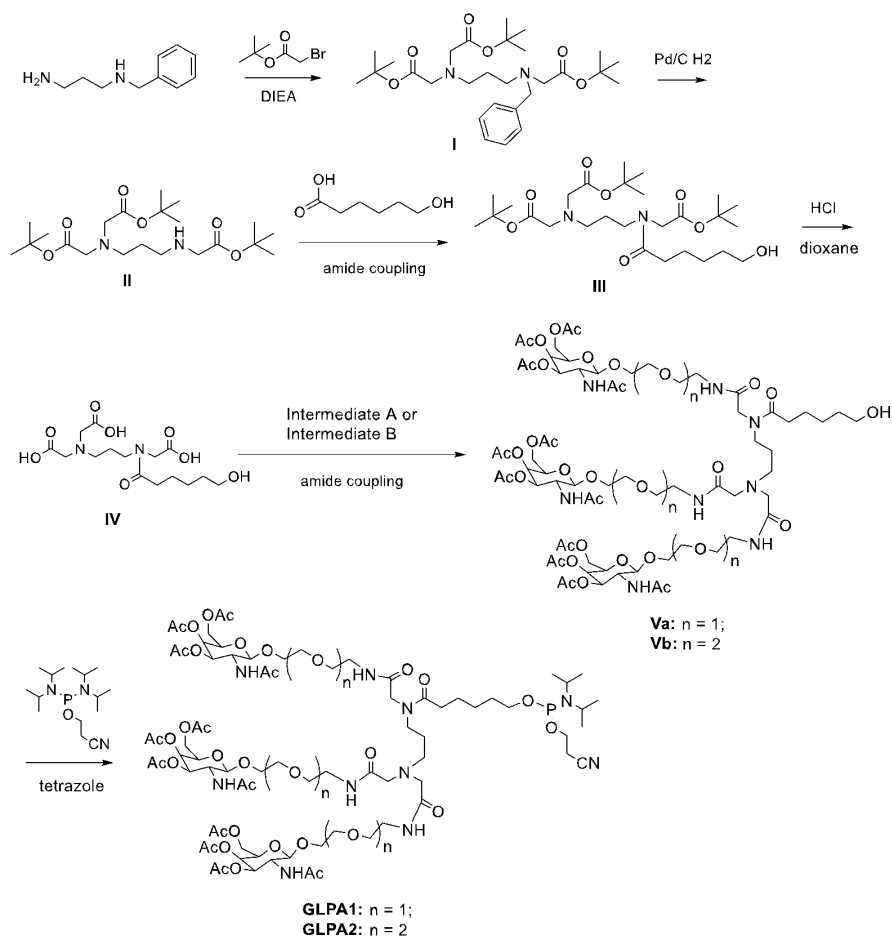
Example 4. Synthesis of HMGCR RNAi Agents.

HMGCR RNAi agent duplexes shown in Table 2-3, above, were synthesized in accordance with the following general procedures:

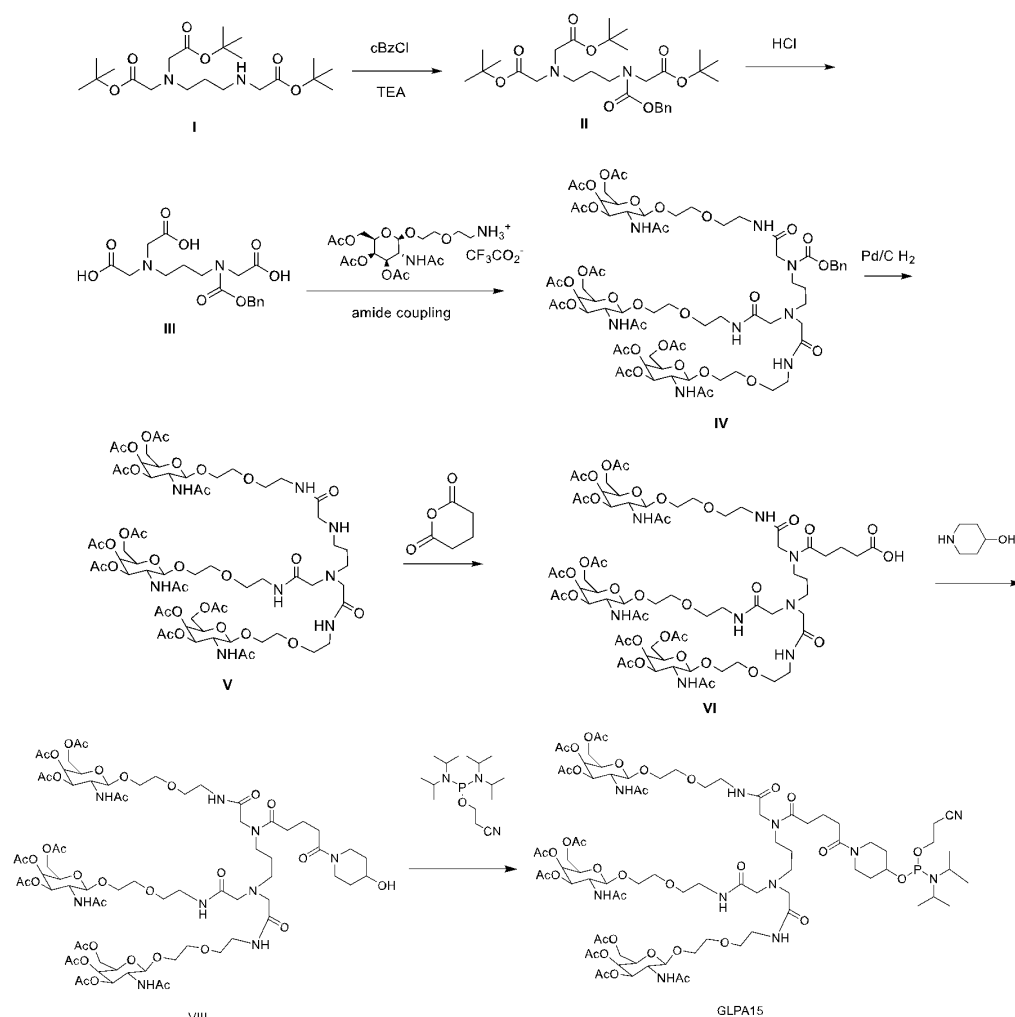
Sense and antisense strand sequences of siRNA were synthesized on oligonucleotide synthesizers using a well-established solid phase synthesis method based on phosphoramidite chemistry. Oligonucleotide chain propagation is achieved through 4-step cycles: a deprotection, a coupling, a capping and an oxidation or a sulfurization step for addition of each nucleotide. Syntheses were performed on a solid support made of controlled pore glass (CPG, 1000 Å). Monomer phosphoramidites may be purchased from commercial sources or may be the phosphoramidite compounds in Examples 1-2 or in WO2023/045995. The phosphoramidite compounds herein may be attached to the 3'-end of a CPG or polystyrene solid support as a monomeric nucleotide. In the case of attachment at the 5'-end, the phosphoramidite compounds may be used for the final coupling reaction, and can be further conjugated to target ligands if necessary.

Phosphoramidites with GalNAc ligand cluster (GLPA1, GLPA2 and GLPA15 as non-limiting examples) were synthesized according to the procedures shown in scheme 1 and scheme 2 or according to the procedures in WO2023/045995. In the case where the GalNAc ligand (GLO-0 as a non-limiting example, wherein GLO-0 refers to the compound GalNAc3 in Jayaprakash, et al., (2014) J. Am. Chem. Soc., 136, 16958–16961.) is attached at 3'-end of sense strand, GalNAc ligand attached CPG solid support was used. In the case where the GalNAc ligand

(GLS-5* or GLS-15* as non-limiting example) is attached at 5'-end of sense strand, a GalNAc phosphoramidite (GLPA1, GLPA2 or GLPA15 as a non-limiting example) was used for the last coupling reaction. Trichloroacetic acid (TCA) 3% in dichloromethane was used for deprotection of 4,4'-dimethoxytrityl protecting group (DMT). 5-Ethylthio-1H-tetrazole was used as an activator. I₂ in THF/Py/H₂O and phenylacetyl disulfide (PADS) in pyridine/MeCN was used for oxidation and sulfurization reactions, respectively. After the final solid phase synthesis step, solid support bound oligomer was cleaved and protecting groups were removed by treating with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution. For the synthesis of siRNAs used for in vitro screening, crude mixture was concentrated. The remaining solid was dissolved in 1.0 M NaOAc, and ice cold EtOH was added to precipitate out the single strand product as the sodium salt, which was used for annealing without further purification. For the synthesis of multi-targeted molecules used for in vivo testing, crude single strand product was further purified by ion pairing reversed phase HPLC (IP-RP-HPLC). Purified single strand oligonucleotide product from IP-RP-HPLC was converted to sodium salt by dissolving in 1.0 M NaOAc and precipitation by addition of ice cold EtOH. Annealing of equimolar complementary sense strand and antisense strand oligonucleotide in water was performed to form the double strand siRNA product, which was lyophilized to afford a fluffy white solid.



Scheme 1



Scheme 2

5 Example 5. *In Vitro* Screening of HMGCR siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 (Invitrogen-11668-019) and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at different concentrations (0.2 nM and 1 nM, 0.5nM and 5nM) in triplicate.

Day 1, psiCHECK(TM)-2 Vector transfection (one plate)

(1) Transfer 2.5 μ g psiCHECK(TM)-2 Vector plasmid into an RNASE free Eppendorf tube (solution mix#1)

(2) Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to $1 \times 10^5/\text{ml}$

(3) Transfer 7.5 μL Lipofectamine 2000 (Invitrogen-11668-019) into solution mix#1 tube, mix.

5 (4) Add solution in Step 3 into cell suspension, mix, and dispense suspension into the 96 well plate (100 $\mu\text{L}/\text{well}$)

Day 2, siRNAs transfection

(1) Dilute Lipofectamine®RNAiMAX Reagent with Opti-MEM® Medium.

(2) Dilute the siRNA with RNA-free water to make $12 \times$ stock.

10 (3) Mix equal volume of diluted RNAiMax and siRNA. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Add 45 μL /well compound Lipofectamine® RNAiMAX(Opti-MEM) mix into 225 μL /well DMEM fresh medium, and discard the supernatants in assay plate, add 120 μL /well compound mix into 96 well plates.

15 (5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

(1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.

(2) Transfer 100 μL cell lysates into a plate, then measure the firefly luminescence.

20 (3) Add 50 μL of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.

(4) Calculate the relative expression

Data analysis

25 Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

% inhibition= $100 - (\text{Ratio of sample well} / \text{the average Ratio of no compound control}) \times 100\%$

30 Table 5 provides experimental results of *in vitro* studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean $\pm$ SD)	
	1 nM	0.2 nM
AV00810	82.69 $\pm$ 0.79	56.87 $\pm$ 4.72

AV00811	76.37 $\pm$ 1.38	52.94 $\pm$ 2.42
AV00812	63.22 $\pm$ 0.79	35.89 $\pm$ 4.98
AV00813	77.39 $\pm$ 1.72	50.36 $\pm$ 2.66
AV00814	63.55 $\pm$ 2.15	37.97 $\pm$ 1.05
AV00815	66.44 $\pm$ 3.75	36.56 $\pm$ 3.21
AV00816	75.40 $\pm$ 2.18	45.76 $\pm$ 7.47
AV00817	47.42 $\pm$ 8.88	25.20 $\pm$ 9.45
AV00818	6.01 $\pm$ 7.57	22.64 $\pm$ 5.57
AV00819	45.30 $\pm$ 1.49	14.05 $\pm$ 6.48
AV00820	44.00 $\pm$ 3.05	11.90 $\pm$ 7.08
AV00821	39.73 $\pm$ 5.65	9.19 $\pm$ 8.83
AV00822	45.93 $\pm$ 2.14	15.25 $\pm$ 7.00
AV00823	35.73 $\pm$ 1.40	6.73 $\pm$ 2.80
AV00824	44.43 $\pm$ 4.88	23.68 $\pm$ 4.36
AV00825	34.36 $\pm$ 5.55	7.53 $\pm$ 14.23
AV00826	46.27 $\pm$ 4.21	28.73 $\pm$ 1.99
AV00828	63.38 $\pm$ 2.01	38.39 $\pm$ 1.37
AV00829	73.86 $\pm$ 3.46	45.29 $\pm$ 5.59
AV00830	61.30 $\pm$ 3.31	30.68 $\pm$ 6.17
AV00831	26.72 $\pm$ 3.85	7.57 $\pm$ 1.56
AV00833	41.86 $\pm$ 3.56	15.83 $\pm$ 9.99
AV00834	39.47 $\pm$ 2.25	4.93 $\pm$ 5.32
AV00835	25.96 $\pm$ 3.13	18.37 $\pm$ 10.93
AV00836	52.32 $\pm$ 5.22	34.59 $\pm$ 6.12
AV00837	32.60 $\pm$ 2.13	11.77 $\pm$ 5.08
AV00838	43.43 $\pm$ 3.41	28.60 $\pm$ 4.86
AV00839	39.27 $\pm$ 2.33	19.28 $\pm$ 5.63
AV00840	48.08 $\pm$ 1.12	26.10 $\pm$ 2.55
AV00841	53.49 $\pm$ 6.40	35.30 $\pm$ 2.24
AV00842	16.00 $\pm$ 7.31	-1.88 $\pm$ 5.01
AV00843	48.08 $\pm$ 6.65	18.33 $\pm$ 4.75
AV00844	22.63 $\pm$ 3.05	0.86 $\pm$ 4.33
AV00845	41.61 $\pm$ 4.94	16.86 $\pm$ 8.45
AV00846	58.88 $\pm$ 1.78	27.40 $\pm$ 2.12
AV00847	44.07 $\pm$ 0.57	23.25 $\pm$ 9.02
AV00848	36.40 $\pm$ 3.16	12.07 $\pm$ 6.40
AV00849	8.34 $\pm$ 5.39	4.98 $\pm$ 6.30
AV00850	31.01 $\pm$ 5.01	15.62 $\pm$ 6.81
AV00851	9.69 $\pm$ 8.19	5.16 $\pm$ 6.25
AV00852	13.75 $\pm$ 2.03	5.03 $\pm$ 7.09
AV00853	9.82 $\pm$ 7.19	-4.48 $\pm$ 13.77
AV00854	17.43 $\pm$ 6.12	-0.18 $\pm$ 2.07
AV00855	8.29 $\pm$ 4.22	7.00 $\pm$ 4.07
AV00856	-1.90 $\pm$ 14.24	-11.02 $\pm$ 12.09
AV00857	7.22 $\pm$ 6.62	-7.75 $\pm$ 4.22

AV00858	26.46±5.05	6.30±4.05
AV00859	14.30±5.03	-2.86±5.08
AV00860	24.93±4.36	5.67±3.55
AV00861	17.48±10.95	10.22±10.96
AV00862	36.76±1.38	17.61±3.09
AV00863	38.84±0.65	19.35±6.25
AV00864	25.48±4.11	11.71±1.64
AV00866	11.64±3.89	0.43±2.21
AV00867	16.09±7.95	5.97±4.54
AV00869	11.49±10.10	1.64±10.62
AV00870	35.18±2.89	5.97±10.17
AV00871	22.24±2.40	12.00±7.08
AV00872	17.68±9.64	5.36±7.01
AV00873	21.52±5.51	2.77±12.92
AV00874	9.98±3.50	9.17±6.66
AV00875	21.91±3.45	6.31±10.56
AV00876	15.38±0.42	6.77±5.81
AV00877	11.08±5.33	0.86±2.68
AV00879	27.70±2.42	3.45±3.96
AV00880	19.91±1.16	-1.54±7.84
AV00881	32.10±3.27	7.97±9.25
AV00882	18.08±5.34	3.35±5.95
AV00883	11.38±8.45	-11.39±4.75
AV00884	15.53±2.53	-1.14±10.43
AV00885	17.44±5.11	-5.89±5.25
AV00886	1.82±1.25	-1.02±22.63
AV00887	32.36±5.08	11.51±5.25
AV00888	34.32±5.28	12.09±4.61
AV00889	2.57±5.67	6.63±7.92
AV00894	8.27±7.00	0.70±7.64
AV00895	6.74±2.58	-4.49±6.69
AV00896	13.15±2.42	2.50±7.71
AV00897	1.68±8.14	-1.99±4.87
AV00898	5.97±4.97	-0.53±1.92
AV00899	13.88±4.39	-3.70±9.45
AV00900	9.36±9.74	6.55±2.30
AV00901	21.49±5.31	-3.94±5.12
AV00902	11.45±7.02	-5.78±5.10
AV00903	7.21±8.19	-1.14±6.56
AV00905	5.62±8.04	0.07±5.61
AV00906	16.07±4.57	3.94±5.32
AV00907	31.11±3.79	5.16±2.79
AV00908	12.21±6.72	7.42±0.53
AV00909	11.84±2.71	8.00±12.25
AV00910	26.26±5.38	7.35±2.67

AV00911	45.90±3.13	28.40±5.81
AV00912	42.60±1.98	25.78±5.65
AV00913	20.76±1.49	0.72±7.04
AV00914	43.24±5.38	9.96±5.03
AV00915	38.07±1.81	17.68±10.56
AV00916	32.98±2.75	18.96±5.67
AV00917	28.65±2.84	11.71±2.94
AV00918	52.57±3.41	32.66±8.42
AV00919	35.55±6.93	6.17±6.25
AV00920	3.15±9.54	9.74±5.41
AV00921	30.58±1.91	8.68±7.59
AV00922	24.77±5.78	7.52±6.03
AV00923	22.01±2.64	6.43±10.28
AV00924	47.83±1.42	19.03±3.36
AV00925	4.30±6.60	0.91±5.46
AV00926	29.11±2.75	17.99±8.36
AV00927	15.41±7.01	1.16±6.07

Table 6 provides experimental results of *in vitro* studies using various HMGCRC RNAi agents to inhibit HMGCRC expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ±SD)	
	1 nM	0.2 nM
AV01321	13.64±7.07	-0.84±9.51
AV01322	47.09±3.44	7.78±9.38
AV01323	41.02±6.24	19.92±8.29
AV01324	66.59±6.95	38.79±5.73
AV01325	76.43±7.22	44.71±2.77
AV01326	39.03±13.45	8.03±8.64
AV01328	13.71±1.43	6.38±7.29
AV01329	8.11±7.07	12.66±7.43
AV01330	13.31±1.34	13.81±3.43
AV01331	58.24±1.74	28.29±4.03
AV01332	13.45±5.27	5.92±11.25
AV01333	38.98±2.21	19.54±2.23
AV01334	24.14±5.00	-2.96±11.89
AV01335	40.27±10.57	12.57±3.54
AV01336	32.07±3.73	10.58±7.65
AV01338	63.27±5.49	26.55±24.80
AV01339	40.00±0.58	15.09±13.78
AV01340	30.41±0.00	-1.09±9.95
AV01341	8.07±9.82	9.75±8.57
AV01342	55.66±6.36	23.32±10.32
AV01343	59.62±7.58	21.78±10.08
AV01344	41.05±1.28	16.60±3.93
AV01345	41.22±1.67	13.92±7.57

AV01346	16.98 $\pm$ 3.24	-2.41 $\pm$ 2.44
AV01347	32.49 $\pm$ 3.49	-9.46 $\pm$ 3.70
AV01348	23.18 $\pm$ 4.92	6.11 $\pm$ 5.67
AV01349	34.62 $\pm$ 4.64	7.15 $\pm$ 1.96
AV01350	41.50 $\pm$ 2.79	14.84 $\pm$ 3.86
AV01351	58.55 $\pm$ 8.88	27.82 $\pm$ 2.47
AV01352	40.09 $\pm$ 4.65	11.78 $\pm$ 4.24
AV01353	44.91 $\pm$ 1.59	11.36 $\pm$ 0.87
AV01360	22.13 $\pm$ 8.18	1.16 $\pm$ 8.55
AV01361	49.72 $\pm$ 9.61	34.62 $\pm$ 7.37
AV01362	39.10 $\pm$ 4.40	16.42 $\pm$ 4.21

Table 7 provides experimental results of *in vitro* studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean $\pm$ SD)	
	1 nM	0.2 nM
AV04242	-2.39 $\pm$ 3.02	-13.56 $\pm$ 4.86
AV04243	27.42 $\pm$ 3.57	-7.74 $\pm$ 3.65
AV04244	55.75 $\pm$ 7.12	-10.75 $\pm$ 1.76
AV04245	42.77 $\pm$ 8.42	-2.50 $\pm$ 7.64
AV04246	78.01 $\pm$ 3.57	26.25 $\pm$ 5.50
AV04247	73.47 $\pm$ 2	31.52 $\pm$ 5.94
AV04248	81.9 $\pm$ 2.41	33.28 $\pm$ 8.47
AV04249	53.75 $\pm$ 1.76	5.95 $\pm$ 0.06
AV04250	58.99 $\pm$ 1.25	19.54 $\pm$ 4.67
AV04251	59.28 $\pm$ 4.2	9.00 $\pm$ 20.48
AV04252	44.31 $\pm$ 4.53	0.79 $\pm$ 21.73
AV04253	32.08 $\pm$ 3.93	5.54 $\pm$ 8.27
AV04254	33.46 $\pm$ 5.99	17.55 $\pm$ 4.93
AV04255	61.85 $\pm$ 2.31	-4.04 $\pm$ 5.34
AV04256	46.19 $\pm$ 5.48	-5.16 $\pm$ 26.30
AV04257	35.09 $\pm$ 0.76	-4.16 $\pm$ 8.10
AV04258	43.89 $\pm$ 0.29	0.57 $\pm$ 2.00
AV04259	61.3 $\pm$ 2.83	14.62 $\pm$ 5.42
AV04260	74.63 $\pm$ 8.59	39.68 $\pm$ 1.37
AV04261	52.23 $\pm$ 7.84	6.08 $\pm$ 13.90
AV04262	49.18 $\pm$ 4.49	-1.04 $\pm$ 7.50
AV04263	25.34 $\pm$ 0.46	-1.69 $\pm$ 1.16
AV04264	51.7 $\pm$ 7.9	3.63 $\pm$ 30.90
AV04265	61.61 $\pm$ 3.17	16.81 $\pm$ 5.50
AV04266	63.45 $\pm$ 0.64	19.54 $\pm$ 0.84
AV04268	20.51 $\pm$ 1.57	-7.25 $\pm$ 0.83
AV04270	58.16 $\pm$ 1.83	35.55 $\pm$ 43.80

AV04271	70.63±3.26	23.43±2.30
AV04272	43.99±7	-3.35±3.70
AV04273	45.35±5.8	-9.74±0.13
AV04274	33.9±8.73	-2.72±4.56
AV04275	29.76±3.83	2.86±7.49
AV04276	18.1±6.89	-5.34±4.37
AV04277	41.46±7.42	-4.48±3.82
AV04278	57.28±3.84	13.44±5.47
AV04280	30.8±0.35	-9.60±3.35
AV04282	52.89±9.27	-1.07±21.66
AV04284	78.47±5.33	47.58±5.23
AV04285	62.9±1.91	25.02±5.27
AV04286	67.82±4.2	30.45±7.95
AV04287	39.39±4.46	11.20±8.12
AV04288	62.79±3.61	15.76±0.33
AV04289	65.93±0.57	18.66±4.65
AV04290	64.08±7.36	31.87±5.67
AV04291	58.62±0.69	36.96±3.54
AV04292	34.71±7.43	9.47±3.18
AV04293	55.95±2.73	17.44±5.41
AV04294	22.94±7.81	2.67±2.25
AV04295	61.14±3.17	24.27±3.12
AV04296	40.79±5.31	9.02±4.09
AV04297	46.03±8.86	17.84±25.19
AV04298	58.1±8.62	1.18±3.49
AV04299	43.43±5.74	-0.35±4.38
AV04300	47.28±2.44	-0.44±6.86
AV04301	55.49±0.8	-1.16±5.61
AV04302	45.37±9.92	-1.92±1.49
AV04303	28.89±5.72	-2.95±7.29
AV04304	33.71±2.57	-3.40±0.42
AV04305	42.47±4.13	8.42±4.21
AV04310	9.77±6.91	-12.20±20.20
AV04311	36.73±3.46	-5.49±3.88
AV04312	34.72±8.28	-5.32±11.11
AV04314	40.93±7	3.19±7.89
AV04315	13.41±4.42	-20.22±8.87
AV04316	40.72±9.58	19.19±5.07
AV04317	22.46±10.8	-20.83±6.26
AV04318	46.26±3.69	20.49±9.69
AV04319	25.06±11.26	-21.53±3.61
AV04320	32.28±5.46	-10.89±1.91
AV04321	40.85±4.37	-1.14±8.63
AV04322	53.51±6.39	8.09±5.41
AV04324	20.89±9.86	2.68±11.57

AV04325	15.91±7.22	-3.98±6.25
AV04328	18.95±5.18	-3.27±9.23
AV04329	22.74±2.84	-8.91±1.77
AV04330	15.72±7.59	0.13±4.86
AV04331	25.07±24.56	-8.02±9.87
AV04332	48.68±5.76	9.01±2.64
AV04335	26.53±1.96	-7.75±0.01
AV04336	12.71±2.69	-23.20±9.63
AV04337	14.7±5.85	-21.58±2.49
AV04340	18.48±0.71	-11.68±2.50
AV04341	26.65±2.03	-10.71±4.22
AV04342	49.15±9.47	16.87±9.89
AV04344	47.95±6.79	16.78±5.92
AV04345	34.69±3.24	-2.48±5.87
AV04346	10.94±1.12	14.16±2.46
AV04347	23.81±1.4	12.20±3.74
AV04348	31.54±5.1	6.10±3.84
AV04349	9.46±5.65	0.84±6.45
AV04350	24.1±8.12	6.58±4.41
AV04352	34.03±0.18	8.52±4.65
AV04354	36.84±8.38	2.28±2.61
AV04355	38.88±6.44	6.46±9.49
AV04356	25.35±3.41	-7.51±0.61
AV04358	13.81±4.97	0.84±9.59
AV04359	13.83±9.61	5.49±5.50
AV04360	34.95±1.85	14.99±5.58
AV04361	15.96±5.22	-7.82±4.41
AV04363	25.52±1.29	-2.52±7.56
AV04365	9.99±6.36	5.47±1.00
AV04366	25.42±3.38	-0.88±2.63
AV04368	31.89±5.17	11.64±5.38
AV04369	18.39±1.86	-7.56±1.80
AV04371	27.28±8.09	-6.28±4.72
AV04373	29.01±4	-4.75±7.77
AV04374	28.97±1.14	-1.47±2.43
AV04375	14.77±5.44	2.75±5.94
AV04377	41.32±5.92	2.13±9.56
AV04382	23.17±3	3.07±3.39
AV04384	33.09±5.22	14.71±2.23
AV04385	48.31±1.15	25.67±0.59
AV04386	16.74±6.66	-1.37±3.01
AV04387	20.79±3.86	4.26±5.61
AV04388	12.78±4.04	-9.04±9.82
AV04389	23.38±4.75	10.88±3.30
AV04390	11.25±6.6	18.73±6.89

AV04391	30.79 $\pm$ 4.28	14.30 $\pm$ 2.86
AV04395	8.86 $\pm$ 7.03	-0.46 $\pm$ 5.95
AV04396	11.05 $\pm$ 4.79	-0.28 $\pm$ 3.39
AV04397	18.15 $\pm$ 8.01	-0.49 $\pm$ 4.84
AV04398	15.23 $\pm$ 0.45	-0.57 $\pm$ 9.44
AV04399	29.89 $\pm$ 2.49	-0.99 $\pm$ 8.41
AV04400	36.85 $\pm$ 4.6	-1.25 $\pm$ 5.33
AV04403	12.64 $\pm$ 8.07	-5.07 $\pm$ 6.69
AV04405	19.55 $\pm$ 5.3	-4.37 $\pm$ 5.42

Table 8 provides experimental results of *in vitro* studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean $\pm$ SD)	
	5 nM	0.5 nM
AV04243	51.74 $\pm$ 3.19	14.66 $\pm$ 12.20
AV04244	54.49 $\pm$ 5.53	-2.91 $\pm$ 7.89
AV04245	52.24 $\pm$ 7.80	-16.88 $\pm$ 8.33
AV04246	79.47 $\pm$ 2.04	21.17 $\pm$ 4.53
AV04247	71.24 $\pm$ 2.80	19.76 $\pm$ 5.54
AV04248	83.34 $\pm$ 1.88	26.66 $\pm$ 6.78
AV04249	70.89 $\pm$ 1.09	18.94 $\pm$ 1.81
AV04250	26.20 $\pm$ 8.84	-28.64 $\pm$ 7.33
AV04251	71.12 $\pm$ 2.43	29.44 $\pm$ 4.44
AV04252	36.94 $\pm$ 3.72	16.49 $\pm$ 3.33
AV04253	18.58 $\pm$ 9.29	11.05 $\pm$ 7.73
AV04254	48.40 $\pm$ 6.45	8.74 $\pm$ 3.10
AV04255	52.76 $\pm$ 6.08	12.70 $\pm$ 4.31
AV04256	47.84 $\pm$ 9.21	-1.21 $\pm$ 4.92
AV04257	63.43 $\pm$ 0.89	6.20 $\pm$ 4.20
AV04258	53.54 $\pm$ 3.87	8.01 $\pm$ 6.62
AV04259	67.12 $\pm$ 7.18	-5.26 $\pm$ 5.65
AV04260	69.83 $\pm$ 2.08	11.82 $\pm$ 9.21
AV04261	48.15 $\pm$ 4.76	-1.93 $\pm$ 5.82
AV04262	52.71 $\pm$ 5.04	13.99 $\pm$ 5.93
AV04263	25.21 $\pm$ 3.50	10.88 $\pm$ 4.14
AV04264	61.40 $\pm$ 8.60	13.93 $\pm$ 1.10
AV04265	75.00 $\pm$ 3.96	16.93 $\pm$ 3.82
AV04266	64.31 $\pm$ 2.71	11.43 $\pm$ 8.90
AV04270	45.86 $\pm$ 9.68	1.62 $\pm$ 1.93
AV04272	35.67 $\pm$ 4.59	11.65 $\pm$ 2.54
AV04273	41.72 $\pm$ 1.08	-1.74 $\pm$ 7.00
AV04274	29.46 $\pm$ 5.76	-1.48 $\pm$ 5.39
AV04275	48.04 $\pm$ 4.75	4.37 $\pm$ 5.25

AV04277	51.52±4.43	10.00±7.37
AV04278	62.73±2.31	9.12±10.82
AV04280	47.80±8.38	-8.30±5.60
AV04282	69.97±3.22	7.65±6.94
AV04284	75.57±3.63	38.29±3.98
AV04285	66.27±1.70	19.96±5.09
AV04286	74.00±4.66	29.42±5.74
AV04287	62.14±1.89	11.82±4.80
AV04288	71.06±1.96	18.25±7.85
AV04289	65.89±2.96	4.97±7.83
AV04290	56.19±4.74	13.77±7.82
AV04291	45.82±4.25	25.55±12.19
AV04292	41.14±6.58	5.65±5.62
AV04293	44.58±4.96	8.31±1.35
AV04295	55.36±2.89	34.10±4.99
AV04296	40.45±9.50	0.50±9.82
AV04297	54.63±3.11	20.01±4.13
AV04298	56.44±2.19	25.99±7.42
AV04299	35.16±3.30	-2.79±3.38
AV04300	44.90±3.49	2.86±15.60
AV04301	50.71±4.89	3.86±8.28
AV04302	36.77±5.26	0.49±2.36
AV04303	42.27±4.33	4.15±8.22
AV04304	28.25±5.04	6.25±5.95
AV04305	45.21±1.36	3.74±6.14
AV04311	38.35±3.77	-0.12±2.35
AV04312	19.38±5.75	15.98±1.44
AV04314	34.22±7.43	16.20±5.18
AV04316	34.82±5.09	16.32±4.16
AV04318	52.42±4.42	16.42±12.71
AV04319	26.17±7.84	16.27±10.18
AV04320	44.91±1.96	16.70±5.28
AV04321	51.41±3.14	17.03±1.50
AV04322	27.89±6.62	-11.33±6.54
AV04331	6.93±1.74	-25.35±7.34
AV04332	42.77±4.80	-8.55±9.04
AV04335	27.78±4.97	-4.78±22.37
AV04341	40.51±1.60	8.56±3.54
AV04342	52.01±5.40	14.82±9.57
AV04344	59.51±2.23	36.97±3.89
AV04345	59.07±2.91	7.57±3.00
AV04348	50.93±4.91	22.22±8.31
AV04352	46.31±6.63	30.66±9.03
AV04354	39.69±2.13	20.49±5.21
AV04355	37.27±4.03	28.99±4.28

AV04356	31.39±7.60	3.38±3.71
AV04360	50.31±6.40	22.64±2.42
AV04363	55.30±5.06	34.39±8.86
AV04366	50.00±3.57	6.49±10.46
AV04368	52.74±3.99	17.89±5.58
AV04371	49.22±3.47	22.01±5.29
AV04373	47.00±5.01	11.43±4.43
AV04374	52.25±4.37	14.45±11.92
AV04377	48.07±4.67	27.25±11.73
AV04384	51.23±4.46	26.41±9.17
AV04385	53.11±2.72	40.95±6.29
AV04391	45.00±8.60	18.46±10.99
AV04399	34.29±11.95	2.35±14.42
AV04400	41.62±5.88	15.16±6.53
AV04415	40.50±5.84	11.05±10.38
AV04416	44.76±5.96	35.44±2.35
AV04417	40.51±7.72	25.13±11.42
AV04424	51.28±6.09	26.95±8.58
AV04429	40.43±5.12	22.93±4.89
AV04431	46.64±2.34	13.54±2.69
AV04456	14.36±4.57	6.22±14.13
AV04457	26.46±2.83	14.70±8.46
AV04458	38.65±0.69	14.85±8.72
AV04459	-3.25±5.43	9.34±15.60
AV04460	33.09±5.59	12.65±5.65
AV04461	37.00±4.26	4.09±4.97
AV04462	43.43±7.40	17.94±4.12
AV04463	41.41±11.55	11.07±5.63
AV04464	36.66±7.65	10.02±13.85
AV04465	17.48±2.65	6.61±7.57
AV04488	15.65±11.35	-1.39±0.54
AV04489	10.07±4.75	3.17±6.33
AV04490	9.62±5.89	-2.39±7.88
AV04491	43.60±4.15	22.16±6.13
AV04492	44.40±11.63	18.64±5.03
AV04493	48.50±9.07	25.13±6.16
AV04494	24.48±4.44	-8.12±11.72
AV04495	32.28±8.28	6.20±6.30
AV04496	26.71±6.55	1.92±0.87
AV04497	45.55±3.81	13.13±4.18
AV04499	56.06±2.06	31.07±6.88
AV04500	51.80±3.56	36.87±4.29
AV04501	56.02±2.46	25.64±14.17
AV04502	52.89±4.75	24.49±4.11
AV04503	50.79±5.74	28.51±6.66

AV04504	39.10±12.62	12.43±4.13
AV04508	43.71±10.31	21.74±9.03
AV04510	48.51±1.44	28.21±4.26
AV04511	45.91±3.36	23.93±6.49
AV04512	56.20±3.74	43.36±3.20
AV04516	48.04±6.19	37.25±2.09
AV04519	54.14±3.71	40.62±1.54
AV04525	50.96±3.08	30.63±8.29
AV04526	56.83±4.12	39.60±4.32
AV04527	47.34±7.98	38.40±6.39
AV04528	47.35±2.65	23.27±5.07
AV04530	41.02±5.36	30.49±9.48

Huh7 cells were trypsinized and adjusted to appropriate density seeded into 96-well plates. Cells were transfected with the complexes of psiCHECK(TM)-2 Vector plasmid, blank vector pCNDNA 3.0, siRNAs or a control siRNA using Lipofectamine 2000 (Invitrogen-11668-019) at the next day of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at different concentrations (0.2 nM and 1 nM) in triplicate.

Day 1, Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to 1×10^5 /ml and culture with DMEM medium.

Day 2, psiCHECK(TM)-2 Vector/blank vector pCDNA3.0/siRNAs/ Lipofectamine 2000 mixture transfection.

(1) Mix appropriate Lipofectamine 2000 (Invitrogen-11668-019) with Opti-MEM® Medium (solution mix#1). Final equal 0.3 µl Lipofectamine 2000 and Opti-MEM® Medium 4.7 µl per well.

(2) Mix appropriate psiCHECK(TM)-2 Vector, blank pCNDNA 3.0 vector and siRNAs with Opti-MEM® Medium (solution mix#2).

(3) Mix equal volume of solution mix#1 and mix#2 (mix#3), final 10 µl per well. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Remove DMEM medium, add 10 µl mixed solution mix#3 and 90 µl fresh DMEM medium.

(5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and blank vector pCNDNA 3.0 and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

(1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.

(2) Transfer 100 µl cell lysates into a plate, then measure the firefly luminescence.

(3) Add 50µl of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.

(4) Calculate the relative expression

5 Data analysis

Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

10 % inhibition= 100-(Ratio of sample well/ the average Ratio of no compound control) ×100%

Table 9 provides experimental results of *in vitro* studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ±SD)	
	1 nM	0.2 nM
AV06076	72.62±1.88	36.19±4.64
AV06077	93.98±0.54	81.16±1.13
AV06078	88.52±0.75	67.58±2.10
AV06079	96.76±0.38	90.93±0.25
AV06080	96.31±0.16	93.40±0.35
AV06081	75.24±1.57	35.69±3.70
AV06082	85.37±0.92	52.56±5.28
AV06083	28.48±3.40	3.46±4.79
AV06084	62.07±2.37	34.19±3.85
AV06085	37.82±6.17	32.57±4.74
AV06086	61.72±1.29	15.77±10.63
AV06087	26.27±2.68	16.30±4.72
AV06088	18.06±8.25	21.60±6.95
AV06089	69.96±2.07	27.37±4.72
AV06090	53.45±5.18	17.25±1.88
AV06091	38.09±4.67	10.27±3.34
AV06117	30.18±1.95	6.76±7.24
AV06118	17.21±3.91	-0.43±9.93
AV06119	26.00±0.88	1.95±9.74
AV06120	42.94±3.19	9.71±6.12
AV06128	39.86±1.13	10.35±2.14
AV06129	45.11±1.86	16.29±1.99
AV06130	-2.55±3.75	-1.30±5.51
AV06131	39.03±3.85	7.45±5.85

AV06132	52.81±3.40	4.54±1.61
AV06133	3.09±7.93	6.96±7.42
AV06134	17.10±0.76	7.32±2.77
AV06135	11.34±9.25	0.38±2.96
AV06136	7.37±2.95	-0.89±1.29
AV06137	56.67±4.33	9.90±1.75
AV06138	78.05±1.76	37.41±1.17
AV06139	16.17±7.22	-2.62±8.02
AV06140	17.44±3.42	1.30±3.40
AV06141	79.73±3.48	54.20±1.66
AV06142	58.48±1.50	13.12±6.40
AV06143	61.74±2.09	19.41±5.54
AV06144	79.46±1.12	41.57±2.05
AV06145	32.43±1.64	1.80±5.38
AV06146	73.24±0.33	33.71±7.53
AV06147	27.16±1.99	-3.48±6.00
AV06148	44.68±3.26	7.77±5.33
AV06149	30.62±2.94	3.29±5.24
AV06150	54.69±2.15	10.17±1.72
AV06151	26.66±5.25	13.62±0.97
AV06152	82.88±1.18	41.90±5.98
AV06153	59.27±2.98	21.46±4.22
AV06154	72.05±0.87	27.52±3.85
AV06155	84.96±0.27	57.24±0.25
AV06156	67.96±1.07	22.02±6.18
AV06157	64.73±4.58	41.28±0.80
AV06158	88.57±0.53	74.03±2.27
AV06159	85.73±0.87	59.21±1.55
AV06160	70.18±2.89	34.74±4.97
AV06161	49.79±4.29	33.11±3.97
AV06162	79.61±1.00	54.38±2.34
AV06163	87.24±0.83	74.48±0.08
AV06164	80.86±0.18	57.58±0.63
AV06165	77.56±1.97	45.75±1.55
AV06166	90.01±0.63	66.33±1.60
AV06167	54.84±1.09	31.58±4.91
AV06168	68.92±0.76	35.60±6.88
AV06169	82.77±2.11	61.22±2.59
AV06170	72.37±2.29	36.56±4.99
AV06171	80.27±0.44	47.59±2.47
AV06172	84.77±0.28	57.43±2.86
AV06173	58.72±3.24	21.51±4.00
AV06174	88.76±0.32	70.14±2.66

AV06175	70.58 $\pm$ 4.15	40.86 $\pm$ 2.70
AV06176	56.76 $\pm$ 2.80	34.86 $\pm$ 1.90
AV06177	70.98 $\pm$ 2.78	35.79 $\pm$ 3.14
AV06178	80.78 $\pm$ 1.79	60.62 $\pm$ 0.98
AV06179	75.12 $\pm$ 0.56	50.03 $\pm$ 2.12
AV06180	78.33 $\pm$ 1.46	45.54 $\pm$ 2.72
AV06181	89.40 $\pm$ 0.74	67.20 $\pm$ 1.08
AV06182	78.45 $\pm$ 2.09	42.72 $\pm$ 7.60
AV06183	80.49 $\pm$ 2.15	49.01 $\pm$ 4.70
AV06184	68.29 $\pm$ 1.48	27.16 $\pm$ 8.89
AV06185	40.93 $\pm$ 2.51	16.40 $\pm$ 4.22
AV06186	74.55 $\pm$ 0.86	29.33 $\pm$ 5.21
AV06187	55.17 $\pm$ 2.26	29.18 $\pm$ 1.36
AV06188	80.74 $\pm$ 0.75	55.43 $\pm$ 3.17
AV06189	66.31 $\pm$ 2.03	28.06 $\pm$ 2.31
AV06190	10.92 $\pm$ 5.54	4.43 $\pm$ 3.84
AV06191	70.36 $\pm$ 3.66	37.56 $\pm$ 1.92
AV06192	38.64 $\pm$ 2.70	14.55 $\pm$ 4.47
AV06193	75.21 $\pm$ 1.88	50.42 $\pm$ 2.15
AV06194	57.71 $\pm$ 2.28	31.04 $\pm$ 3.08
AV06195	15.63 $\pm$ 3.58	4.72 $\pm$ 0.28
AV06196	73.97 $\pm$ 0.78	29.85 $\pm$ 8.15
AV06197	50.08 $\pm$ 2.00	18.76 $\pm$ 4.30
AV06198	71.07 $\pm$ 3.03	41.88 $\pm$ 3.78
AV06199	56.87 $\pm$ 2.68	18.84 $\pm$ 12.56
AV06200	71.46 $\pm$ 2.50	23.86 $\pm$ 3.56
AV06201	23.34 $\pm$ 1.57	7.51 $\pm$ 8.08
AV06203	75.98 $\pm$ 1.92	32.77 $\pm$ 1.74
AV06204	83.90 $\pm$ 0.45	49.45 $\pm$ 3.97
AV06205	88.15 $\pm$ 0.33	66.39 $\pm$ 2.07
AV06206	84.01 $\pm$ 1.48	63.06 $\pm$ 0.11
AV06207	12.99 $\pm$ 5.35	5.76 $\pm$ 0.67
AV06208	31.00 $\pm$ 5.37	13.98 $\pm$ 3.91
AV06209	86.83 $\pm$ 0.69	73.61 $\pm$ 1.68
AV06210	83.70 $\pm$ 0.60	73.27 $\pm$ 1.69
AV06211	75.85 $\pm$ 3.47	48.55 $\pm$ 1.48
AV06212	71.36 $\pm$ 0.35	43.55 $\pm$ 8.47
AV06213	90.95 $\pm$ 0.45	78.63 $\pm$ 1.31
AV06214	82.59 $\pm$ 0.21	54.27 $\pm$ 3.67
AV06215	90.30 $\pm$ 0.48	67.12 $\pm$ 3.12
AV06216	82.80 $\pm$ 0.65	54.35 $\pm$ 2.25
AV06217	90.81 $\pm$ 0.16	62.97 $\pm$ 2.58
AV06218	78.64 $\pm$ 0.58	42.23 $\pm$ 5.57

AV06219	89.61±0.51	68.98±1.06
AV06220	66.03±2.15	31.64±3.64
AV06221	62.62±1.95	49.41±1.20
AV06222	88.40±0.47	77.30±2.01
AV06223	75.44±2.06	48.17±0.71
AV06224	82.70±1.50	67.68±1.18
AV06225	87.15±0.22	73.90±1.64
AV06226	84.37±2.08	76.10±1.50

Example 6 *In Vivo* testing of HMGCR siRNA Duplexes

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human HMGCR and luciferase gene. At day 8, mice were subcutaneously administered a single 3 mg/kg of HMGCR siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 15 and at the terminal day 22. Serum samples were collected, and luciferase activity of serum samples was measured per manufacturer's recommended protocol. The results are shown in Tables 10.

Table 10 provides experimental results of *in vivo* studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean ± SD)	D22 remaining percent relative to D8 (Mean ±SD)	Dosage (mg/kg)
AD00619	0.12 ±0.04	0.14 ±0.05	3
AD00620	0.12 ±0.03	0.15 ±0.05	3
AD00621	0.07 ±0.02	0.11 ±0.02	3
AD00622	0.16 ±0.07	0.23 ±0.10	3
AD00623	0.23 ±0.12	0.24 ±0.06	3
AD00624	0.56 ±0.20	0.36 ±0.11	3
AD00625	0.43 ±0.12	0.38 ±0.07	3
AD00626	0.21 ±0.03	0.43 ±0.32	3
AD00627	0.34 ±0.09	0.42 ±0.20	3
AD00628	0.27 ±0.07	0.19 ±0.06	3
AD00629	0.30 ±0.07	0.31 ±0.05	3
AD00630	0.26 ±0.06	0.27 ±0.10	3
AD00631	0.28 ±0.14	0.30 ±0.13	3
AD00632	0.33 ±0.09	0.27 ±0.15	3

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human

HMGCR and luciferase gene. At day 8, mice were subcutaneously administered a single 2 mg/kg or a single 1 mg/kg of HMGCR siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 15 and at the terminal day 22. Serum samples were collected, and luciferase activity of serum samples was measured per manufacturer's recommended protocol. The results are shown in Tables 11-16.

Table 11 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD00611	0.41 $\pm$ 0.08	1.12 $\pm$ 0.25	2
AD00619	0.16 $\pm$ 0.02	0.21 $\pm$ 0.06	2
AD00842	0.09 $\pm$ 0.01	0.14 $\pm$ 0.02	2
AD00844	0.10 $\pm$ 0.01	0.18 $\pm$ 0.03	2
AD00845	0.13 $\pm$ 0.02	0.25 $\pm$ 0.05	2
AD00846	0.21 $\pm$ 0.02	0.24 $\pm$ 0.04	2
AD00847	0.20 $\pm$ 0.02	0.23 $\pm$ 0.06	2
AD00849	0.28 $\pm$ 0.08	0.23 $\pm$ 0.09	2
AD00850	0.10 $\pm$ 0.02	0.15 $\pm$ 0.06	2
AD00851	0.16 $\pm$ 0.02	0.19 $\pm$ 0.01	2
AD00852	0.07 $\pm$ 0.01	0.10 $\pm$ 0.03	2
AD00853	0.29 $\pm$ 0.08	0.29 $\pm$ 0.10	2
AD00854	0.36 $\pm$ 0.05	0.32 $\pm$ 0.11	2
AD00855	0.17 $\pm$ 0.03	0.23 $\pm$ 0.04	2
AD00856	0.25 $\pm$ 0.02	0.24 $\pm$ 0.05	2
AD00857	0.33 $\pm$ 0.07	0.30 $\pm$ 0.06	2
AD00858	0.14 $\pm$ 0.02	0.15 $\pm$ 0.02	2
AD00859	0.53 $\pm$ 0.09	0.75 $\pm$ 0.10	2
AD00860	0.20 $\pm$ 0.02	0.31 $\pm$ 0.07	2
AD00861	0.32 $\pm$ 0.03	0.37 $\pm$ 0.16	2
AD00862	0.57 $\pm$ 0.08	0.44 $\pm$ 0.14	2
AD00863	0.31 $\pm$ 0.05	0.30 $\pm$ 0.06	2

Table 12 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD00621	0.14 $\pm$ 0.07	0.20 $\pm$ 0.13	2
AD00843	0.13 $\pm$ 0.07	0.10 $\pm$ 0.01	2
AD00848	0.1 $\pm$ 0.09	0.17 $\pm$ 0.11	2
AD01021	0.17 $\pm$ 0.04	0.19 $\pm$ 0.05	2
AD01022	0.22 $\pm$ 0.14	0.43 $\pm$ 0.06	2
AD01023	0.18 $\pm$ 0.1	0.34 $\pm$ 0.14	2
AD01024	0.15 $\pm$ 0.03	0.2 $\pm$ 0.09	2
AD01025	0.31 $\pm$ 0.05	0.66 $\pm$ 0.24	2
AD01026	0.09 $\pm$ 0.06	0.24 $\pm$ 0.07	2

Table 13 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD02071	0.2 $\pm$ 0.02	0.23 $\pm$ 0.05	2
AD02067	0.23 $\pm$ 0.07	0.16 $\pm$ 0.02	2
AD02066	0.32 $\pm$ 0.01	0.21 $\pm$ 0.02	2
AD02069	0.35 $\pm$ 0.06	0.16 $\pm$ 0.03	2
AD02073	0.41 $\pm$ 0.07	0.42 $\pm$ 0.14	2
AD02074	0.48 $\pm$ 0.13	0.58 $\pm$ 0.13	2
AD02068	0.53 $\pm$ 0.14	0.42 $\pm$ 0.14	2
AD02070	0.58 $\pm$ 0.13	0.26 $\pm$ 0.09	2
AD02072	1.32 $\pm$ 0.35	0.71 $\pm$ 0.11	2

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Table 14 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD02039	0.76 $\pm$ 0.23	0.87 $\pm$ 0.17	2
AD02040	0.18 $\pm$ 0.03	0.15 $\pm$ 0.03	2
AD02041	0.19 $\pm$ 0.04	0.09 $\pm$ 0.02	2
AD02042	0.57 $\pm$ 0.15	0.16 $\pm$ 0.03	2

AD02043	0.68±0.32	0.21±0.06	2
AD02044	0.33±0.04	0.16±0.05	2
AD02046	0.49±0.06	0.16±0.05	2
AD02047	0.3±0.09	0.16±0.02	2
AD02048	0.42±0.07	0.33±0.08	2
AD02049	0.42±0.06	0.4±0.11	2
AD02050	0.3±0.06	0.46±0.15	2
AD02051	0.23±0.07	0.24±0.07	2
AD02052	0.42±0.16	0.25±0.15	2
AD02053	0.32±0.05	0.17±0.03	2
AD02054	0.43±0.12	0.22±0.03	2
AD02055	0.34±0.07	0.09±0.03	2
AD02056	0.27±0.05	0.15±0.02	2
AD02057	0.59±0.13	0.14±0.04	2
AD02058	0.31±0.07	0.2±0.08	2
AD02059	0.18±0.04	0.2±0.03	2
AD02060	0.2±0.05	0.23±0.05	2
AD02061	0.36±0.09	0.13±0.01	2
AD02062	0.46±0.13	0.52±0.19	2
AD02063	0.51±0.19	0.33±0.1	2
AD02064	0.62±0.14	0.15±0.04	2
AD02065	0.86±0.12	0.48±0.13	2

Table 15 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean ± SD)	D22 remaining percent relative to D8 (Mean ± SD)	Dosage (mg/kg)
Saline	1±0.21	1±0.09	/
AD00850	0.46±0.11	0.41±0.22	1
AD02303	0.41±0.09	0.75±0.22	1
AD02302	0.47±0.15	0.3±0.08	1
AD02304	0.53±0.17	0.48±0.15	1
AD02305	0.54±0.19	0.35±0.12	1
AD02306	0.68±0.16	0.79±0.13	1
AD02310	0.78±0.22	0.68±0.19	1
AD02311	1.06±0.35	0.91±0.11	1

AD02307	1.44±0.36	2.16±0.27	1
AD02308	1.81±0.73	1.28±0.58	1
AD02309	1.91±0.55	2.27±0.87	1

Table 16 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean ± SD)	D22 remaining percent relative to D8 (Mean ± SD)	Dosage (mg/kg)
Saline	1±0.15	1±0.36	/
AD02312	0.42±0.14	0.33±0.18	1
AD02313	0.51±0.15	0.71±0.27	1
AD02314	0.62±0.15	0.34±0.06	1

5

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human HMGCR and luciferase gene. At day 8, mice were subcutaneously administered a single 1 mg/kg of HMGCR siRNA agents or Saline. Blood samples were collected at day 8, before dosing of siRNA, at day 21 and at the terminal day 28. Serum samples were collected, and luciferase activity of serum samples was measured per manufacturer's recommended protocol. The results are shown in Tables 17-18.

Table 17 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

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Duplex AD#	D21 remaining percent relative to D8 (Mean ± SD)	D28 remaining percent relative to D8 (Mean ± SD)	Dosage (mg/kg)
Saline	1±0.11	1±0.11	/
AD00850	0.62±0.12	0.42±0.11	1
AD00619	0.37±0.07	0.32±0.07	1
AD00620	0.28±0.12	0.16±0.05	1
AD00621	0.2±0.03	0.16±0.01	1
AD00622	0.63±0.03	0.43±0.13	1
AD00842	0.42±0.08	0.2±0.07	1
AD00843	0.29±0.15	0.29±0.05	1
AD00844	0.35±0.1	0.18±0.04	1
AD00845	0.54±0.16	0.3±0.1	1
AD00848	0.32±0.06	0.52±0.11	1

AD00851	0.18±0.06	0.26±0.06	1
AD00852	0.15±0.03	0.11±0.03	1
AD00858	0.27±0.04	0.21±0.06	1
AD01021	0.53±0.17	0.21±0.06	1
AD01023	0.33±0.04	0.35±0.12	1
AD01024	0.34±0.07	0.36±0.04	1
AD01026	0.15±0.02	0.19±0.02	1
AD02040	0.16±0.04	0.2±0.07	1
AD02041	0.24±0.05	0.19±0.02	1
AD02044	0.66±0.15	0.62±0.13	1
AD02047	0.33±0.04	0.61±0.14	1
AD02051	0.46±0.11	0.59±0.09	1
AD02053	0.53±0.13	0.73±0.19	1
AD02055	0.29±0.03	0.18±0.02	1
AD02056	0.69±0.26	0.82±0.39	1
AD02058	0.31±0.06	0.32±0.03	1
AD02059	0.29±0.04	0.14±0.04	1
AD02060	0.3±0.15	0.15±0.05	1
AD02061	0.34±0.07	0.22±0.01	1
AD02302	0.32±0.05	0.3±0.09	1
AD02303	0.58±0.12	0.45±0.04	1
AD02305	0.58±0.22	0.48±0.13	1

Table 18 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean ± SD)	D22 remaining percent relative to D8 (Mean ± SD)	Dosage (mg/kg)
Saline	1±0.16	1±0.08	/
AD00863	0.68±0.17	1.91±0.24	1
AD02067	0.85±0.09	0.99±0.14	1
AD02071	0.56±0.15	0.83±0.14	1
AD02312	0.45±0.17	0.53±0.07	1

5

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human HMGCR and luciferase gene. At day 8, mice were subcutaneously administered a single 1 mg/kg of HMGCR siRNA agents or Saline. Blood samples were collected at day 8, before

dosing of siRNA, at day 15 and at the terminal day 22. Plasma samples were collected, and luciferase activity of plasma samples was measured per manufacturer's recommended protocol. The results are shown in Tables 19.

- 5 Table 19 provides experimental results of in vivo studies using various HMGCR RNAi agents to inhibit HMGCR expression. The duplex sequences used correspond to those shown in Table 3.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
Saline	1 $\pm$ 0.1	1 $\pm$ 0.05	/
AD02602	0.19 $\pm$ 0.04	0.16 $\pm$ 0.02	1
AD02603	0.12 $\pm$ 0.02	0.11 $\pm$ 0.02	1
AD02604	0.22 $\pm$ 0.09	0.14 $\pm$ 0.05	1
AD02605	0.19 $\pm$ 0.04	0.09 $\pm$ 0.02	1
AD02606	0.2 $\pm$ 0.02	0.16 $\pm$ 0.03	1
AD02607	0.2 $\pm$ 0.06	0.05 $\pm$ 0.02	1
AD02608	0.35 $\pm$ 0.11	0.23 $\pm$ 0.06	1
AD02609	0.37 $\pm$ 0.1	0.11 $\pm$ 0.02	1
AD02610	0.33 $\pm$ 0.09	0.12 $\pm$ 0.04	1
AD02611	0.14 $\pm$ 0.02	0.08 $\pm$ 0.02	1
AD02612	0.22 $\pm$ 0.02	0.09 $\pm$ 0.04	1
AD02613	0.44 $\pm$ 0.07	0.29 $\pm$ 0.03	1
AD02614	0.2 $\pm$ 0.05	0.19 $\pm$ 0.03	1
AD02615	0.39 $\pm$ 0.09	0.3 $\pm$ 0.11	1
AD02616	0.16 $\pm$ 0.03	0.1 $\pm$ 0.03	1

Equivalents

- 10 Although several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art
- 15 will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific
- 20 embodiments of the invention described herein. It is, therefore, to be understood that the

foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto; the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any
5 combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary
10 meanings of the defined terms.

The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

The term "or" as used herein means "and/or," and is used interchangeably with the latter, unless clearly excluded from context. The phrase "and/or," as used herein in the
15 specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. If there are more than two elements and are separated by commas, the commas before "and/or" have the same meaning as "and/or", correspondingly representing "and" or "or". Other elements may optionally be present other than the elements specifically
20 identified by the "and/or" clause, whether related or unrelated to those elements specifically identified, unless clearly indicated to the contrary.

All references, patents and patent applications and publications that are cited or referred to in this application are incorporated herein in their entirety herein by reference.

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.
2. The dsRNA agent of claim 1, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.
3. The dsRNA agent of claim 1, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.
4. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to an HMGCR RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand.
5. The dsRNA agent of claim 4, wherein the region of complementarity to an HMGCR RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3.
6. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent including a sense strand and an antisense strand, wherein the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and preferably the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3.
7. The dsRNA agent of claim 6, wherein the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the dsRNA

agent, preferably, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3.

8. The dsRNA agent of any one of claims 1-7, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

9. The dsRNA of any one of claims 1-8, wherein the dsRNA agent comprises at least one modified nucleotide.

10. The dsRNA agent of any one of claims 1-9, wherein all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

11. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HMGCR, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand sequence may be represented by formula (I):



wherein:

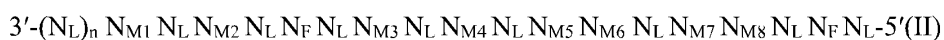
each N'_F represents a 2'-fluoro-modified nucleotide;

each N'_{N1} , N'_{N2} , N'_{N3} , N'_{N4} , N'_{N5} , and N'_{N6} independently represents a modified or unmodified nucleotide;

each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;

and m' and n' are each independently an integer of 0 to 7.

12. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding HMGCR, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand sequence may be represented by formula (II):



wherein:

each N_F represents a 2'-fluoro-modified nucleotide;

each N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N_{M6} , N_{M7} and N_{M8} independently represents a modified or unmodified nucleotide;

each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;

and n is an integer of 0 to 7.

- 5 13. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to an mRNA encoding HMGCR,
- 10 wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex represented by formula (III):

sense: 5'-(N'_L) $_n$ N'_L N'_L N'_L N'_{N1} N'_{N2} N'_{N3} N'_L N'_F N'_L N'_{N4} N'_{N5} N'_{N6} N'_L N'_L N'_L (N'_L) $_m$ -3'
 antisense: 3'-(N_L) $_n$ N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} N_L N_{M4} N_L N_{M5} N_{M6} N_L N_{M7} N_{M8} N_L N_F N_L -5'

(III)

- 15 wherein:
- each strand is independently about 17 to about 30 nucleotides in length;
- each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide;
- N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N_{M6} , N_{M7} , N_{M8} , N'_{N1} , N'_{N2} , N'_{N3} , N'_{N4} , N'_{N5} , and N'_{N6} each independently represents a modified or unmodified nucleotide;
- 20 each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide;
- and m' , n' and n are each independently an integer of 0 to 7.

14. The dsRNA agent of any one of claims 9-13, wherein the one or more modified nucleotides
- 25 are independently selected from the group consisting of: a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, a 2'-deoxy nucleotide, a 2'3'-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2'-F-Arabino nucleotide, a 2'-methoxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2'-Ome
- 30 nucleotide, an inverted 2'-deoxy nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a mopholino nucleotide, a 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

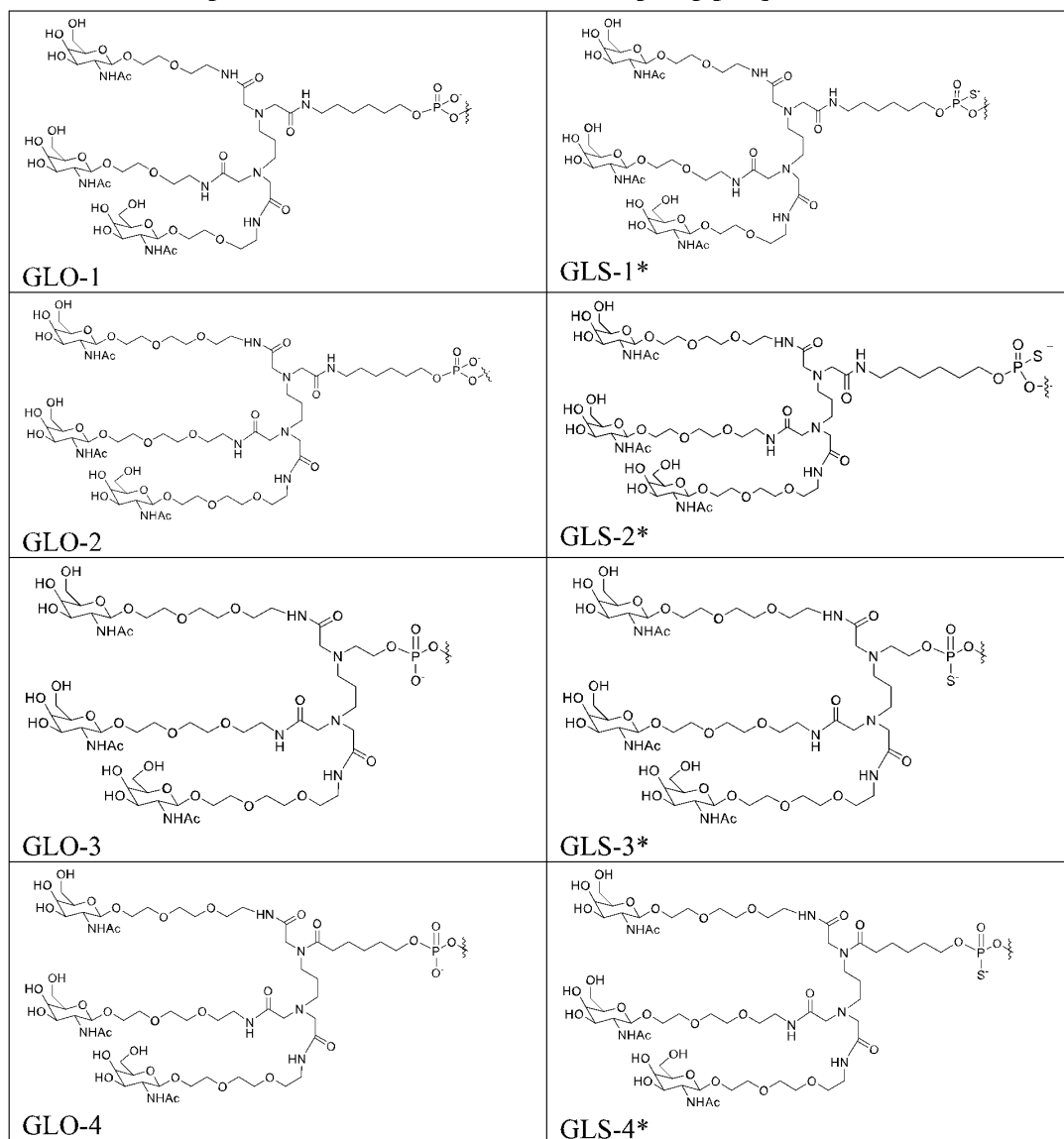
- 35 15. The dsRNA agent of any one of claims 1-14, comprises an E-vinylphosphonate nucleotide at the 5' end of the guide strand.

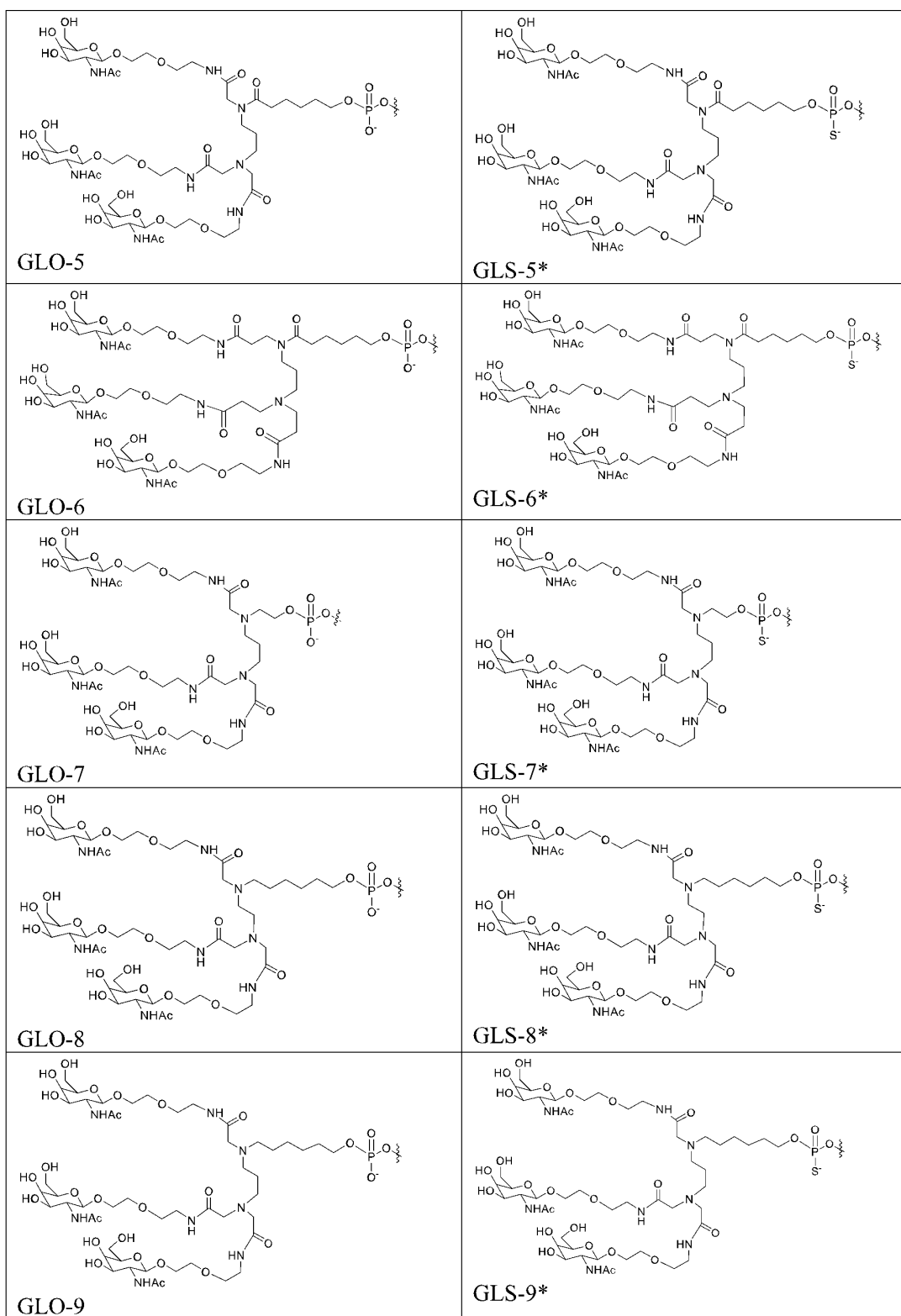
16. The dsRNA agent of any one of claims 1-15, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage.
17. The dsRNA agent of any one of claims 1-15, wherein the sense strand comprises at least one phosphorothioate internucleoside linkage.
18. The dsRNA agent of any one of claims 1-15, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage.
19. The dsRNA agent of any one of claims 1-15, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
20. The dsRNA agent of any one of claims 1-15, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
21. The dsRNA agent of any one of claims 1-20, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3.
22. The dsRNA agent of any one of claims 1-20, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.
23. The dsRNA agent of any one of claims 1-22, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length.
24. The dsRNA agent of any one of claims 1-23, wherein the region of complementarity is 19-21 nucleotides in length.
25. The dsRNA agent of any one of claims 1-24, wherein each strand is no more than 30 nucleotides in length.
26. The dsRNA agent of any one of claims 1-24, wherein each strand is no more than 25 nucleotides in length.
27. The dsRNA agent of any one of claims 1-24, wherein each strand is no more than 23 nucleotides in length.
28. The dsRNA agent of any one of claims 1-27, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups.

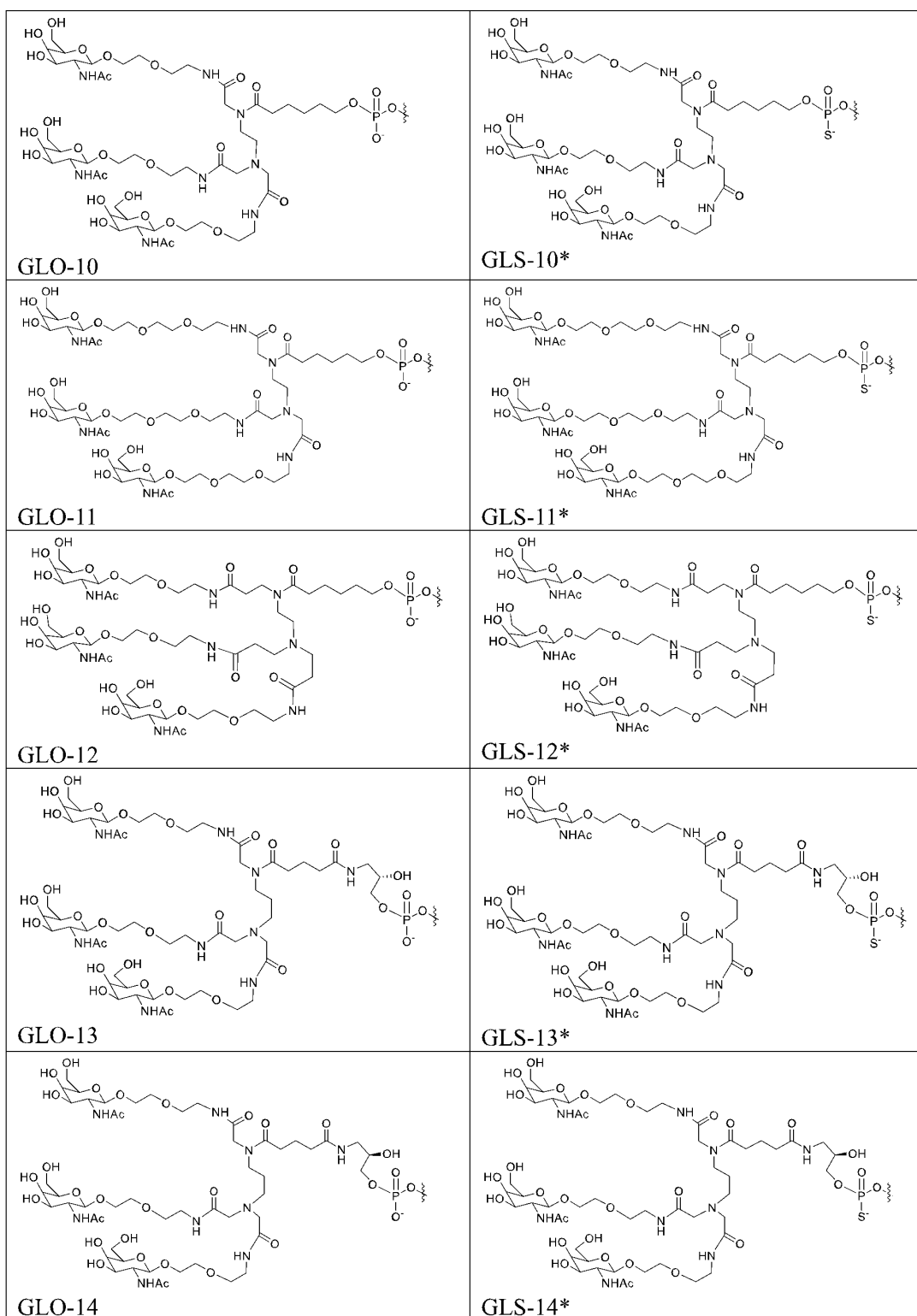
29. The dsRNA agent of claim 28, wherein the one or more targeting groups or linking groups are conjugated to the sense strand.

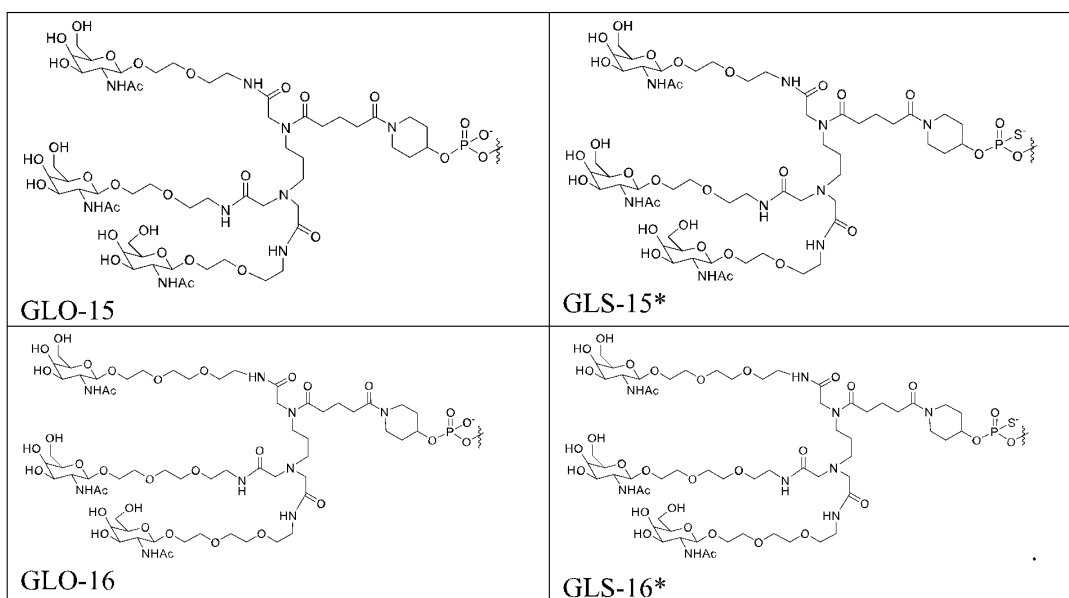
30. The dsRNA agent of claim 28 or 29, wherein the targeting group or linking group
5 comprises N-acetyl-galactosamine (GalNAc).

31. The dsRNA agent of claim 28 or 29, wherein the targeting group has a structure:









32. The dsRNA agent of any one of claims 1-31, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand.

5 33. The dsRNA agent of any one of claims 1-31, wherein the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.

34. The dsRNA agent of any one of claims 1-31, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end.

10

35. The dsRNA agent of any one of claims 1-31, wherein the sense strand comprises one or two inverted abasic residues or imann residues at 3' or/and 5' terminal end.

36. The dsRNA agent of any one of claims 1-35, wherein the dsRNA agent has two blunt ends.

15

37. The dsRNA agent of any one of claims 1-35, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

38. The dsRNA agent of any one of claims 1-35, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

20

39. A composition comprising a dsRNA agent of any one of claims 1-38.

40. The composition of claim 39, further comprising a pharmaceutically acceptable carrier.

25

41. The composition of claim 40, further comprising one or more additional therapeutic agents.
42. The composition of claim 41, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial.
- 5 43. The composition of any one of claims 39-42, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.
- 10 44. A cell comprising a dsRNA agent of any one of claims 1-38, optionally, the cell is a mammalian cell, optionally a human cell.
45. A method of inhibiting the expression of an HMGCR gene in a cell, the method comprising:
- 15 (i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-38 or a composition of any one of claims 39-43.
46. The method of claim 45, further comprising:
- (ii) maintaining the cell prepared in claim 45(i) for a time sufficient to obtain degradation of the mRNA transcript of an HMGCR gene, thereby inhibiting expression of the
- 20 HMGCR gene in the cell.
47. The method of any one of claims 45-46, wherein the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously.
- 25 48. The method of any one of claims 45-46, wherein the cell is in a subject and the dsRNA agent is administered to the subject by IV administration.
49. The method of claim 47 or 48, further comprising assessing inhibition of the HMGCR gene, following the administration of the dsRNA agent to the subject, wherein a means for the
- 30 assessing comprises:
- (i) determining one or more physiological characteristics of an HMGCR-associated disease or condition in the subject and
- (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition and/or to a control
- 35 physiological characteristic of the HMGCR-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HMGCR gene in the subject.

50. The method of claim 49, wherein the determined physiological characteristic is one or more of: the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.

51. The method of claim 50, wherein a reduction in one or more of the subject's HMGCR mRNA level, the HMGCR protein level in the subject, and/or a decrease in one or more of cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum indicates reduction of HMGCR gene expression in the subject.

52. A method of inhibiting expression of an HMGCR gene in a subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-38 or a composition of any one of claims 39-43.

53. The method of claim 52, wherein the dsRNA agent is administered to the subject subcutaneously.

54. The method of claim 52, wherein the dsRNA agent is administered to the subject by IV administration.

55. The method of any one of claims 52-54, further comprising assessing inhibition of the HMGCR gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises:

- (i) determining one or more physiological characteristics of an HMGCR-associated disease or condition in the subject and
- (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition and/or to a control physiological characteristic of the HMGCR-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HMGCR gene in the subject.

56. The method of claim 55, wherein the determined physiological characteristic is one or more of: the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein

cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C level), and lipid level in blood or serum.

- 5 57. The method of claim 56, wherein a reduction in one or more of the subject's HMGCR mRNA level, the HMGCR protein level in the subject, and/or a decrease in one or more of cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum indicates reduction of HMGCR gene
10 expression in the subject.

58. A method of treating a disease or condition associated with the presence of HMGCR protein, the method comprising administering to a subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-38, or a composition of any
15 one of claims 39-43, to inhibit HMGCR gene expression.

59. The method of claim 58, wherein the disease or condition is one or more of: hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, congestive
20 heart disease (CHD) and atherosclerosis, atherosclerosis, dyslipidemia, acute pancreatitis associated with hypertriglyceridemia, chylomicron syndrom, familial chylomicronemia, Apo-E deficiency or resistance, LPL deficiency or hypoactivity, familial partial lipodystrophy type 1 (FPLD1), polycystic ovarian syndrome related to insulin resistance, renal transplantation, nephrotic syndrome, Cushing's syndrome, acromegaly, systemic lupus erythematosus,
25 dysglobulinemia, lipodystrophy, glycogenosis type I, and Addison's disease, or other disorders of lipid metabolism related to HMGCR.

60. The method of claim 59, further comprising administering an additional therapeutic regimen to the subject.
30

61. The method of claim 60, wherein the additional therapeutic regimen comprises: administering to the subject one or more HMGCR antisense polynucleotides of the invention, administering to the subject a non-HMGCR dsRNA therapeutic agent, and a behavioral modification in the subject.
35

62. The method of claim 61, wherein the non-HMGCR dsRNA therapeutic agent is one of more of: a statin, a bile sequestering agent, a VLDL secretion inhibitor, a lipophilic antioxidant, an acyl- CoA cholesterol acyl transferase inhibitor, a farnesoid X receptor antagonist, a sterol regulatory binding protein cleavage activating protein (SCAP) activator, a

microsomal triglyceride transfer protein (MTP) inhibitor, an ApoE-related peptide, a cholesteryl ester transfer protein (CETP) inhibitor, a therapeutic antibody against HMGCR, and a combination of any of the foregoing.

5 63. The method of any one of claims 58-62, wherein the dsRNA agent is administered to the subject subcutaneously.

64. The method of any one of claims 58-62, wherein the dsRNA agent is administered to the subject by IV administration.

10

65. The method of any one of claims 58-64, further comprising determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.

15 66. The method of claim 65, wherein a means of determining an efficacy of the treatment in the subject comprises:

(i) determining one or more physiological characteristics of the HMGCR-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HMGCR-associated disease or condition

20 wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

67. The method of claim 66, wherein the determined physiological characteristic is: the HMGCR mRNA level, the HMGCR protein level in the subject, or cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.

30 68. The method of claim 66, wherein a reduction in one or more of the HMGCR mRNA level, the HMGCR protein level in the subject, and/or a decrease in one or more of cholesteryl ester (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum indicates the presence of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

35

69. A method of decreasing a level of HMGCR protein in a subject compared to a baseline pre-treatment level of HMGCR protein in the subject, the method comprising administering to the

subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-38, or a composition of any one of claims 39-43, to decrease the level of HMGCR gene expression.

- 5 70. The method of claim 69, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

71. A method of altering a physiological characteristic of an HMGCR-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the
10 HMGCR-associated disease or condition in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-38, or a composition of any one of claims 39-43, to alter the physiological characteristic of the HMGCR-associated disease or condition in the subject.

- 15 72. The method of claim 71, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

73. The method of any one of claims 71-72, wherein the physiological characteristic is one or more of: the HMGCR mRNA level, the HMGCR protein level in the subject, cholesteryl ester
20 (CE) levels, triglyceride levels, cholesterol levels (such as high-density lipoprotein cholesterol (HDL-C), intermediate-density lipoprotein cholesterol (IDL-C), low-density lipoprotein cholesterol (LDL-C) level, very-low-density lipoprotein cholesterol (VLDL-C) level), and lipid level in blood or serum.

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