DOUBLE-STRANDED OLIGONUCLEOTIDE AND CONJUGATE FOR INHIBITING EXPRESSION OF C3 GENES, AND USES THEREOF

FIELD

[0001] The present disclosure relates to the field of pharmacy, in particular to a double-stranded oligonucleotide for inhibiting expression of C3 gene, conjugates and uses thereof.

BACKGROUND

[0002] The complement system is a crucial component of the body's innate immunity, composed of more than 50 soluble proteins and membrane-bound proteins. The complement system plays a vital role in various life activities, such as defending the body against foreign substances, cell lysis, inflammatory responses, the dissolution of immune complexes, the clearance of apoptotic cells, and the enhancement of humoral immune responses.

[0003] Complement activation occurs through three main pathways: the classical pathway, the alternative pathway, and the mannose-binding lectin (MBL) pathway.

[0004] Given the important role of the complement system in defending against foreign substances, clearing immune complexes within the body, and participating in adaptive immunity, abnormalities in the complement system are closely associated with numerous diseases, such as kidney diseases and autoimmune disorders. For example, atypical hemolytic uremic syndrome (aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Over 50% of aHUS cases are associated with mutations or polymorphisms in complement regulatory factors such as Factor H, Factor I, MCP, C4BP, Factor B, and C3, as well as the production of autoantibodies against Factor H. These mutations or polymorphisms typically occur in a heterozygous state and affect the secretion and function of these proteins. Another example is type II membranoproliferative glomerulonephritis (MPGN), a severe class of kidney disease typically characterized by electron-dense deposits visible under electron microscopy, accompanied by the proliferation of the glomerular basement membrane and mesangial cells. Individuals with Factor H or C3 deficiency are susceptible to this disease. Furthermore, MPGN is also associated with the body's production of autoantibodies against the C3 convertase of the

alternative pathway (also known as C3 nephritic factor, C3NeF). Glomerulonephritis is a disease characterized by kidney damage caused by excessive complement activation triggered by immune complexes in the renal blood vessels. C3 and its regulatory proteins, Factor I and Factor H, are closely linked to the onset and progression of glomerulonephritis. A deficiency in Factor I and Factor H leads to the dysregulation of C3. In addition, C1q knockout mice can produce autoantibodies, which make the apoptotic cells unable to be effectively cleared, so the mice are susceptible to immune complex-mediated glomerulonephritis.

[0005] Within the classical, lectin, and alternative pathways of the complement system, theuraputic targets currently under development include C1 (C1q, C1r, C1s), MASP, C2, C3, C5, and C6. For targeting the key complement protein C3, several companies are developing peptide drugs (e.g., AMY-101, APL-1) or recombinant enzymes (CB2782) for the treatment of diseases such as paroxysmal nocturnal hemoglobinuria (PNH), chronic obstructive pulmonary disease (COPD), and age-related macular degeneration (AMD). However, very few drugs targeting the key complement protein C3 are currently being developed for the treatment of kidney diseases.

[0006] Therefore, providing a double-stranded oligonucleotide that inhibits C3 gene expression is of great significance for improving the disease course in patients with C3 deposition in renal tissue, and for the alleviation, prevention, and/or treatment of diseases or conditions mediated by the C3 gene.

SUMMARY

[0007] In view of the foregoing, the present disclosure provides a double-stranded oligonucleotide for inhibiting the expression of C3 gene, a conjugate thereof and uses thereof.

[0008] To achieve the foregoing objects, the present disclosure provides the following technical solutions:

[0009] In a first aspect, the present disclosure provides a double-stranded oligonucleotide for inhibiting expression of C3 gene, comprising a sense strand and an antisense strand;

[0010] from 5'-end to 3'-end, nucleotides of positions 2 to 19 of the antisense strand comprise a complementary region to a C3 RNA transcript, wherein the complementary region comprises at

least 17 contiguous nucleotides of any one of the nucleotide sequences as set forth in SEQ ID NOs: 213 to 424 or a nucleotide sequence having 1, 2 or 3 nucleotide differences from the at least 17 contiguous nucleotides; and

[0011] the sense strand comprises at least 17 nucleotides, and the sense strand and the antisense strand are complementary or substantially complementary to form a duplex region, wherein being substantial complementary means that the sense strand and the antisense strand have no more than 3 nucleotide mismatches in the duplex region.

[0012] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide differences from any one of the sequences as set forth in SEQ ID NOs: 213 to 424.

[0013] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0 or 1 nucleotide difference from any one of the sequences as set forth in SEQ ID NOs: 213 to 424.

[0014] In some specific embodiments of the present disclosure, the antisense strand is selected from or comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 213 to 424.

[0015] In some optional embodiments of the present disclosure, the sense strand comprises at least 17 contiguous nucleotides of any one of the nucleotide sequences as set forth in SEQ ID NOs: 1 to 212 or a nucleotide sequence having 1, 2 or 3 nucleotide differences from the at least 17 contiguous nucleotides.

[0016] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide differences from any one of the sequences as set forth in SEQ ID NOs: 1 to 212.

[0017] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0 or 1 nucleotide difference from any one of the nucleotide sequences as set forth in SEQ ID NOs: 1 to 212.

[0018] In some specific embodiments of the present disclosure, the sense strand is selected from or comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 1 to 212.

[0019] In some specific embodiments of the present disclosure, the antisense strand is selected

from or comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 213 to 424, and the sense strand is selected from or comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 1 to 212.

[0020] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0 or 1 nucleotide difference from any one of the nucleotide sequences as set forth in SEQ ID NOs: 241, 242, 285, 357 or 403;

[0021] In some specific embodiments of the present disclosure, the antisense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 241, 242, 285, 357 or 403.

[0022] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0 or 1 nucleotide difference from any one of the nucleotide sequences as set forth in SEQ ID NOs: 29, 30, 73, 145 or 191.

[0023] In some optional embodiments of the present disclosure, the sense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 29, 30, 73, 145 or 191.

[0024] In some specific embodiments of the present disclosure, the antisense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 241, 242, 285, 357 or 403, and the sense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 29, 30, 73, 145 or 191.

[0025] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

[0026] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 241 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 29 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom;

[0027] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 242 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 30 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom;

[0028] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 285 or a

nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 73 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom;

[0029] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 357 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 145 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom; and

[0030] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 403 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 191 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom.

[0031] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

[0032] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 241, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 29;

[0033] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 242, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 30;

[0034] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 285, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 73;

[0035] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 357, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 145; and

[0036] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 403, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 191.

[0037] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises:

[0038] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 241 or a nucleotide sequence having 0 or 1 nucleotide difference therefrom, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 29 or a nucleotide sequence having 0 or 1

nucleotide difference therefrom.

[0039] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises:

[0040] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 241, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 29.

[0041] In some specific embodiments of the present disclosure, each nucleotide of the double-stranded oligonucleotide is independently selected from a modified or unmodified nucleotide.

[0042] In some specific embodiments of the present disclosure, substantially all nucleotides of the double-stranded oligonucleotide are independently selected from modified nucleotides, wherein "substantially all nucleotides of the double-stranded oligonucleotide" means that most but not all of the nucleotides of the double-stranded oligonucleotide are modified nucleotides, and the double-stranded oligonucleotide comprises no more than 5, 4, 3, 2 or 1 unmodified nucleotides.

[0043] In some specific embodiments of the present disclosure, all nucleotides of the double-stranded oligonucleotide are independently selected from modified nucleotides.

[0044] In some specific embodiments of the present disclosure, each nucleotide of the double-stranded oligonucleotide is independently selected from the group consisting of:

[0045] a 2'-halogen-modified nucleotide, a 2'-deoxy-modified nucleotide, a 2'-O-optionally substituted C_{1-6} alkyl-modified nucleotide, a 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide, a 2'-amino-modified nucleotide, an abasic nucleotide or a nucleotide analog, wherein the nucleotide analog is one or more selected from peptide nucleic acid (PNA), Morpholino (MNA), bridged nucleic acid (BNA), locked nucleic acid (LNA), glycol nucleic acid (GNA), threose nucleic acid (TNA) and unlocked nucleic acid (UNA);

[0046] wherein n is selected from 1 or 2, R_1 is selected from an optionally substituted C_{1-6} alkyl or an optionally substituted C_{1-6} alkoxy; when R_1 comprises a substituent, the substituent is selected from a halogen, a C_{1-6} alkoxy, a hydroxyl and an amino.

[0047] In some specific embodiments of the present disclosure, each nucleotide of the sense strand and/or the antisense strand is independently selected from a modified or unmodified nucleotide.

[0048] In some optional embodiments of the present disclosure, substantially all nucleotides of the sense strand and/or the antisense strand are selected from modified nucleotides, wherein "substantially all nucleotides are selected from modified nucleotides" means that most but not all of the nucleotides of the strand are modified nucleotides, and the strand comprises no more than 5, 4, 3, 2 or 1 unmodified nucleotides.

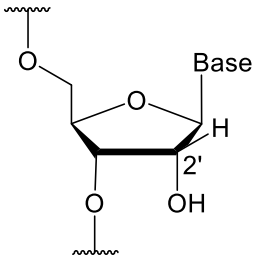
[0049] In some specific embodiments of the present disclosure, all nucleotides of the sense strand and/or the antisense strand are independently selected from a modified or unmodified nucleotide.

[0050] In some specific embodiments of the present disclosure, each nucleotide of the sense strand and/or the antisense strand is independently selected from the group consisting of:

[0051] a 2'-halogen-modified nucleotide, a 2'-deoxy-modified nucleotide, a 2'-O-optionally substituted C_{1-6} alkyl-modified nucleotide, a 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide, a 2'-amino-modified nucleotide, an abasic nucleotide or a nucleotide analog, wherein the nucleotide analog is one or more selected from peptide nucleic acid (PNA), Morpholino (MNA), bridged nucleic acid (BNA), locked nucleic acid (LNA), glycol nucleic acid (GNA), threose nucleic acid (TNA) and unlocked nucleic acid (UNA);

[0052] wherein n is selected from 1 and 2;

[0053] R_1 is selected from an optionally substituted C_{1-6} alkyl or an optionally substituted C_{1-6} alkoxy; when R_1 comprises a substituent, the substituent is selected from a halogen, a C_{1-6} alkoxy, a hydroxyl and an amino.

[0054] Wherein, a nucleotide has a structure of: 

, where Base represents a nucleoside base, and the nucleoside base of each nucleotide is selected from Uracil (U), thymine (T), cytosine (C), adenine (A), and guanine (G).

[0055] In the present diclsoure, a 2'-halogen-modified nucleotide is a nucleotide in which the 2'-hydroxyl of the ribosyl is substituted by a halogen, such as a 2'-fluoro-modified nucleotide.

[0056] In some specific embodiments of the present disclosure, the 2'-halogen-modified nucleotide is a 2'-fluoro-modified nucleotide.

[0057] In the present diclsoure, a 2'-deoxy-modified nucleotide is a nucleotide in which the 2'-hydroxyl of the ribosyl is substituted by hydrogen.

[0058] In the present diclsoure, a 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is a nucleotide in which the hydrogen of the 2'-hydroxyl of the ribosyl is substituted by -$(CH_2)_n$-O-R_1. Wherein: when n is 1, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from a 2'-O-ethoxymethyl-modified nucleotide and a 2'-O-2,2,2-trifluoroethoxymethyl-modified nucleotide; when n is 2, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from 2'-O-methoxyethyl-modified nucleotide (also known as a 2'-O-moe modified nucleotide).

[0059] In some optional embodiments of the present disclosure, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from a 2'-O-methoxyethyl-modified nucleotide, a 2'-O-ethoxymethyl-modified nucleotide and a 2'-O-2,2,2-trifluoroethoxymethyl-modified nucleotide.

[0060] In some optional embodiments of the present disclosure, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from a 2'-O-methoxyethyl-modified nucleotide.

[0061] Wherein, in the present disclosure, "optionally substituted" is used to define a variable, which may be unsubstituted, and may be substituted.

[0062] In some optional embodiments of the present disclosure, each nucleotide of the sense strand and/or the antisense strand is independently selected from the group consisting of:

[0063] a 2'-O-methyl-modified nucleotide, a 2'-fluoro-modified nucleotide, a 2'-O-methoxyethyl-modified nucleotide and a 2'-deoxy-modified nucleotide.

[0064] In some specific embodiments of the present disclosure, each nucleotide of the sense strand and/or the antisense strand is independently selected from the group consisting of:

[0065] a 2'-O-methyl-modified nucleotide, a 2'-fluoro-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0066] In some specific embodiments of the present disclosure, each nucleotide of the sense

strand and/or the antisense strand is independently selected from the group consisting of:

[0067] a 2'-O-methyl-modified nucleotide, a 2'-fluoro-modified nucleotide and a 2'-deoxy-modified nucleotide.

[0068] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises at least one 2'-O-methoxyethyl-modified nucleotide.

[0069] In some specific embodiments of the present disclosure, the sense strand has a length selected from 18 to 21 nucleotides, and the antisense strand has a length selected from 19 to 23 nucleotides.

[0070] In some specific embodiments of the present disclosure, the sense strand has a length selected from 17 to 21 nucleotides, and the antisense strand has a length selected from 19 to 23 nucleotides.

[0071] In some specific embodiments of the present disclosure, the sense strand has a length of 19 nucleotides, and the antisense strand has a length 21 nucleotides.

[0072] In some specific embodiments of the present disclosure, the antisense strand comprises at least one 2'-O-methoxyethyl-modified nucleotide; and the sense strand comprises no more than one 2'-O-methoxyethyl-modified nucleotide.

[0073] In some specific embodiments of the present disclosure, the sense strand comprises no 2'-O-methoxyethyl-modified nucleotide; and the antisense strand comprises one 2'-O-methoxyethyl-modified nucleotide. Wherein, each nucleotide of the sense strand is independently selected from a 2'-fluoro-modified nucleotide and a 2'-O-methyl-modified nucleotide; and each nucleotide of the antisense strand is independently selected from a 2'-fluoro-modified nucleotide, a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide, and the antisense strand comprise one 2'-O-methoxyethyl-modified nucleotide.

[0074] In some specific embodiments of the present disclosure, the sense strand comprises one 2'-O-methoxyethyl-modified nucleotide; and the antisense strand comprises one 2'-O-methoxyethyl-modified nucleotide. Wherein, each nucleotide of the sense strand is independently selected from a 2'-fluoro-modified nucleotide, a 2'-O-methyl-modified nucleotide and a 2'-O-

methoxyethyl-modified nucleotide; and each nucleotide of the antisense strand is independently selected from a 2'-fluoro-modified nucleotide, a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0075] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0076] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than 2 nucleotides at positions 5, 12, 13, and 18 are selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0077] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than 1 nucleotide at positions 5, 12, 13, and 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0078] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than 1 nucleotide at positions 5, 12, 13, and 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0079] In some specific embodiments of the present disclosure, the sense strand has a modification pattern selected from (SS-1) to (SS-5):

[0080] (SS-1) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0081] (SS-2) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, nucleotide at

position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0082] (SS-3) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0083] (SS-4) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0084] (SS-5) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0085] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 9 to 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0086] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 9 to 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0087] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[0088] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0089] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, nucleotide at position 8 or 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0090] In some specific embodiments of the present disclosure, the antisense strand has a modification pattern selected from (AS-1) to (AS-8):

[0091] (AS-1) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0092] (AS-2) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0093] (AS-3) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0094] (AS-4) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the

remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0095] (AS-5) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0096] (AS-6) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0097] (AS-7) rom 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

[0098] (AS-8) from 5'-end to 3'-end, in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide.

[0099] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide;

[00100] in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 9 to 12, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[00101] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide;

[00102] in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 9 to 12, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotides at positions 2, 6, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

[00103] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than 2 nucleotides at positions 5, 12, 13 and 18 are selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00104] in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 9 to 12, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, nucleotides at positions 2, 6, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00105] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than 1 nucleotide at positions 5, 12, 13 and 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00106] in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14 and 16 are selected from a 2'-fluoro-modified nucleotide, any one of nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00107] In some specific embodiments of the present disclosure, the sense strand and the antisense strand of the double-stranded oligonucleotide have a modification pattern selected from (ds-1) to (ds-32):

[00108] (ds-1) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the

nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00109] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00110] (ds-2) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00111] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00112] (ds-3) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00113] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00114] (ds-4) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00115] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00116] (ds-5) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the

nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00117] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00118] (ds-6) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00119] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00120] (ds-7) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00121] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00122] (ds-8) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00123] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00124] (ds-9) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the

nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00125] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00126] (ds-10) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00127] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00128] (ds-11) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00129] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00130] (ds-12) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00131] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected

from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00132] (ds-13) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00133] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00134] (ds-14) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 5 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00135] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00136] (ds-15) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00137] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00138] (ds-16) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining

nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00139] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00140] (ds-17) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00141] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00142] (ds-18) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00143] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00144] (ds-19) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00145] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00146] (ds-20) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 12 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00147] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00148] (ds-21) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00149] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00150] (ds-22) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00151] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00152] (ds-23) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00153] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11,

14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00154] (ds-24) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00155] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00156] (ds-25) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00157] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00158] (ds-26) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 13 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00159] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00160] (ds-27) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at

position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00161] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00162] (ds-28) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00163] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00164] (ds-29) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00165] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00166] (ds-30) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00167] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a

2'-O-methyl-modified nucleotide;

[00168] (ds-31) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00169] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00170] (ds-32) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00171] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00172] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00173] in the nucleotide sequence of the antisense strand, at least 4 of the nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00174] In some specific embodiments of the present disclosure, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-

modified nucleotide; and

[00175] in the nucleotide sequence of the antisense strand, at least 4 of the nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 or 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00176] In some specific embodiments of the present disclosure, the sense strand and the antisense strand of the double-stranded oligonucleotide have a modification pattern selected from (ds-1) to (ds-8):

[00177] (ds-1) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00178] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00179] (ds-2) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00180] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00181] (ds-3) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00182] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected

from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00183] (ds-4) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00184] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00185] (ds-5) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00186] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00187] (ds-6) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00188] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

[00189] (ds-7) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00190] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is

selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00191] (ds-8) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

[00192] in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide.

[00193] In some specific embodiments of the present disclosure, the sense strand and/or the antisense strand independently comprise one or more internucleotide phosphorothioate linkages.

[00194] In some specific embodiments of the present disclosure, the sense strand comprises two contiguous internucleotide phosphorothioate linkages at 5'-end.

[00195] In some specific embodiments of the present disclosure, the antisense strand comprises two contiguous internucleotide phosphorothioate linkages at 5'-end, and two contiguous internucleotide phosphorothioate linkages at 3'-end.

[00196] In some specific embodiments of the present disclosure, the sense strand comprises two internucleotide phosphorothioate linkages at 5'-end, and the antisense strand comprises two internucleotide phosphorothioate linkages at 5'-end and two internucleotide phosphorothioate linkages at 3'-end.

[00197] In some optional embodiments of the present disclosure, the sense strand or the antisense strand comprises a 3'-overhang having at least 1 nucleotide.

[00198] In some optional embodiments of the present disclosure, the antisense strand comprises a 3'-overhang having at least 1 nucleotide.

[00199] In some optional embodiments of the present disclosure, the antisense strand comprises a 3'-overhang having 2 nucleotides.

[00200] In some specific embodiments of the present disclosure, each nucleotide of the double-stranded oligonucleotide is independently selected from a modified nucleotide;

[00201] wherein the sense strand is selected from any one of the sequences as set forth in SEQ ID NOs: 887 to 907; and/or the antisense strand is selected from any one of the sequences as set forth in SEQ ID NOs: 908 to 943; wherein

[00202] the sense strand, from 5'-end to 3'-end,

[00203] SEQ ID NO: 887: CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm;

[00204] SEQ ID NO: 888: CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm;

[00205] SEQ ID NO: 889: CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm;

[00206] SEQ ID NO: 890: CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm;

[00207] SEQ ID NO: 891: CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um;

[00208] SEQ ID NO: 892: CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm;

[00209] SEQ ID NO: 893: CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm;

[00210] SEQ ID NO: 894: CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm;

[00211] SEQ ID NO: 895: CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm;

[00212] SEQ ID NO: 896: CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um;

[00213] SEQ ID NO: 897: GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm;

[00214] SEQ ID NO: 898: GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAmCmAmA

mAm;

[00215] SEQ ID NO: 899: GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmA mAm;

[00216] SEQ ID NO: 900: GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmA mAm;

[00217] SEQ ID NO: 901: GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(mo e)Am;

[00218] SEQ ID NO: 902: CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmU m;

[00219] SEQ ID NO: 903: CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmA mUm;

[00220] SEQ ID NO: 904: CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmA mUm;

[00221] SEQ ID NO: 905: CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmA mUm;

[00222] SEQ ID NO: 906: CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(mo e)Um; and

[00223] SEQ ID NO: 907: AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmA m; and

[00224] the antisense strand, from 5'-end to 3'-end,

[00225] SEQ ID NO: 908: AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmC mGmsUmsAm;

[00226] SEQ ID NO: 909: AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmC mGmsUmsAm;

[00227] SEQ ID NO: 910: AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmC mGmsUmsAm;

[00228] SEQ ID NO: 911: AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCm

GmsUmsAm;

[00229] SEQ ID NO: 912: AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm;

[00230] SEQ ID NO: 913: AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm;

[00231] SEQ ID NO: 914: AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm;

[00232] SEQ ID NO: 915: AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm;

[00233] SEQ ID NO: 916: UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfT(moe)UfCmUmCmsCmsUm;

[00234] SEQ ID NO: 917: UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm;

[00235] SEQ ID NO: 918: UmsUfsUmGmUmAfUmGmAmAmGfCmAmAfT(moe)UfCmUmCmsCmsUm;

[00236] SEQ ID NO: 919: UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm;

[00237] SEQ ID NO: 920: AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm;

[00238] SEQ ID NO: 921: AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm;

[00239] SEQ ID NO: 922: AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm;

[00240] SEQ ID NO: 923: AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm;

[00241] SEQ ID NO: 924: AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm;

[00242] SEQ ID NO: 925: AmsUfsGmUmAmGfUmA(moe)GmAmAfUmUmUfCmUfCmUmGmsUmsAm;

[00243] SEQ ID NO: 926: AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm;

[00244] SEQ ID NO: 927: AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm;

[00245] SEQ ID NO: 928: UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm;

[00246] SEQ ID NO: 929: UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm;

[00247] SEQ ID NO: 930: UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm;

[00248] SEQ ID NO: 931: AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm;

[00249] SEQ ID NO: 932: AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm;

[00250] SEQ ID NO: 933: AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm;

[00251] SEQ ID NO: 934: AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm;

[00252] SEQ ID NO: 935: AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm;

[00253] SEQ ID NO: 936: AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm;

[00254] SEQ ID NO: 937: AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm;

[00255] SEQ ID NO: 938: AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGm

sUmsAm;

[00256] SEQ ID NO: 939: UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm;

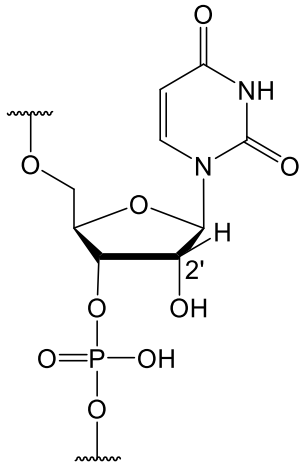
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[00258] SEQ ID NO: 941: UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm;

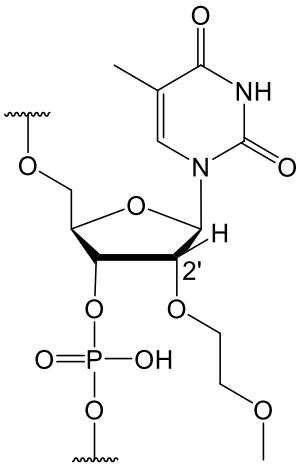
[00259] SEQ ID NO: 942: UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm; and

[00260] SEQ ID NO: 943: UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm.

[00261] Wherein, C represents cytidine-3'-monophosphate, G represents guanosine-3'-monophosphate, U represents uridine-3'-monophosphate, A represents adenosine-3'-monophosphate, and T represents thymidine-3'-monophosphate; m indicates that a nucleotide immediately to the left of the letter m is a 2'-O-methyl-modified nucleotide; f indicates that a nucleotide immediately to the left of the letter f is a 2'-fluoro-modified nucleotide; (moe) indicates that a nucleotide immediately to the left of the combined identifier (moe) is a 2'-O-methoxyethyl-modified nucleotide; and s indicates that two adjacent nucleotides are linked by a phosphorothioate diester bond.

[00262] Wherein, the structural formula of U is 

, and the structural

formula of T(moe) is . Herein, T(moe) is considered as a modification of U.

[00263] It is particularly noted that: in the context of the present disclosure, since sequences in which all nucleotides are modified cannot be properly validated and thus a sequence list cannot be generated, all sequences involving modifications in the present disclosure cannot be presented by a sequence list, and for all such sequences, the descriptions in the specification shall prevail.

[00264] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002245	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RX002246	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002247	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002248	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002249	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002250	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002251	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002252	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002253	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002254	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002255	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002256	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002	CmsAmsGmAmGmAmAfAfUfUfCmU	SEQ ID	AmsUfsGmUmAmGfUmAmGmAfAmUm	SEQ ID

257	mAmCmUmAmCmAmUm	NO: 892	UmUfC(moe)UfCmUmGmsUmsAm	NO: 913
RX002 258	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002 259	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 260	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 261	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 262	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 263	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 264	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 265	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 266	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 267	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 916
RX002 268	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 269	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGfCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 918
RX002 270	GmsAmsGmAmA(moe)UmUfGfCfUfU mCmAmUmAmCmAmAmAm	SEQ ID NO: 898	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 271	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm	SEQ ID NO: 899	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 272	GmsAmsGmAmAmUmUfGfCfUfUmC mA(moe)UmAmCmAmAmAm	SEQ ID NO: 900	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 273	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmA(moe)Am	SEQ ID NO: 901	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 274	GmsAmsGmAmA(moe)UmUfGfCfUfU mCmAmUmAmCmAmAmAm	SEQ ID NO: 898	UmsUfsUmGmUmAfUmG(moe)AmAfGm CmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 275	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm	SEQ ID NO: 899	UmsUfsUmGmUmAfUmG(moe)AmAfGm CmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 276	GmsAmsGmAmAmUmUfGfCfUfUmC mA(moe)UmAmCmAmAmAm	SEQ ID NO: 900	UmsUfsUmGmUmAfUmG(moe)AmAfGm CmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 277	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmA(moe)Am	SEQ ID NO: 901	UmsUfsUmGmUmAfUmG(moe)AmAfGm CmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 278	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RX002 279	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAfGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 280	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGfGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RX002 281	CmsAmsAmCmT(moe)CmAfCfCfUfG mUmAmAmUmAmAmAmUm	SEQ ID NO: 903	AmsUfsUmUmAmUfUmAmCmAfGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 282	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm	SEQ ID NO: 904	AmsUfsUmUmAmUfUmAmCmAfGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 283	CmsAmsAmCmUmCmAfCfCfUfGmU mA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmAmCmAfGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 284	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmAmCmAfGmGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 285	CmsAmsAmCmT(moe)CmAfCfCfUfG mUmAmAmUmAmAmAmUm	SEQ ID NO: 903	AmsUfsUmUmAmUfUmA(moe)CmAfGm GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 286	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm	SEQ ID NO: 904	AmsUfsUmUmAmUfUmA(moe)CmAfGm GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923

RX002 287	CmsAmsAmCmUmCmAfCfCfUfGmU mA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmA(moe)CmAfGm GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 288	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmA(moe)CmAfGm GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 289	CmsGmsAmAmG(moe)CmUfCfAfUfG mAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAmUfGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 290	CmsGmsAmAmGmCmUfCfAfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAmUfGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 291	CmsGmsAmAmGmCmUfCfAfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAmUf GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RX002 292	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAmUf GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RX002 293	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAmAfUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002 294	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmA(moe)GmAmAf UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 925
RX002 295	CmsAmsAmCmUmCmAfCfCfUfGmU mA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmAmCmAmGfGm UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RX002 296	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmA(moe)CmAmGf GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
RX002 297	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUf UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RX002 298	AmsAmsAmUmUmCmUfAfCfUfAmC mAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUf AmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RX002 299	AmsAmsAmUmUmCmUfAfCfUfAmC mAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUm AmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RX002 300	AmsAmsAmUmUmCmUfAfCfUfAmC mAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUf AmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RX002 301	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGm AmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RX002 302	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGf AmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RX002 303	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGf AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RX002 304	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGm UmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RX002 305	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGf UmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RX002 306	CmsAmsAmCmUmCmAfCfCfUfGmU mAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGf UmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RX002 307	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUm UmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RX002 308	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUf UmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RX002 309	AmsAmsAmUmUmCmUfAfCfUfAmC mAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUm AmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RX002 310	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCm AmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RX002 311	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCf AmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RX002 312	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCm AmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002 313	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCf AmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

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[00265] In some specific embodiments of the present disclosure, the sense strand is selected from any one of the sequences as set forth in SEQ ID NO: 887, 892, 897, 902, and 907; and/or

[00266] the antisense strand is selected from any one of the sequences as set forth in SEQ ID NO: 908, 912, 914, 920, and 927 to 943.

[00267] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002245	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RX002256	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002258	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002278	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RX002297	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RX002298	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RX002299	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RX002300	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RX002301	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RX002302	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RX002303	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RX002304	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RX002305	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RX002306	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RX002307	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RX002308	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RX002309	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RX002310	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RX002311	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RX002312	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002313	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

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[00268] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises the pair of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002258	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914

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[00269] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide is selected from siRNA.

[00270] In a second aspect, the present disclosure provides a double-stranded oligonucleotide for inhibiting the expression of C3 gene, wherein the double-stranded oligonucleotide comprises a sense strand and an antisense strand, and each nucleotide of the double-stranded nucleotide is independently selected from a modified nucleotide;

[00271] wherein the nucleotide sequence from positions 2 to 19 of the antisense strand comprises at least 17 contiguous nucleotides from any one of the nucleotide sequences as set forth in SEQ ID NOs: 908 to 943 or a nucleotide sequence having 1, 2 or 3 nucleotide base differences from the contiguous nucleotides; and

[00272] the sense strand comprises at least 17 nucleotides, and the sense strand and the antisense strand are complementary or substantially complementary to form a duplex region, wherein being substantial complementary means that the sense strand and the antisense strand have no more than 3 nucleotide mismatches in the duplex region.

[00273] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide base differences from any one of the sequences as set forth in SEQ ID NOs: 908 to 943.

[00274] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0 or 1 nucleotide base difference from any one of the sequences as set forth in SEQ ID NOs: 908 to 943.

[00275] In some optional embodiments of the present disclosure, the antisense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 908 to 943.

[00276] In some optional embodiments of the present disclosure, the sense strand comprises at least 17 contiguous nucleotides of any one of the nucleotide sequences as set forth in SEQ ID NOs: 887 to 907 or a nucleotide sequence having 1, 2 or 3 nucleotide base differences from the at least

17 contiguous nucleotides.

[00277] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide base differences from any one of the sequences as set forth in SEQ ID NOs: 887 to 907.

[00278] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0 or 1 nucleotide base difference from any one of the nucleotide sequences as set forth in SEQ ID NOs: 887 to 907.

[00279] In some optional embodiments of the present disclosure, the sense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 887 to 907.

[00280] In some optional embodiments of the present disclosure, the antisense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 908 to 943, and the sense strand comprises any one of the nucleotide sequences as set forth in SEQ ID NOs: 887 to 907.

[00281] In some optional embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

[00282] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 908, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00283] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 909, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00284] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 910, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00285] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 909, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 888;

[00286] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 909, and a sense strand having a nucleotide sequence

with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 889;

[00287] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 909, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 890;

[00288] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 909, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 891;

[00289] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 911, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 888;

[00290] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 911, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 889;

[00291] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 911, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 890;

[00292] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 911, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 891;

[00293] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 912, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00294] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 913, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00295] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 914, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00296] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 913, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 893;

[00297] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 913, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 894;

[00298] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 913, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 895;

[00299] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 913, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 896;

[00300] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 915, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 893;

[00301] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 915, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 894;

[00302] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 915, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 895;

[00303] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 915, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 896;

[00304] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 916, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00305] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference

from the sequence as set forth in SEQ ID NO: 917, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00306] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 918, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00307] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 917, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 898;

[00308] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 917, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 899;

[00309] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 917, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 900;

[00310] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 917, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 901;

[00311] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 919, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 898;

[00312] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 919, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 899;

[00313] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 919, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 900;

[00314] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 919, and a sense strand having a nucleotide sequence

with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 901;

[00315] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 920, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00316] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 921, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00317] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 922, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00318] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 921, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 903;

[00319] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 921, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 904;

[00320] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 921, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 905;

[00321] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 921, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 906;

[00322] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 923, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 903;

[00323] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 923, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 904;

[00324] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 923, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 905;

[00325] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 923, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 906;

[00326] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 910, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 888;

[00327] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 910, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 890;

[00328] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 924, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 890;

[00329] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 924, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 891;

[00330] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 914, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 895;

[00331] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 925, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 896;

[00332] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 922, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 905;

[00333] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference

from the sequence as set forth in SEQ ID NO: 926, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 906;

[00334] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 927, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00335] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 928, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00336] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 929, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00337] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 930, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00338] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 931, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00339] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 932, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00340] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 933, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00341] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 934, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00342] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 935, and a sense strand having a nucleotide sequence

with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00343] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 936, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00344] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 937, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00345] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 938, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00346] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 939, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00347] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 940, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00348] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 941, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00349] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 942, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897; and

[00350] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 943, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897.

[00351] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

Pair	Sense strand (5'-3')	Antisense strand (5'-3')

RX002 245	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RX002 246	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 247	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUfGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 248	CmsGmsAmAmG(moe)CmUfCfAfUfG mAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 249	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 250	CmsGmsAmAmGmCmUfCfAfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 251	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 252	CmsGmsAmAmG(moe)CmUfCfAfUfG mAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 253	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 254	CmsGmsAmAmGmCmUfCfAfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 255	CmsGmsAmAmGmCmUfCfAfUfGmA mAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 256	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002 257	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 258	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002 259	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 260	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 261	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 262	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 263	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 264	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 265	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 266	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RX002 267	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 916
RX002 268	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 269	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGfCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 918
RX002 270	GmsAmsGmAmA(moe)UmUfGfCfUfU mCmAmUmAmCmAmAmAm	SEQ ID NO: 898	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 271	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm	SEQ ID NO: 899	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 272	GmsAmsGmAmAmUmUfGfCfUfUmC mA(moe)UmAmCmAmAmAm	SEQ ID NO: 900	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002 273	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmA(moe)Am	SEQ ID NO: 901	UmsUfsUmGmUmAfUmGmAmAfGmCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RX002	GmsAmsGmAmA(moe)UmUfGfCfUfU	SEQ ID	UmsUfsUmGmUmAfUmG(moe)AmAfGm	SEQ ID

274	mCmAmUmAmCmAmAmAm	NO: 898	CmAmAfUmUfCmUmCmsCmsUm	NO: 919
RX002 275	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm	SEQ ID NO: 899	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 276	GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmAmAm	SEQ ID NO: 900	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 277	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(moe)Am	SEQ ID NO: 901	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RX002 278	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RX002 279	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 280	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RX002 281	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 903	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 282	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm	SEQ ID NO: 904	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 283	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 284	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RX002 285	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 903	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 286	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm	SEQ ID NO: 904	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 287	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 288	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RX002 289	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 290	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 291	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RX002 292	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RX002 293	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002 294	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmA(moe)GmAmAfUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 925
RX002 295	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm	SEQ ID NO: 905	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RX002 296	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
RX002 297	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RX002 298	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RX002 299	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RX002 300	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RX002 301	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RX002 302	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RX002 303	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933

RX002304	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RX002305	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RX002306	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RX002307	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RX002308	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RX002309	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RX002310	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RX002311	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RX002312	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002313	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

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[00352] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence with 0, 1, 2 or 3 nucleotide base differences from any one of the sequences as set forth in SEQ ID NOs: 908, 912, 914, 920 and 927 to 943.

[00353] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence with 0 or 1 nucleotide base difference from any one of the sequences as set forth in SEQ ID NOs: 908, 912, 914, 920 and 927 to 943.

[00354] In some optional embodiments of the present disclosure, the antisense strand comprises any one of the sequences as set forth in SEQ ID NOs: 908, 912, 914, 920 and 927 to 943.

[00355] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence with 0, 1, 2 or 3 nucleotide base differences from any one of the sequences as set forth in SEQ ID NOs: 887, 892, 897, 902 and 907.

[00356] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence with 0 or 1 nucleotide base difference from any one of the sequences as set forth in SEQ ID NOs: 887, 892, 897, 902 and 907.

[00357] In some optional embodiments of the present disclosure, the sense strand comprises any one of the sequences as set forth in SEQ ID NOs: 887, 892, 897, 902 and 907.

[00358] In some optional embodiments of the present disclosure, the antisense strand comprises

any one of the sequences as set forth in SEQ ID NOs: 908, 912, 914, 920 and 927 to 943, and the sense strand comprises any one of the sequences as set forth in SEQ ID NOs: 887, 892, 897, 902 and 907.

[00359] In some optional embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

[00360] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 908, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00361] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 931, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00362] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 932, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00363] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 933, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 887;

[00364] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 912, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00365] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 914, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00366] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 927, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00367] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 937, and a sense strand having a nucleotide sequence

with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00368] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 938, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892;

[00369] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 940, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00370] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 941, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00371] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 942, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00372] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 943, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 897;

[00373] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 920, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00374] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 934, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00375] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 935, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00376] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 936, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 902;

[00377] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 928, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00378] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 929, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907;

[00379] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 930, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907; and

[00380] an antisense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 939, and a sense strand having a nucleotide sequence with 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 907.

[00381] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002245	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RX002256	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002258	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002278	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RX002297	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RX002298	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RX002299	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RX002300	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RX002301	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RX002302	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RX002303	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RX002304	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RX002305	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RX002306	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm	SEQ ID NO: 902	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936

RX002307	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RX002308	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RX002309	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RX002310	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RX002311	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RX002312	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002313	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

.

[00382] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide base differences from the sequence as set forth in SEQ ID NO: 914.

[00383] In some optional embodiments of the present disclosure, the antisense strand comprises a nucleotide sequence having 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 914.

[00384] In some optional embodiments of the present disclosure, the antisense strand comprises the sequence as set forth in SEQ ID NO: 914.

[00385] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0, 1, 2 or 3 nucleotide base differences from the sequence as set forth in SEQ ID NO: 892.

[00386] In some optional embodiments of the present disclosure, the sense strand comprises a nucleotide sequence having 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892.

[00387] In some optional embodiments of the present disclosure, the sense strand comprises the sequence as set forth in SEQ ID NO: 892.

[00388] In some optional embodiments of the present disclosure, the double-stranded oligonucleotide comprises:

[00389] an antisense strand comprising a nucleotide sequence having 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 914, and a sense strand comprising a

nucleotide sequence having 0 or 1 nucleotide base difference from the sequence as set forth in SEQ ID NO: 892.

[00390] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide comprises:

[00391] an antisense strand having a nucleotide sequence as set forth in SEQ ID NO: 914, and a sense strand having a nucleotide sequence as set forth in SEQ ID NO: 892.

[00392] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide is selected from siRNA.

[00393] In a third aspect, the present disclosure provides a conjugate comprising the double-stranded oligonucleotide of the first and/or second aspect, and one or more gene delivery carriers.

[00394] In some optional embodiments of the present disclosure, the gene delivery carrier is selected from a lipid, a nanoparticle, a polymer, and a ligand.

[00395] In some optional embodiments of the present disclosure, the lipid includes cholesterol and cholesterol derivatives; the polymer includes an amphiphilic polymer and a membrane active polymer; the ligand is selected from a ligand capable of binding to a cell surface receptor.

[00396] In some specific embodiments of the present disclosure, the gene delivery carrier is selected from a ligand capable of binding to a cell surface receptor.

[00397] In some specific embodiments of the present disclosure, the ligand specifically targets the liver tissue.

[00398] In some specific embodiments of the present disclosure, the ligand is selected from a ligand of asialoglycoprotein receptor (ASGPR). Binding between the ASGPR ligand and ASGPR can promote the specific targeting and the endocytosis of the conjugate into the hepatocytes.

[00399] In some specific embodiments of the present disclosure, the ASGPR ligand comprises galactose or a derivative thereof.

[00400] In some specific embodiments of the present disclosure, the galactose or the derivative thereof include but are not limited to galactose, galactosamine, N-formyl galactosamine, N-acetyl galactosamine, N-propionyl galactosamine, N-n-butyryl galactosamine and N-isobutyryl

galactosamine.

[00401] In some specific embodiments of the present disclosure, the galactose or the derivative thereof is N-acetyl galactosamine (GalNAc).

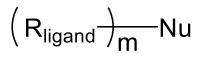
[00402] In some specific embodiments of the present disclosure, the ASGPR ligand comprises N-acetyl galactosamine.

[00403] In some optional embodiments of the present disclosure, the ligand is conjugated to 3'-end of the sense strand, 5'-end of the sense strand, 3'-end of the antisense strand and/or 5'-end of the antisense strand.

[00404] In some specific embodiments of the present disclosure, the number of the ASGPR ligand is one, and the one ASGPR ligand is conjugated to 3'-end of the sense strand.

[00405] In some specific embodiments of the present disclosure, the double-stranded oligonucleotide is siRNA. The conjugate is a conjugate of siRNA.

[00406] In some optional embodiments of the present disclosure, the conjugate comprises a structure as shown by formula (101):



(101) ;

[00407] wherein, Nu represents the double-stranded oligonucleotide;

[00408] each R_{ligand} is independently selected from an ASGPR ligand; and

[00409] m is selected from 1, 2, 3 and 4.

[00410] In some optional embodiments of the present disclosure, when m is one, the one R_{ligand} is conjugated to 3'-end of the sense strand, the one R_{ligand} is conjugated to 5'-end of the sense strand, the one R_{ligand} is conjugated to 3'-end of the antisense strand, or the one R_{ligand} is conjugated to 5'-end of the antisense strand;

[00411] when m is two, the two R_{ligand} are conjugated to 3'-end of the sense strand and 5'-end of the sense strand respectively; the two R_{ligand} are conjugated to 3'-end of the sense strand and 3'-end of the antisense strand respectively; the two R_{ligand} are conjugated to 5'-end of the sense strand and 3'-end of the antisense strand respectively; the two R_{ligand} are conjugated to 5'-end of the sense

strand and 3'-end of the antisense strand respectively; the two R_{ligand} are conjugated to 5'-end of the sense strand and 5'-end of the antisense strand respectively; the two R_{ligand} are conjugated to 3'-end of the antisense strand and 5'-end of the antisense strand respectively;

[00412] when m is three, the three R_{ligand} are conjugated to 3'-end of the sense strand, 5'-end of the sense strand, and the 3'-end of the antisense strand, respectively; the three R_{ligand} are conjugated to 3'-end of the sense strand, 5'-end of the sense strand, and the 5'-end of the antisense strand, respectively; the three R_{ligand} are conjugated to 3'-end of the sense strand, 3'-end of the antisense strand, and the 5'-end of the antisense strand, respectively; the three R_{ligand} are conjugated to 5'-end of the sense strand, 3'-end of the antisense strand, and the 5'-end of the antisense strand, respectively;

[00413] when m is four, the four R_{ligand} are conjugated to 3'-end of the sense strand, 5'-end of the sense strand, 3'-end of the antisense strand, and 5'-end of the antisense strand.

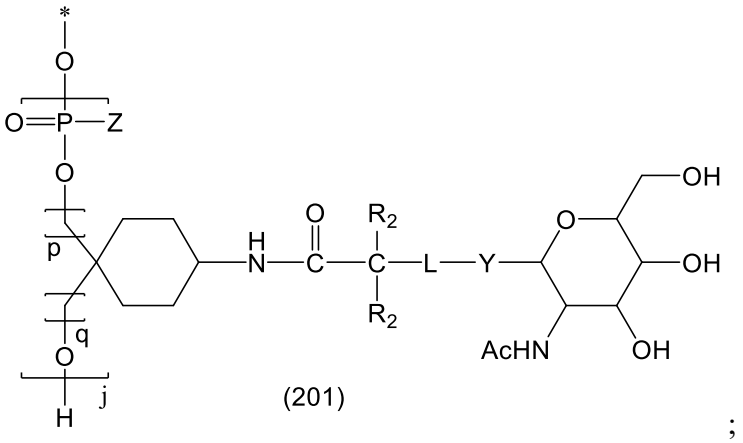
[00414] In some specific embodiments of the present disclosure, m is one.

[00415] In some specific embodiments of the present disclosure, m is one, and the R_{ligand} is conjugated to 3'-end of the sense strand.

[00416] In some specific embodiments of the present disclosure, m is two.

[00417] In some specific embodiments of the present disclosure, m is two, and the two R_{ligand} are conjugated to 3'-end and 5'-end of the sense strand, respectively.

[00418] In some optional embodiments of the present disclosure, each R_{ligand} is independently selected from a structure as shown by formula (201), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



(201)

;

[00419] wherein * represents a conjugation site of the ligand on the sense strand or the antisense strand;

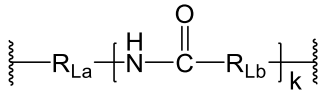
[00420] j is selected from 1, 2, 3 and 4;

[00421] each Z is selected from hydroxy and sulfydryl;

[00422] each p is selected from 1, 2 and 3;

[00423] each q is selected from 1, 2 and 3;

[00424] each R_2 is independently selected from H, any optionally substituted C_{1-6} alkyl and optionally substituted C_{1-6} alkoxy;

[00425] each L is selected from optionally substituted C_{2-20} alkylene and , wherein R_{La} and R_{Lb} are independently selected from any optionally substituted C_{1-10} alkylene, and k is selected from 1, 2, 3, 4 and 5; and

[00426] each Y is selected from O, S and NH.

[00427] In some optional embodiments of the present disclosure, [[m]]j is selected from 1, 2 or 3.

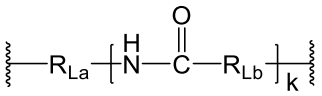
[00428] In some specific embodiments of the present disclosure, [[m]]j is 3.

[00429] In some specific embodiments of the present disclosure, Z is hydroxy.

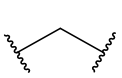
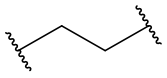
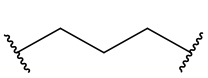
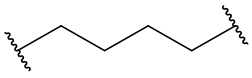
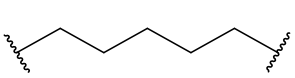
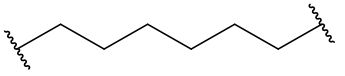
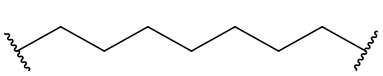
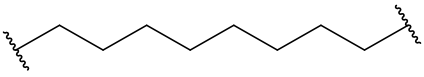
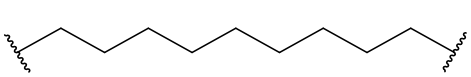
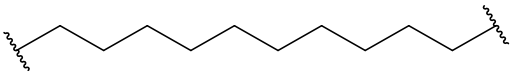
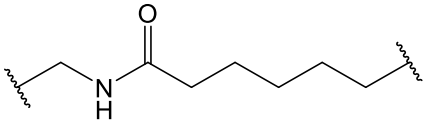
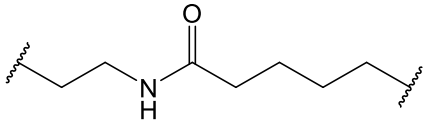
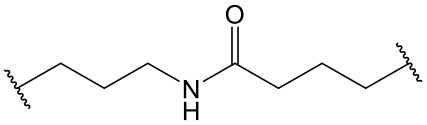
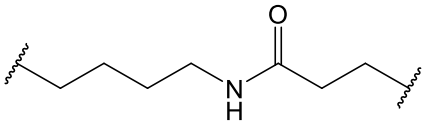
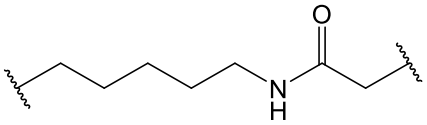
[00430] In some specific embodiments of the present disclosure, p is 1.

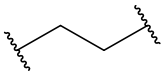
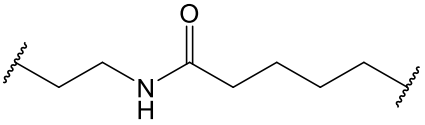
[00431] In some specific embodiments of the present disclosure, q is 1.

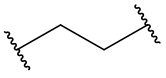
[00432] In some specific embodiments of the present disclosure, R_2 is H.

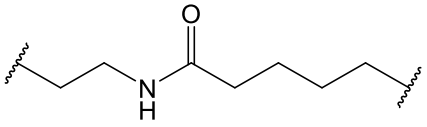
[00433] In some optional embodiments of the present disclosure, each L is selected from optionally substituted C_{2-10} alkylene and , wherein R_{La} and R_{Lb} are independently selected from any optionally substituted C_{1-10} alkylene, and k is selected from 1, 2 and 3.

[00434] In some specific embodiments of the present disclosure, k is 1.

[00435] In some optional embodiments of the present disclosure, each L is selected from , , , , , , , , , , , , , ,  and .

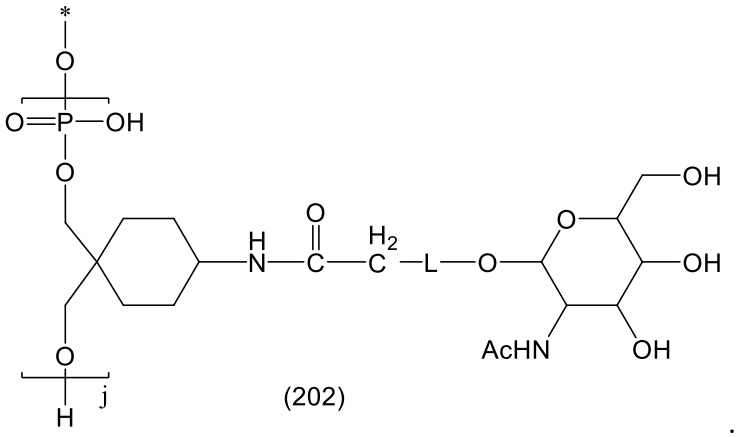
[00436] In some optional embodiments of the present disclosure, each L is selected from  and .

[00437] In some specific embodiments of the present disclosure, L is .

[00438] In some specific embodiments of the present disclosure, L is .

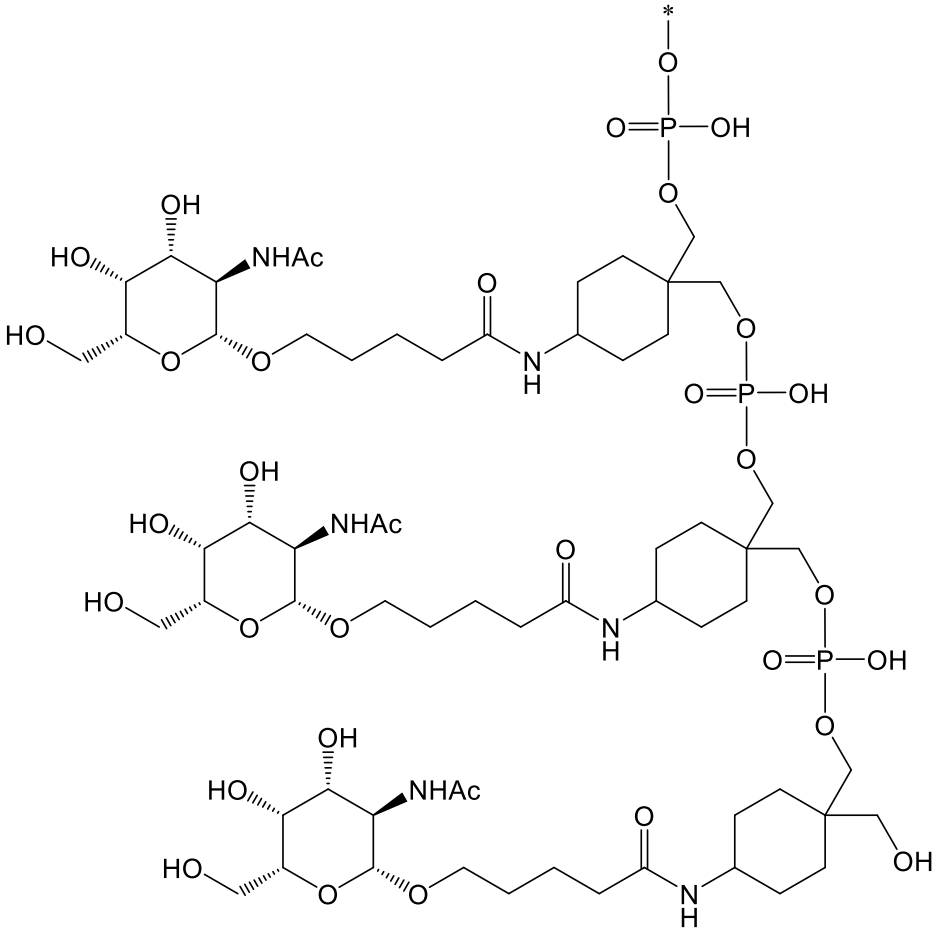
[00439] In some specific embodiments of the present disclosure, Y is O.

[00440] In some optional embodiments of the present disclosure, each R_{ligand} is independently selected from a structure as shown by formula (202), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



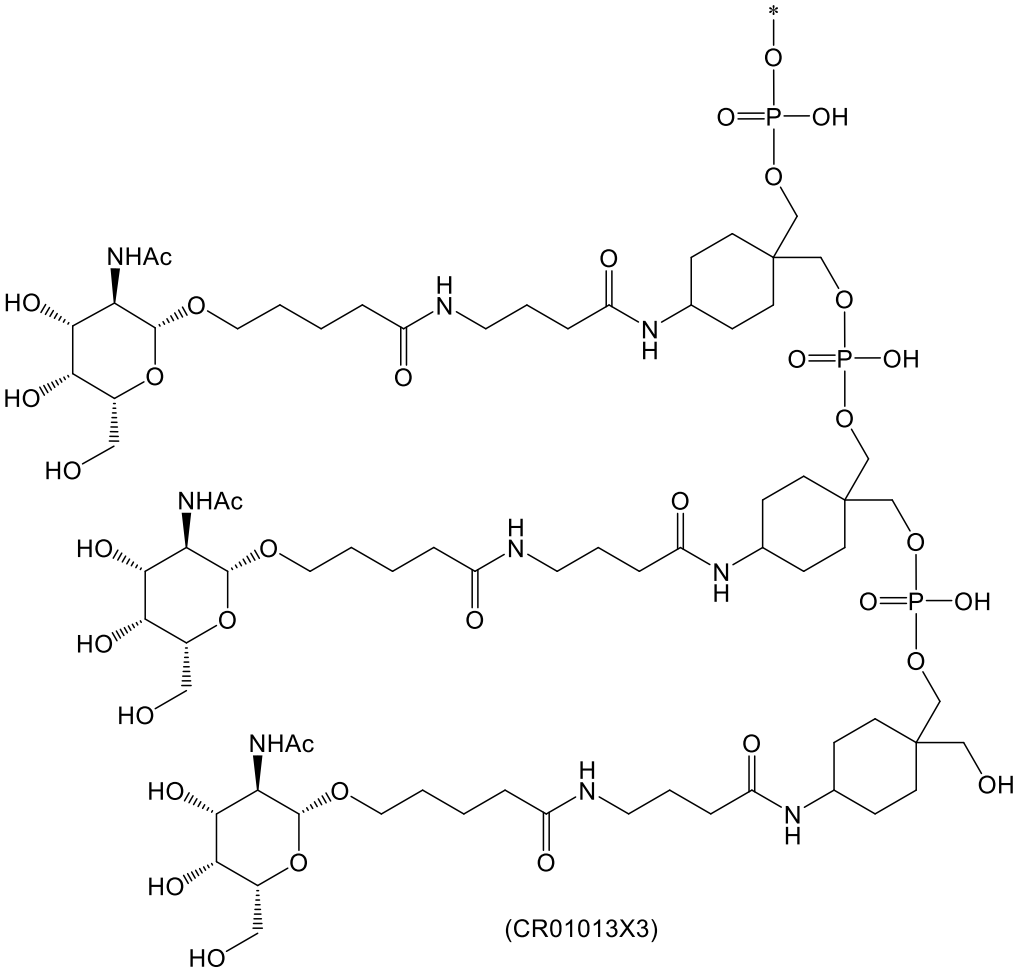
(202)

[00441] In some optional embodiments of the present disclosure, each R_{ligand} is independently selected from a structure as shown by formula (CR01008×3), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



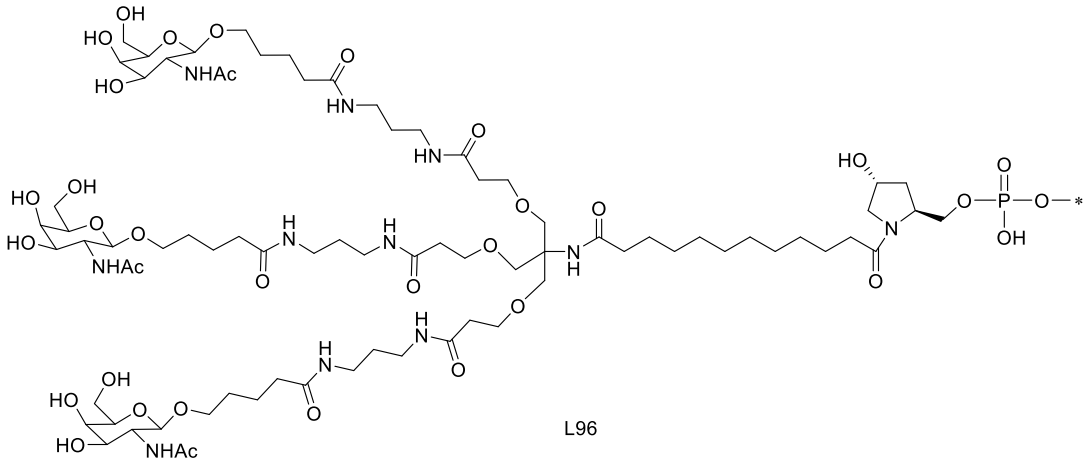
(CR01008X3)

[00442] In some optional embodiments of the present disclosure, each R_{ligand} is independently selected from a structure as shown by formula (CR01013×3), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



(CR01013X3)

[00443] In some optional embodiments of the present disclosure, each R_{ligand} is independently selected from a structure as shown by formula L96, and a pharmaceutically acceptable salt thereof:



[00444] In some specific embodiments of the present disclosure, the conjugate comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RZ002033	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RZ002034	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002036	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002037	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 889_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002038	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002039	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002040	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002041	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 889_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002042	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002043	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002050	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RZ002051	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_	SEQ ID NO: 892_(CR01008	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmG	SEQ ID NO: 913

	(CR01008×3)	×3)	msUmsAm	
RZ002053	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002054	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002055	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002056	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002057	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002058	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002059	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002060	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002066	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 916
RZ002067	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002068	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGfCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 918
RZ002069	GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 898_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002070	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 899_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002071	GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 900_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002072	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(moe)Am_(CR01008×3)	SEQ ID NO: 901_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002073	GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 898_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002074	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 899_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002075	GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 900_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002076	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(moe)	SEQ ID NO: 901_(CR01008	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCm	SEQ ID NO: 919

	Am_(CR01008×3)	×3)	sCmsUm	
RZ002082	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RZ002083	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002084	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RZ002085	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 903_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002086	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 904_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002087	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002088	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002089	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 903_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002090	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 904_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002091	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002092	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002099	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002100	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002101	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002102	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002103	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002107	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002108	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)	SEQ ID NO: 896_(CR01008	AmsUfsGmUmAmGfUmA(moe)GmAmAfUmUmUfCmUfCmUmGm	SEQ ID NO: 925

	Um_(CR01008×3)	×3)	sUmsAm	
RZ002112	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RZ002113	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
RZ002115	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RZ002116	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RZ002117	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RZ002118	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RZ002119	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RZ002120	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RZ002121	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RZ002122	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RZ002123	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RZ002124	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RZ002125	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RZ002126	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RZ002130	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RZ002131	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RZ002132	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RZ002133	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RZ002134	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_	SEQ ID NO: 897_(CR01008	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCm	SEQ ID NO: 943

	(CR01008×3)	×3)	sCmsUm	

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[00445] as an illustrative example, "SEQ ID NO: 892_(CR01008×3)" indicates that the ligand represented by formula (CR01008×3) is conjugated to 3'-end of the sense strand as set forth in SEQ ID NO: 892.

[00446] In some specific embodiments of the present disclosure, the conjugate comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RZ002033	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RZ002050	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RZ002082	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002115	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RZ002116	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RZ002117	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RZ002118	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RZ002119	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RZ002120	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RZ002121	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RZ002122	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RZ002123	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RZ002124	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936

		×3)		
RZ002125	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RZ002126	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RZ002130	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RZ002131	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RZ002132	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RZ002133	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RZ002134	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

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[00447] as an illustrative example, "SEQ ID NO: 892_(CR01008×3)" indicates that the ligand represented by formula (CR01008×3) is conjugated to 3'-end of the sense strand as set forth in SEQ ID NO: 892.

[00448] In some specific embodiments of the present disclosure, the conjugate comprises:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914

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[00449] wherein, "SEQ ID NO: 892_(CR01008×3)" indicates that the ligand represented by formula (CR01008×3) is conjugated to 3'-end of the sense strand as set forth in SEQ ID NO: 892.

[00450] In a fourth aspect, the present disclosure provides a use of the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect, in the manufacture of a medicament for ameliorating, preventing and/or treating a disease or disorder mediated by C3 gene.

[00451] In some optional embodiments of the present disclosure, the disease or disorder mediated by C3 gene includes but is not limited to IgA nephropathy, atypical hemolytic uremic syndrome

(aHUS), paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulopathy, lupus nephritis, and membranous nephropathy.

[00452] In a fifth aspect, the present disclosure provides a pharmaceutical composition comprising the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect.

[00453] In some optional embodiments of the present disclosure, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients or adjuvants.

[00454] In the present disclosure, a "pharmaceutical composition" may refer to one for use in the treatment of a disease, or for use in in vitro cell culture experiments. When used for the treatment of a disease, the term "pharmaceutical composition" usually refers to a unit dosage form, and can be prepared by any of the methods well known in the pharmaceutical art. The methods include the step of bringing an active ingredient into association with an excipient which constitutes one or more accessory ingredients. Generally, compositions are prepared by uniformly and intimately bringing an active siRNA into association with a liquid excipient, a finely divided solid excipient, or both.

[00455] In the present disclosure, the term "pharmaceutically acceptable" means that a substance or composition must be chemically and/or toxicologically compatible with the other ingredients comprising a formulation and/or the mammal to be treated therewith. Preferably, "pharmaceutically acceptable" as described in the present disclosure refers to what is approved by a federal regulatory agency or a national government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[00456] In the present disclosure, the term "pharmaceutically acceptable excipient" include any solvents, solid excipients, diluents, or other liquid excipients, and the like, that are suitable for a particular target dosage form. The use of any conventional excipient is contemplated herein, except to the extent that such excipients are incompatible with an siRNA of the present disclosure, for example, by producing any undesirable biological effect or interacting in a deleterious manner with any other component of the pharmaceutically acceptable composition.

[00457] The use of any conventional excipient is contemplated herein, except to the extent that

such excipients are incompatible with an siRNA of the present disclosure, for example, by producing any undesirable biological effect or interacting in a deleterious manner with any other component of the pharmaceutically acceptable composition.

[00458] The pharmaceutical compositions of the present disclosure include formulations suitable for parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The amount of an active ingredient that can be combined with excipient materials to produce a single dosage form will generally be that amount of the siRNA which produces a therapeutic effect.

[00459] In a sixth aspect, the present disclosure provides a medicament, wherein the medicament comprises the pharmaceutical composition according to the fifth aspect.

[00460] In a seventh aspect, the present disclosure provides a medicament combination, comprising the medicament according to the sixth aspect and any other active ingredient.

[00461] In an eighth aspect, the present disclosure provides a kit comprising the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect, and/or the pharmaceutical composition according to the fifth aspect, and/or the medicament according to the sixth aspect, and/or the medicament combination according to the seventh aspect.

[00462] In a ninth aspect, the present disclosure provides a method for inhibiting expression of C3 gene, comprising administering to a subject in need thereof the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect, and/or the pharmaceutical composition according to the fifth aspect, and/or the medicament according to the sixth aspect, and/or the medicament combination according to the seventh aspect.

[00463] In some specific embodiments of the present disclosure, the present disclosure provides a method for inhibiting C3 gene expression in a cell in vitro, comprising contacting the cell with the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect, and/or the pharmaceutical composition according to the fifth aspect, and/or the medicament according to the sixth aspect, and/or the medicament combination according to the seventh aspect.

[00464] In some optional embodiments of the present disclosure, the inhibition of the expression of the C3 gene is that the cell is maintained for a time sufficient to obtain degradation of the mRNA transcript of the C3 gene.

[00465] More practically, in a tenth aspect of, the present disclosure provides a method for ameliorating, treating and/or preventing a disease or disorder mediated by C3 gene, comprising administering the double-stranded oligonucleotide according to the first aspect, and/or the double-stranded oligonucleotide according to the second aspect, and/or the conjugate according to the third aspect, and/or the pharmaceutical composition according to the fifth aspect, and/or the medicament according to the sixth aspect, and/or the medicament combination according to the seventh aspect, to a subject in need thereof.

[00466] In some specific embodiments of the present disclosure, the subject is a human.

[00467] In some specific embodiments of the present disclosure, the medicament is administered at a dose of 0.01 mg/kg to 10 mg/kg, or 0.5 mg/kg to 50 mg/kg.

[00468] In some specific embodiments of the present disclosure, the mode of administration of the medicament includes subcutaneous administration or intravenous administration.

[00469] In some specific embodiments of the present disclosure, the disease or disorder mediated by C3 gene is associated with the mRNA expression level of C3 gene.

[00470] In some specific embodiments of the present disclosure, the disease or disorder is selected from IgA nephropathy, atypical hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulopathy, lupus nephritis and membranous nephropathy.

[00471] The double-stranded oligonucleotides or conjugates thereof provided by the present disclosure significantly inhibit C3 gene mRNA expression in HepG2 cells, significantly inhibit C3 gene mRNA expression in animals, significantly reduce the protein level of the C3 gene in the serum of *Macaca fascicularis* and the inhibitory effect lasts until day 42, significantly inhibit the alternative complement pathway in the serum of *Macaca fascicularis* but has no effect on the classical complement pathway in the serum, reduce C3 gene mRNA and protein levels in CFA-IgA mice, reduce C3 deposition in renal tissue and improve the disease course in patients with C3 deposition in renal tissue, and no significant abnormalities are observed in animal hematology and blood biochemistry. The double-stranded oligonucleotide or a conjugate thereof provided by the

present disclosure is useful for alleviating, preventing, and/or treating a disease or disorder mediated by C3 gene.

BRIEF DESCRIPTION OF DRAWINGS

[00472] FIG. 1 shows the inhibitory activity on C3 mRNA in BALB/c-HDI mice after administration of the siRNA conjugate as described in Example 2;

[00473] FIG. 2 shows representative histopathological images (H&E staining, 200x magnification) for each experimental group in Example 3;

[00474] FIG. 3 shows the inhibitory activity on C3 mRNA in HepG2 cells after administration of the siRNA conjugate as described in Example 4;

[00475] FIG. 4 shows the inhibitory activity on C3 mRNA in the liver of *Macaca fascicularis* after administration of the siRNA conjugate as described in Example 5;

[00476] FIG. 5 shows the change in the C3 protein level in the serum of *Macaca fascicularis* after administration of the siRNA conjugate as described in Example 6;

[00477] FIG. 6 shows the change in the activity of the alternative complement pathway in the serum of *Macaca fascicularis* after administration of the siRNA conjugate as described in Example 7;

[00478] FIG. 7 shows the change in the activity of the classical complement pathway in the serum of *Macaca fascicularis* after administration of the siRNA conjugate as described in Example 7;

[00479] FIG. 8 shows the inhibitory activity on the target gene in the liver of CFA-hIgA mice after administration of the siRNA conjugate as described in Example 8;

[00480] FIG. 9 shows the change in the C3 protein level in the serum of CFA-hIgA mice after administration of the siRNA conjugate as described in Example 8; and

[00481] FIG. 10 shows the change in C3 deposition in the kidneys of CFA-hIgA mice after administration of the siRNA conjugate as described in Example 8.

DETAILED DESCRIPTION

[00482] The present disclosure provides a double-stranded oligonucleotide for inhibiting C3 gene expression, a conjugate thereof, and uses thereof. A person skilled in the art can implement the present disclosure by referring to the content herein and appropriately modifying the process parameters. It is to be noted that all similar substitutions and modifications are obvious to a person skilled in the art and are considered to be included in the present disclosure. The methods and applications of the present disclosure have been described through preferred embodiments, and a person skilled in the art can obviously make modifications or appropriate changes and combinations to the methods and applications described herein without departing from the content, spirit, and scope of the present disclosure to realize and apply the technology of the present disclosure.

[00483] Term Explanation

[00484] In the present disclosure, the term "comprising" or "including" is an open-ended expression, meaning that it specifies certain contents described in the present disclosure, but does not exclude the presence of other, unlisted contents.

[00485] In the present disclosure, the terms "optionally", "optional", or "option" generally refer to an event or condition that is subsequently described that may or may not occur, and this description includes instances in which the event or condition occurs and instances in which it does not.

[00486] In the present disclosure, the term "small interfering RNA (siRNA)" is a double-stranded RNA of 17 to 25 nucleotides in length, comprising a sense strand and an antisense strand. An siRNA mediates target cleavage of an RNA transcript via the RISC pathway by forming an RNA-induced silencing complex (RISC). Specifically, an siRNA directs sequence-specific degradation of an mRNA through the known RNA interference (RNAi) process, thereby inhibiting the translation of the mRNA into amino acids and its conversion into a protein. For example, an siRNA can regulate (e.g., inhibit) the expression of C3 in a cell.

[00487] In the present disclosure, the term "antisense strand (or guide strand)" includes a region that is substantially complementary to a target sequence, such as the mRNA of C3. The "sense strand (or passenger strand)" refers to a siRNA strand that contains a sequence substantially complementary to the antisense strand. The term "substantially complementary" means fully complementary or at least partially complementary, for example, the antisense strand is fully

complementary or at least partially complementary to the target sequence. In the case of partial complementarity, mismatches can be present within the internal or terminal regions of the molecule, wherein the most tolerated mismatches are present within the terminal regions, for example, within 5, 4, 3, or 2 nucleotides of the 5'-end and/or 3'-end of the siRNA.

[00488] It should be noted that an antisense strand being "at least partially substantially complementary" to an mRNA means that the antisense strand has a polynucleotide that is substantially complementary to a contiguous portion of an mRNA of interest (e.g., an mRNA encoding C3). Alternatively, the antisense strand is complementary to at least a portion of the mRNA of C3 if a polynucleotide is substantially uninterruptedly complementary to a portion of the mRNA encoding C3.

[00489] In the present disclosure, the term "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of the C3 gene, including an mRNA that is a product of RNA processing of a primary transcript. C3 can be within a cell, for example, a cell in a subject.

[00490] In the present disclosure, the term "substantially complementary" means that the sense strand and the antisense strand have no more than 3 nucleotide mismatches, no more than 2 nucleotide mismatches, or no more than 1 nucleotide mismatch in the duplex region, for example, 3 nucleotide mismatches, 2 nucleotide mismatches, 1 nucleotide mismatch, or 0 nucleotide mismatches.

[00491] In the present disclosure, the terms "nucleotide difference" and "nucleotide base difference" are used interchangeably. A "nucleotide difference" exists between one nucleotide sequence and another nucleotide sequence when the type of base of the nucleotide at the same position has changed in the former compared to the latter. For example, when a nucleotide base at a certain position in the latter is A, and the corresponding nucleotide base at the same position in the former is U, C, G, or T, it is considered that a nucleotide difference exists between the two nucleotide sequences at that position. In some embodiments, when a nucleotide at the original position is replaced by an abasic nucleotide or an equivalent thereof, a nucleotide difference can also be considered to have been created at that position.

[00492] In the present disclosure, the term "overhang" refers to at least one unpaired nucleotide

that protrudes from the double-helical structure of a double-stranded oligonucleotide, and also refers to the nucleotide sequence in a siRNA structure other than the duplex region. For example, when the 3'-end of one strand in the sense strand and/or the antisense strand extends beyond the 5'-end of the other strand, or when the 5'-end of one strand in the sense strand and/or the antisense strand extends beyond the 3'-end of the other strand, a nucleotide overhang is present. The overhang may comprise at least one nucleotide, at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides, or more nucleotides. The nucleotide overhang may comprise or be composed of nucleotides or nucleoside analogs, including deoxynucleotides and deoxynucleosides. The overhang can be located on the sense strand, the antisense strand, or any combination thereof. In addition, the nucleotides of the overhang can appear at the 5'-end, the 3'-end, or both ends of the antisense or sense strand.

[00493] In the present disclosure, the term "DEPC H_2O" is ultrapure water (Type I water) that has been treated with diethyl pyrocarbonate (DEPC) and sterilized by high-temperature, high-pressure autoclaving.

[00494] In the present disclosure, the term "subject" refers to any animal being examined, studied, or treated, and is not intended to limit the present disclosure to any particular type of subject. In some embodiments of the present disclosure, a human is a preferred subject, while in other embodiments, a non-human animal is a preferred subject, including but not limited to a mouse, monkey, ferret, cow, sheep, goat, pig, chicken, turkey, dog, cat, horse, and reptile.

[00495] In the present disclosure, the term "inhibiting the expression of C3 gene" refers to any level of inhibition of the C3 gene expression, for example, at least partial inhibition of C3 gene expression, such as inhibition of at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%. Herein, the expression of the C3 gene can be evaluated based on the level of any variable associated with C3 gene expression, for example, the mRNA level or protein level of C3. Inhibition can be evaluated by a decrease in the absolute or relative level of one or more of these variables compared to a control level. A control level can be any type of control level utilized in

the art, for example, a baseline level before administration, or a level determined from a similar subject, cell, or sample that was not treated or was treated with a control (e.g., a buffer-only control or an inactive agent control).

[00496] In the present disclosure, unless otherwise specified, the siRNA sequences were synthesized by Kunshan Aotai Biotechnology Co., Ltd.; the PCR primers were synthesized by Sangon Biotech (Shanghai) Co., Ltd.; the human liver cancer HepG2 cells were purchased from Wuhan Procell Life Science & Technology Co., Ltd.; the experimental animal BALB/c mice were purchased from Zhejiang Vital River Laboratory Animal Technology Co. Ltd.; the CFA-hIgA nephropathy model mice were constructed by Peking University First Hospital; and the healthy *Macaca fascicularis* were purchased from Guangzhou Landao Biotechnology Co., Ltd.

[00497] In the present disclosure, unless otherwise specified, the base compositions and modifications are represented as follows: capital letters A, U, G, C, and T represent the base composition of the nucleotides, respectively; a lowercase letter m indicates that the nucleotide immediately to the left of the letter m is a 2'-O-methyl modified (alsonamed: 2'-methoxy modified) nucleotide; a lowercase letter f indicates that the nucleotide immediately to the left of the letter f is a 2'-fluoro modified nucleotide; a lowercase letter d indicates that the nucleotide immediately to the left of the letter d is a 2'-deoxy modified ribonucleic acid (also named: deoxyribonucleic acid); (moe) indicates that the nucleotide immediately to the left of the combination identifier (moe) is a 2'-O-methoxyethyl modified nucleotide; and a lowercase letter s indicates a phosphorothioate linkage between the two nucleotides immediately adjacent to the left and right of the letter s.

[00498] In the present disclosure, unless otherwise specified, the Real-time PCR detection data of the in vivo activity experiments described herein were subjected to relative quantification of the target gene mRNA in each test group using the ΔΔCt method. The calculation method is summarized as follows:

[00499] ΔCt (test group) = Ct (target gene in the test group) – Ct (internal reference gene in the test group)

[00500] ΔCt (control group) = Ct (target gene in the control group) – Ct (internal reference gene in the control group)

[00501] ΔΔCt (test group) = ΔCt (test group) - average ΔCt (control group)

[00502] ΔΔCt (control group) = ΔCt (control group) - average ΔCt (control group)

[00503] The mRNA expression level of the target gene in the test group is normalized with the control group as the baseline, and the remaining mRNA expression level of the target gene in the control group is defined as 100%.

[00504] Relative remaining mRNA expression level of the target gene in the test group = $2^{-\Delta\Delta Ct\ (test\ group)} \times 100\%$

[00505] mRNA inhibition rate of the target gene in the test group = 100% - relative remaining mRNA expression level of the target gene in the test group

[00506] For the C3 protein detection data at different time points in the in vivo activity experiments of the present disclosure, the calculation formula is:

$$\text{Relative remaining expression level of C3 protein} = \frac{Dx}{Pre-dose} \times 100\%$$

[00507] wherein, "pre-dose" represents the C3 protein concentration in the serum before administration, and "Dx" represents the C3 protein concentration in the serum on day x after administration.

[00508] For the CCP and CAP activity detection data at different time points in the in vivo activity experiments of the present disclosure, the calculation formula is:

$$\text{Relative remaining activity of CAP or CCP} = \frac{Dx}{Pre-dose} \times 100\%$$

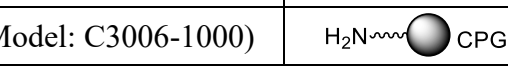
[00509] wherein, pre-dose represents the CCP activity or CAP activity in the serum before administration, and Dx represents the CCP activity or CAP activity in the serum on day x after administration.

[00510] In the present disclosure, unless otherwise specified, the in vivo activity experimental data are expressed as mean ± SD (X ± STDEV), and the experimental data were all plotted and analyzed using GraphPad Prism 8.0 software.

[00511] In the present disclosure, unless otherwise specified, the proportions of the reagents are calculated by volume ratio (v/v).

[00512] Unless otherwise specified, the reagents used in the preparation of the compounds in the present disclosure were purchased from Beijing Ouhe Technology Co., Ltd., and information of the main reagents is shown in Table 1.

[00513] Table 1: Main reagents

Reagent Name	Abbreviation	CAS No.
Lithium aluminum hydride ($LiAlH_4$)	-	16853-85-3
Wet palladium on carbon (10 wt%)	Pd/C	-
Palladium hydroxide on carbon (10 wt%)	$Pd(OH)_2/C$	-
O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate	HBTU	94790-37-1
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate	HATU	148893-10-1
4,4'-Dimethoxytrityl chloride / 4,4'-Dimethoxytriphenylchloromethane	DMTrCl	40615-36-9
bis(diisopropylamino)(2-cyanoethoxy)phosphine	-	102691-36-1
4,5-Dicyanoimidazole	DCI	1122-28-7
4-Dimethylaminopyridine	DMAP	1122-58-3
Amino-CPG (Aminoalkyl-CPG, Model: C3006-1000)		-
4M Hydrochloric acid in 1,4-dioxane solution	-	-
trans-4-(Boc-amino)cyclohexanecarboxaldehyde	-	181308-57-6
N-Benzyloxycarbonyl-4-aminobutanoic acid	-	5105-78-2
5-[[(2R,3R,4R,5R,6R)-3-Acetamido-4,5-diacetoxy-6-(acetoxymethyl)2-tetrahydropyranyl]oxy]pentanoic acid	Compound 4	1159408-54-4

[00514] wherein, CPG represents a Controlled Pore Glass support.

[00515] Unless otherwise specified, the reagents, consumables, instruments, and equipment used in the biological detection experiments in the present disclosure are all commercially available products. The main reagents and consumables and their sources are shown in Table 2, and the main instruments and equipment and their sources are shown in Table 3.

[00516] Table 2: Main reagents and consumables

Name	Manufacturer
Opti-MEM	GENOM Bio
MEM Medium	Gibco
FBS	Gibco
Penicilin-streptomycin	HyClone
Trypsin	Gibco

Power SYBR Green RNA-to-CT™ 1-Step	Thermo Fisher
1×PBS	Zhongke Maichen (Beijing) Technology Co., Ltd.
DMEM Medium	Zhongke Maichen (Beijing) Technology Co., Ltd.
Opti-MEM™ Medium	Gibco
Serum	Sigma
Trypsin	Zhongke Maichen (Beijing) Technology Co., Ltd.
Penicilin-streptomycin	BBI
Lipofectamine RNAiMax	Invitrogen
Nucleic Acid Extraction/Purification Kit	Zhejiang Hanwei Technology Co ltd
RevertAid First Strand cDNA Synthesis Kit	Thermo Fisher Scientific
TaqMan Fast Advanced Master Mix	Thermo Fisher Scientific
SYBR Select Master Mix	Thermo Fisher Scientific
Hanwei RNA Extraction Kit	Zhejiang Hanwei Technology Co ltd
RNALater™	Thermo Fisher Scientific
Ambion® RNAlater®	Invitrogen
Human Complement C3 ELISA Kit	Hycult Biotech
WIESLAB® Complement System Alternative Pathway - RUO	IBL America
WIESLAB® Complement System Classical Pathway- RUO	IBL America

[00517] Table 3: Main instruments and equipment

Name	Manufacturer
Automatic Nucleic Acid Extractor	Zhejiang Hanwei Technology Co ltd
High-Speed Refrigerated Centrifuge	Eppendorf
CO_2 Incubator	Thermo Fisher Scientific
Biosafety Cabinet	Shanghai Lishen
Constant Temperature Water Bath	Shanghai Boxun
Automatic Cell Counter	Shanghai Ruiyu
Inverted Microscope	Olympus
NANODROP OneC	Thermo Fisher Scientific
Gradient PCR Thermal Cycler	Eppendorf
CFX Opus 384	Bio-Rad
LightCycler 480	Roche
Gel Imaging System	Shanghai Tanon Life Science Co.,Ltd.
Electrophoresis System	BEIJING LIUYI BIOTECHNOLOGY CO.,LTD.

Tissuelyser II Automatic Tissue Homogenizer	Shanghaijingxin Experimental Technology
Real-Time Quantitative PCR System	Roche
Paraffin Microtome	JINHUA YIDI MEDICAL APPLIANCE CO.,LTD.
Tissue Processor	Leica
Automatic Biological Tissue Embedding System	JINHUA YIDI MEDICAL APPLIANCE CO.,LTD.
Automatic Modular Hematology and Body Fluid Analyzer	SYSMEX

[00518] The raw materials and reagents used for the double-stranded oligonucleotide for inhibiting C3 gene expression, the conjugate thereof, and the use thereof provided by the present disclosure are all commercially available.

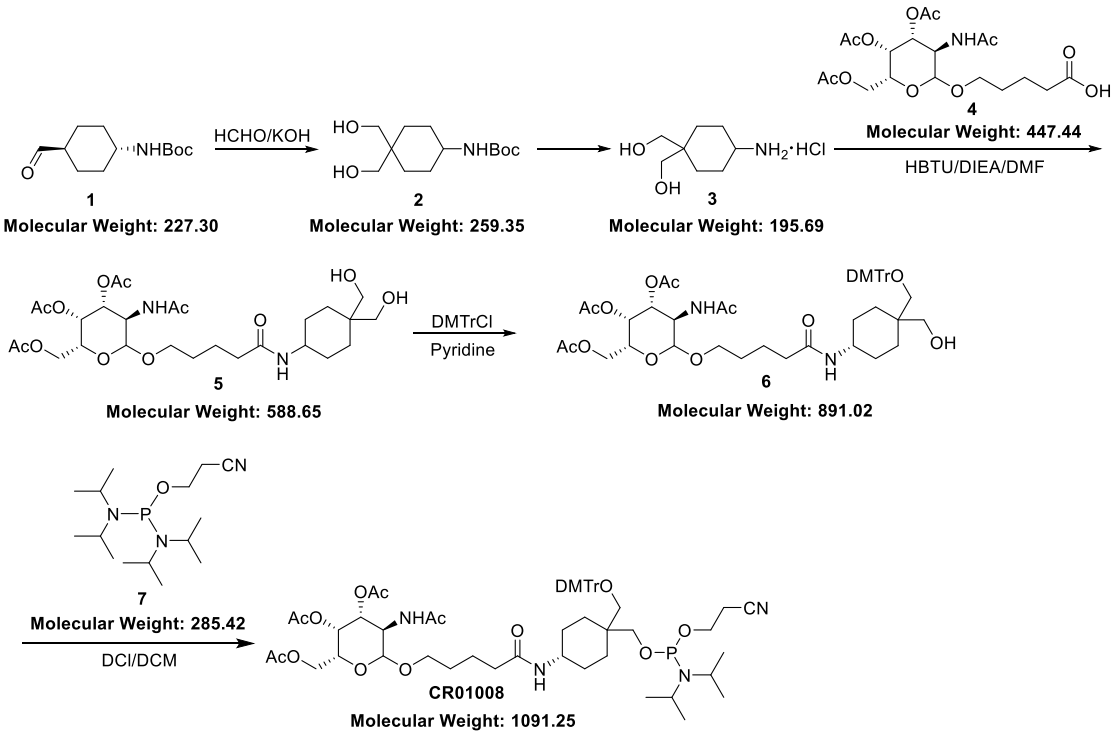
[00519] The present disclosure is further described below in conjunction with examples:

Preparation of compounds

Preparation Example 1: Preparation of Compound CR01008 and Compound CR01008Z

[00520] (1.1) Synthesis of Compound CR01008

[00521] In this preparation example, the synthetic route for compound CR01008 was:



[00522] (1.1.1) Synthesis of compound 2

[00523] Compound 1 (trans-4-(Boc-amino)cyclohexanecarboxaldehyde, 10.0 g, 1.0 eq) and an aqueous formaldehyde solution (8.9 g, 37 %, 2.4 eq) were dissolved in 33 mL of methanol. 13 mL of an aqueous KOH solution with a concentration of 45.3 % was added dropwise. After the addition was completed, the mixture was stirred and reacted at 25°C for 30 min, heated to 60°C, and reacted under reflux at 60°C for 2 h. After the reaction was completed, the reaction solution was cooled to room temperature and then evaporated to dryness under reduced pressure and a white solid crude product was obtained. A small amount of water was added to the crude product to form a slurry, which was then filtered, and compound 2 (9 g, yield 78.9%) was obtained as a white solid. MS-ESI (m/z) = 260 $[M+H]^+$.

[00524] (1.1.2) Synthesis of compound 3

[00525] Compound 2 (9 g, 1 eq) prepared according to step (1.1.1) was dissolved in 70 mL of 1,4-dioxane. A solution of hydrogen chloride in 1,4-dioxane (45 mL, 4 M) was added, and the mixture was stirred and reacted at 25°C for 1 hour. After the reaction was completed, the reaction solution was evaporated to dryness under reduced pressure, and compound 3 (6.8 g, yield 100%) was obtained as a white solid.

[00526] (1.1.3) Synthesis of compound 5

[00527] Compound 3 (1.8 g, 2.0 eq) prepared according to step (1.1.2), compound 4 (5-[[(2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)2-tetrahydropyranyl]oxy]pentanoic acid, 2.1 g, 1.0 eq), and DIEA (N,N-diisopropylethylamine, 3.5 g, 6.0 eq) were dissolved in 15 mL of DMF. HBTU (1.9 g, 1.1 eq) was added, and the mixture was stirred and reacted at 25°C for 3 h under an N_2 atmosphere. After the reaction was completed, the reaction solution was evaporated to dryness under reduced pressure and purified by reverse-phase chromatography (using a 22 vol% aqueous acetonitrile solution). Compound 5 (1.78 g, yield 64.4%) was obtained as a white solid. MS-ESI (m/z) = 589 $[M+H]^+$.

[00528] (1.1.4) Synthesis of compound 6

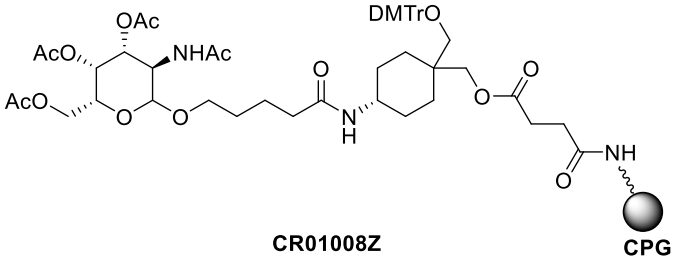
[00529] Compound 5 (1.54 g, 1.0 eq) prepared according to step (1.1.3) was dissolved in 15 mL of pyridine. The reaction system was cooled to 0°C with an ice-water bath, and DMTrCl (4,4'-dimethoxytrityl chloride, 1.32 g, 1.5 eq) was added at 0°C. The mixture was reacted at 25°C for 3 h, and the reaction was quenched by adding 15 mL of methanol to the reaction solution. After the reaction was completed, the reaction solution was evaporated to dryness under reduced pressure and the residue was purified by reverse-phase chromatography (using a 60 vol% aqueous solution of acetonitrile). Compound 6 (1 g, yield 42.7%) was obtained as a yellow solid. MS-ESI (m/z) = 891 $[M+H]^+$.

[00530] (1.1.5) Synthesis of compound CR01008

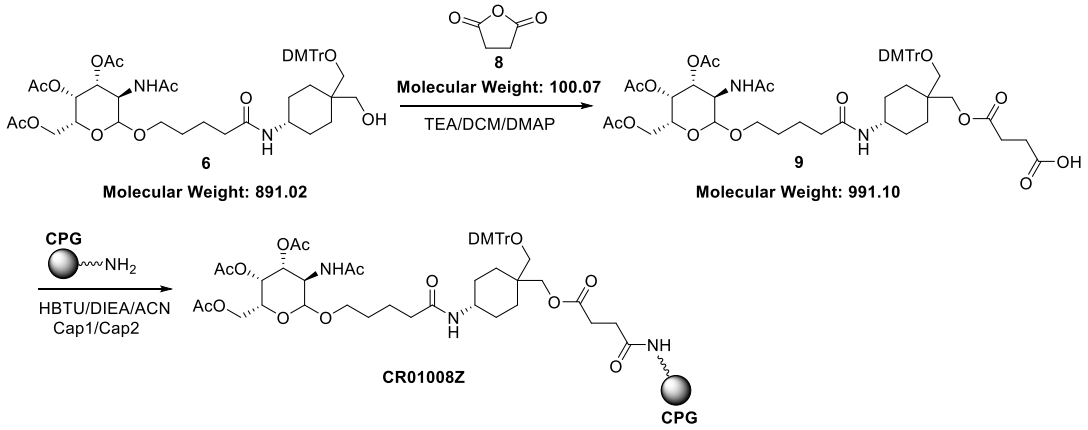
[00531] Compound 6 (1.08 g, 1.0 eq) prepared according to step (1.1.4) was dissolved in 20 mL of anhydrous dichloromethane. DCI (115 mg, 0.8 eq) and compound 7 (bis(diisopropylamino)(2-cyanoethoxy)phosphine, 732 mg, 2.1 eq) were added respectively. The atmosphere was purged with nitrogen 3 times, and the mixture was stirred and reacted at 25°C for 2 h. After the reaction was completed, 20 mL of a saturated aqueous sodium bicarbonate solution was added to the reaction solution, and the mixture was extracted 3 times with 20 mL of dichloromethane (3×20 mL). The organic phases were combined and evaporated to dryness under reduced pressure, and the residue was purified by reverse-phase chromatography (using a 72 vol% aqueous acetonitrile solution), and then dried under vacuum for 12 h. Compound CR01008 (1 g, yield 76.0%) was obtained as a white powder. MS-ESI (m/z) = 1091 $[M+Na]^+$.

[00532] 1H NMR (400 MHz, DMSO-d6) δ 1.05 (d, J = 6.7 Hz, 6H).1.14 (d, J = 6.7 Hz, 6H), 1.37 – 1.17 (m, 5H), 1.60 – 1.40 (m, 6H),1.68 – 1.62 (m, 1H),1.80 (s, 3H),1.80 (s, 3H),1.92 (s, 3H), 2.02 (s, 5H),2.13 (s, 3H),2.71 (t, J = 5.9 Hz, 2H), 2.79 (d, J = 8.4 Hz, 1H), 2.87 (d, J = 8.4 Hz, 1H),3.36 (s, 1H), 3.58 – 3.39 (m, 3H), 3.69 – 3.60 (m, 2H), 3.75 (s, 7H), 3.90 (dt, J = 11.2, 8.8 Hz, 1H), 4.05 (s, 3H),4.51 (d, J = 8.4 Hz, 1H), 4.99 (dd, J = 11.3, 3.4 Hz, 1H), 5.24 (d, J = 3.4 Hz, 1H), 5.78 (s, 1H), 6.93 – 6.87 (m, 4H),7.35 – 7.21 (m, 7H), 7.44 – 7.37 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H).

[00533] (1.2) Synthesis of Compound CR01008Z



[00534] In this preparation example, the synthetic route for compound CR01008Z was:



[00535] (1.2.1) Synthesis of compound 9

[00536] Compound 6 (500 mg) prepared according to step (1.1.4) was dissolved in 10 mL of dichloromethane. Compound 8 (succinic anhydride, 112 mg), DMAP (6.8 mg), and TEA (226.2 mg) were added. The atmosphere was purged with nitrogen 3 times, and the mixture was stirred and reacted at 25°C for 16 h. The residue was purified by flash chromatography, and compound 9 (300 mg, yield 53.6%) was obtained. MS-ESI (m/z) = 1013 $[M+Na]^+$.

[00537] (1.2.2) Synthesis of compound CR01008Z

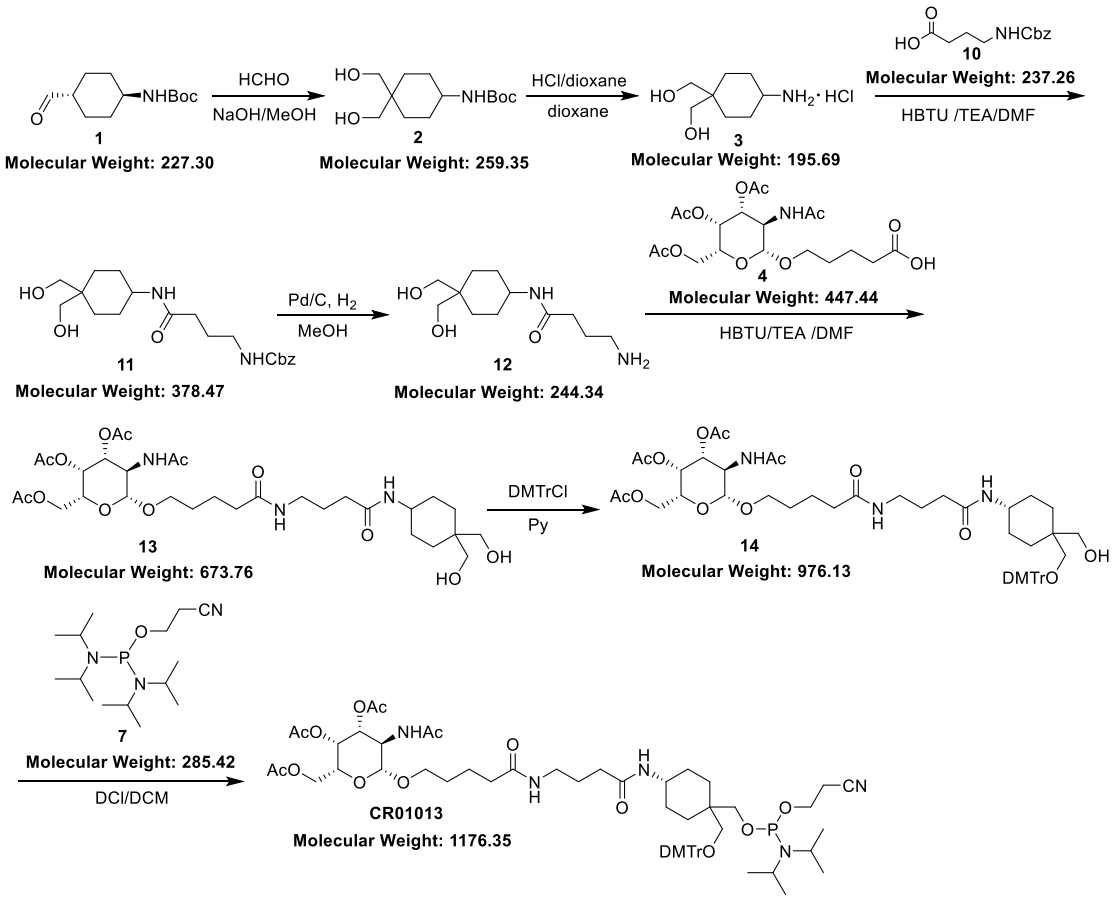
[00538] Compound 9 (50 mg) prepared according to step (1.2.1), amino-CPG (1.25 g, 80 μmol/g, 0.1 mmol), HBTU (27 mg), and DIEA (12 mg) were added to a 20 mL vial. The mixture was reacted on a shaker for 16 h. After the reaction was completed, the reaction mixture was filtered and a filter cake was obtained. The filter cake was first washed once with 10 mL of acetonitrile (1 × 10 mL) and then dried under vacuum. The dried filter cake, DMAP (3 mg), Cap1 (10 mL, 200V), and Cap2 (1 mL, 20V) were added to a 20 mL vial. The mixture was reacted on a shaker for 6 h. After the reaction was completed, the reaction mixture was filtered and a filter cake was obtained. The filter cake was first washed once with 10 mL of acetonitrile (1 × 10 mL) and then dried under vacuum, and compound CR01008Z (1.03 g, loading capacity 20 to 30 μmol/g) was obtained.

[00539] Wherein Cap1 and Cap2 are capping reagents, Cap1 is a 20 vol% solution of N-methylimidazole in a mixed solution of pyridine/acetonitrile, with a volume ratio of pyridine to acetonitrile of 3:5; and Cap2 is a 20 vol% solution of acetic anhydride in acetonitrile.

Preparation Example 2: Preparation of Compound CR01013 and Compound CR01013Z

[00540] (2.1) Preparation of Compound CR01013

[00541] In this preparation example, the synthetic route for compound CR01013 was:



[00542] (2.1.1) Synthesis of compound 2

[00543] Compound 1 (trans-4-(Boc-amino)cyclohexanecarbaldehyde, 4.9 g) was dissolved in 17 mL of methanol. An aqueous formaldehyde solution (4.21 g, with a concentration of 37 %) and an aqueous sodium hydroxide solution (6.5 mL, with a concentration of 45.3 %) were added dropwise. After the addition was completed, the mixture was heated to 60°C and stirred and reacted at 60°C for 2 h. After the reaction was completed, the reaction solution was cooled to 25°C and then evaporated to dryness under reduced pressure. A white solid crude product was obtained. A small amount of water was added to the crude product to form a slurry, which was then filtered and dried, and compound 2 (4.8 g, yield 85.9%) was obtained as a white solid. ESI-MS (m/z) = 260.2 $[M+H]^+$.

[00544] (2.1.2) Synthesis of compound 3

[00545] Compound 2 (4.8 g) prepared according to step (2.1.1) was dissolved in 25 mL of 1,4-dioxane. A solution of hydrochloric acid in 1,4-dioxane (25 mL, 4 M) was added, and the mixture was stirred and reacted at 25°C for 2 h. After the reaction was completed, the reaction solution was

evaporated to dryness under reduced pressure and compound 3 (3.6 g, yield 99.4%) was obtained as a white solid.

[00546] (2.1.3) Synthesis of compound 11

[00547] Compound 3 (3.6 g) prepared according to step (2.1.2) was dissolved in 36 mL of DMF, and then TEA (5.62 g), compound 10 (N-benzyloxycarbonyl-4-aminobutanoic acid, 5.28 g), and HBTU (8.43 g) were added. The mixture was stirred and reacted at 25°C for 16 h. After the reaction was completed, the reaction solution was added to 200 mL of a saturated aqueous sodium bicarbonate solution and extracted three times with 100 mL of ethyl acetate (3 × 100 mL). The organic phases were combined. The combined organic phase was first washed once with 50 mL of a saturated aqueous sodium chloride solution (1 × 50 mL) and then dried over anhydrous sodium sulfate. The organic phase was evaporated to dryness under reduced pressure and the residue was purified by normal-phase column chromatography (eluent: dichloromethane/methanol = 10/1, v/v). Compound 11 (2.3 g, yield 33.0%) was obtained as a white solid. ESI-MS (m/z) = 379.5 $[M+H]^+$.

[00548] (2.1.4) Synthesis of compound 12

[00549] Compound 11 (2.3 g) prepared in step (2.1.3) was dissolved in 23 mL of methanol. Wet palladium on carbon (230 mg, 10 % loading) was added. The atmosphere was purged with hydrogen three times, and the reaction system was stirred and reacted at 25°C for 16 h under a hydrogen atmosphere (15 psi). After the reaction was completed, the reaction mixture was filtered and a filtrate was obtained. The filtrate was evaporated to dryness under reduced pressure and compound 12 (1.48 g, yield 99.8%) was obtained as a yellow oil.

[00550] (2.1.5) Synthesis of compound 13

[00551] Compound 12 (1.48 g) prepared in step (2.1.4) was dissolved in 15 mL of DMF. Triethylamine (TEA, 1.22 g), compound 4 (1.35 g), and HBTU (3.45 g) were added, and the mixture was stirred and reacted at 25°C for 16 h. After the reaction was completed, the reaction solution was added to 150 mL of a saturated aqueous sodium bicarbonate solution and extracted three times with 50 mL of ethyl acetate (3 × 50 mL). The organic phases were combined. The combined organic phase was first washed once with 30 mL of a saturated aqueous sodium chloride solution (1 × 30 mL) and then dried over anhydrous sodium sulfate. The organic phase was evaporated to dryness under reduced pressure and the residue was purified by reverse-phase

column chromatography (C18 column, eluent: water/acetonitrile = 5/1, v/v). Compound 13 (1.3 g, yield 31.8%) was obtained as a white solid. ESI-MS (m/z): 674.3 [M+H]+.

[00552] (2.1.6) Synthesis of compound 14

[00553] Compound 13 (1.1 g) prepared in step (2.1.5) was dissolved in 11 mL of pyridine. The reaction system was cooled to 0°C with an ice-water bath, and DMTrCl (813 mg) was added in portions at 0°C. The reaction system was stirred at 0°C for 1 hour. After the reaction was completed, the reaction was quenched by adding methanol to the reaction solution, the solvent was evaporated, and the residue was purified by reverse-phase column chromatography (eluent: water/acetonitrile = 1/4, v/v). Compound 14 (800 mg, yield 50.3%) was obtained as a white solid. ESI-MS (m/z): 976.5 $[M+H]^+$.

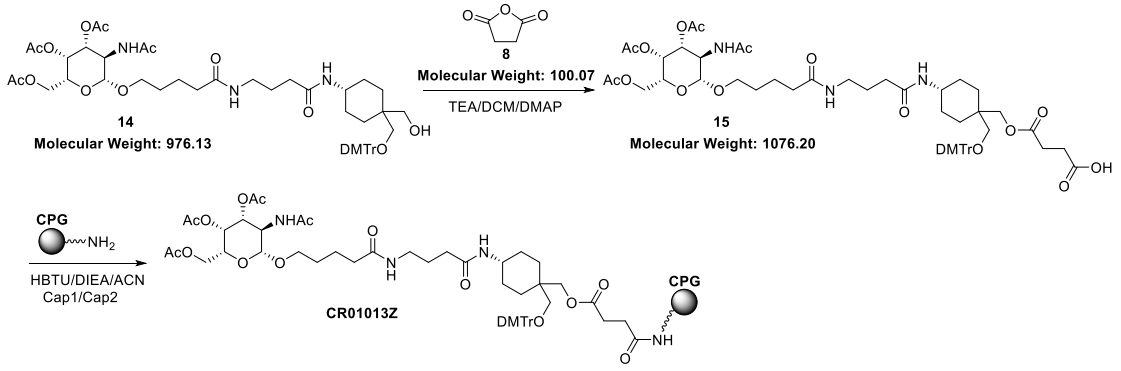
[00554] (2.1.7) Synthesis of compound CR01013

[00555] At 25°C, compound 14 (550 mg) prepared according to step (2.1.6) was dissolved in 5 mL of dichloromethane (DCM). 4,5-dicyanoimidazole (DCI, 53.2 mg) and compound 7 (2-cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite, 255.4 mg) were added. The atmosphere was purged with nitrogen three times, and the reaction system was stirred and reacted at 25°C for 1 hour under a nitrogen atmosphere. After the reaction was completed, the reaction solution was first washed twice with 5 mL of a saturated aqueous sodium bicarbonate solution (2 × 5 mL) and then washed once with 30 mL of a saturated aqueous sodium chloride solution (1 × 30 mL). The organic phase was separated, dried over anhydrous sodium sulfate, and the solvent in the organic phase was evaporated under reduced pressure. The residue was purified by normal-phase column chromatography (eluent: dichloromethane/methanol = 20/1, v/v) and compound CR01013 (532 mg, yield 80.4%) was obtained as a white solid. ESI-MS (m/z): 1176.7 $[M+H]^+$.

[00556] 1H NMR (400 MHz, DMSO-d6) δ 0.95 – 1.05 (d, J = 6.7 Hz, 5H), 1.06 – 1.15 (q, J = 7.6 Hz, 8H), 1.15 – 1.21 (t, J = 7.2 Hz, 14H), 1.72 – 1.80 (s, 3H), 1.84 – 1.92 (s, 3H), 1.94 – 2.07 (d, J = 16.0 Hz, 7H), 2.07 – 2.14 (s, 3H), 2.64 – 2.72 (q, J = 5.8 Hz, 2H), 2.74 – 2.89 (d, J = 8.5 Hz, 2H), 3.35 – 3.56 (m, 4H), 3.57 – 3.70 (m, 4H), 3.71 – 3.77 (s, 6H), 3.81 – 3.93 (m, 1H), 3.96 – 4.09 (d, J = 6.4 Hz, 3H), 6.82 – 6.97 (d, J = 8.7 Hz, 4H), 7.17 – 7.27 (t, J = 8.7 Hz, 5H), 7.27 – 7.34 (t, J = 7.6 Hz, 2H), 7.34 – 7.43 (d, J = 7.5 Hz, 2H).

[00557] (2.2) Preparation of Compound CR01013Z

[00558] In this preparation example, the synthetic route for compound CR01013Z was:



[00559] (2.2.1) Synthesis of compound 15

[00560] At 25°C, compound 14 (100 mg, 0.10 mmol) prepared according to step (2.1.6) was dissolved in 2 mL of dichloromethane. Triethylamine (25.9 mg, 0.25 mmol), DMAP (1.25 mg, 0.01 mmol), and compound 8 (succinic anhydride, 15.4 mg, 0.15 mmol) were added. The reaction system was stirred at 25°C for 16 h. After the reaction was completed, the solvent in the reaction solution was evaporated, and the residue was purified by reverse-phase column chromatography (C18 column, eluent: water/acetonitrile = 2/1, v/v). Compound 15 (110 mg, 0.10 mmol, yield 100%) was obtained as a yellow oil. ESI-MS (m/z) = 1099.3 $[M+Na]^+$.

[00561] (2.2.2) Synthesis of compound CR01013Z

[00562] Compound 15 (50 mg, 0.04 mmol) prepared according to step (2.2.1) was dissolved in 10 mL of acetonitrile. HBTU (24.2 mg, 0.06 mmol), DIEA (11.0 mg, 0.08 mmol), and amino-CPG (1.06 g, loading capacity 80 μmol/g) were added. The reaction system was stirred and reacted at 25°C for 16 h. After the reaction was completed, the reaction mixture was filtered to obtain a filter cake. The filter cake was first washed sequentially twice with 50 mL of dichloromethane (2 × 50 mL), three times with 50 mL of acetonitrile (3 × 50 mL), and once with 50 mL of ethyl acetate (1 × 50 mL), and then dried under vacuum. To the dried filter cake were added Cap1 (4.8 mL), Cap2 (0.54 mL), and DMAP (2.59 mg). The reaction system was stirred and reacted at 25°C for 5 h. After the reaction was completed, the reaction mixture was filtered and a filter cake was obtained. The filter cake was washed three times with 50 mL of acetonitrile (3 × 50 mL) and dried under vacuum. Compound CR01013Z (900 mg, with a loading capacity of 20 to 30 μmol/g) was obtained.

[00563] Wherein Cap1 and Cap2 are capping reagents, Cap1 is a 20 vol% solution of N-

methylimidazole in a mixed solution of pyridine/acetonitrile with a volume ratio of pyridine to acetonitrile of 3:5; and Cap2 is a 20 vol% solution of acetic anhydride in acetonitrile.

Preparation of siRNA/siRNA Conjugates

Preparation Example 3: Preparation of siRNA

[00564] (3.1) Synthesis of sense strand (SS)

[00565] Using the phosphoramidite solid-phase nucleic acid synthesis method, nucleoside monomers were linked sequentially in a 3' to 5' direction. Each cycle of nucleoside monomer addition included four reaction steps: deprotection, coupling, capping, and oxidation or sulfurization. The synthesis conditions were as follows.

[00566] The nucleoside monomers were prepared as 0.1 M solutions of the nucleoside monomer in acetonitrile.

[00567] The conditions for the deprotection reaction were the same for each step. The conditions for the deprotection reaction were: a temperature of 25°C, a reaction time of 70 s, and the deprotection reagent was a 3 vol% solution of dichloroacetic acid in dichloromethane, wherein the molar ratio of dichloroacetic acid to the 4,4'-dimethoxytrityl protecting group on the solid-phase support was 5:1.

[00568] The conditions for the coupling reaction were the same for each step. The conditions for the coupling reaction were: a temperature of 25°C, a molar ratio of the nucleic acid sequence linked on the solid-phase support to the nucleoside monomer of 1:10, a molar ratio of the nucleic acid sequence linked on the solid-phase support to the coupling reagent of 1:65, a reaction time of 600 s, the coupling reagent was a 0.5 M solution of 5-ethylthio-1H-tetrazole in acetonitrile, and the thiolation reagent was a 0.2 M solution of xanthane hydride in a mixed solution of acetonitrile/pyridine (the volume ratio of acetonitrile to pyridine was 1:1).

[00569] The conditions for the capping reaction were the same for each step. The conditions for the capping reaction were: a temperature of 25°C; a reaction time of 2 min; the capping reagent solution was a mixed solution of Cap1 and Cap2 in a molar ratio of 1:1, where Cap1 was a 20 vol% solution of N-methylimidazole in a mixed solution of pyridine/acetonitrile with a volume ratio of

pyridine to acetonitrile of 3:5, and Cap2 was a 20 vol% solution of acetic anhydride in acetonitrile; the molar ratio of N-methylimidazole in the Cap1 capping reagent, acetic anhydride in the Cap2 capping reagent, and the nucleic acid sequence linked on the solid-phase support was 1:1:1.

[00570] The conditions for the oxidation reaction were the same for each step. The conditions for the oxidation reaction were: a temperature of 25°C; a reaction time of 3 s; the oxidizing reagent was a 0.05 M aqueous iodine solution, with a molar ratio of iodine to the nucleic acid sequence linked on the solid-phase support of 30:1; and the oxidation reaction was performed in a mixed solvent of water/pyridine (the volume ratio of water to pyridine was 1:9). The conditions for the sulfurization reaction were: a temperature of 25°C; a reaction time of 360 s; the thiolation reagent was a 0.2 M solution of xanthane hydride in pyridine, with a molar ratio of the thiolation reagent to the nucleic acid sequence linked on the solid-phase support of 4:1; and the sulfurization reaction was performed in a mixed solvent of water/pyridine (the volume ratio of water to pyridine was 1:9).

[00571] After the last nucleoside monomer was linked, the nucleic acid moleculars linked on the solid-phase support was subjected to cleavage, deprotection, purification, desalting, and lyophilization sequentially, and the sense strands were obtained.

[00572] Cleavage and deprotection conditions were as follows: the synthesized nucleotide molecular linked to the solid-phase support was added to a 25 % aqueous ammonia solution, with the amount of aqueous ammonia being 0.5 mL/μmol, and the mixture was reacted at 55°C for 16 h. The solvent was removed, and the residue was concentrated to dryness under vacuum. After the aqueous ammonia treatment, the product was dissolved using 0.4 mL of N-methylpyrrolidone per μmol of the single-stranded nucleic acid, and 0.3 mL of triethylamine per μmol and 0.6 mL of triethylamine trihydrofluoride per μmol were added to remove the 2'-O-TBDMS protecting group on the ribose.

[00573] Purification and desalting conditions: Purification of the nucleic acid was accomplished by NaCl gradient elution using a preparative ion-exchange chromatography column (Source 15Q). Specifically: Eluent 1 was 20 mM sodium phosphate (pH=8.1) in a mixed solvent of water/acetonitrile (volume ratio of water to acetonitrile was 9:1); Eluent 2 was 1.5 M sodium chloride, 20 mM sodium phosphate (pH=8.1), in a mixed solvent of water/acetonitrile (volume ratio of water to acetonitrile was 9:1); and the elution gradient was from Eluent 1:Eluent 2 = (100:0)

to (50:50). The product elution fractions were collected and combined, and desalting was performed using a reverse-phase chromatography column. The desalting conditions included desalting using a dextran gel column, with the packing material being dextran gel G25, and eluting with deionized water.

[00574] Detection: Purity was detected using ion-exchange chromatography (IEX-HPLC); molecular weight was detected using liquid chromatography-mass spectrometry (LC-MS). The measured value of the molecular weight was compared with the theoretical value. If the measured value and the theoretical value were consistent, it indicated that the sense strand of the siRNA was obtained.

[00575] (3.2) Synthesis of antisense strand (AS)

[00576] A universal solid-phase support was used to synthesize the antisense strand. The conditions for deprotection, coupling, capping, and oxidation or sulfurization reactions, the conditions for cleavage and deprotection, and the processes and conditions for purification and desalting in the solid-phase synthesis method of the antisense strand were the same as those for the synthesis of the sense strand in step (3.1).

[00577] Detection: Purity was detected using ion-exchange chromatography (IEX-HPLC); molecular weight was detected using liquid chromatography-mass spectrometry (LC-MS). The measured value of the molecular weight was compared with the theoretical value. If the measured value and the theoretical value were consistent, it indicated that the antisense strand of the siRNA was obtained.

[00578] (3.3) Synthesis of siRNA duplex

[00579] The sense strand synthesized in step (3.1) and the antisense strand synthesized in step (3.2) were mixed in an equimolar ratio, dissolved in water for injection, and heated to 95°C. The mixture was slowly cooled to room temperature and held at room temperature for 10 min. The sense and antisense strands were allowed to form a double-stranded structure through hydrogen bonds, and siRNAs having the sense and antisense strands shown in Tables 4 to 7 were obtained.

[00580] Table 4: Sequence Information of siRNAs

siRNA No.	sense strand (5'-3')	antisense strand (5'-3')

RN002001	GUCCACGACUUCCCAGGCA	SEQ ID NO: 1	UGCCUGGGAAGUCGUGGACAG	SEQ ID NO: 213
RN002002	CCACGACUUCCCAGGCAAA	SEQ ID NO: 2	UUUGCCUGGGAAGUCGUGGAC	SEQ ID NO: 214
RN002003	CACGACUUCCCAGGCAAAA	SEQ ID NO: 3	UUUUGCCUGGGAAGUCGUGGA	SEQ ID NO: 215
RN002004	GUGCUGUCCAGUGAGAAGA	SEQ ID NO: 4	UCUUCUCACUGGACAGCACUA	SEQ ID NO: 216
RN002005	GCUGUCCAGUGAGAAGACU	SEQ ID NO: 5	AGUCUUCUCACUGGACAGCAC	SEQ ID NO: 217
RN002006	CAGAGCGGGUACCUCUUCA	SEQ ID NO: 6	UGAAGAGGUACCCGCUCUGCA	SEQ ID NO: 218
RN002007	GCGGGUACCUCUUCAUCCA	SEQ ID NO: 7	UGGAUGAAGAGGUACCCGCUC	SEQ ID NO: 219
RN002008	CAGACAGACAAGACCAUCU	SEQ ID NO: 8	AGAUGGUCUUGUCUGUCUGGA	SEQ ID NO: 220
RN002009	GGAUCUUCACCGUCAACCA	SEQ ID NO: 9	UGGUUGACGGUGAAGAUCCGA	SEQ ID NO: 221
RN002010	CCGUCAACCACAAGCUGCU	SEQ ID NO: 10	AGCAGCUUGUGGUUGACGGUG	SEQ ID NO: 222
RN002011	CGUCAACCACAAGCUGCUA	SEQ ID NO: 11	UAGCAGCUUGUGGUUGACGGU	SEQ ID NO: 223
RN002012	CGGUCAAGCAGGACUCCUU	SEQ ID NO: 12	AAGGAGUCCUGCUUGACCGGG	SEQ ID NO: 224
RN002013	GUCAAGCAGGACUCCUUGU	SEQ ID NO: 13	ACAAGGAGUCCUGCUUGACCG	SEQ ID NO: 225
RN002014	CAAGCAGGACUCCUUGUCU	SEQ ID NO: 14	AGACAAGGAGUCCUGCUUGAC	SEQ ID NO: 226
RN002015	CUUGGGACAUUCCGGAACU	SEQ ID NO: 15	AGUUCCGGAAUGUCCCAAGAC	SEQ ID NO: 227
RN002016	GGGACAUUCCGGAACUCGU	SEQ ID NO: 16	ACGAGUUCCGGAAUGUCCCAA	SEQ ID NO: 228
RN002017	CAGUGGAAGAUCCGAGCCU	SEQ ID NO: 17	AGGCUCGGAUCUUCCACUGGC	SEQ ID NO: 229
RN002018	AGUGGAAGAUCCGAGCCUA	SEQ ID NO: 18	UAGGCUCGGAUCUUCCACUGG	SEQ ID NO: 230
RN002019	GGAAGAUCCGAGCCUACUA	SEQ ID NO: 19	UAGUAGGCUCGGAUCUUCCAC	SEQ ID NO: 231
RN002020	GAAGAUCCGAGCCUACUAU	SEQ ID NO: 20	AUAGUAGGCUCGGAUCUUCCA	SEQ ID NO: 232
RN002021	GAUCCGAGCCUACUAUGAA	SEQ ID NO: 21	UUCAUAGUAGGCUCGGAUCUU	SEQ ID NO: 233
RN002022	AGUUUGAGGUGAAGGAGUA	SEQ ID NO: 22	UACUCCUUCACCUCAAACUCA	SEQID No.234
RN002023	GCCCAGUUUCGAGGUCAUA	SEQ ID NO: 23	UAUGACCUCGAAACUGGGCAG	SEQ ID NO: 235
RN002024	CCAGUUUCGAGGUCAUAGU	SEQ ID NO: 24	ACUAUGACCUCGAAACUGGGC	SEQ ID NO: 236
RN002025	CAGUUUCGAGGUCAUAGUG	SEQ ID NO: 25	CACUAUGACCUCGAAACUGGG	SEQ ID NO: 237
RN002026	GUUUCGAGGUCAUAGUGGA	SEQ ID NO: 26	UCCACUAUGACCUCGAAACUG	SEQ ID NO: 238
RN002027	CGAGGUCAUAGUGGAGCCU	SEQ ID NO: 27	AGGCUCCACUAUGACCUCGAA	SEQ ID NO: 239
RN002028	AGUGGAGCCUACAGAGAAA	SEQ ID NO: 28	UUUCUCUGUAGGCUCCACUAU	SEQ ID NO: 240
RN002029	CAGAGAAAUUCUACUACAU	SEQ ID NO: 29	AUGUAGUAGAAUUUCUCUGUA	SEQ ID NO: 241
RN002030	AAAUUCUACUACAUCUAUA	SEQ ID	UAUAGAUGUAGUAGAAUUUCU	SEQ ID

		NO: 30		NO: 242
RN002031	GGAACUGCCUUUGUCAUCU	SEQ ID NO: 31	AGAUGACAAAGGCAGUUCCCU	SEQ ID NO: 243
RN002032	GAACUGCCUUUGUCAUCUU	SEQ ID NO: 32	AAGAUGACAAAGGCAGUUCCC	SEQ ID NO: 244
RN002033	CCUUUGUCAUCUUCGGGAU	SEQ ID NO: 33	AUCCCGAAGAUGACAAAGGCA	SEQ ID NO: 245
RN002034	CUGAAUCCCUCAAGCGCAU	SEQ ID NO: 34	AUGCGCUUGAGGGAUUCAGGC	SEQ ID NO: 246
RN002035	CAGGCAGUGACAUGGUGCA	SEQ ID NO: 35	UGCACCAUGUCACUGCCUGAG	SEQ ID NO: 247
RN002036	GUGACCUCUCCCUACCAGA	SEQ ID NO: 36	UCUGGUAGGGAGAGGUCACGA	SEQ ID NO: 248
RN002037	GAAUGCCCUUUGACCUCAU	SEQ ID NO: 37	AUGAGGUCAAAGGGCAUUCCU	SEQ ID NO: 249
RN002038	CCUUUGACCUCAUGGUGUU	SEQ ID NO: 38	AACACCAUGAGGUCAAAGGGC	SEQ ID NO: 250
RN002039	GACCUCAUGGUGUUCGUGA	SEQ ID NO: 39	UCACGAACACCAUGAGGUCAA	SEQ ID NO: 251
RN002040	CUCAUGGUGUUCGUGACGA	SEQ ID NO: 40	UCGUCACGAACACCAUGAGGU	SEQ ID NO: 252
RN002041	UCAUGGUGUUCGUGACGAA	SEQ ID NO: 41	UUCGUCACGAACACCAUGAGG	SEQ ID NO: 253
RN002042	CUGUGCAGUCUCUAACCCA	SEQ ID NO: 42	UGGGUUAGAGACUGCACAGUG	SEQ ID NO: 254
RN002043	GCCAGAAGCCCUUGAGCAU	SEQ ID NO: 43	AUGCUCAAGGGCUUCUGGCUG	SEQ ID NO: 255
RN002044	CAGAAGCCCUUGAGCAUCA	SEQ ID NO: 44	UGAUGCUCAAGGGCUUCUGGC	SEQ ID NO: 256
RN002045	GCAUCACGGUGCGCACGAA	SEQ ID NO: 45	UUCGUGCGCACCGUGAUGCUC	SEQ ID NO: 257
RN002046	CGGUGCGCACGAAGAAGCA	SEQ ID NO: 46	UGCUUCUUCGUGCGCACCGUG	SEQ ID NO: 258
RN002047	CCGUGGGCAACUCCAACAA	SEQ ID NO: 47	UUGUUGGAGUUGCCCACGGUG	SEQ ID NO: 259
RN002048	CGUGGGCAACUCCAACAAU	SEQ ID NO: 48	AUUGUUGGAGUUGCCCACGGU	SEQ ID NO: 260
RN002049	GUGGGCAACUCCAACAAUU	SEQ ID NO: 49	AAUUGUUGGAGUUGCCCACGG	SEQ ID NO: 261
RN002050	GCAACUCCAACAAUUACCU	SEQ ID NO: 50	AGGUAAUUGUUGGAGUUGCCC	SEQ ID NO: 262
RN002051	CUCCAACAAUUACCUGCAU	SEQ ID NO: 51	AUGCAGGUAAUUGUUGGAGUU	SEQ ID NO: 263
RN002052	GGGGAGACCCUCAACGUCA	SEQ ID NO: 52	UGACGUUGAGGGUCUCCCCGG	SEQ ID NO: 264
RN002053	GGGAGACCCUCAACGUCAA	SEQ ID NO: 53	UUGACGUUGAGGGUCUCCCCG	SEQ ID NO: 265
RN002054	GAGACCCUCAACGUCAACU	SEQ ID NO: 54	AGUUGACGUUGAGGGUCUCCC	SEQ ID NO: 266
RN002055	CCCUCAACGUCAACUUCCU	SEQ ID NO: 55	AGGAAGUUGACGUUGAGGGUC	SEQ ID NO: 267
RN002056	UCAACUUCCUCCUGCGAAU	SEQ ID NO: 56	AUUCGCAGGAGGAAGUUGACG	SEQ ID NO: 268
RN002057	GAGGCCAAGAUCCGCUACU	SEQ ID NO: 57	AGUAGCGGAUCUUGGCCUCGU	SEQ ID NO: 269
RN002058	AGAUCCGCUACUACACCUA	SEQ ID NO: 58	UAGGUGUAGUAGCGGAUCUUG	SEQ ID NO: 270
RN002059	CGCUACUACACCUACCUGA	SEQ ID NO: 59	UCAGGUAGGUGUAGUAGCGGA	SEQ ID NO: 271

RN002060	GCUACUACACCUACCUGAU	SEQ ID NO: 60	AUCAGGUAGGUGUAGUAGCGG	SEQ ID NO: 272
RN002061	CCGUGUGGGUGGACGUCAA	SEQ ID NO: 61	UUGACGUCCACCCACACGGAG	SEQ ID NO: 273
RN002062	GGGCUCGCUGGUGGUAAAA	SEQ ID NO: 62	UUUUACCACCAGCGAGCCCAC	SEQ ID NO: 274
RN002063	CCCUGAAGAUAGAGGGUGA	SEQ ID NO: 63	UCACCCUCUAUCUUCAGGGUC	SEQ ID NO: 275
RN002064	CGGGAGAACCCCAUGAGGU	SEQ ID NO: 64	ACCUCAUGGGGUUCUCCCGCA	SEQ ID NO: 276
RN002065	GGGAGAACCCCAUGAGGUU	SEQ ID NO: 65	AACCUCAUGGGGUUCUCCCGC	SEQ ID NO: 277
RN002066	GAGAACCCCAUGAGGUUCU	SEQ ID NO: 66	AGAACCUCAUGGGGUUCUCCC	SEQ ID NO: 278
RN002067	CUGCUGCAACUACAUCACA	SEQ ID NO: 67	UGUGAUGUAGUUGCAGCAGUC	SEQ ID NO: 279
RN002068	GGAGUAACCUGGAUGAGGA	SEQ ID NO: 68	UCCUCAUCCAGGUUACUCCUG	SEQ ID NO: 280
RN002069	GUAACCUGGAUGAGGACAU	SEQ ID NO: 69	AUGUCCUCAUCCAGGUUACUC	SEQ ID NO: 281
RN002070	GCAGAAGAGAACAUCGUUU	SEQ ID NO: 70	AAACGAUGUUCUCUUCUGCAA	SEQ ID NO: 282
RN002071	GAGAACAUCGUUUCCCGAA	SEQ ID NO: 71	UUCGGGAAACGAUGUUCUCUU	SEQ ID NO: 283
RN002072	CCCGAAGUGAGUUCCCAGA	SEQ ID NO: 72	UCUGGGAACUCACUUCGGGAA	SEQ ID NO: 284
RN002073	CGAAGCUCAUGAAUAUAUU	SEQ ID NO: 73	AAUAUAUUCAUGAGCUUCGUA	SEQ ID NO: 285
RN002074	GAAGCUCAUGAAUAUAUUU	SEQ ID NO: 74	AAAUAUAUUCAUGAGCUUCGU	SEQ ID NO: 286
RN002075	CCCUUCGAGGUCACAGUAA	SEQ ID NO: 75	UUACUGUGACCUCGAAGGGGU	SEQ ID NO: 287
RN002076	CCUUCGAGGUCACAGUAAU	SEQ ID NO: 76	AUUACUGUGACCUCGAAGGGG	SEQ ID NO: 288
RN002077	UCACAGUAAUGCAGGACUU	SEQ ID NO: 77	AAGUCCUGCAUUACUGUGACC	SEQ ID NO: 289
RN002078	CCUGCGGCUACCCUACUCU	SEQ ID NO: 78	AGAGUAGGGUAGCCGCAGGUC	SEQ ID NO: 290
RN002079	GCGGCUACCCUACUCUGUU	SEQ ID NO: 79	AACAGAGUAGGGUAGCCGCAG	SEQ ID NO: 291
RN002080	GGCUACCCUACUCUGUUGU	SEQ ID NO: 80	ACAACAGAGUAGGGUAGCCGC	SEQ ID NO: 292
RN002081	GCUACCCUACUCUGUUGUU	SEQ ID NO: 81	AACAACAGAGUAGGGUAGCCG	SEQ ID NO: 293
RN002082	ACCCUACUCUGUUGUUCGA	SEQ ID NO: 82	UCGAACAACAGAGUAGGGUAG	SEQ ID NO: 294
RN002083	CCCUACUCUGUUGUUCGAA	SEQ ID NO: 83	UUCGAACAACAGAGUAGGGUA	SEQ ID NO: 295
RN002084	CCUACUCUGUUGUUCGAAA	SEQ ID NO: 84	UUUCGAACAACAGAGUAGGGU	SEQ ID NO: 296
RN002085	CGAAACGAGCAGGUGGAAA	SEQ ID NO: 85	UUUCCACCUGCUCGUUUCGAA	SEQ ID NO: 297
RN002086	GAAACGAGCAGGUGGAAAU	SEQ ID NO: 86	AUUUCCACCUGCUCGUUUCGA	SEQ ID NO: 298
RN002087	CGAGCAGGUGGAAAUCCGA	SEQ ID NO: 87	UCGGAUUUCCACCUGCUCGUU	SEQ ID NO: 299
RN002088	CAAUUACCGGCAGAACCAA	SEQ ID NO: 88	UUGGUUCUGCCGGUAAUUGUA	SEQ ID NO: 300
RN002089	GGGUGGAACUACUCCACAA	SEQ ID	UUGUGGAGUAGUUCCACCCUC	SEQ ID

		NO: 89		NO: 301
RN002090	GGUGGAACUACUCCACAAU	SEQ ID NO: 90	AUUGUGGAGUAGUUCCACCCU	SEQ ID NO: 302
RN002091	GGAACUACUCCACAAUCCA	SEQ ID NO: 91	UGGAUUGUGGAGUAGUUCCAC	SEQ ID NO: 303
RN002092	CGUCACCAGCAGACCGUAA	SEQ ID NO: 92	UUACGGUCUGCUGGUGACGCC	SEQ ID NO: 304
RN002093	CACCAGCAGACCGUAACCA	SEQ ID NO: 93	UGGUUACGGUCUGCUGGUGAC	SEQ ID NO: 305
RN002094	GGAAGUCCCUGAAGGUCGU	SEQ ID NO: 94	ACGACCUUCAGGGACUUCCUG	SEQ ID NO: 306
RN002095	GUCGUGCCGGAAGGAAUCA	SEQ ID NO: 95	UGAUUCCUUCCGGCACGACCU	SEQ ID NO: 307
RN002096	CGUGCCGGAAGGAAUCAGA	SEQ ID NO: 96	UCUGAUUCCUUCCGGCACGAC	SEQ ID NO: 308
RN002097	GUGCCGGAAGGAAUCAGAA	SEQ ID NO: 97	UUCUGAUUCCUUCCGGCACGA	SEQ ID NO: 309
RN002098	CCGGAAGGAAUCAGAAUGA	SEQ ID NO: 98	UCAUUCUGAUUCCUUCCGGCA	SEQ ID NO: 310
RN002099	CGGAAGGAAUCAGAAUGAA	SEQ ID NO: 99	UUCAUUCUGAUUCCUUCCGGC	SEQ ID NO: 311
RN002100	UGCAGACCUCAGUGACCAA	SEQ ID NO: 100	UUGGUCACUGAGGUCUGCAGG	SEQ ID NO: 312
RN002101	GACCAGAAUUCUCCUGCAA	SEQ ID NO: 101	UUGCAGGAGAAUUCUGGUCUC	SEQ ID NO: 313
RN002102	GAACGGCUGAAGCACCUCA	SEQ ID NO: 102	UGAGGUGCUUCAGCCGUUCCG	SEQ ID NO: 314
RN002103	CGCUGUGCAUUACCUGGAU	SEQ ID NO: 103	AUCCAGGUAAUGCACAGCGAU	SEQ ID NO: 315
RN002104	GCAUUACCUGGAUGAAACG	SEQ ID NO: 104	CGUUUCAUCCAGGUAAUGCAC	SEQ ID NO: 316
RN002105	CCUUGGAGCUCAUCAAGAA	SEQ ID NO: 105	UUCUUGAUGAGCUCCAAGGCC	SEQ ID NO: 317
RN002106	GCAGCUGGCCUUCAGACAA	SEQ ID NO: 106	UUGUCUGAAGGCCAGCUGCUG	SEQ ID NO: 318
RN002107	CCGCCUACGUGGUCAAGGU	SEQ ID NO: 107	ACCUUGACCACGUAGGCGGUC	SEQ ID NO: 319
RN002108	CCUACGUGGUCAAGGUCUU	SEQ ID NO: 108	AAGACCUUGACCACGUAGGCG	SEQ ID NO: 320
RN002109	CGUGGUCAAGGUCUUCUCU	SEQ ID NO: 109	AGAGAAGACCUUGACCACGUA	SEQ ID NO: 321
RN002110	CUCUGGCUGUCAACCUCAU	SEQ ID NO: 110	AUGAGGUUGACAGCCAGAGAG	SEQ ID NO: 322
RN002111	CUCUGCGGGGCUGUUAAAU	SEQ ID NO: 111	AUUUAACAGCCCCGCAGAGGA	SEQ ID NO: 323
RN002112	CUGUUAAAUGGCUGAUCCU	SEQ ID NO: 112	AGGAUCAGCCAUUUAACAGCC	SEQ ID NO: 324
RN002113	GGAGGAUGCGCCCGUGAUA	SEQ ID NO: 113	UAUCACGGGCGCAUCCUCCUG	SEQ ID NO: 325
RN002114	GGCCCUCACGGCCUUUGUU	SEQ ID NO: 114	AACAAAGGCCGUGAGGGCCAU	SEQ ID NO: 326
RN002115	CUCACGGCCUUUGUUCUCA	SEQ ID NO: 115	UGAGAACAAAGGCCGUGAGGG	SEQ ID NO: 327
RN002116	CCUUUGUUCUCAUCUCGCU	SEQ ID NO: 116	AGCGAGAUGAGAACAAAGGCC	SEQ ID NO: 328
RN002117	CUUGAAGCCAACUACAUGA	SEQ ID NO: 117	UCAUGUAGUUGGCUUCAAGGA	SEQ ID NO: 329
RN002118	CCAACUACAUGAACCUACA	SEQ ID NO: 118	UGUAGGUUCAUGUAGUUGGCU	SEQ ID NO: 330

RN002119	CCUACAGAGAUCCUACACU	SEQ ID NO: 119	AGUGUAGGAUCUCUGUAGGUU	SEQ ID NO: 331
RN002120	CUGACCACAGCCAAAGAUA	SEQ ID NO: 120	UAUCUUUGGCUGUGGUCAGAA	SEQ ID NO: 332
RN002121	CCACAGCCAAAGAUAAGAA	SEQ ID NO: 121	UUCUUAUCUUUGGCUGUGGUC	SEQ ID NO: 333
RN002122	GCCAAAGAUAAGAACCGCU	SEQ ID NO: 122	AGCGGUUCUUAUCUUUGGCUG	SEQ ID NO: 334
RN002123	GCCACAUCCUAUGCCCUCU	SEQ ID NO: 123	AGAGGGCAUAGGAUGUGGCCU	SEQ ID NO: 335
RN002124	CCACAUCCUAUGCCCUCUU	SEQ ID NO: 124	AAGAGGGCAUAGGAUGUGGCC	SEQ ID NO: 336
RN002125	GGCCCUACUGCAGCUAAAA	SEQ ID NO: 125	UUUUAGCUGCAGUAGGGCCAA	SEQ ID NO: 337
RN002126	CUACUGCAGCUAAAAGACU	SEQ ID NO: 126	AGUCUUUUAGCUGCAGUAGGG	SEQ ID NO: 338
RN002127	CAGCUAAAAGACUUUGACU	SEQ ID NO: 127	AGUCAAAGUCUUUUAGCUGCA	SEQ ID NO: 339
RN002128	GCUAAAAGACUUUGACUUU	SEQ ID NO: 128	AAAGUCAAAGUCUUUUAGCUG	SEQ ID NO: 340
RN002129	CCGUCGUGCGUUGGCUCAA	SEQ ID NO: 129	UUGAGCCAACGCACGACGGGA	SEQ ID NO: 341
RN002130	CGUCGUGCGUUGGCUCAAU	SEQ ID NO: 130	AUUGAGCCAACGCACGACGGG	SEQ ID NO: 342
RN002131	CGUGCGUUGGCUCAAUGAA	SEQ ID NO: 131	UUCAUUGAGCCAACGCACGAC	SEQ ID NO: 343
RN002132	CGUUGGCUCAAUGAACAGA	SEQ ID NO: 132	UCUGUUCAUUGAGCCAACGCA	SEQ ID NO: 344
RN002133	GGCUCAAUGAACAGAGAUA	SEQ ID NO: 133	UAUCUCUGUUCAUUGAGCCAA	SEQ ID NO: 345
RN002134	CUCAAUGAACAGAGAUACU	SEQ ID NO: 134	AGUAUCUCUGUUCAUUGAGCC	SEQ ID NO: 346
RN002135	CCACCUUCAUGGUGUUCCA	SEQ ID NO: 135	UGGAACACCAUGAAGGUGGCC	SEQ ID NO: 347
RN002136	CACCUUCAUGGUGUUCCAA	SEQ ID NO: 136	UUGGAACACCAUGAAGGUGGC	SEQ ID NO: 348
RN002137	GGUGUUCCAAGCCUUGGCU	SEQ ID NO: 137	AGCCAAGGCUUGGAACACCAU	SEQ ID NO: 349
RN002138	CCGUAUCCACUGGGAAUCU	SEQ ID NO: 138	AGAUUCCCAGUGGAUACGGUG	SEQ ID NO: 350
RN002139	GCCUCCUGCGAUCAGAAGA	SEQ ID NO: 139	UCUUCUGAUCGCAGGAGGCUG	SEQ ID NO: 351
RN002140	UGCGAUCAGAAGAGACCAA	SEQ ID NO: 140	UUGGUCUCUUCUGAUCGCAGG	SEQ ID NO: 352
RN002141	GAUCAGAAGAGACCAAGGA	SEQ ID NO: 141	UCCUUGGUCUCUUCUGAUCGC	SEQ ID NO: 353
RN002142	GUUUCACAGUCACAGCUGA	SEQ ID NO: 142	UCAGCUGUGACUGUGAAACCC	SEQ ID NO: 354
RN002143	UGACAAUGUACCAUGCUAA	SEQ ID NO: 143	UUAGCAUGGUACAUUGUCACC	SEQ ID NO: 355
RN002144	GUACCAUGCUAAGGCCAAA	SEQ ID NO: 144	UUUGGCCUUAGCAUGGUACAU	SEQ ID NO: 356
RN002145	CAACUCACCUGUAAUAAAU	SEQ ID NO: 145	AUUUAUUACAGGUGAGUUGAU	SEQ ID NO: 357
RN002146	CCUGUAAUAAAUUCGACCU	SEQ ID NO: 146	AGGUCGAAUUUAUUACAGGUG	SEQ ID NO: 358
RN002147	GUAAUAAAUUCGACCUCAA	SEQ ID NO: 147	UUGAGGUCGAAUUUAUUACAG	SEQ ID NO: 359
RN002148	CGACCUCAAGGUCACCAUA	SEQ ID	UAUGGUGACCUUGAGGUCGAA	SEQ ID

		NO: 148		NO: 360
RN002149	GACCUCAAGGUCACCAUAA	SEQ ID NO: 149	UUAUGGUGACCUUGAGGUCGA	SEQ ID NO: 361
RN002150	CAAGGUCACCAUAAAACCA	SEQ ID NO: 150	UGGUUUUAUGGUGACCUUGAG	SEQ ID NO: 362
RN002151	CCAGCACCGGAAACAGAAA	SEQ ID NO: 151	UUUCUGUUUCCGGUGCUGGUU	SEQ ID NO: 363
RN002152	GCACCGGAAACAGAAAAGA	SEQ ID NO: 152	UCUUUUCUGUUUCCGGUGCUG	SEQ ID NO: 364
RN002153	GGCCUCAGGAUGCCAAGAA	SEQ ID NO: 153	UUCUUGGCAUCCUGAGGCCUC	SEQ ID NO: 365
RN002154	CAGGAUGCCAAGAACACUA	SEQ ID NO: 154	UAGUGUUCUUGGCAUCCUGAG	SEQ ID NO: 366
RN002155	GAUGCCAAGAACACUAUGA	SEQ ID NO: 155	UCAUAGUGUUCUUGGCAUCCU	SEQ ID NO: 367
RN002156	CCAAGAACACUAUGAUCCU	SEQ ID NO: 156	AGGAUCAUAGUGUUCUUGGCA	SEQ ID NO: 368
RN002157	AGAACACUAUGAUCCUUGA	SEQ ID NO: 157	UCAAGGAUCAUAGUGUUCUUG	SEQ ID NO: 369
RN002158	GAGACCAGGAUGCCACUAU	SEQ ID NO: 158	AUAGUGGCAUCCUGGUCUCCC	SEQ ID NO: 370
RN002159	CCAGGAUGCCACUAUGUCU	SEQ ID NO: 159	AGACAUAGUGGCAUCCUGGUC	SEQ ID NO: 371
RN002160	CAGGAUGCCACUAUGUCUA	SEQ ID NO: 160	UAGACAUAGUGGCAUCCUGGU	SEQ ID NO: 372
RN002161	GGAUGCCACUAUGUCUAUA	SEQ ID NO: 161	UAUAGACAUAGUGGCAUCCUG	SEQ ID NO: 373
RN002162	GAUGCCACUAUGUCUAUAU	SEQ ID NO: 162	AUAUAGACAUAGUGGCAUCCU	SEQ ID NO: 374
RN002163	GUUGACAGAUACAUCUCCA	SEQ ID NO: 163	UGGAGAUGUAUCUGUCAACAC	SEQ ID NO: 375
RN002164	GACAGAUACAUCUCCAAGU	SEQ ID NO: 164	ACUUGGAGAUGUAUCUGUCAA	SEQ ID NO: 376
RN002165	CAGAUACAUCUCCAAGUAU	SEQ ID NO: 165	AUACUUGGAGAUGUAUCUGUC	SEQ ID NO: 377
RN002166	AGAUACAUCUCCAAGUAUG	SEQ ID NO: 166	CAUACUUGGAGAUGUAUCUGU	SEQ ID NO: 378
RN002167	GAUACAUCUCCAAGUAUGA	SEQ ID NO: 167	UCAUACUUGGAGAUGUAUCUG	SEQ ID NO: 379
RN002168	CCAAGUAUGAGCUGGACAA	SEQ ID NO: 168	UUGUCCAGCUCAUACUUGGAG	SEQ ID NO: 380
RN002169	GGACAAAGCCUUCUCCGAU	SEQ ID NO: 169	AUCGGAGAAGGCUUUGUCCAG	SEQ ID NO: 381
RN002170	GACAAAGCCUUCUCCGAUA	SEQ ID NO: 170	UAUCGGAGAAGGCUUUGUCCA	SEQ ID NO: 382
RN002171	GCCUUCUCCGAUAGGAACA	SEQ ID NO: 171	UGUUCCUAUCGGAGAAGGCUU	SEQ ID NO: 383
RN002172	CCGAUAGGAACACCCUCAU	SEQ ID NO: 172	AUGAGGGUGUUCCUAUCGGAG	SEQ ID NO: 384
RN002173	GAUAGGAACACCCUCAUCA	SEQ ID NO: 173	UGAUGAGGGUGUUCCUAUCGG	SEQ ID NO: 385
RN002174	CUGGACAAGGUCUCACACU	SEQ ID NO: 174	AGUGUGAGACCUUGUCCAGGU	SEQ ID NO: 386
RN002175	GCUUUCAAAGUUCACCAAU	SEQ ID NO: 175	AUUGGUGAACUUUGAAAGCUA	SEQ ID NO: 387
RN002176	CUUUCAAAGUUCACCAAUA	SEQ ID NO: 176	UAUUGGUGAACUUUGAAAGCU	SEQ ID NO: 388
RN002177	CAGUCAAGGUCUACGCCUA	SEQ ID NO: 177	UAGGCGUAGACCUUGACUGCU	SEQ ID NO: 389

RN002178	GUCAAGGUCUACGCCUAUU	SEQ ID NO: 178	AAUAGGCGUAGACCUUGACUG	SEQ ID NO: 390
RN002179	AGGUCUACGCCUAUUACAA	SEQ ID NO: 179	UUGUAAUAGGCGUAGACCUUG	SEQ ID NO: 391
RN002180	GCUGUACCCGGUUCUACCA	SEQ ID NO: 180	UGGUAGAACCGGGUACAGCUU	SEQ ID NO: 392
RN002181	CUGUACCCGGUUCUACCAU	SEQ ID NO: 181	AUGGUAGAACCGGGUACAGCU	SEQ ID NO: 393
RN002182	CCGGAAAAGGAGGAUGGAA	SEQ ID NO: 182	UUCCAUCCUCCUUUUCCGGAU	SEQ ID NO: 394
RN002183	CGGAAAAGGAGGAUGGAAA	SEQ ID NO: 183	UUUCCAUCCUCCUUUUCCGGA	SEQ ID NO: 395
RN002184	GAGGAUGGAAAGCUGAACA	SEQ ID NO: 184	UGUUCAGCUUUCCAUCCUCCU	SEQ ID NO: 396
RN002185	GCCGCUGUGCUGAGGAGAA	SEQ ID NO: 185	UUCUCCUCAGCACAGCGGCAC	SEQ ID NO: 397
RN002186	CCGCUGUGCUGAGGAGAAU	SEQ ID NO: 186	AUUCUCCUCAGCACAGCGGCA	SEQ ID NO: 398
RN002187	CGCUGUGCUGAGGAGAAUU	SEQ ID NO: 187	AAUUCUCCUCAGCACAGCGGC	SEQ ID NO: 399
RN002188	GUGCUGAGGAGAAUUGCUU	SEQ ID NO: 188	AAGCAAUUCUCCUCAGCACAG	SEQ ID NO: 400
RN002189	GCUGAGGAGAAUUGCUUCA	SEQ ID NO: 189	UGAAGCAAUUCUCCUCAGCAC	SEQ ID NO: 401
RN002190	GGAGAAUUGCUUCAUACAA	SEQ ID NO: 190	UUGUAUGAAGCAAUUCUCCUC	SEQ ID NO: 402
RN002191	GAGAAUUGCUUCAUACAAA	SEQ ID NO: 191	UUUGUAUGAAGCAAUUCUCCU	SEQ ID NO: 403
RN002192	GUGAGCCAGGAGUGGACUA	SEQ ID NO: 192	UAGUCCACUCCUGGCUCACAG	SEQ ID NO: 404
RN002193	CCAGGAGUGGACUAUGUGU	SEQ ID NO: 193	ACACAUAGUCCACUCCUGGCU	SEQ ID NO: 405
RN002194	CAGGAGUGGACUAUGUGUA	SEQ ID NO: 194	UACACAUAGUCCACUCCUGGC	SEQ ID NO: 406
RN002195	GGAGUGGACUAUGUGUACA	SEQ ID NO: 195	UGUACACAUAGUCCACUCCUG	SEQ ID NO: 407
RN002196	GAGUGGACUAUGUGUACAA	SEQ ID NO: 196	UUGUACACAUAGUCCACUCCU	SEQ ID NO: 408
RN002197	GUGGACUAUGUGUACAAGA	SEQ ID NO: 197	UCUUGUACACAUAGUCCACUC	SEQ ID NO: 409
RN002198	CCAAUGACUUUGACGAGUA	SEQ ID NO: 198	UACUCGUCAAAGUCAUUGGAC	SEQ ID NO: 410
RN002199	GACUUUGACGAGUACAUCA	SEQ ID NO: 199	UGAUGUACUCGUCAAAGUCAU	SEQ ID NO: 411
RN002200	ACUUUGACGAGUACAUCAU	SEQ ID NO: 200	AUGAUGUACUCGUCAAAGUCA	SEQ ID NO: 412
RN002201	GACGAGUACAUCAUGGCCA	SEQ ID NO: 201	UGGCCAUGAUGUACUCGUCAA	SEQ ID NO: 413
RN002202	CAUCAAGUCAGGCUCGGAU	SEQ ID NO: 202	AUCCGAGCCUGACUUGAUGGU	SEQ ID NO: 414
RN002203	CAGGCUCGGAUGAGGUGCA	SEQ ID NO: 203	UGCACCUCAUCCGAGCCUGAC	SEQ ID NO: 415
RN002204	GCUCGGAUGAGGUGCAGGU	SEQ ID NO: 204	ACCUGCACCUCAUCCGAGCCU	SEQ ID NO: 416
RN002205	CGUUCAUCAGCCCCAUCAA	SEQ ID NO: 205	UUGAUGGGGCUGAUGAACGUG	SEQ ID NO: 417
RN002206	GGGGUCUCUCCUCCGAUUU	SEQ ID NO: 206	AAAUCGGAGGAGAGACCCCAC	SEQ ID NO: 418
RN002207	CCGAUUUCUGGGGAGAGAA	SEQ ID	UUCUCUCCCCAGAAAUCGGAG	SEQ ID

		NO: 207		NO: 419
RN002208	CUCAGCUACAUCAUCGGGA	SEQ ID NO: 208	UCCCGAUGAUGUAGCUGAGGU	SEQ ID NO: 420
RN002209	GCUACAUCAUCGGGAAGGA	SEQ ID NO: 209	UCCUUCCCGAUGAUGUAGCUG	SEQ ID NO: 421
RN002210	CCGAGGAGGACGAAUGCCA	SEQ ID NO: 210	UGGCAUUCGUCCUCCUCGGGC	SEQ ID NO: 422
RN002211	CGAGGAGGACGAAUGCCAA	SEQ ID NO: 211	UUGGCAUUCGUCCUCCUCGGG	SEQ ID NO: 423
RN002212	CUUUGGGUGCCCCAACUGA	SEQ ID NO: 212	UCAGUUGGGGCACCCAAAGAC	SEQ ID NO: 424

[00581] The software for preparing the sequence listing requires that U be represented as T when generating RNA sequences. Therefore, the siRNA sequences of the present disclosure cannot be correctly represented in the sequence listing. All sequences are as set forth in the description.

[00582] Table 5: Sequence Information of siRNAs

siRNA No.	sense strand (5'-3')		antisense strand (5'-3')	
RX002001	GmsUmsCmCmAmCmGfAfCfUmUmCmCmCmAmGmGmCmAm	SEQ ID NO: 425	UmsGfsCmCmUmGfGmGmAmAmGmUmCmGfUmGfGmAmCmsAmsGm	SEQ ID NO: 637
RX002002	CmsCmsAmCmGmAmCfUfUfCmCmCmAmGmGmCmAmAmAm	SEQ ID NO: 426	UmsUfsUmGmCmCfUmGmGmGmAmAmGmUfCmGfUmGmGmsAmsCm	SEQ ID NO: 638
RX002003	CmsAmsCmGmAmCmUfUfCfCmCmAmGmGmCmAmAmAmAm	SEQ ID NO: 427	UmsUfsUmUmGmCfCmUmGmGmGmAmAmGfUmCfGmUmGmsGmsAm	SEQ ID NO: 639
RX002004	GmsUmsGmCmUmGmUfCfCfAmGmUmGmAmGmAmAmGmAm	SEQ ID NO: 428	UmsCfsUmUmCmUfCmAmCmUmGmGmAmCfAmGfCmAmCmsUmsAm	SEQ ID NO: 640
RX002005	GmsCmsUmGmUmCmCfAfGfUmGmAmGmAmAmGmAmCmUm	SEQ ID NO: 429	AmsGfsUmCmUmUfCmUmCmAmCmUmGmGfAmCfAmGmCmsAmsCm	SEQ ID NO: 641
RX002006	CmsAmsGmAmGmCmGfGfGfUmAmCmCmUmCmUmUmCmAm	SEQ ID NO: 430	UmsGfsAmAmGmAfGmGmUmAmCmCmCmGfCmUfCmUmGmsCmsAm	SEQ ID NO: 642
RX002007	GmsCmsGmGmGmUmAfCfCfUmCmUmUmCmAmUmCmCmAm	SEQ ID NO: 431	UmsGfsGmAmUmGfAmAmGmAmGmGmUmAfCmCfCmGmCmsUmsCm	SEQ ID NO: 643
RX002008	CmsAmsGmAmCmAmGfAfCfAmAmGmAmCmCmAmUmCmUm	SEQ ID NO: 432	AmsGfsAmUmGmGfUmCmUmUmGmUmCmUfGmUfCmUmGmsGmsAm	SEQ ID NO: 644
RX002009	GmsGmsAmUmCmUmUfCfAfCmCmGmUmCmAmAmCmCmAm	SEQ ID NO: 433	UmsGfsGmUmUmGfAmCmGmGmUmGmAmAfGmAfUmCmCmsGmsAm	SEQ ID NO: 645
RX002010	CmsCmsGmUmCmAmAfCfCfAmCmAmAmGmCmUmGmCmUm	SEQ ID NO: 434	AmsGfsCmAmGmCfUmUmGmUmGmGmUmUfGmAfCmGmGmsUmsGm	SEQ ID NO: 646
RX002011	CmsGmsUmCmAmAmCfCfAfCmAmAmGmCmUmGmCmUmAm	SEQ ID NO: 435	UmsAfsGmCmAmGfCmUmUmGmUmGmGmUfUmGfAmCmGmsGmsUm	SEQ ID NO: 647
RX002012	CmsGmsGmUmCmAmAfGfCfAmGmGmAmCmUmCmCmUmUm	SEQ ID NO: 436	AmsAfsGmGmAmGfUmCmCmUmGmCmUmUfGmAfCmCmGmsGmsGm	SEQ ID NO: 648
RX002013	GmsUmsCmAmAmGmCfAfGfGmAmCmUmCmCmUmUmGmUm	SEQ ID NO: 437	AmsCfsAmAmGmGfAmGmUmCmCmUmGmCfUmUfGmAmCmsCmsGm	SEQ ID NO: 649
RX002014	CmsAmsAmGmCmAmGfGfAfCmUmCmCmUmUmGmUmCmUm	SEQ ID NO: 438	AmsGfsAmCmAmAfGmGmAmGmUmCmCmUfGmCfUmUmGmsAmsCm	SEQ ID NO: 650
RX002015	CmsUmsUmGmGmGmAfCfAfUmUmCmCmGmGmAmAmCmUm	SEQ ID NO: 439	AmsGfsUmUmCmCfGmGmAmAmUmGmUmCfCmCfAmAmGmsAmsCm	SEQ ID NO: 651
RX002016	GmsGmsGmAmCmAmUfUfCfCmGmGmAmAmCmUmCmGmUm	SEQ ID NO: 440	AmsCfsGmAmGmUfUmCmCmGmGmAmAmUfGmUfCmCmCmsAmsAm	SEQ ID NO: 652
RX002017	CmsAmsGmUmGmGmAfAfGfAmUmCmCmGmAmGmCmCmUm	SEQ ID NO: 441	AmsGfsGmCmUmCfGmGmAmUmCmUmUmCfCmAfCmUmGmsGmsCm	SEQ ID NO: 653

RX002018	AmsGmsUmGmGmAmAfGfAfUmCmCmGmAmGmCmCmUmAm	SEQ ID NO: 442	UmsAfsGmGmCmUfCmGmGmAmUmCmUmUfCmCfAmCmUmsGmsGm	SEQ ID NO: 654
RX002019	GmsGmsAmAmGmAmUfCfCfGmAmGmCmCmUmAmCmUmAm	SEQ ID NO: 443	UmsAfsGmUmAmGfGmCmUmCmGmGmAmUfCmUfUmCmCmsAmsCm	SEQ ID NO: 655
RX002020	GmsAmsAmGmAmUmCfCfGfAmGmCmCmUmAmCmUmAmUm	SEQ ID NO: 444	AmsUfsAmGmUmAfGmGmCmUmCmGmGmAfUmCfUmUmCmsCmsAm	SEQ ID NO: 656
RX002021	GmsAmsUmCmCmGmAfGfCfCmUmAmCmUmAmUmGmAmAm	SEQ ID NO: 445	UmsUfsCmAmUmAfGmUmAmGmGmCmUmCfGmGfAmUmCmsUmsUm	SEQ ID NO: 657
RX002022	AmsGmsUmUmUmGmAfGfGfUmGmAmAmGmGmAmGmUmAm	SEQ ID NO: 446	UmsAfsCmUmCmCfUmUmCmAmCmCmUmCfAmAfAmCmUmsCmsAm	SEQ ID NO: 658
RX002023	GmsCmsCmCmAmGmUfUfUfCmGmAmGmGmUmCmAmUmAm	SEQ ID NO: 447	UmsAfsUmGmAmCfCmUmCmGmAmAmAmCfUmGfGmGmCmsAmsGm	SEQ ID NO: 659
RX002024	CmsCmsAmGmUmUmUfCfGfAmGmGmUmCmAmUmAmGmUm	SEQ ID NO: 448	AmsCfsUmAmUmGfAmCmCmUmCmGmAmAfAmCfUmGmGmsGmsCm	SEQ ID NO: 660
RX002025	CmsAmsGmUmUmUmCfGfAfGmGmUmCmAmUmAmGmUmGm	SEQ ID NO: 449	CmsAfsCmUmAmUfGmAmCmCmUmCmGmAfAmAfCmUmGmsGmsGm	SEQ ID NO: 661
RX002026	GmsUmsUmUmCmGmAfGfGfUmCmAmUmAmGmUmGmGmAm	SEQ ID NO: 450	UmsCfsCmAmCmUfAmUmGmAmCmCmUmCfGmAfAmAmCmsUmsGm	SEQ ID NO: 662
RX002027	CmsGmsAmGmGmUmCfAfUfAmGmUmGmAmGmGmCmCmUm	SEQ ID NO: 451	AmsGfsGmCmUmCfCmAmCmUmAmUmGmAfCmCfUmCmGmsAmsAm	SEQ ID NO: 663
RX002028	AmsGmsUmGmGmAmGfCfCfUmAmCmAmGmAmGmAmAmAm	SEQ ID NO: 452	UmsUfsUmCmUmCfUmGmUmAmGmGmCmUfCmCfAmCmUmsAmsUm	SEQ ID NO: 664
RX002029	CmsAmsGmAmGmAmAfAfUfUmCmUmAmCmUmAmCmAmUm	SEQ ID NO: 453	AmsUfsGmUmAmGfUmAmGmAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 665
RX002030	AmsAmsAmUmUmCmUfAfCfUmAmCmAmUmCmUmAmUmAm	SEQ ID NO: 454	UmsAfsUmAmGmAfUmGmUmAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 666
RX002031	GmsGmsAmAmCmUmGfCfCfUmUmUmGmUmCmAmUmCmUm	SEQ ID NO: 455	AmsGfsAmUmGmAfCmAmAmAmGmGmCmAfGmUfUmCmCmsCmsUm	SEQ ID NO: 667
RX002032	GmsAmsAmCmUmGmCfCfUfUmUmGmUmCmAmUmCmUmUm	SEQ ID NO: 456	AmsAfsGmAmUmGfAmCmAmAmAmGmGmCfAmGfUmUmCmsCmsCm	SEQ ID NO: 668
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RX002036	GmsUmsGmAmCmCmUfCfUfCmCmCmUmAmCmCmCmAmGmAm	SEQ ID NO: 460	UmsCfsUmGmGmUfAmGmGmGmAmGmAmGfGmUfCmAmCmsGmsAm	SEQ ID NO: 672
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RX002 115	CmsUmsCmAmCmGmGfCfCfUmUm UmGmUmUmCmUmCmAm	SEQ ID NO: 539	UmsGfsAmGmAmAfCmAmAmAmGm GmCmCfGmUfGmAmGmsGmsGm	SEQ ID NO: 751
RX002 116	CmsCmsUmUmUmGmUfUfCfUmCm AmUmCmUmCmGmCmUm	SEQ ID NO: 540	AmsGfsCmGmAmGfAmUmGmAmGm AmAmCfAmAfAmGmGmsCmsCm	SEQ ID NO: 752
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RX002 122	GmsCmsCmAmAmAmGfAfUfAmAm GmAmAmCmCmGmCmUm	SEQ ID NO: 546	AmsGfsCmGmGmUfUmCmUmUmAm UmCmUfUmUfGmGmCmsUmsGm	SEQ ID NO: 758
RX002 123	GmsCmsCmAmCmAmUfCfCfUmAm UmGmCmCmCmUmCmUm	SEQ ID NO: 547	AmsGfsAmGmGmGfCmAmUmAmGm GmAmUfGmUfGmGmCmsCmsUm	SEQ ID NO: 759
RX002 124	CmsCmsAmCmAmUmCfCfUfAmUm GmCmCmCmUmCmUmUm	SEQ ID NO: 548	AmsAfsGmAmGmGfGmCmAmUmAm GmGmAfUmGfUmGmGmsCmsCm	SEQ ID NO: 760
RX002 125	GmsGmsCmCmCmUmAfCfUfGmCm AmGmCmUmAmAmAmAm	SEQ ID NO: 549	UmsUfsUmUmAmGfCmUmGmCmAm GmUmAfGmGfGmCmCmsAmsAm	SEQ ID NO: 761
RX002 126	CmsUmsAmCmUmGmCfAfGfCmUm AmAmAmAmGmAmCmUm	SEQ ID NO: 550	AmsGfsUmCmUmUfUmUmAmGmCm UmGmCfAmGfUmAmGmsGmsGm	SEQ ID NO: 762
RX002 127	CmsAmsGmCmUmAmAfAfAfGmAm CmUmUmUmGmAmCmUm	SEQ ID NO: 551	AmsGfsUmCmAmAfAmGmUmCmUm UmUmUfAmGfCmUmGmsCmsAm	SEQ ID NO: 763
RX002 128	GmsCmsUmAmAmAmAfGfAfCmUm UmUmGmAmCmUmUmUm	SEQ ID NO: 552	AmsAfsAmGmUmCfAmAmAmGmUm CmUmUfUmUfAmGmCmsUmsGm	SEQ ID NO: 764
RX002 129	CmsCmsGmUmCmGmUfGfCfGmUm UmGmGmCmUmCmAmAm	SEQ ID NO: 553	UmsUfsGmAmGmCfCmAmAmCmGm CmAmCfGmAfCmGmGmsGmsAm	SEQ ID NO: 765
RX002 130	CmsGmsUmCmGmUmGfCfGfUmUm GmGmCmUmCmAmAmUm	SEQ ID NO: 554	AmsUfsUmGmAmGfCmCmAmAmCm GmCmAfCmGfAmCmGmsGmsGm	SEQ ID NO: 766
RX002 131	CmsGmsUmGmCmGmUfUfGfGmCm UmCmAmAmUmGmAmAm	SEQ ID NO: 555	UmsUfsCmAmUmUfGmAmGmCmCm AmAmCfGmCfAmCmGmsAmsCm	SEQ ID NO: 767
RX002 132	CmsGmsUmUmGmGmCfUfCfAmAm UmGmAmAmCmAmGmAm	SEQ ID NO: 556	UmsCfsUmGmUmUfCmAmUmUmGm AmGmCfCmAfAmCmGmsCmsAm	SEQ ID NO: 768
RX002 133	GmsGmsCmUmCmAmAfUfGfAmAm CmAmGmAmGmAmUmAm	SEQ ID NO: 557	UmsAfsUmCmUmCfUmGmUmUmCm AmUmUfGmAfGmCmCmsAmsAm	SEQ ID NO: 769

RX002 134	CmsUmsCmAmAmUmGfAfAfCmAm GmAmGmAmUmAmCmUm	SEQ ID NO: 558	AmsGfsUmAmUmCfUmCmUmGmUm UmCmAfUmUfGmAmGmsCmsCm	SEQ ID NO: 770
RX002 135	CmsCmsAmCmCmUmUfCfAfUmGm GmUmGmUmUmCmCmAm	SEQ ID NO: 559	UmsGfsGmAmAmCfAmCmCmAmUm GmAmAfGmGfUmGmGmsCmsCm	SEQ ID NO: 771
RX002 136	CmsAmsCmCmUmUmCfAfUfGmGm UmGmUmUmCmCmAmAm	SEQ ID NO: 560	UmsUfsGmGmAmAfCmAmCmCmAm UmGmAfAmGfGmUmGmsGmsCm	SEQ ID NO: 772
RX002 137	GmsGmsUmGmUmUmCfCfAfAmGm CmCmUmUmGmGmCmUm	SEQ ID NO: 561	AmsGfsCmCmAmAfGmGmCmUmUm GmGmAfAmCfAmCmCmsAmsUm	SEQ ID NO: 773
RX002 138	CmsCmsGmUmAmUmCfCfAfCmUm GmGmGmAmAmUmCmUm	SEQ ID NO: 562	AmsGfsAmUmUmCfCmCmAmGmUm GmGmAfUmAfCmGmGmsUmsGm	SEQ ID NO: 774
RX002 139	GmsCmsCmUmCmCmUfGfCfGmAm UmCmAmGmAmAmGmAm	SEQ ID NO: 563	UmsCfsUmUmCmUfGmAmUmCmGm CmAmGfGmAfGmGmCmsUmsGm	SEQ ID NO: 775
RX002 140	UmsGmsCmGmAmUmCfAfGfAmAm GmAmGmAmCmCmAmAm	SEQ ID NO: 564	UmsUfsGmGmUmCfUmCmUmUmCm UmGmAfUmCfGmCmAmsGmsGm	SEQ ID NO: 776
RX002 141	GmsAmsUmCmAmGmAfAfGfAmGm AmCmCmAmAmGmGmAm	SEQ ID NO: 565	UmsCfsCmUmUmGfGmUmCmUmCm UmUmCfUmGfAmUmCmsGmsCm	SEQ ID NO: 777
RX002 142	GmsUmsUmUmCmAmCfAfGfUmCm AmCmAmGmCmUmGmAm	SEQ ID NO: 566	UmsCfsAmGmCmUfGmUmGmAmCm UmGmUfGmAfAmAmCmsCmsCm	SEQ ID NO: 778
RX002 143	UmsGmsAmCmAmAmUfGfUfAmCm CmAmUmGmCmUmAmAm	SEQ ID NO: 567	UmsUfsAmGmCmAfUmGmGmUmAm CmAmUfUmGfUmCmAmsCmsCm	SEQ ID NO: 779
RX002 144	GmsUmsAmCmCmAmUfGfCfUmAm AmGmGmCmCmAmAmAm	SEQ ID NO: 568	UmsUfsUmGmGmCfCmUmUmAmGm CmAmUfGmGfUmAmCmsAmsUm	SEQ ID NO: 780
RX002 145	CmsAmsAmCmUmCmAfCfCfUmGm UmAmAmUmAmAmAmUm	SEQ ID NO: 569	AmsUfsUmUmAmUfUmAmCmAmGm GmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 781
RX002 146	CmsCmsUmGmUmAmAfUfAfAmAm UmUmCmGmAmCmCmUm	SEQ ID NO: 570	AmsGfsGmUmCmGfAmAmUmUmUm AmUmUfAmCfAmGmGmsUmsGm	SEQ ID NO: 782
RX002 147	GmsUmsAmAmUmAmAfAfUfUmCm GmAmCmCmUmCmAmAm	SEQ ID NO: 571	UmsUfsGmAmGmGfUmCmGmAmAm UmUmUfAmUfUmAmCmsAmsGm	SEQ ID NO: 783
RX002 148	CmsGmsAmCmCmUmCfAfAfGmGm UmCmAmCmCmAmUmAm	SEQ ID NO: 572	UmsAfsUmGmGmUfGmAmCmCmUm UmGmAfGmGfUmCmGmsAmsAm	SEQ ID NO: 784
RX002 149	GmsAmsCmCmUmCmAfAfGfGmUm CmAmCmCmAmUmAmAm	SEQ ID NO: 573	UmsUfsAmUmGmGfUmGmAmCmCm UmUmGfAmGfGmUmCmsGmsAm	SEQ ID NO: 785
RX002 150	CmsAmsAmGmGmUmCfAfCfCmAm UmAmAmAmAmCmCmAm	SEQ ID NO: 574	UmsGfsGmUmUmUfUmAmUmGmGm UmGmAfCmCfUmUmGmsAmsGm	SEQ ID NO: 786
RX002 151	CmsCmsAmGmCmAmCfCfGfGmAm AmAmCmAmGmAmAmAm	SEQ ID NO: 575	UmsUfsUmCmUmGfUmUmUmCmCm GmGmUfGmCfUmGmGmsUmsUm	SEQ ID NO: 787
RX002 152	GmsCmsAmCmCmGmGfAfAfAmCm AmGmAmAmAmAmGmAm	SEQ ID NO: 576	UmsCfsUmUmUmUfCmUmGmUmUm UmCmCfGmGfUmGmCmsUmsGm	SEQ ID NO: 788
RX002 153	GmsGmsCmCmUmCmAfGfGfAmUm GmCmCmAmAmGmAmAm	SEQ ID NO: 577	UmsUfsCmUmUmGfGmCmAmUmCm CmUmGfAmGfGmCmCmsUmsCm	SEQ ID NO: 789
RX002 154	CmsAmsGmGmAmUmGfCfCfAmAm GmAmAmCmAmCmUmAm	SEQ ID NO: 578	UmsAfsGmUmGmUfUmCmUmUmGm GmCmAfUmCfCmUmGmsAmsGm	SEQ ID NO: 790
RX002 155	GmsAmsUmGmCmCmAfAfGfAmAm CmAmCmUmAmUmGmAm	SEQ ID NO: 579	UmsCfsAmUmAmGfUmGmUmUmCm UmUmGfGmCfAmUmCmsCmsUm	SEQ ID NO: 791
RX002 156	CmsCmsAmAmGmAmAfCfAfCmUm AmUmGmAmUmCmCmUm	SEQ ID NO: 580	AmsGfsGmAmUmCfAmUmAmGmUm GmUmUfCmUfUmGmGmsCmsAm	SEQ ID NO: 792
RX002 157	AmsGmsAmAmCmAmCfUfAfUmGm AmUmCmCmUmUmGmAm	SEQ ID NO: 581	UmsCfsAmAmGmGfAmUmCmAmUm AmGmUfGmUfUmCmUmsUmsGm	SEQ ID NO: 793
RX002 158	GmsAmsGmAmCmCmAfGfGfAmUm GmCmCmAmCmUmAmUm	SEQ ID NO: 582	AmsUfsAmGmUmGfGmCmAmUmCm CmUmGfGmUfCmUmCmsCmsCm	SEQ ID NO: 794
RX002 159	CmsCmsAmGmGmAmUfGfCfCmAm CmUmAmUmGmUmCmUm	SEQ ID NO: 583	AmsGfsAmCmAmUfAmGmUmGmGm CmAmUfCmCfUmGmGmsUmsCm	SEQ ID NO: 795
RX002 160	CmsAmsGmGmAmUmGfCfCfAmCm UmAmUmGmUmCmUmAm	SEQ ID NO: 584	UmsAfsGmAmCmAfUmAmGmUmGm GmCmAfUmCfCmUmGmsGmsUm	SEQ ID NO: 796
RX002 161	GmsGmsAmUmGmCmCfAfCfUmAm UmGmUmCmUmAmUmAm	SEQ ID NO: 585	UmsAfsUmAmGmAfCmAmUmAmGm UmGmGfCmAfUmCmCmsUmsGm	SEQ ID NO: 797
RX002 162	GmsAmsUmGmCmCmAfCfUfAmUm GmUmCmUmAmUmAmUm	SEQ ID NO: 586	AmsUfsAmUmAmGfAmCmAmUmAm GmUmGfGmCfAmUmCmsCmsUm	SEQ ID NO: 798

RX002163	GmsUmsUmGmAmCmAfGfAfUmAmCmAmUmCmUmCmCmAm	SEQ ID NO: 587	UmsGfsGmAmGmAfUmGmUmAmUmCmUmGfUmCfAmAmCmsAmsCm	SEQ ID NO: 799
RX002164	GmsAmsCmAmGmAmUfAfCfAmUmCmUmCmCmAmAmGmUm	SEQ ID NO: 588	AmsCfsUmUmGmGfAmGmAmUmGmUmAmUfCmUfGmUmCmsAmsAm	SEQ ID NO: 780
RX002165	CmsAmsGmAmUmAmCfAfUfCmUmCmCmAmAmGmUmAmUm	SEQ ID NO: 589	AmsUfsAmCmUmUfGmGmAmGmAmUmGmUfAmUfCmUmGmsUmsCm	SEQ ID NO: 801
RX002166	AmsGmsAmUmAmCmAfUfCfUmCmCmAmAmGmUmAmUmGm	SEQ ID NO: 590	CmsAfsUmAmCmUfUmGmGmAmGmAmUmGfUmAfUmCmUmsGmsUm	SEQ ID NO: 802
RX002167	GmsAmsUmAmCmAmUfCfUfCmCmAmAmGmUmAmUmGmAm	SEQ ID NO: 591	UmsCfsAmUmAmCfUmUmGmGmAmGmAmUfGmUfAmUmCmsUmsGm	SEQ ID NO: 803
RX002168	CmsCmsAmAmGmUmAfUfGfAmGmCmUmGmGmAmCmAmAm	SEQ ID NO: 592	UmsUfsGmUmCmCfAmGmCmUmCmAmUmAfCmUfUmGmGmsAmsGm	SEQ ID NO: 804
RX002169	GmsGmsAmCmAmAmAfGfCfCmUmUmCmUmCmCmGmAmUm	SEQ ID NO: 593	AmsUfsCmGmGmAfGmAmAmGmGmCmUmUfUmGfUmCmCmsAmsGm	SEQ ID NO: 805
RX002170	GmsAmsCmAmAmAmGfCfCfUmUmCmUmCmCmGmAmUmAm	SEQ ID NO: 594	UmsAfsUmCmGmGfAmGmAmAmGmGmCmUfUmUfGmUmCmsCmsAm	SEQ ID NO: 806
RX002171	GmsCmsCmUmUmCmUfCfCfGmAmUmAmGmGmAmAmCmAm	SEQ ID NO: 595	UmsGfsUmUmCmCfUmAmUmCmGmGmAmGfAmAfGmGmCmsUmsUm	SEQ ID NO: 807
RX002172	CmsCmsGmAmUmAmGfGfAfAmCmAmCmCmCmUmCmAmUm	SEQ ID NO: 596	AmsUfsGmAmGmGfGmUmGmUmUmCmCmUfAmUfCmGmGmsAmsGm	SEQ ID NO: 808
RX002173	GmsAmsUmAmGmGmAfAfCfAmCmCmCmUmCmAmUmCmAm	SEQ ID NO: 597	UmsGfsAmUmGmAfGmGmGmUmGmUmUmCfCmUfAmUmCmsGmsGm	SEQ ID NO: 809
RX002174	CmsUmsGmGmAmCmAfAfGfGmUmCmUmCmAmCmAmCmUm	SEQ ID NO: 598	AmsGfsUmGmUmGfAmGmAmCmCmUmUmGfUmCfCmAmGmsGmsUm	SEQ ID NO: 810
RX002175	GmsCmsUmUmUmCmAfAfAfGmUmUmCmAmCmCmCmAmAmUm	SEQ ID NO: 599	AmsUfsUmGmGmUfGmAmAmCmUmUmUmGfAmAfAmGmCmsUmsAm	SEQ ID NO: 811
RX002176	CmsUmsUmUmCmAmAfAfGfUmUmCmAmCmCmCmAmAmUmAm	SEQ ID NO: 600	UmsAfsUmUmGmGfUmGmAmAmCmUmUmUfGmAfAmAmGmsCmsUm	SEQ ID NO: 812
RX002177	CmsAmsGmUmCmAmAfGfGfUmCmUmAmCmGmCmCmUmAm	SEQ ID NO: 601	UmsAfsGmGmCmGfUmAmGmAmCmCmUmUfGmAfCmUmGmsCmsUm	SEQ ID NO: 813
RX002178	GmsUmsCmAmAmGmGfUfCfUmAmCmGmCmCmUmAmUmUm	SEQ ID NO: 602	AmsAfsUmAmGmGfCmGmUmAmGmAmCmCmUfGmAmCmsUmsGm	SEQ ID NO: 814
RX002179	AmsGmsGmUmCmUmAfCfGfCmCmUmAmUmUmAmCmAmAm	SEQ ID NO: 603	UmsUfsGmUmAmAfUmAmGmGmCmGmUmAfGmAfCmCmUmsUmsGm	SEQ ID NO: 815
RX002180	GmsCmsUmGmUmAmCfCfCfGmGmUmUmCmUmAmCmCmAm	SEQ ID NO: 604	UmsGfsGmUmAmGfAmAmCmCmGmGmGmUfAmCfAmGmCmsUmsUm	SEQ ID NO: 816
RX002181	CmsUmsGmUmAmCmCfCfGfGmUmUmCmUmAmCmCmAmUm	SEQ ID NO: 605	AmsUfsGmGmUmAfGmAmAmCmCmGmGmGfUmAfCmAmGmsCmsUm	SEQ ID NO: 817
RX002182	CmsCmsGmGmAmAmAfAfGfGmAmGmGmAmUmGmGmAmAm	SEQ ID NO: 606	UmsUfsCmCmAmUfCmCmUmCmCmUmUmUfUmCfCmGmGmsAmsUm	SEQ ID NO: 818
RX002183	CmsGmsGmAmAmAmAfGfGfAmGmGmAmUmGmGmAmAmAm	SEQ ID NO: 607	UmsUfsUmCmCmAfUmCmCmUmCmCmUmUfUmUfCmCmGmsGmsAm	SEQ ID NO: 819
RX002184	GmsAmsGmGmAmUmGfGfAfAmAmGmCmUmGmAmAmCmAm	SEQ ID NO: 608	UmsGfsUmUmCmAfGmCmUmUmUmCmCmAfUmCfCmUmCmsCmsUm	SEQ ID NO: 820
RX002185	GmsCmsCmGmCmUmGfUfGfCmUmGmAmGmGmAmGmAmAm	SEQ ID NO: 609	UmsUfsCmUmCmCfUmCmAmGmCmAmCmAfGmCfGmGmCmsAmsCm	SEQ ID NO: 821
RX002186	CmsCmsGmCmUmGmUfGfCfUmGmAmGmGmAmGmAmAmUm	SEQ ID NO: 610	AmsUfsUmCmUmCfCmUmCmAmGmCmAmCfAmGfCmGmGmsCmsAm	SEQ ID NO: 822
RX002187	CmsGmsCmUmGmUmGfCfUfGmAmGmGmAmGmAmAmUmUm	SEQ ID NO: 611	AmsAfsUmUmCmUfCmCmUmCmAmGmCmAfCmAfGmCmGmsGmsCm	SEQ ID NO: 823
RX002188	GmsUmsGmCmUmGmAfGfGfAmGmAmAmUmUmGmCmUmUm	SEQ ID NO: 612	AmsAfsGmCmAmAfUmUmCmUmCmCmUmCfAmGfCmAmCmsAmsGm	SEQ ID NO: 824
RX002189	GmsCmsUmGmAmGmGfAfGfAmAmUmUmGmCmUmUmUmCmAm	SEQ ID NO: 613	UmsGfsAmAmGmCfAmAmUmUmCmUmCmCfUmCfAmGmCmsAmsCm	SEQ ID NO: 825
RX002190	GmsGmsAmGmAmAmUfUfGfCmUmUmCmAmUmAmCmAmAm	SEQ ID NO: 614	UmsUfsGmUmAmUfGmAmAmGmCmAmAmUfUmCfUmCmCmsUmsCm	SEQ ID NO: 826
RX002191	GmsAmsGmAmAmUmUfGfCfUmUmCmAmUmAmCmAmAmAm	SEQ ID NO: 615	UmsUfsUmGmUmAfUmGmAmAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 827

RX002192	GmsUmsGmAmGmCmCfAfGfGmAmGmUmGmGmAmCmUmAm	SEQ ID NO: 616	UmsAfsGmUmCmCfAmCmUmCmCmUmGmGfCmUfCmAmCmsAmsGm	SEQ ID NO: 828
RX002193	CmsCmsAmGmGmAmGfUfGfGmAmCmUmAmUmGmUmGmUm	SEQ ID NO: 617	AmsCfsAmCmAmUfAmGmUmCmCmAmCmUfCmCfUmGmGmsCmsUm	SEQ ID NO: 829
RX002194	CmsAmsGmGmAmGmUfGfGfAmCmUmAmUmGmUmGmUmAm	SEQ ID NO: 618	UmsAfsCmAmCmAfUmAmGmUmCmCmAmCfUmCfCmUmGmsGmsCm	SEQ ID NO: 830
RX002195	GmsGmsAmGmUmGmGfAfCfUmAmUmGmUmGmUmAmCmAm	SEQ ID NO: 619	UmsGfsUmAmCmAfCmAmUmAmGmUmCmCfAmCfUmCmCmsUmsGm	SEQ ID NO: 831
RX002196	GmsAmsGmUmGmGmAfCfUfAmUmGmUmGmUmAmCmAmAm	SEQ ID NO: 620	UmsUfsGmUmAmCfAmCmAmUmAmGmUmCfCmAfCmUmCmsCmsUm	SEQ ID NO: 832
RX002197	GmsUmsGmGmAmCmUfAfUfGmUmGmUmAmCmAmAmGmAm	SEQ ID NO: 621	UmsCfsUmUmGmUfAmCmAmCmAmUmAmGfUmCfCmAmCmsUmsCm	SEQ ID NO: 833
RX002198	CmsCmsAmAmUmGmAfCfUfUmUmGmAmCmGmAmGmUmAm	SEQ ID NO: 622	UmsAfsCmUmCmGfUmCmAmAmAmGmUmCfAmUfUmGmGmsAmsCm	SEQ ID NO: 834
RX002199	GmsAmsCmUmUmUmGfAfCfGmAmGmUmAmCmAmUmCmAm	SEQ ID NO: 623	UmsGfsAmUmGmUfAmCmUmCmGmUmCmAfAmAfGmUmCmsAmsUm	SEQ ID NO: 835
RX002200	AmsCmsUmUmUmGmAfCfGfAmGmUmAmCmAmUmCmAmUm	SEQ ID NO: 624	AmsUfsGmAmUmGfUmAmCmUmCmGmUmCfAmAfAmGmUmsCmsAm	SEQ ID NO: 836
RX002201	GmsAmsCmGmAmGmUfAfCfAmUmCmAmUmGmGmCmCmAm	SEQ ID NO: 625	UmsGfsGmCmCmAfUmGmAmUmGmUmAmCfUmCfGmUmCmsAmsAm	SEQ ID NO: 837
RX002202	CmsAmsUmCmAmAmGfUfCfAmGmGmCmUmCmGmGmAmUm	SEQ ID NO: 626	AmsUfsCmCmGmAfGmCmCmUmGmAmCmUfUmGfAmUmGmsGmsUm	SEQ ID NO: 838
RX002203	CmsAmsGmGmCmUmCfGfGfAmUmGmAmGmGmUmGmCmAm	SEQ ID NO: 627	UmsGfsCmAmCmCfUmCmAmUmCmCmGmAfGmCfCmUmGmsAmsCm	SEQ ID NO: 839
RX002204	GmsCmsUmCmGmGmAfUfGfAmGmGmUmGmCmAmGmGmUm	SEQ ID NO: 628	AmsCfsCmUmGmCfAmCmCmUmCmAmUmCfCmGfAmGmCmsCmsUm	SEQ ID NO: 840
RX002205	CmsGmsUmUmCmAmUfCfAfGmCmCmCmAmUmCmAmAm	SEQ ID NO: 629	UmsUfsGmAmUmGfGmGmGmCmUmGmAmUfGmAfAmCmGmsUmsGm	SEQ ID NO: 841
RX002206	GmsGmsGmGmUmCmUfCfUfCmCmUmCmCmGmAmUmUmUm	SEQ ID NO: 630	AmsAfsAmUmCmGfGmAmGmGmAmGmAmGfAmCfCmCmCmsAmsCm	SEQ ID NO: 842
RX002207	CmsCmsGmAmUmUmUfCfUfGmGmGmAmGmAmGmAmAm	SEQ ID NO: 631	UmsUfsCmUmCmUfCmCmCmCmAmGmAmAfAmUfCmGmGmsAmsGm	SEQ ID NO: 843
RX002208	CmsUmsCmAmGmCmUfAfCfAmUmCmAmUmCmGmGmGmAm	SEQ ID NO: 632	UmsCfsCmCmGmAfUmGmAmUmGmUmAmGfCmUfGmAmGmsGmsUm	SEQ ID NO: 844
RX002209	GmsCmsUmAmCmAmUfCfAfUmCmGmGmGmAmAmGmGmAm	SEQ ID NO: 633	UmsCfsCmUmUmCfCmCmGmAmUmGmAmUfGmUfAmGmCmsUmsGm	SEQ ID NO: 845
RX002210	CmsCmsGmAmGmGmAfGfGfAmCmGmAmAmUmGmCmCmAm	SEQ ID NO: 634	UmsGfsGmCmAmUfUmCmGmUmCmCmUmCfCmUfCmGmGmsGmsCm	SEQ ID NO: 846
RX002211	CmsGmsAmGmGmAmGfGfAfCmGmAmAmUmGmCmCmAmAm	SEQ ID NO: 635	UmsUfsGmGmCmAfUmUmCmGmUmCmCmUfCmCfUmCmGmsGmsGm	SEQ ID NO: 847
RX002212	CmsUmsUmUmGmGmGfUfGfCmCmCmCmAmAmCmCmUmGmAm	SEQ ID NO: 636	UmsCfsAmGmUmUfGmGmGmGmCmAmCmCfCmAfAmAmGmsAmsCm	SEQ ID NO: 848

[00583] Table 6: Sequence Information of siRNAs

siRNA No.	sense strand (5'-3')		antisense strand (5'-3')	
RX002213	CmsAmsGmAmCmAmGfAdCfAmAmGmAmCmCmAmUmCmUm	SEQ ID NO: 849	AmsGfsAmUmGmGfUmCmUmUmGmUmCmUfGmUfCmUmGmsGmsAm	SEQ ID NO: 644
RX002214	CmsAmsAmGmCmAmGfGdAfCmUmCmCmUmUmGmUmCmUm	SEQ ID NO: 850	AmsGfsAmCmAmAfGmGmAmGmUmCmCmUfGmCfUmUmGmsAmsCm	SEQ ID NO: 650
RX002215	CmsAmsGmAmGmAmAfAdUfUmCmUmAmCmUmAmCmAmUm	SEQ ID NO: 851	AmsUfsGmUmAmGfUmAmGmAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 665
RX002216	UmsCmsAmAmCmUmUfCdCfUmCmCmUmGmCmGmAmAmUm	SEQ ID NO: 852	AmsUfsUmCmGmCfAmGmGmAmGmGmAmAfGmUfUmGmAmsCmsGm	SEQ ID NO: 692
RX002217	GmsCmsAmGmAmAmGfAdGfAmAmCmAmUmCmGmUmUmUm	SEQ ID NO: 853	AmsAfsAmCmGmAfUmGmUmUmCmUmCmUfUmCfUmGmCmsAmsAm	SEQ ID NO: 706

RX002218	CmsGmsAmAmGmCmUfCdAfUmGmAmAmUmAmUmAmUmUm	SEQ ID NO: 854	AmsAfsUmAmUmAfUmUmCmAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 709
RX002219	CmsCmsUmAmCmUmCfTdGfUmUmGmUmUmCmGmAmAmAm	SEQ ID NO: 855	UmsUfsUmCmGmAfAmCmAmAmCmAmGmAfGmUfAmGmGmsGmsUm	SEQ ID NO: 720
RX002220	CmsCmsAmAmCmUmAfCdAfUmGmAmAmCmCmUmAmCmAm	SEQ ID NO: 856	UmsGfsUmAmGmGfUmUmCmAmUmGmUmAfGmUfUmGmGmsCmsUm	SEQ ID NO: 754
RX002221	CmsAmsGmCmUmAmAfAdAfGmAmCmUmUmUmGmAmCmUm	SEQ ID NO: 857	AmsGfsUmCmAmAfAmGmUmCmUmUmUmUfAmGfCmUmGmsCmsAm	SEQ ID NO: 763
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RX000002	UmsUmsCmUmCmCmGfAdAfCmGm UmGmUmCmAmCmGmUm	SEQ ID NO: 885	AmsCfsGmUmGmAfCmAmCmGmUmU mCmGfGmAfGmAmAmsCmsUm	SEQ ID NO: 886

[00584] Table 7: Sequence Information of siRNAs

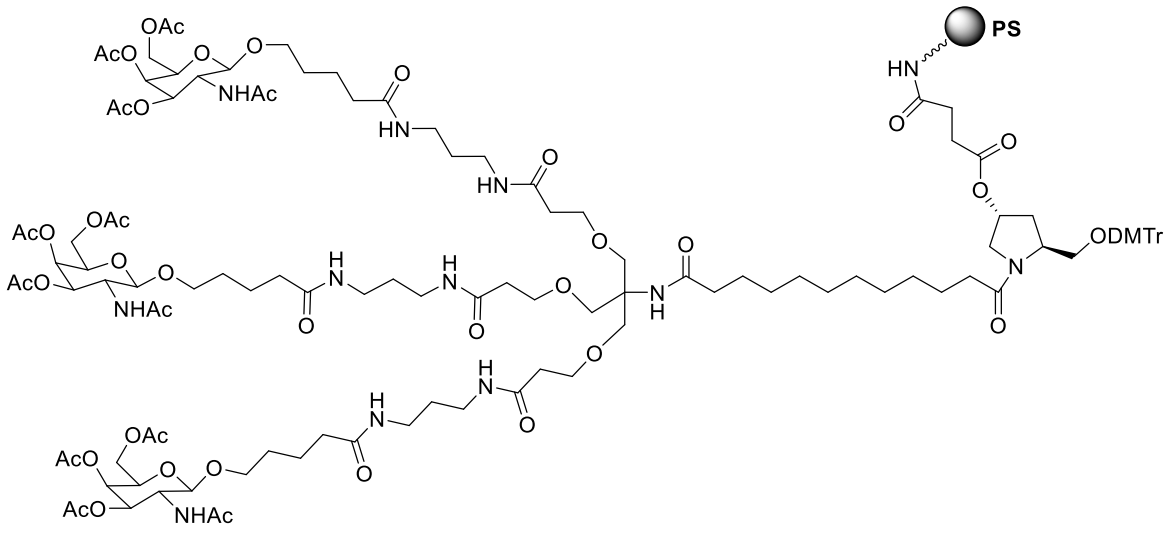
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RX002 246	CmsGmsAmAmGmCmUfCfAfUfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 247	CmsGmsAmAmGmCmUfCfAfUfUfGmA mAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUfGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002 248	CmsGmsAmAmG(moe)CmUfCfAfUfG mAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 249	CmsGmsAmAmGmCmUfCfAfUfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 250	CmsGmsAmAmGmCmUfCfAfUfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 251	CmsGmsAmAmGmCmUfCfAfUfUfGmA mAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmUmCmAfUmGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002 252	CmsGmsAmAmG(moe)CmUfCfAfUfG mAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 253	CmsGmsAmAmGmCmUfCfAfUfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 254	CmsGmsAmAmGmCmUfCfAfUfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 255	CmsGmsAmAmGmCmUfCfAfUfUfGmA mAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAfUm GmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002 256	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002 257	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 258	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002 259	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 260	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 261	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 262	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmAmGmAfAmUm UmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002 263	CmsAmsGmAmG(moe)AmAfAfUfUfC mUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
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RX002 265	CmsAmsGmAmGmAmAfAfUfUfCmU mA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmA(moe)GmAfAm UmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
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RX002 269	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGfCm AmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 918

RX002 270	GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 898	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
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RX002 296	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um	SEQ ID NO: 906	AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
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RX002309	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm	SEQ ID NO: 907	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RX002310	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RX002311	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RX002312	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002313	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

Preparation Example 4: Preparation of siRNA Conjugate with L96 Moiety Conjugated to 3'-end of Sense Strand

[00585] Wherein, compound L96-PS was purchased from Asymchem Laboratories (Tianjin) Co., Ltd., with a loading capacity of 120 ± 12 μmol/g (detection method: UV/HPLC). The structural formula of compound L96-PS is:



[00586] Wherein, PS represents a polystyrene resin solid-phase support.

[00587] (4.1) Synthesis of sense strand

[00588] Using the phosphoramidite solid-phase nucleic acid synthesis method, reaction cycles were started with the aforementioned L96-PS compound linked to a solid-phase support, and nucleoside monomers were linked sequentially in a 3' to 5' direction according to the nucleotide sequence. Each cycle of nucleoside monomer addition included four reaction steps: deprotection, coupling, capping, and oxidation or sulfurization. The synthesis method and conditions followed the sense strand synthesis method shown in step (3.1) of Preparation Example 3.

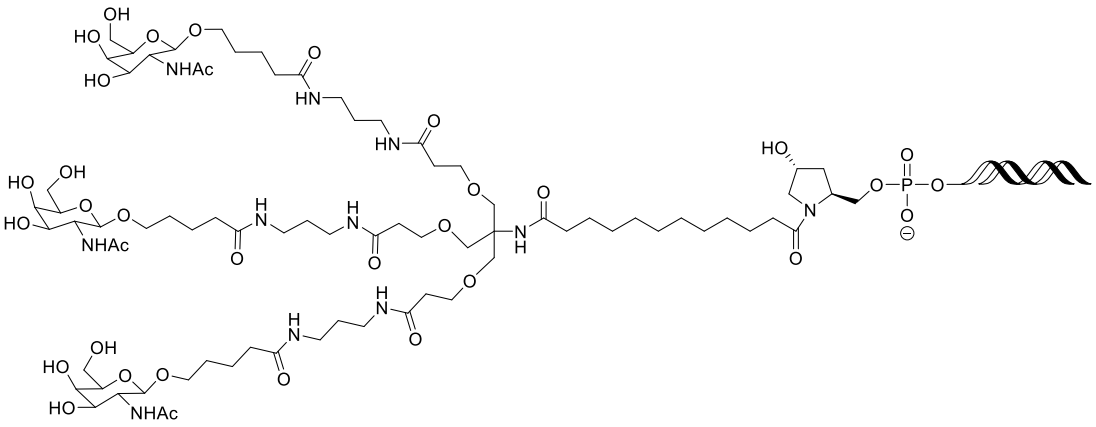
[00589] (4.2) Synthesis of antisense strand

[00590] The siRNA antisense strands in this preparation example were synthesized according to the antisense strand synthesis method shown in step (3.2) of Preparation Example 3.

[00591] (4.3) Synthesis of siRNA conjugate

[00592] The siRNA conjugates of this preparation example were synthesized according to the method shown in step (3.3) of Preparation Example 3.

[00593] Wherein, the structural formula of the siRNA conjugate with the L96 moiety conjugated to the 3'-end of the sense strand is as follows:



[00594] Wherein,  represents siRNA. L96 was conjugated to the 3'-end of the sense strand of the siRNA via a phosphodiester bond.

[00595] Table 8: Sequence Information of siRNA Conjugates with an L96 Moiety Conjugated to the 3'-end of the Sense Strand

siRNA conjugate No.	sense strand (5'-3')		antisense strand (5'-3')	
RZ002001	CmsAmsGmAmCmAmGfAdCfAmAmGmAmCmCmAmUmCmUm_L96	SEQ ID NO: 849_L96	AmsGfsAmUmGmGfUmCmUmUmGmUmCmUfGmUfCmUmGmsGmsAm	SEQ ID NO: 644
RZ002002	CmsAmsAmGmCmAmGfGdAfCmUmCmCmUmUmGmUmCmUm_L96	SEQ ID NO: 850_L96	AmsGfsAmCmAmAfGmGmAmGmUmCmCmUfGmCfUmUmGmsAmsCm	SEQ ID NO: 650
RZ002003	CmsAmsGmAmGmAmAfAdUfUmCmUmAmCmUmAmCmAmUm_L96	SEQ ID NO: 851_L96	AmsUfsGmUmAmGfUmAmGmAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 665
RZ002004	UmsCmsAmAmCmUmUfCdCfUmCmCmUmGmCmGmAmAmUm_L96	SEQ ID NO: 852_L96	AmsUfsUmCmGmCfAmGmGmAmGmGmAmAfGmUfUmGmAmsCmsGm	SEQ ID NO: 692
RZ002005	GmsCmsAmGmAmAmGfAdGfAmAmCmAmUmCmGmUmUmUm_L96	SEQ ID NO: 853_L96	AmsAfsAmCmGmAfUmGmUmUmCmUmCmUfUmCfUmGmCmsAmsAm	SEQ ID NO: 706
RZ002006	CmsGmsAmAmGmCmUfCdAfUmGmAmAmUmAmUmAmUmUm_L96	SEQ ID NO: 854_L96	AmsAfsUmAmUmAfUmUmCmAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 709
RZ002007	CmsCmsUmAmCmUmCfTdGfUmUmGmUmUmCmGmAmAmAm_L96	SEQ ID NO: 855_L96	UmsUfsUmCmGmAfAmCmAmAmCmAmGmAfGmUfAmGmGmsGmsUm	SEQ ID NO: 720
RZ002008	CmsCmsAmAmCmUmAfCdAfUmGmAmAmCmCmUmAmCmAm_L96	SEQ ID NO: 856_L96	UmsGfsUmAmGmGfUmUmCmAmUmGmUmAfGmUfUmGmGmsCmsUm	SEQ ID NO: 754
RZ002009	CmsAmsGmCmUmAmAfAdAfGmAmCmUmUmUmGmAmCmUm_L96	SEQ ID NO: 857_L96	AmsGfsUmCmAmAfAmGmUmCmUmUmUfAmGfCmUmGmsCmsAm	SEQ ID NO: 763
RZ002010	CmsGmsUmCmGmUmGfCdGfUmUmGmGmCmUmCmAmAmUm_L96	SEQ ID NO: 858_L96	AmsUfsUmGmAmGfCmCmAmAmCmGmCmAfCmGfAmCmGmsGmsGm	SEQ ID NO: 766
RZ002011	CmsAmsAmCmUmCmAfCdCfUmGmUmAmAmUmAmAmAmUm_L96	SEQ ID NO:	AmsUfsUmUmAmUfUmAmCmAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO:

		859_L96		781
RZ002012	CmsAmsGmAmUmAmCfAdUfCmUmCmCmAmAmGmUmAmUm_L96	SEQ ID NO: 860_L96	AmsUfsAmCmUmUfGmGmAmGmAmUmGmUfAmUfCmUmGmsUmsCm	SEQ ID NO: 801
RZ002013	CmsCmsGmAmUmAmGfGdAfAmCmAmCmCmCmUmCmAmUm_L96	SEQ ID NO: 861_L96	AmsUfsGmAmGmGfGmUmGmUmUmCmCmUfAmUfCmGmGmsAmsGm	SEQ ID NO: 808
RZ002014(AD570714)	GmsAmsGmCmCmGmUfUmCfUfCfUmAmCmAmAmUmUmAmCmUm_L96	SEQ ID NO: 862_L96	AmsGfsUmAmAmUfUmGfUfAmGmAmGmAfAmCfGmGmCmUmCmsGmsGm	SEQ ID NO: 881
RZ002015	AmsAmsAmUmUmCmUfAdCfUmAmCmAmUmCmUmAmUmAm_L96	SEQ ID NO: 863_L96	UmsAfsUmAmGmAfUmGmUmAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 666
RZ002016	CmsUmsCmCmAmAmCfAdAfUmUmAmCmCmUmGmCmAmUm_L96	SEQ ID NO: 864_L96	AmsUfsGmCmAmGfGmUmAmAmUmUmGmUfUmGfGmAmGmsUmsUm	SEQ ID NO: 687
RZ002017	CmsUmsGmCmUmGmCfAdAfCmUmAmCmAmUmCmAmCmAm_L96	SEQ ID NO: 865_L96	UmsGfsUmGmAmUfGmUmAmGmUmUmGmCfAmGfCmAmGmsUmsCm	SEQ ID NO: 703
RZ002018	GmsAmsAmGmCmUmCfAdUfGmAmAmUmAmUmAmUmUmUm_L96	SEQ ID NO: 866_L96	AmsAfsAmUmAmUfAmUmUmCmAmUmGmAfGmCfUmUmCmsGmsUm	SEQ ID NO: 710
RZ002019	CmsCmsUmUmCmGmAfGdGfUmCmAmCmAmGmUmAmAmUm_L96	SEQ ID NO: 867_L96	AmsUfsUmAmCmUfGmUmGmAmCmCmUmCfGmAfAmGmGmsGmsGm	SEQ ID NO: 712
RZ002020	CmsCmsGmGmAmAmGfGdAfAmUmCmAmGmAmAmUmGmAm_L96	SEQ ID NO: 868_L96	UmsCfsAmUmUmCfUmGmAmUmUmCmCmUfUmCfCmGmGmsCmsAm	SEQ ID NO: 734
RZ002021	CmsGmsCmUmGmUmGfCdAfUmUmAmCmCmUmGmGmAmUm_L96	SEQ ID NO: 869_L96	AmsUfsCmCmAmGfGmUmAmAmUmGmCmAfCmAfGmCmGmsAmsUm	SEQ ID NO: 739
RZ002022	CmsUmsUmGmAmAmGfCdCfAmAmCmUmAmCmAmUmGmAm_L96	SEQ ID NO: 870_L96	UmsCfsAmUmGmUfAmGmUmUmGmGmCmCmUfUmCfAmAmGmsGmsAm	SEQ ID NO: 753
RZ002023	CmsUmsAmCmUmGmCfAdGfCmUmAmAmAmAmGmAmCmUm_L96	SEQ ID NO: 871_L96	AmsGfsUmCmCmUfUmUmAmGmCmUmGmCfAmGfUmAmGmsGmsGm	SEQ ID NO: 762
RZ002024	GmsCmsUmAmAmAmAfGdAfCmUmUmUmGmAmCmUmUmUm_L96	SEQ ID NO: 872_L96	AmsAfsAmGmUmCfAmAmAmGmUmCmUmUfUmUfAmGmCmsUmsGm	SEQ ID NO: 764
RZ002025	AmsGmsAmAmCmAmCfUdAfUmGmAmUmCmCmUmUmGmAm_L96	SEQ ID NO: 873_L96	UmsCfsAmAmGmGfAmUmCmAmUmAmGmUfGmUfUmCmUmsUmsGm	SEQ ID NO: 793
RZ002026	GmsAmsUmAmCmAmUfCdUfCmCmAmAmGmUmAmUmGmAm_L96	SEQ ID NO: 874_L96	UmsCfsAmUmAmCfUmUmGmGmAmGmAmUfGmUfAmUmCmsUmsGm	SEQ ID NO: 803
RZ002027	GmsGmsAmCmAmAmAfGdCfCmUmUmCmUmCmCmGmAmUm_L96	SEQ ID NO: 875_L96	AmsUfsCmGmGmAfGmAmAmGmGmCmUmUfUmGfUmCmCmsAmsGm	SEQ ID NO: 805
RZ002028	CmsUmsUmUmCmAmAfAdGfUmUmCmAmCmCmCmAmAmUmAm_L96	SEQ ID NO: 876_L96	UmsAfsUmUmGmGfUmGmAmAmCmUmUmUfGmAfAmAmGmsCmsUm	SEQ ID NO: 812
RZ002029	CmsAmsGmUmCmAmAfGdGfUmCmUmAmCmGmCmCmUmAm_L96	SEQ ID NO: 877_L96	UmsAfsGmGmCmGfUmAmGmAmCmCmUmUfGmAfCmUmGmsCmsUm	SEQ ID NO: 813
RZ002030	GmsUmsCmAmAmGmGfUdCfUmAmCmGmCmCmUmAmUmUm_L96	SEQ ID NO: 878_L96	AmsAfsUmAmGmGfCmGmUmAmGmAmCmCfUmUfGmAmCmsUmsGm	SEQ ID NO: 814
RZ002031	GmsAmsGmAmAmUmUfGdCfUmUmCmAmUmAmCmAmAmAm_L96	SEQ ID NO:	UmsUfsUmGmUmAfUmGmAmAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO:

		879_L96		827
RZ002032	CmsGmsAmGmGmAmGfGdAfCmGmAmAmUmGmCmCmAmAm_L96	SEQ ID NO: 880_L96	UmsUfsGmGmCmAfUmUmCmGmUmCmCmUfCmCfUmCmGmsGmsGm	SEQ ID NO: 847

[00596] As an exemplary explanation, "SEQ ID NO: 849_L96" indicates that the L96 moiety is conjugated to the 3'-end of the sense strand as shown in SEQ ID NO: 849 via a phosphodiester bond.

[00597] Table 9: Sequence Information of Murine siRNA Conjugates with an L96 Moiety Conjugated to the 3'-end of the Sense Strand

siRNA conjugate No.	sense strand (5'-3')		antisense strand (5'-3')	
RZM02003	AmsGmsAmAmGmAmAfGfAfUfAmUmUmAmUmCmUmCmUm_L96	SEQ ID NO: 882_L96	AmsGfsAmGmAmUfAmAmUmAmUmCmUmUfCmUfUmCmUmsGmsGm	SEQ ID NO: 883

[00598] Table 10: Sequence Information of siRNA Conjugates with an L96 Moiety Conjugated to the 3'-end of the Sense Strand

siRNA conjugate No.	sense strand (5'-3')		antisense strand (5'-3')	
RZ000001	UmsUmsCmUmCmCmGfAfAfCmGmUmGmUmCmAmCmGmUm_L96	SEQ ID NO: 884_L96	AmsCfsGmUmGmAfCmAmCmGmUmUmCmGfGmAfGmAmAmsCmsUm	SEQ ID NO: 886
RZ000002	UmsUmsCmUmCmCmGfAdAfCmGmUmGmUmCmAmCmGmUm_L96	SEQ ID NO: 885_L96	AmsCfsGmUmGmAfCmAmCmGmUmUmCmGfGmAfGmAmAmsCmsUm	SEQ ID NO: 886

Preparation Example 5: Synthesis of siRNA Conjugate with (CR01008×3) Moiety Conjugated to 3'-end of Sense Strand

[00599] (5.1) Synthesis of sense strand

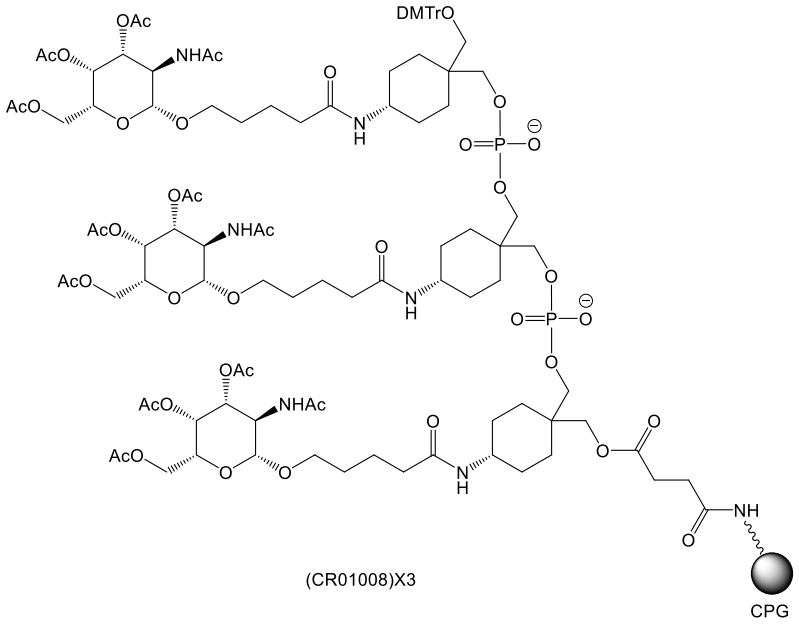
[00600] Using the phosphoramidite solid-phase nucleic acid synthesis method, starting with the aforementioned compound CR01008Z linked to a solid-phase support, nucleoside monomers were linked sequentially in cycles in a 3' to 5' direction according to the nucleotide sequence (compound CR01008 was regarded as a nucleoside monomer).

[00601] Each cycle of nucleoside monomer addition included four reaction steps: deprotection, coupling, capping, and oxidation or sulfurization. In the synthesis of the sense strand of this preparation example, the conditions for deprotection, coupling, capping, and oxidation or

sulfurization reactions, the conditions for cleavage and deprotection, and the conditions for purification and desalting were the same as those for the synthesis of the sense strand in step (3.1) of Preparation Example 3.

[00602] In this step, three clusters of CR01008 were synthesized during the synthesis of the sense strand, denoted as (CR01008)×3 or (CR01008×3).

[00603] The structural formula of the three clusters of CR01008 is:



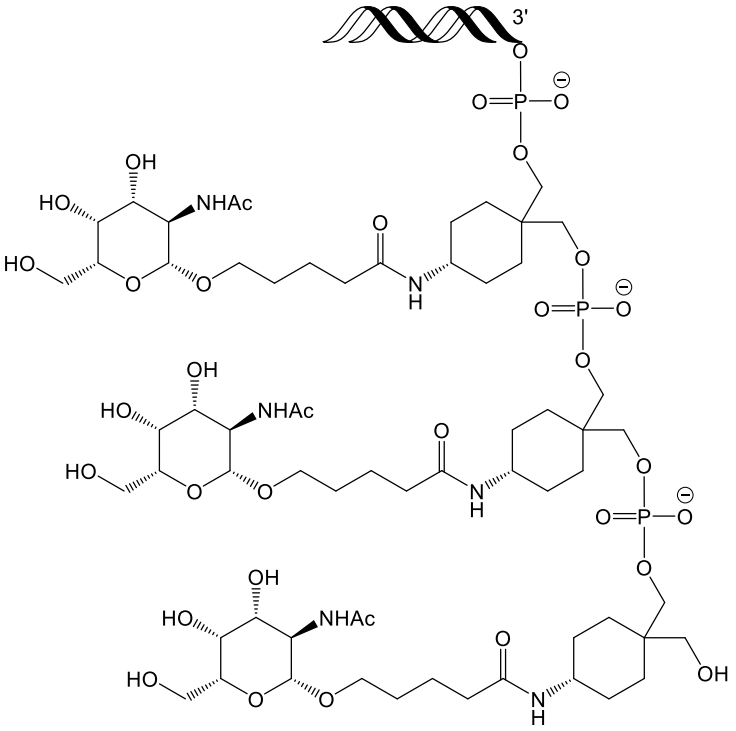
[00604] (5.2) Synthesis of antisense strand:

[00605] The antisense strands of this preparation example were synthesized according to the antisense strand synthesis method shown in step (3.2) of Preparation Example 3.

[00606] (5.3) Synthesis of siRNA conjugate

[00607] The siRNA conjugates of this preparation example were synthesized according to the method shown in step (3.3) of Preparation Example 3.

[00608] Wherein, when the ligand is the three clusters of CR01008, the structural formula of the siRNA conjugate is:


3'
OH
HO
NHAc
HO
O
O
O
N
H
O
P
O
O
O

	mT(moe)Um_(CR01008×3)		mGmsUmsAm	909
RZ002040	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002041	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 889_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002042	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002043	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002050	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RZ002051	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002053	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002054	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002055	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002056	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002057	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002058	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002059	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002060	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002066	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 916
RZ002067	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002068	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGfCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 918
RZ002069	GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAm	SEQ ID NO: 898_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmU	SEQ ID NO:

	CmAmAmAm_(CR01008×3)		mCmsCmsUm	917
RZ002070	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 899_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002071	GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 900_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002072	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(moe)Am_(CR01008×3)	SEQ ID NO: 901_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002073	GmsAmsGmAmA(moe)UmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 898_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002074	GmsAmsGmAmAmUmUfGfCfUfUmC(moe)AmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 899_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002075	GmsAmsGmAmAmUmUfGfCfUfUmCmA(moe)UmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 900_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002076	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmA(moe)Am_(CR01008×3)	SEQ ID NO: 901_(CR01008×3)	UmsUfsUmGmUmAfUmG(moe)AmAfGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 919
RZ002082	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RZ002083	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002084	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RZ002085	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 903_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002086	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 904_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002087	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002088	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAfGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 921
RZ002089	CmsAmsAmCmT(moe)CmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 903_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002090	CmsAmsAmCmUmCmAfCfCfUfGmT(moe)AmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 904_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002091	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUm	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmU	SEQ ID NO:

	AmAmAmUm_(CR01008×3)		mGmsAmsUm	923
RZ002092	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAfGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 923
RZ002099	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002100	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002101	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002102	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002103	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002107	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002108	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAmAfUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 925
RZ002112	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RZ002113	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
RZ002115	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RZ002116	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RZ002117	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RZ002118	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RZ002119	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RZ002120	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RZ002121	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933

RZ002122	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RZ002123	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RZ002124	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RZ002125	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RZ002126	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RZ002130	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RZ002131	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RZ002132	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RZ002133	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RZ002134	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

[00611] For the table above, as an exemplary explanation, "SEQ ID NO: 858_(CR01008×3)" indicates that the (CR01008×3) moiety is conjugated to the 3'-end of the sense strand as shown in SEQ ID NO: 858.

Biological Assays

Example 1: *In vitro* Activity Assessment of Complement C3 (C3) siRNA

[00612] In this example, the inhibitory activity of RX002001 to RX002212 targeting the same C3 target region on the C3 mRNA (Accession No. NM_000064.4) in cells, was assessed using a target gene inhibition activity assay in the liver cancer HepG2 cell line.

[00613] Preparation of test sample

[00614] After the above siRNA test samples were centrifuged, an appropriate amount of DEPC H_2O was added to each tube to dissolve the siRNA, and 20 μM stock solutions was prepared. The

stock solutions were then further serially diluted with DEPC H_2O into 0.04 μM and 0.004 μM working solutions. Dose screening experiments were performed at final duplex concentrations of 1 nM and 0.1 nM.

[00615] 96-well transfection and detection:

[00616] HepG2 cells grown to near confluence were digested with trypsin, the cells were washed, and a cell suspension was prepared for plating in 96-well plates.

[00617] 5 μL of 0.4 μM and 0.04 μM working solutions were dispersed in 20 μL of Opti-MEM to form siRNA mixtures. 0.2 μL of RNAiMAX was dispersed in 24.8 μL of Opti-MEM, and after incubating for 5 min, was mixed with each siRNA mixture and incubated for 10 min to form transfection complexes. 150 μL of cell suspension (12,000 cells) was added to each well of a 96-well plate containing the transfection complex, and the 96-well plate was placed in an incubator for continued culture for 24 h.

[00618] For the mock control group, 0.2 μL of RNAiMAX was dispersed in 24.8 μL of Opti-MEM, and after incubating for 5 min, 25 μL of Opti-MEM was added, followed by incubation for 10 min to form the transfection complex. 150 μL of cell suspension (12,000 cells) was added to each well of a 96-well plate containing the transfection complex, and the 96-well plate was placed in an incubator for continued culture for 24 h.

[00619] The 96-well plate was taken out, the cells were lysed, and the lysate was diluted. A one-step qPCR kit (Thermo Fisher, Power SYBR Green RNA-to-CT™ 1-Step, 4389986) was used to detect the expression level of the target gene mRNA in HepG2 cells on a real-time quantitative PCR system (Roche, LightCycler 480). In this real-time quantitative PCR method, the TATA-box binding protein (TBP) gene was used as an internal reference gene, and primers for the target gene and primers for the TBP internal reference gene were used to detect the target gene and the TBP internal reference gene, respectively. The sequences of the detection primers are shown in Table 12.

[00620] Table 12: Sequences of Detection Primers

Gene		Primer type	Primer sequence
Target gene	C3	Forward primer	5'-AAGCGCATTCCGATTGAGGA-3' (SEQ ID NO: 944)

		Reverse primer	5'-CCTGAGTGCAAGATGACGGT-3' (SEQ ID NO: 945)
Reference gene	TBP	Forward primer	5'-TGCTCACCCACCAACAATTTAG-3' (SEQ ID NO: 946)
		Reverse primer	5'-TCTGCTCTGACTTTAGCACCTG-3' (SEQ ID NO: 947)

[00621] In the real-time quantitative PCR method, the ΔΔCt method was used to perform relative quantitative calculations on the expression level and inhibition rate of the target gene mRNA in each test group according to the technical method described above in DETAILED DESCRIPTION.

[00622] Table 13: Inhibitory Activity of siRNAs on the Target Gene in HepG2 Cells after Administration of the siRNAs

Group	10 nM		1 nM	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
Mock	100.00	6.32	100.00	6.36
RX002001	88.92	8.70	91.03	7.28
RX002002	32.08	2.72	78.55	4.62
RX002003	97.20	2.38	96.63	0.32
RX002004	59.07	5.59	83.87	8.89
RX002005	21.55	0.46	74.79	5.74
RX002006	21.20	0.45	70.17	0.80
RX002007	53.48	0.17	87.91	2.58
RX002008	16.50	4.86	66.24	7.99
RX002009	47.33	4.79	85.36	4.74
RX002010	33.17	9.10	80.28	8.77
RX002011	19.57	4.56	68.58	5.15
RX002012	36.59	10.84	83.70	7.37
RX002013	69.76	4.67	106.55	5.57
RX002014	13.88	0.59	59.50	4.56
RX002015	59.80	15.93	96.89	4.11
RX002016	34.05	6.58	66.32	11.21
RX002017	71.24	1.86	94.47	4.32
RX002018	40.33	8.05	77.44	3.29
RX002019	60.78	10.67	84.84	3.46
RX002020	21.11	4.79	64.86	0.11
RX002021	17.12	5.23	73.89	12.49
RX002022	53.64	6.29	115.88	7.00

RX002023	72.78	15.69	131.80	4.09
RX002024	16.74	1.82	90.86	16.02
RX002025	28.19	1.01	88.20	4.18
RX002026	35.77	11.82	108.83	23.81
RX002027	85.79	13.68	131.81	29.89
RX002028	14.71	0.96	97.87	10.69
RX002029	5.33	1.17	47.14	6.11
RX002030	8.26	3.42	42.37	9.47
RX002031	28.29	17.54	81.26	22.92
RX002032	47.25	23.91	99.86	0.49
RX002033	40.09	2.62	99.54	10.07
RX002034	24.25	2.73	77.37	2.02
RX002035	79.47	6.23	97.35	6.36
RX002036	86.71	7.78	104.42	36.74
RX002037	27.42	11.56	60.53	15.07
RX002038	35.63	0.17	86.48	7.20
RX002039	109.95	4.31	126.48	6.40
RX002040	90.28	7.95	121.25	8.31
RX002041	19.33	0.38	70.01	7.48
RX002042	63.06	8.01	95.41	11.04
RX002043	32.88	3.00	68.85	5.84
RX002044	18.42	0.42	64.59	4.74
RX002045	15.61	5.58	68.67	12.50
RX002046	71.98	10.89	79.60	1.69
RX002047	71.96	19.85	80.73	6.32
RX002048	28.40	6.35	70.45	8.72
RX002049	15.93	1.55	80.72	23.46
RX002050	21.72	1.08	79.15	2.59
RX002051	9.52	4.02	47.97	19.35
RX002052	63.67	4.94	85.52	2.65
RX002053	30.14	12.56	78.96	7.73
RX002054	81.67	20.07	100.44	8.03
RX002055	21.17	9.45	73.13	13.78
RX002056	10.46	3.33	13.82	3.77
RX002057	71.21	7.89	76.89	1.38
RX002058	79.01	5.74	93.15	2.59
RX002059	92.56	2.80	82.44	3.64
RX002060	26.23	0.94	72.29	6.37
RX002061	21.32	0.38	70.21	9.66
RX002062	73.05	10.94	91.82	15.08
RX002063	43.75	1.22	85.30	1.25
RX002064	95.49	8.57	86.94	9.50
RX002065	74.28	3.03	96.80	4.74
RX002066	70.54	6.10	86.38	13.07

RX002067	18.88	13.32	58.14	14.29
RX002068	24.77	5.04	78.19	8.80
RX002069	64.37	5.25	98.77	10.55
RX002070	6.53	1.20	33.94	10.05
RX002071	74.34	5.22	81.50	14.17
RX002072	83.25	13.81	83.11	1.43
RX002073	5.62	2.25	20.36	8.12
RX002074	7.28	3.89	29.56	5.24
RX002075	86.15	4.64	93.48	3.66
RX002076	10.73	0.28	37.74	3.88
RX002077	29.35	2.49	65.25	4.69
RX002078	83.30	4.35	91.22	2.53
RX002079	25.47	3.44	86.01	22.64
RX002080	86.76	18.29	82.78	2.03
RX002081	29.17	6.20	66.34	0.65
RX002082	37.01	12.34	79.57	3.51
RX002083	40.56	0.53	111.30	38.65
RX002084	7.50	2.02	29.94	1.22
RX002085	78.59	11.51	104.16	4.76
RX002086	11.51	0.11	59.01	22.83
RX002087	26.78	5.00	72.22	5.89
RX002088	59.94	4.40	98.15	0.80
RX002089	95.37	7.01	94.88	9.52
RX002090	92.87	2.88	94.77	3.17
RX002091	73.63	10.31	102.08	1.17
RX002092	27.46	7.01	75.38	6.52
RX002093	82.63	0.81	99.27	6.16
RX002094	43.09	10.08	95.26	11.49
RX002095	91.65	3.22	111.33	2.91
RX002096	61.23	3.40	89.27	5.83
RX002097	41.10	0.77	82.72	9.71
RX002098	12.61	2.35	32.95	1.29
RX002099	43.88	11.55	72.18	1.06
RX002100	42.55	5.41	82.51	5.12
RX002101	50.21	0.16	68.39	5.58
RX002102	40.12	3.67	88.41	11.52
RX002103	11.74	2.96	65.23	1.12
RX002104	62.66	5.52	93.37	10.96
RX002105	23.86	1.68	89.66	5.71
RX002106	21.00	2.60	57.57	2.44
RX002107	73.21	12.09	88.31	2.67
RX002108	16.40	0.42	79.88	14.15
RX002109	18.45	1.10	63.84	10.85
RX002110	18.44	7.13	51.16	1.34

RX002111	77.15	4.66	68.32	3.57
RX002112	56.80	1.62	90.03	7.35
RX002113	68.05	1.89	89.83	16.63
RX002114	90.74	12.71	92.74	6.66
RX002115	41.90	9.50	90.01	3.09
RX002116	33.60	10.84	67.39	10.85
RX002117	14.28	1.21	45.74	1.42
RX002118	7.93	1.94	27.30	2.94
RX002119	23.35	10.29	70.12	12.14
RX002120	65.79	5.21	75.26	5.77
RX002121	24.86	2.43	84.69	40.29
RX002122	20.41	0.37	87.12	9.23
RX002123	14.56	1.61	83.55	33.96
RX002124	35.75	4.49	86.63	18.12
RX002125	19.33	4.28	61.15	10.24
RX002126	14.48	1.51	37.15	21.28
RX002127	15.10	5.36	38.05	6.98
RX002128	13.02	4.30	54.98	15.68
RX002129	72.17	14.29	95.39	20.41
RX002130	12.03	4.38	43.21	3.60
RX002131	84.28	21.12	89.93	8.66
RX002132	77.35	16.18	94.03	24.15
RX002133	43.46	13.55	89.19	24.95
RX002134	27.71	3.21	61.83	6.85
RX002135	37.92	5.37	83.08	15.25
RX002136	60.48	2.86	88.08	10.34
RX002137	39.71	1.88	77.74	16.51
RX002138	20.58	1.78	52.71	6.78
RX002139	92.08	31.70	104.80	27.75
RX002140	50.22	7.36	72.04	4.70
RX002141	72.00	8.92	112.40	10.45
RX002142	22.40	4.18	75.67	11.94
RX002143	17.15	0.13	67.91	9.95
RX002144	18.54	3.25	65.58	3.21
RX002145	7.54	1.73	17.61	0.86
RX002146	57.03	14.65	92.90	0.30
RX002147	66.15	12.67	99.91	6.52
RX002148	18.72	7.22	79.84	16.51
RX002149	108.94	9.95	96.51	0.47
RX002150	15.27	0.02	52.75	13.30
RX002151	41.59	17.34	84.58	21.86
RX002152	79.40	26.60	96.65	16.34
RX002153	108.89	22.61	117.10	4.59
RX002154	15.25	2.92	46.49	2.73

RX002155	59.28	5.90	99.20	8.90
RX002156	11.88	4.97	41.07	3.35
RX002157	10.00	6.13	29.95	7.55
RX002158	31.99	3.18	63.43	12.66
RX002159	15.88	2.97	48.71	1.03
RX002160	35.89	3.10	75.98	17.71
RX002161	25.16	3.56	82.42	3.23
RX002162	27.58	6.60	68.42	1.90
RX002163	40.79	4.46	102.03	1.83
RX002164	21.86	4.29	76.61	1.13
RX002165	10.83	2.25	37.09	2.66
RX002166	49.92	13.14	93.55	0.31
RX002167	13.42	5.35	55.49	14.43
RX002168	71.33	2.68	93.66	0.46
RX002169	12.19	2.98	45.76	15.61
RX002170	14.00	0.75	51.64	5.64
RX002171	92.05	0.00	95.86	9.54
RX002172	10.02	2.64	36.70	0.84
RX002173	33.36	1.25	80.30	9.03
RX002174	69.36	12.40	92.65	21.30
RX002175	16.98	2.49	74.89	6.11
RX002176	10.83	0.88	20.50	1.94
RX002177	9.00	0.25	31.74	2.98
RX002178	14.11	1.31	45.92	3.07
RX002179	18.55	2.96	55.38	4.07
RX002180	102.34	16.65	106.61	7.66
RX002181	89.85	14.69	90.17	3.68
RX002182	100.82	0.99	105.62	4.14
RX002183	65.10	2.87	90.89	12.73
RX002184	38.38	0.88	93.89	3.99
RX002185	86.78	2.84	100.14	2.62
RX002186	25.42	8.44	62.34	5.90
RX002187	22.25	0.15	72.57	14.25
RX002188	30.98	6.83	94.67	13.72
RX002189	72.25	3.89	109.49	8.93
RX002190	13.96	2.92	56.74	9.37
RX002191	7.54	2.97	30.24	10.27
RX002192	101.65	12.26	105.80	8.03
RX002193	67.68	0.33	98.30	2.25
RX002194	76.28	15.10	105.19	6.18
RX002195	36.19	7.80	96.71	0.32
RX002196	32.28	10.34	64.29	5.56
RX002197	52.12	4.85	81.45	3.06
RX002198	47.23	8.21	74.57	8.75

RX002199	57.00	2.61	84.64	4.42
RX002200	46.22	12.82	80.84	7.52
RX002201	87.15	9.24	104.87	5.65
RX002202	19.06	7.03	83.61	7.10
RX002203	68.75	6.73	93.46	12.48
RX002204	78.25	2.30	107.51	7.72
RX002205	41.98	14.13	81.37	0.27
RX002206	101.99	8.65	108.83	9.59
RX002207	92.20	6.77	113.75	7.61
RX002208	78.89	2.19	106.14	1.04
RX002209	60.79	3.28	105.51	17.33
RX002210	52.75	11.21	101.34	0.33
RX002211	14.45	0.09	36.90	7.25
RX002212	109.84	14.32	107.61	7.20

Example 2: *In vivo* Activity Assessment of siRNA Conjugates with L96 Moiety Conjugated to 3'-end of Sense Strand in BALB/c-HDI Mice

[00623] In this example, a BALB/c mouse hydrodynamic tail vein injection model was used to assess the inhibitory activity of siRNA conjugates RZ002001-RZ002032, with an L96 moiety conjugated to the 3'-end of the sense strand targeting the same C3 target region on the C3 mRNA, with RZ000001 as a negative control.

[00624] Plasmid construction

[00625] A pcDNA-CMV-RG002 plasmid (ID: NM_000064.4) was constructed by Sangon Biotech (Shanghai) Co., Ltd.

[00626] Mouse model construction

[00627] The BALB/c mouse hydrodynamic injection model was established by rapidly injecting a pcDNA-CMV-RG002 plasmid solution into the mice via tail vein under high pressure. On day 3 of the experiment, mice were injected with 10 μg of pcDNA-CMV-RG002 via hydrodynamic tail vein injection within 5 s, with an injection volume equivalent to 8% of the mouse's body weight. The plasmid DNA for injection was diluted with PBS. The solution was prepared before injection and stored at 4°C.

[00628] Animal grouping, administration, and tissue sample collection

[00629] 6 to 7-week-old female BALB/c mice were randomly grouped by body weight, with 5 mice per group. Each test group was administered a predetermined dose of the drug conjugate, and a PBS control group was included. The administration dose for all mice was calculated based on their body weight. A single dose was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 0.1 mg/mL (calculated as siRNA) solution in PBS, with a dosing volume of 10 mL/kg (mouse body weight). That is, the administration dose of each drug conjugate was 1 mg/kg (siRNA/mouse body weight). The PBS control group was administered 10 mL/kg (mouse body weight) of a PBS solution without the siRNA conjugate. The day of administration was recorded as day 0 (D0). Plasmid injection was performed on day 3 (D3) after administration, and all 5 mice in each group were sacrificed on day 4 (D4). Dissection was performed on the sacrificed mice, and the liver tissue from each sacrificed mouse was collected. The liver tissue was cut into approximately 2 mm^3 small pieces and preserved in RNAlater™ solution.

[00630] For each mouse, an appropriate amount of liver tissue sample was taken out from RNAlater™ solution. The liver tissue sample was disrupted for 60 s in a Tissuelyser II automatic tissue homogenizer. Then, total RNA was extracted using an automatic nucleic acid extractor (purchased from Zhejiang Hanwei Technology Co., Ltd.) and a nucleic acid extraction kit (purchased from Zhejiang Hanwei Technology Co., Ltd., GO-MNTR-100) according to the standard operating procedure for total RNA extraction.

[00631] For each mouse, 1 μg of total RNA was used for reverse-transcription using a reverse transcription kit (Thermo Fisher Scientific, RevertAid First Strand cDNA Synthesis Kit, K1622) with Oligo(dT)18 as the reverse transcription primer. A 20 μL reverse transcription system was prepared, and the reverse transcription reaction was completed according to the instruction manual. After the reaction, 60 μL of RNase-Free water was added to the reverse transcription system to obtain a cDNA solution. Next, the expression level of the target gene mRNA in the animals was detected on a real-time quantitative PCR system (Bio-Rad, CFX Opus 384) using a real-time quantitative PCR kit (Thermo Fisher Scientific, TaqMan Fast Advanced Master Mix, 4444557). In this real-time quantitative PCR method, the Nero gene on the plasmid backbone was used as an internal reference gene, and primers for the target gene and primers for the Nero internal reference gene were used to detect the target gene and the Nero internal reference gene, respectively. The

sequences of the detection primers are shown in Table 14.

[00632] Table 14: Sequences of Detection Primers

Gene		Primer type	Primer sequence	Fluorescent group
Target gene	C3	Forward primer	5'-AGTCTCCTGCTTTAGTGATGC-3' (SEQ ID NO: 948)	/
		Reverse primer	5'-GCCTTTGTTCTCATCTCGCT-3' (SEQ ID NO: 949)	/
		Probe primer	5'-CTGTTGACCTGCTCCTCGCAAATATCT-3' (SEQ ID NO: 950)	5'FAM; 3'MGB
Reference gene	Nero	Forward primer	5'-CGTTGGCTACCCGTGATATT-3' (SEQ ID NO: 951)	/
		Reverse primer	5'-CTCGTCAAGAAGGCGATAGAAG-3' (SEQ ID NO: 952)	/
		Probe primer	5'-CCGCTTCCTCGTGCTTTACGGTAT-3' (SEQ ID NO: 953)	5'VIC; 3'MGB

[00633] A 10 μL Real-time PCR reaction system was prepared for each PCR detection well according to the method described in the instruction manual of the real-time quantitative PCR kit. Each reaction system contained 4 μL of the cDNA solution obtained from the reverse transcription reaction described above, 5 μL of TaqMan™ Fast Advanced Master Mix (2×), 0.15 μL of 10 μM forward primer, 0.15 μL of 10 μM reverse primer (for primer information, see Table 8), 0.15 μL of 10 μM probe primer, and 0.55 μL of RNase-Free H_2O. The prepared reaction system was placed on a real-time quantitative PCR system (Bio-Rad, CFX Opus 384), and Real-time PCR amplification was performed using a two-step method. The amplification program was: 50°C for 2 min, pre-denaturation at 95°C for 20 s, and then 40 cycles of denaturation at 95°C for 3 s and annealing and extension at 60°C for 30 s. In this real-time quantitative PCR method, the ΔΔCt method was used to perform relative quantitative calculations on the expression level and inhibition rate of the target gene mRNA in each test group according to the technical method described above in DETAILED DESCRIPTION.

[00634] The results of Example 2 showed that at a dose of 1 mg/kg, RZ002003, RZ002006, RZ002011, RZ002015, and RZ002031 significantly inhibited the expression of C3 gene mRNA in

mouse liver tissue (FIG. 1, Table 15).

[00635] Table 15: Inhibitory Activity of siRNA Conjugates on C3 Gene mRNA in Liver Tissue of BALB/c-HDI Mice after Administration of the siRNA Conjugates

Group	1 mg/kg	
	Relative remaining expression level (%)	STDEV
PBS	100.00	21.64
RZ000001	107.29	21.82
RZ002001	71.27	40.59
RZ002002	49.64	13.24
RZ002003	27.97	15.06
RZ002004	47.73	9.78
RZ002005	60.75	11.91
RZ002006	23.39	4.50
RZ002007	40.26	10.97
RZ002008	49.83	7.77
RZ002009	43.55	9.71
RZ002010	57.71	14.87
RZ002011	39.12	16.78
RZ002012	109.83	39.57
RZ002013	90.25	15.70
RZ002015	12.45	3.11
RZ002016	39.26	6.37
RZ002017	75.85	16.85
RZ002018	42.00	16.33
RZ002019	66.95	11.04
RZ002020	91.29	24.69
RZ002021	55.92	17.25
RZ002022	117.15	74.63
RZ002023	33.31	27.44
RZ002024	45.34	13.76
RZ002025	74.24	33.05
RZ002026	68.33	25.03
RZ002027	53.43	13.26
RZ002028	63.89	28.42
RZ002029	58.55	20.98
RZ002030	63.63	19.14
RZ002031	17.91	7.95
RZ002032	67.48	23.43

Example 3: Toxicological Assessment of siRNA Conjugates with L96 Moiety Conjugated to 3'-end of Sense Strand in ICR Mice

[00636] This example assessed the nature and extent of toxic reactions of L96 moiety conjugates RZ002003, RZ002006, RZ002011, RZ002015, and RZ002031 in ICR mice via a single subcutaneous injection at 300 mg/kg.

[00637] Animal grouping, administration, and tissue sample collection

[00638] 6 to 8-week-old ICR mice (purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd.) were randomly grouped by body weight, with 10 mice per group, half male and half female. Each test group was administered a predetermined dose of the drug conjugate, and a PBS control group was included. The administration dose for all mice was calculated based on their body weight. A single dose was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 30 mg/mL (calculated as siRNA) solution in PBS, with a dosing volume of 10 mL/kg (mouse body weight). That is, the administration dose of each drug conjugate was 300 mg/kg (siRNA/mouse body weight). The PBS control group was administered 10 mL/kg (mouse body weight) of a PBS solution without the siRNA conjugate and observed for 14 days. The day of administration was recorded as day 0 (D0). During the experiment, clinical observations were performed at least once daily after the first administration, and body weight and food consumption were measured twice a week. On day 14 (D14) of the experiment, blood was collected from all animals (mice were fasted for no less than 12 h before sampling and detection, with free access to water) for hematology and blood biochemistry tests. Collected blood was anticoagulated with EDTA-K2, and a complete blood count was performed using an automatic modular hematology and body fluid analyzer (Sysmex XN-10B1). Blood samples (without anticoagulant) were collected and left at room temperature for about 30 min. After blood coagulation, the samples were centrifuged at 2000 g for 10 min at 4°C, and blood biochemistry was tested using a fully automatic biochemical analyzer (Sysmex BX-4000). On day 14 (D14) of the experiment, all animals were desected. Before desection, the mice to be desected were fasted for at least 12 h with free access to water, anesthetized with Zoletil 50 (Virbac, France, 8G4VA), and then euthanized by exsanguination from the abdominal aorta after blood collection, followed by gross necropsy observation. Histopathological examinations were performed on the livers and kidneys of all animals, as shown in FIG. 2 (using hematoxylin-eosin staining). The results showed

that each test sample had no significant effect on the general condition, body weight, food consumption, and gross necropsy observations of the ICR mice. Compared to the PBS group, at a dose of 300 mg/kg (siRNA/mouse body weight), no significant abnormalities were observed in the hematology and blood biochemistry of animals in the RZ002003, RZ002006, RZ002011, and RZ002015 groups; no significant abnormalities were observed in the hematology of animals in the RZ002031 group, with slight elevations in ALT and AST.

Example 4: *In vitro* Activity Assessment of siRNA Conjugates with (CR01008)×3 Moiety Conjugated to 3'-end of Sense Strand

[00639] In this example, the inhibitory activity of (CR01008)×3 moiety siRNA conjugates on the target gene C3 mRNA in cells was assessed using a target gene inhibition activity assay in the human liver cancer HepG2 cell line.

[00640] Preparation of test samples

[00641] After each of the above siRNA test samples was centrifuged, an appropriate amount of PBS was added to each tube to dissolve the siRNA, and 20 μM stock solutions were prepared. The stock solutions were then further serially diluted with PBS into 0.5 μM and 0.05 μM working solutions. Dose experiments were performed at final duplex concentrations of 5 nM and 0.5 nM.

[00642] 96-well transfection and detection

[00643] HepG2 cells grown to near confluence were digested with trypsin, the cells were washed to prepare a cell suspension, and 100 μL of the cell suspension, containing 12,000 cells, was added to each well of a 96-well plate and cultured in an incubator at 37°C with 5% CO_2. After the cells had adhered for 24 h, the DMEM medium in the 96-well plate was aspirated, 80 μL of Opti-MEM™ medium was added to each well, and the 96-well plate was then placed back in the incubator for continued culture. 1 μL of 0.1 μM and 0.01 μM working solutions were dispersed in 9 μL of Opti-MEM to form siRNA mixtures, and 0.3 μL of RNAiMAX was dispersed in 9.7 μL of Opti-MEM and mixed with each siRNA mixture to form transfection complexes. The transfection complexes were incubated at room temperature for 10 min and then added to the 96-well plate at 20 μL/well. After culturing for 4 h, 100 μL of DMEM medium containing 20% FBS was added to each well, and the 96-well plate was placed in the incubator for continued culture for 24 h. For the Mock

control group: 0.3 μL of RNAiMAX was dispersed in 9.7 μL of Opti-MEM, and then 10 μL of Opti-MEM was added, followed by incubation at room temperature for 10 min; it was then added to the 96-well plate at 20 μL/well. After culturing for 4 h, 100 μL of DMEM medium containing 20% FBS was added to each well, and the 96-well plate was placed in the incubator for continued culture for 24 h.

[00644] The 96-well plate was taken out, and total RNA was extracted using an automatic nucleic acid extractor (purchased from Zhejiang Hanwei Technology Co., Ltd.) and a nucleic acid extraction kit (purchased from Zhejiang Hanwei Technology Co., Ltd., GO-MNTR-100) according to the standard operating procedure for total RNA extraction.

[00645] A reverse transcription kit (Thermo Fisher Scientific, RevertAid First Strand cDNA Synthesis Kit, K1622) was used with Oligo(dT)18 as the reverse transcription primer. A 20 μL reverse transcription system was prepared, and the reverse transcription reaction was completed according to the method described in the instruction manual. Next, a real-time quantitative PCR kit (Thermo Fisher Scientific, TaqMan Fast Advanced Master Mix, 4444557) was used to detect the expression level of the target gene mRNA in HepG2 cells on a real-time quantitative PCR system (Bio-Rad, CFX Opus 384). In this real-time quantitative PCR method, the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as an internal reference gene, and primers for the target gene and primers for the GAPDH internal reference gene were used to detect the target gene and the GAPDH internal reference gene, respectively. The sequences of the detection primers are shown in Table 16.

[00646] Table 16: Sequences of Detection Primers

Gene		Primer type	Primer sequence	Fluorescent group
Target gene	C3	Forward primer	5'-AGTCTCCTGCTTTAGTGATGC-3' (SEQ ID NO: 948)	/
		Reverse primer	5'-GCCTTTGTTCTCATCTCGCT-3' (SEQ ID NO: 949)	/
		Probe primer	5'-CTGTTGACCTGCTCCTCGCAAATATCT-3' (SEQ ID NO: 951)	5'FAM; 3'MGB

Reference gene	GAPDH	Forward primer	5'-AAGAAGGTGGTGAAGCAGG-3' (SEQ ID NO: 954)	/
		Reverse primer	5'-CAAAGTGGTCGTTGAGGG-3' (SEQ ID NO: 955)	/
		Probe primer	5'-CAACAGCGACACCCACTC-3' (SEQ ID NO: 956)	5'VIC; 3'MGB

[00647] A 10 μL Real-time PCR reaction system was prepared for each PCR detection well according to the method described in the instruction manual of the real-time quantitative PCR kit. Each reaction system contained 4 μL of the cDNA solution obtained from the reverse transcription reaction described above, 5 μL of TaqMan™ Fast Advanced Master Mix (2×), 0.15 μL of 10 μM forward primer, 0.15 μL of 10 μM reverse primer (for primer information, see Table 14), 0.15 μL of 10 μM probe primer, and 0.55 μL of RNase-Free H_2O. The prepared reaction system was placed on a real-time quantitative PCR system (Bio-Rad, CFX Opus 384), and Real-time PCR amplification was performed using a two-step method. The amplification program was: 50°C for 2 min, followed by pre-denaturation at 95°C for 20 s, and then 40 cycles of denaturation at 95°C for 3 s and annealing and extension at 60°C for 30 s. In this real-time quantitative PCR method, the ΔΔCt method was used to perform relative quantitative calculations on the expression level and inhibition rate of the target gene mRNA in each test group according to the technical method described above in DETAILED DESCRIPTION.

[00648] Table 17: Inhibitory Activity of siRNA Conjugates on the Target Gene C3 mRNA in HepG2 Cells After Administration of the siRNA Conjugates

Name	5 nM		0.5 nM	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
Mock	100.00	3.12	100.00	3.12
RZ002033	9.16	0.94	31.05	0.71
RZ002034	8.80	0.76	24.48	6.22
RZ002099	7.65	1.92	32.10	1.97
RZ002036	11.98	0.18	24.00	1.03
RZ002037	11.26	0.61	27.13	0.60

RZ002038	9.04	1.21	30.71	0.51
RZ002039	10.98	0.37	36.07	1.88
RZ002040	12.62	0.59	31.73	1.40
RZ002041	10.48	1.47	27.68	6.13
RZ002042	9.07	0.71	26.13	1.61
RZ002043	8.04	0.71	30.68	0.16
RZ002050	17.65	2.29	36.54	2.38
RZ002051	16.27	2.17	27.43	6.32
RZ002106	13.92	1.18	30.03	0.72
RZ002053	14.88	4.01	26.00	0.90
RZ002054	17.8	10.42	28.19	2.16
RZ002055	15.57	2.71	24.53	2.19
RZ002056	16.48	2.71	43.19	1.83
RZ002057	17.52	3.31	40.75	5.49
RZ002058	14.75	0.11	31.72	1.35
RZ002059	11.28	1.47	26.63	4.85
RZ002060	10.28	1.48	25.93	0.70
RZ002066	20.09	9.16	42.86	15.61
RZ002067	16.89	4.88	27.44	1.50
RZ002068	15.99	9.04	38.27	2.66
RZ002069	18.44	5.73	31.22	2.43
RZ002070	16.77	8.10	34.34	1.93
RZ002071	16.24	5.08	32.74	1.91
RZ002072	24.64	4.76	53.87	6.33
RZ002073	34.06	3.25	51.24	0.29
RZ002074	14.91	0.16	44.37	1.31
RZ002075	10.69	0.15	41.05	4.82
RZ002076	10.76	1.08	41.10	1.94
RZ002082	21.93	5.23	28.44	2.52
RZ002083	19.48	8.68	25.39	1.18
RZ002084	15.71	8.17	27.85	2.26
RZ002085	23.27	5.75	33.20	2.55
RZ002086	21.12	8.65	34.10	6.23
RZ002087	21.77	0.85	36.53	3.15
RZ002088	34.48	0.91	69.65	6.92
RZ002089	31.49	5.73	54.13	8.64

RZ002090	14.91	0.03	51.77	15.52
RZ002091	11.73	0.65	36.02	0.00
RZ002092	11.67	1.28	37.72	0.36

[00649] The results of Example 4 showed that at doses of 5 nM and 0.5 nM, different siRNA conjugates modified with CR01008 significantly inhibited C3 gene mRNA expression in HepG2 cells (Table 17).

Example 5: Assessment of mRNA Knockdown Effect of siRNA Conjugates with (CR01008)×3 Moiety Conjugated to 3'-end of Sense Strand in Normal *Macaca fascicularis*

[00650] This example assessed the inhibitory activity of RZ002099, RZ002101, RZ002106, and RZ002113 on the target gene C3 mRNA in *Macaca fascicularis*.

[00651] Animal grouping, administration, and tissue sample collection

[00652] Healthy *Macaca fascicularis* weighing 3 to 5 kg were grouped, with 4 *Macaca fascicularis* per group, half male and half female. Each test group was administered a predetermined dose of the drug conjugate, and a PBS control group was included. The administration dose for all animals was calculated based on their body weight. A single dose was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 9 mg/mL (calculated as siRNA) solution in PBS, with a dosing volume of 1 mL/kg (*Macaca fascicularis* body weight). That is, the administration dose of each drug conjugate was 9 mg/kg (siRNA/*Macaca fascicularis* body weight). The PBS control group was administered 1 mL/kg (*Macaca fascicularis* body weight) of a PBS solution without the siRNA conjugate. The day of administration was recorded as day 0 (D0). On day 14 (D14) after administration, liver biopsies were performed on the *Macaca fascicularis* in each group, and the liver biopsy tissues were immediately preserved in RNAlater™ solution.

[00653] For each *Macaca fascicularis*, a liver tissue sample was taken from RNAlater™ solution. The liver tissue sample was disrupted for 60 s in a Tissuelyser II automatic tissue homogenizer. Then, total RNA was extracted using an automatic nucleic acid extractor (purchased from Zhejiang Hanwei Technology Co., Ltd.) and a nucleic acid extraction kit (purchased from Zhejiang Hanwei

Technology Co., Ltd., GO-MNTR-100) according to the standard operating procedure for total RNA extraction.

[00654] For each *Macaca fascicularis*, 1 μg of total RNA was taken for reverse-transcription using a reverse transcription kit (Thermo Fisher Scientific, RevertAid First Strand cDNA Synthesis Kit, K1622) with Oligo(dT)18 as the reverse transcription primer. A 20 μL reverse transcription system was prepared, and the reverse transcription reaction was completed according to the method described in the instruction manual of the reverse transcription kit. After the reaction, 60 μL of RNase-Free water was added to the reverse transcription system to obtain a cDNA solution. Next, the expression level of the target gene mRNA in the animals was detected on a real-time quantitative PCR system (Roche, Lightcycler 480II) using a real-time quantitative PCR kit (Thermo Fisher Scientific, TaqMan Fast Advanced Master Mix, 4444557). In this real-time quantitative PCR method, the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as an internal reference gene, and primers for the target gene and primers for the GAPDH internal reference gene were used to detect the target gene and the GAPDH internal reference gene, respectively. The sequences of the detection primers are shown in Table 18.

[00655] Table 18: Sequences of Detection Primers

Gene		Primer type	Primer sequence	Fluorescent group
Target gene	C3	Forward primer	5'-TCCTGCGATCAGAAGAGACC-3' (SEQ ID NO: 957)	/
		Reverse primer	5'-GACCTTTGGCCTTAGCATGG-3' (SEQ ID NO: 958)	/
		Probe primer	5'-ACCGACAAGGTGCCTTGGCCT-3' (SEQ ID NO: 959)	5'FAM; 3'MGB
Reference gene	GAPDH	Forward primer	5'-TCGTGGAAGGACTCATGACC-3' (SEQ ID NO: 960)	/
		Reverse primer	5'-GCAGGGATGATGTTCTGGAG-3' (SEQ ID NO: 961)	/
		Probe primer	5'-CTCCGCGGCCATCACGCCAC-3' (SEQ ID NO: 962)	5'VIC; 3'MGB

[00656] A 10 μL Real-time PCR reaction system was prepared for each PCR detection well according to the method described in the instruction manual of the real-time quantitative PCR kit. Each reaction system contained 4 μL of the cDNA solution obtained from the reverse transcription reaction described above, 5 μL of TaqMan™ Fast Advanced Master Mix (2×), 0.15 μL of 10 μM forward primer, 0.15 μL of 10 μM reverse primer (for primer information, see Table 16), 0.15 μL of 10 μM probe primer, and 0.55 μL of RNase-Free H_2O. The prepared reaction system was placed on a real-time quantitative PCR system (Bio-Rad, CFX Opus 384), and Real-time PCR amplification was performed using a two-step method. The amplification program was: 50°C for 2 min, followed by pre-denaturation at 95°C for 20 s, and then 40 cycles of denaturation at 95°C for 3 s and annealing and extension at 60°C for 30 s. In this real-time quantitative PCR method, the ΔΔCt method was used to perform relative quantitative calculations on the expression level and inhibition rate of the target gene mRNA in each test group according to the technical method described above in DETAILED DESCRIPTION.

[00657] The results of Example 5 showed that at a single dose of 9 mg/kg, RZ002099, RZ002101, RZ002106, and RZ002113 significantly inhibited C3 gene mRNA expression (Table 19, FIG. 4).

[00658] Table 19: Change of C3 mRNA Level in *Macaca fascicularis* Liver After Administration of the siRNA Conjugates

Group	C3 mRNA level (9 mg/kg, D14)	
	Relative remaining expression level (%)	STDEV
PBS	100.00	28.24
RZ002099	15.51	5.60
RZ002101	22.29	12.07
RZ002106	9.86	1.44
RZ002113	12.96	6.94

Example 6: Assessment of C3 Protein Reduction Caused by siRNA Conjugates with (CR01008)×3 Moiety at 3'-end of Sense Strand in Normal *Macaca fascicularis*

[00659] This example assessed the expression of C3 protein in the serum of *Macaca fascicularis* at different time points after a single administration of (CR01008)×3 moiety conjugates RZ002099, RZ002101, RZ002106, and RZ002113 using an ELISA method.

[00660] Animal grouping, administration, and tissue sample collection

[00661] Healthy *Macaca fascicularis* weighing 3 to 5 kg were grouped according to serum C3 protein levels, with 4 *Macaca fascicularis* per group, half male and half female. Each test group was administered a predetermined dose of the drug conjugate, and a PBS control group was included. The administration dose for all animals was calculated based on their body weight. A single dose was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 9 mg/mL (calculated as siRNA) solution in PBS, with a dosing volume of 1 mL/kg (*Macaca fascicularis* body weight). That is, the administration dose of each drug conjugate was 9 mg/kg (siRNA/*Macaca fascicularis* body weight). The PBS control group was administered 1 mL/kg (*Macaca fascicularis* body weight) of a PBS solution without the siRNA conjugate. *Macaca fascicularis* serum was collected before administration (recorded as pre-dose), on the day of administration recorded as day 0 (D0), and on day 7 (D7), day 14 (D14), day 21 (D21), day 28 (D28), day 35 (D35), day 42 (D42), day 49 (D49), day 56 (D56), day 63 (D63), day 70 (D70), day 77 (D77), day 84 (D84), day 91 (D91), day 98 (D98), and day 105 (D105) after administration. C3 protein expression was measured using a human complement C3 ELISA kit (Hycult Biotech, HK366-01).

[00662] The results of Example 6 showed that at a single dose of 9 mg/kg, RZ002099, RZ002101, RZ002106, and RZ002113 all significantly reduced the C3 protein level in *Macaca fascicularis* serum. Among them, the C3 protein reduction caused by RZ002106 reached up to 90%, with an 80% protein reduction still observed at D70, and the protein level had not returned to the pre-dose level by D105 (FIG. 5, Table 20).

[00663] Table 20: Change of C3 Protein Level in *Macaca fascicularis* Serum after Administration of the siRNA Conjugates

Group	pre-dose		D7		D14		D21	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
PBS	100.00	0.00	100.20	6.80	95.70	14.00	104.10	18.10
RZ002099	100.00	0.00	48.57	12.93	27.63	11.82	30.95	14.81
RZ002101	100.00	0.00	47.87	15.67	26.08	8.71	22.75	10.48
RZ002106	100.00	0.00	44.31	6.21	21.03	5.24	11.88	3.48

RZ002113	100.00	0.00	41.55	13.82	21.54	9.85	17.12	8.27
Group	D28		D35		D42		D49	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
PBS	82.90	10.00	79.30	7.90	80.60	4.50	88.10	8.40
RZ002099	24.25	11.70	26.75	8.80	30.29	15.16	37.84	24.22
RZ002101	19.11	6.12	20.99	4.49	23.77	6.44	21.76	4.33
RZ002106	13.34	6.63	12.15	4.03	11.87	4.67	9.01	1.95
RZ002113	16.91	5.24	15.70	5.49	15.73	5.48	14.45	5.65
Group	D56		D63		D70		D77	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
PBS	79.41	7.84	84.87	17.19	87.71	13.88	103.71	10.45
RZ002099	34.34	26.33	/	/	/	/	/	/
RZ002101	25.18	3.66	/	/	/	/	/	/
RZ002106	9.51	2.59	15.41	5.99	15.17	4.63	24.45	8.90
RZ002113	19.25	8.15	/	/	/	/	/	/
Group	D84		D91		D98		D105	
	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV	Relative remaining expression level (%)	STDEV
PBS	99.52	15.57	91.57	3.00	95.00	1.80	117.08	9.46
RZ002099	/	/	/	/	/	/	/	/
RZ002101	/	/	/	/	/	/	/	/
RZ002106	38.93	16.88	34.23	13.01	36.06	14.85	36.61	13.59
RZ002113	/	/	/	/	/	/	/	/

Example 7: Effect of siRNA Conjugates with (CR01008)×3 Conjugated to 3'-end of Sense Strand on Complement Pathway Activity in Normal *Macaca fascicularis*

[00664] This example evaluated the complement activity in the serum of *Macaca fascicularis* at different time points after a single administration of (CR01008)×3 (i.e., (CR01008×3) ligand) conjugates RZ002099, RZ002101, RZ002106, and RZ002113.

[00665] Animal grouping, administration, and tissue sample collection

[00666] Healthy *Macaca fascicularis* weighing 3 to 5 kg were grouped, with 4 *Macaca fascicularis* per group, half male and half female. Each test group was administered a predetermined dose of the drug conjugate, and a PBS control group was included. The administration dose for all animals was calculated based on their body weight. A single dose was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 9 mg/mL (calculated as siRNA) solution in PBS, with a dosing volume of 1 mL/kg (*Macaca fascicularis* body weight). That is, the administration dose of each drug conjugate was 9 mg/kg (siRNA/*Macaca fascicularis* body weight). The PBS control group was administered 1 mL/kg (*Macaca fascicularis* body weight) of a PBS solution without the siRNA conjugate. *Macaca fascicularis* serum in all groups was collected before administration (recorded as pre-dose), on the day of administration recorded as day 0 (D0), and on day 7 (D7), day 14 (D14), day 21 (D21), day 28 (D28), day 35 (D35), day 42 (D42), day 49 (D49), day 56 (D56), day 63 (D63), day 70 (D70), day 77 (D77), day 84 (D84), day 91 (D91), day 98 (D98), and day 105 (D105) after administration. The activities of the complement system alternative pathway (CAP) and the complement system classical pathway (CCP) were determined using the WIESLAB® Complement System Alternative Pathway Kit (COMPL AP330 RUO, IBL America) and the Complement System Classical Pathway Kit (COMPL CP310 RUO, IBL America).

[00667] The results of Example 7 showed that at a single dose of 9 mg/kg, RZ002099, RZ002101, RZ002106, and RZ002113 all significantly inhibited the complement alternative pathway in the serum of *Macaca fascicularis*, but had no significant effect on the complement classical pathway in the serum (FIG. 6, FIG. 7, Table 21, Table 22).

[00668] Table 21: Change of Serum CAP Activity in *Macaca fascicularis* after Administration of the siRNA Conjugates

Group	pre-dose		D7		D14		D21	
	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV
PBS	100.00	0.00	88.36	21.09	101.24	11.59	92.70	4.88
RZ002099	100.00	0.00	50.06	38.25	37.05	44.75	53.62	38.25
RZ002101	100.00	0.00	70.48	21.06	48.03	13.21	35.31	13.64

RZ002106	100.00	0.00	70.73	32.47	20.20	13.96	9.87	8.83
RZ002113	100.00	0.00	74.86	27.76	32.66	34.63	27.77	27.59
Group	D28		D35		D42		D49	
	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV
PBS	83.52	15.70	88.55	8.63	93.52	6.11	85.74	6.29
RZ002099	33.90	48.51	65.90	33.90	44.33	42.25	53.30	42.55
RZ002101	21.65	17.68	38.20	22.71	35.92	17.57	46.36	15.37
RZ002106	10.69	11.51	4.69	4.04	7.55	10.01	9.04	10.40
RZ002113	22.33	26.74	21.20	26.92	18.09	22.65	37.16	37.55
Group	D56		D63		D70		D77	
	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV
PBS	87.26	12.82	84.05	13.23	85.94	19.26	90.42	10.01
RZ002099	65.11	27.63	/	/	/	/	/	/
RZ002101	58.12	17.72	/	/	/	/	/	/
RZ002106	8.63	10.62	30.58	30.75	31.67	29.63	66.68	38.17
RZ002113	48.77	33.16	/	/	/	/	/	/
Group	D84		D91		D98		D105	
	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV	Relative remaining activity (%)	STDEV
PBS	82.42	17.05	77.47	18.50	82.48	12.97	91.80	10.47
RZ002099	/	/	/	/	/	/	/	/
RZ002101	/	/	/	/	/	/	/	/
RZ002106	59.91	37.62	63.49	32.68	74.24	36.30	72.33	31.73
RZ002113	/	/	/	/	/	/	/	/

[00669] Table 22: Change of Serum CCP Activity in *Macaca fascicularis* after Administration of the siRNA Conjugates

Group	pre-dose	D7	D21	D28	D35	D42

	Relative remaining activity (%)	STD EV	Relative remaining activity (%)	STD EV	Relative remaining activity (%)	STD EV	Relative remaining activity (%)	STD EV	Relative remaining activity (%)	STD EV	Relative remaining activity (%)	STD EV
PBS	100.00	0.00	104.01	11.16	99.79	7.36	104.11	16.23	97.08	6.62	91.57	5.24
RZ002099	100.00	0.00	113.28	16.70	108.76	10.80	109.49	21.92	103.35	3.85	91.43	13.76
RZ002101	100.00	0.00	112.86	9.29	93.61	6.07	108.28	8.23	87.59	6.20	86.39	2.74
RZ002106	100.00	0.00	102.62	8.50	89.24	6.88	91.60	5.93	81.16	3.79	79.86	4.17
RZ002113	100.00	0.00	107.08	6.66	92.17	7.22	104.28	9.25	101.74	11.14	98.14	3.99

Example 8: *In Vivo* Efficacy Evaluation of siRNA Conjugates with L96 Ligand Conjugated to 3'-end of the Sense Strand in CFA-hIgA Mice

[00670] In this embodiment, an IgA nephropathy mouse model was constructed by inducing IgA-humanized mice with Complete Freund's Adjuvant (CFA). The inhibitory effect of RZM02003 on mouse C3 mRNA in CFA-IgA mice was detected by a QPCR method; the expression level of mouse C3 protein in serum at different time points was determined by an enzyme-linked immunosorbent assay (ELISA); the deposition of mouse C3 protein and human IgA immune protein in kidney tissue was observed by an immunofluorescence method; and kidney tissue lesions were observed by a Periodic Acid-Schiff (PAS) staining method.

[00671] Animal grouping, administration, and tissue sample collection

[00672] The CFA-hIgA model mice were randomly grouped, with 3 mice in each group. Each test group was administered a predetermined dose of a drug conjugate, and a PBS control group was included. For all mice, the drug dose was calculated based on body weight, and the administration volume was 10 mL/kg (mouse body weight). A single dose of RZM02003 was administered via subcutaneous injection in the abdomen. Each drug conjugate was administered as a 0.9 mg/mL (calculated as siRNA) solution in PBS. That is, the administration dose of the drug conjugate was 9 mg/kg (siRNA/mouse body weight). The PBS control group (Model PBS Control Group) was administered with a PBS solution without an siRNA conjugate at 10 mL/kg (mouse body weight).

[00673] Before administration, the upper pole of kidney tissue of each mouse after modeling was

collected by an open surgical method. A portion of the kidney tissue was fixed in a 10% formalin solution, embedded in paraffin, and sectioned for PAS staining to observe pre-administration kidney tissue lesions; another portion of the kidney tissue was embedded and fixed with OCT (optimal cutting temperature compound) and then cryosectioned for immunofluorescence staining of kidney tissue to observe pre-administration mouse C3 deposition and human IgA deposition in the kidney. The day of administration was recorded as day 0 (D0). On day 14 (D14) after administration, 3 mice from all groups were euthanized, and on day 28 (D28) after administration, 3 mice from all groups were euthanized. Serum from all euthanized mice was collected, and the C3 protein expression in the serum was detected using a mouse complement C3 ELISA kit (abcam, 157711). Dissection was performed on the euthanized mice, respectively. The liver tissue of each euthanized mouse was collected and cut into small pieces of about 2 mm^3 and stored in RNAlater. The kidney tissue of each euthanized mouse was collected. A portion of the kidney tissue was fixed in a 10% formalin solution, embedded in paraffin, and sectioned for PAS staining to observe kidney tissue lesions on D14 and D28 after administration; another portion of the kidney tissue was embedded and fixed with OCT, and then cryosectioned for immunofluorescence staining of kidney tissue to observe mouse C3 deposition and human IgA deposition in the kidney on D14 and D28 after administration.

[00674] The results of Example 8 showed that at a single dose of 9 mg/kg, RZM02003 significantly reduced the C3 mRNA and protein levels in CFA-IgA mice. On day 14 after administration, the reduction of C3 mRNA and protein reached 98% (FIG. 8, Table 23) and 78% (FIG. 9, Table 24), respectively. On day 28 after administration, the reduction of C3 mRNA was still greater than 98% (FIG. 8, Table 23), and the reduction of C3 protein was about 70% (FIG. 9, Table 24).

[00675] The results of Example 8 showed that at a single dose of 9 mg/kg, RZM02003 could reduce C3 deposition in kidney tissue, and a significant reduction in C3 fluorescence staining in kidney tissue was observed on both day 14 and day 28 after administration (FIG. 10).

[00676] Table 23: Inhibitory Activity of siRNA Conjugates on C3 mRNA in the Liver of CFA-hIgA Mice after Administration of the siRNA Conjugates

Group	C3 mRNA

	Relative remaining expression level (%)	STDEV
Model PBS (D14)	100.00	15.63
RZM02003 (D14)	1.11	1.05
Model PBS (D28)	100.00	8.55
RZM02003 (D28)	1.67	0.38

[00677] Table 24: Change of Serum C3 Protein Level in CFA-hIgA Mice after Administration of the siRNA Conjugate

Group	Serum C3 protein	
	Relative remaining expression level (%)	STDEV
Model PBS (D14)	100.00	22.24
RZM02003 (D14)	21.80	4.17
Model PBS (D28)	100.00	29.70
RZM02003 (D28)	30.14	10.12

[00678] The double-stranded oligonucleotide for inhibiting C3 gene expression, the conjugate thereof, and uses thereof provided by the present disclosure have been described in detail above. Specific examples have been used herein to illustrate the principles and embodiments of the present disclosure, and the description of the above examples is only for the purpose of helping to understand the method of the present disclosure and its core idea. It should be pointed out that, for a person skilled in the art, several improvements and modifications can be made to the present disclosure without departing from the principles of the present disclosure, and these improvements and modifications also fall within the protection scope of the claims of the present disclosure.

CLAIMS

1. A double-stranded oligonucleotide for inhibiting expression of C3 gene, comprising a sense strand and an antisense strand;

from 5'-end to 3'-end, nucleotides of positions 2 to 19 of the antisense strand comprise a complementary region to a C3 RNA transcript, wherein the complementary region comprises at least 17 contiguous nucleotides of any one of the nucleotide sequences as set forth in SEQ ID NO: 241, SEQ ID NOs: 213 to 240 and SEQ ID NOs: 242 to 424 or a nucleotide sequence having 1, 2 or 3 nucleotide differences from the at least 17 contiguous nucleotides; and

the sense strand comprises at least 17 nucleotides, and the sense strand and the antisense strand are complementary or substantially complementary to form a duplex region, wherein being substantial complementary means that the sense strand and the antisense strand have no more than 3 nucleotide mismatches in the duplex region.

2. The double-stranded oligonucleotide according to claim 1, wherein the antisense strand is selected from or comprises any one of the nucleotide sequences as set forth in SEQ ID NO: 241, SEQ ID NOs: 213 to 240 and SEQ ID NOs: 242 to 424; and/or

the sense strand is selected from or comprises any one of the nucleotide sequences as set forth in SEQ ID NO: 29, SEQ ID NOs: 1 to 28 and SEQ ID NOs: 30 to 212.

3. The double-stranded oligonucleotide according to claim 1 or 2, wherein each nucleotide of the double-stranded oligonucleotide is independently selected from a modified or unmodified nucleotide;

optionally, substantially all nucleotides of the double-stranded oligonucleotide are independently selected from modified nucleotides;

optionally, all nucleotides of the double-stranded oligonucleotide are independently selected from modified nucleotides;

optionally, each nucleotide of the double-stranded oligonucleotide is independently selected

from the group consisting of:

a 2'-halogen-modified nucleotide, a 2'-deoxy-modified nucleotide, a 2'-O-optionally substituted C_{1-6} alkyl-modified nucleotide, a 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide, a 2'-amino-modified nucleotide, an abasic nucleotide or a nucleotide analog, wherein the nucleotide analog is one or more selected from PNA, MNA, BNA, LNA, GNA, TNA and UNA;

wherein n is selected from 1 or 2, R_1 is selected from an optionally substituted C_{1-6} alkyl or an optionally substituted C_{1-6} alkoxy; when R_1 is substituted, the substituent is selected from a halogen, a C_{1-6} alkoxy, a hydroxyl and an amino;

optionally, the 2'-halogen-modified nucleotide is a 2'-fluoro-modified nucleotide;

optionally, the 2'-O-optionally substituted C_{1-6} alkyl-modified nucleotide is a 2'-O-methyl-modified nucleotide;

optionally, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from a 2'-O-methoxyethyl-modified nucleotide, a 2'-O-ethoxymethyl-modified nucleotide and a 2'-O-2,2,2-trifluoroethoxymethyl-modified nucleotide;

optionally, the 2'-O-$(CH_2)_n$-O-R_1-modified nucleotide is selected from a 2'-O-methoxyethyl-modified nucleotide;

optionally, each nucleotide of the double-stranded oligonucleotide is independently selected from the group consisting of:

a 2'-fluoro-modified nucleotide, a 2'-deoxy-modified nucleotide, a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide; and

optionally, each nucleotide of the double-stranded oligonucleotide is independently selected from the group consisting of:

a 2'-fluoro-modified nucleotide, a 2'-O-methyl-modified nucleotide and a 2'-O-methoxyethyl-modified nucleotide.

4. The double-stranded oligonucleotide according to claim 3, wherein the double-stranded oligonucleotide comprises at least one 2'-O-methoxyethyl-modified nucleotide;

optionally, the antisense strand comprises at least one 2'-O-methoxyethyl-modified nucleotide; and the sense strand comprises no more than one 2'-O-methoxyethyl-modified nucleotide;

optionally, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, at least 3 nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, no more than one nucleotide at positions 5, 12, 13, and 18 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide; in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

optionally, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, at least one nucleotide at positions 8 and 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

optionally, from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and in the nucleotide sequence of the antisense strand, at least 4 nucleotides at positions 2, 6, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, any one of the nucleotides at positions 9 to 12 is selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 or 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are independently selected from a 2'-O-methyl-modified nucleotide;

optionally, the sense strand and the antisense strand of the double-stranded oligonucleotide have a modification pattern selected from (ds-1) to (ds-8):

(ds-1) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-2) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-3) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-4) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 8 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-5) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 9, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-6) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 10, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide;

(ds-7) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 11, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

(ds-8) from 5'-end to 3'-end, in the nucleotide sequence of the sense strand, the nucleotides at positions 7 to 10 are selected from a 2'-fluoro-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

in the nucleotide sequence of the antisense strand, the nucleotides at positions 2, 6, 12, 14, and 16 are selected from a 2'-fluoro-modified nucleotide, the nucleotide at position 15 is selected from a 2'-O-methoxyethyl-modified nucleotide, and the remaining nucleotides are selected from a 2'-O-methyl-modified nucleotide; and

optionally, the sense strand comprises two contiguous internucleotide phosphorothioate linkages at 5'-end; and

the antisense strand comprises two internucleotide phosphorothioate linkages at 5'-end, and two contiguous internucleotide phosphorothioate linkages at 3'-end.

5. The double-stranded oligonucleotide according to claim 3, wherein each nucleotide of the double-stranded oligonucleotide is independently selected from a modified nucleotide;

wherein the sense strand is selected from any one of the sequences as set forth in SEQ ID NO: 892, SEQ ID NOs: 887 to 891 and SEQ ID NOs: 893 to 907; and/or the antisense strand is selected from any one of the sequences as set forth in SEQ ID NO: 914, SEQ ID NOs: 908 to 913 and SEQ ID NOs: 915 to 943.

6. The double-stranded oligonucleotide according to claim 5, wherein the double-stranded oligonucleotide comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002258	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RX002245	CmsGmsAmAmGmCmUfCfAfUfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RX002246	CmsGmsAmAmGmCmUfCfAfUfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002247	CmsGmsAmAmGmCmUfCfAfUfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 887	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RX002248	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002249	CmsGmsAmAmGmCmUfCfAfUfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002250	CmsGmsAmAmGmCmUfCfAfUfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002251	CmsGmsAmAmGmCmUfCfAfUfUfGmAmAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RX002252	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm	SEQ ID NO: 888	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002253	CmsGmsAmAmGmCmUfCfAfUfUfGmA(moe)AmUmAmUmAmUmUm	SEQ ID NO: 889	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002254	CmsGmsAmAmGmCmUfCfAfUfUfGmAmA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002255	CmsGmsAmAmGmCmUfCfAfUfUfGmAmAmUmAmUmAmT(moe)Um	SEQ ID NO: 891	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RX002256	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RX002	CmsAmsGmAmGmAmAfAfUfUfCmU	SEQ ID	AmsUfsGmUmAmGfUmAmGmAfAmUm	SEQ ID

257	mAmCmUmAmCmAmUm	NO: 892	UmUfC(moe)UfCmUmGmsUmsAm	NO: 913
RX002259	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 893	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002260	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm	SEQ ID NO: 894	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002261	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm	SEQ ID NO: 895	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RX002262	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um	SEQ ID NO: 896	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
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RX002 290	CmsGmsAmAmGmCmUfCfAfUfGmA mA(moe)UmAmUmAmUmUm	SEQ ID NO: 890	AmsAfsUmAmUmAfUmUmCmAmUfGm AmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
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RX002 307	CmsAmsGmAmGmAmAfAfUfUfCmU mAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGfAmAmUm UmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
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RX002 312	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAfAmGmCm AmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RX002 313	GmsAmsGmAmAmUmUfGfCfUfUmC mAmUmAmCmAmAmAm	SEQ ID NO: 897	UmsUfsUmGmUmAfUmGmAmAmGmCf AmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

.

7. The double-stranded oligonucleotide according to claim 3, wherein the sense strand of the double-stranded oligonucleotide comprises SEQ ID NO: 892 and the antisense strand of the

double-stranded oligonucleotide comprises SEQ ID NO: 914.

8. The double-stranded oligonucleotide according to claim 6, wherein the double-stranded oligonucleotide is selected from:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RX002258	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm	SEQ ID NO: 892	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914

.

9. A conjugate comprising the double-stranded oligonucleotide according to any one of claims 1 to 8, and one or more gene delivery carriers;

optionally, the gene delivery carrier is selected from a ligand capable of binding to a cell surface receptor;

optionally, the ligand is selected from a ligand of asialoglycoprotein receptor (ASGPR ligand);

optionally, the ASGPR ligand comprises galactose or a derivative thereof;

the galactose or the derivative thereof is selected from galactose, galactosamine, N-formyl galactosamine, N-acetyl galactosamine, N-propionyl galactosamine, N-n-butyryl galactosamine and N-isobutyryl galactosamine; and

optionally, the number of the ASGPR ligand is one, and the one ASGPR ligand is conjugated to 3'-end of the sense strand of the double-stranded oligonucleotide.

10. The conjugate according to claim 9, wherein the conjugate comprises a structure as shown by formula (101):



(101) ;

wherein Nu represents the double-stranded oligonucleotide;

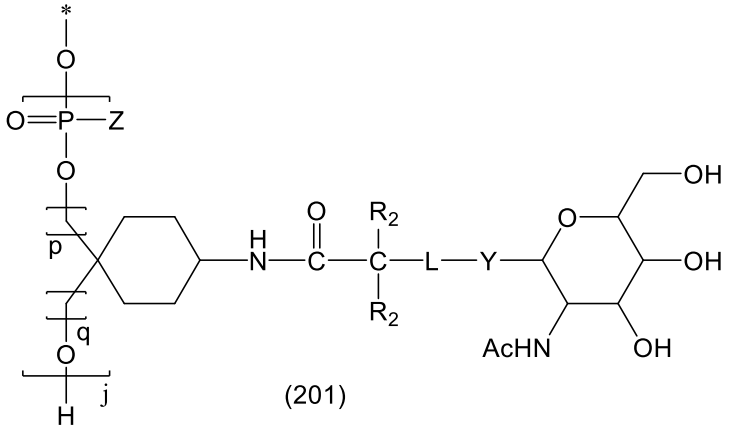
each R_{ligand} is independently selected from an ASGPR ligand; and

m is selected from 1, 2, 3 and 4;

optionally, m is 1; and

optionally, m is one, and the one R_{ligand} is conjugated to 3'-end of the sense strand.

11. The conjugate according to claim 10, wherein each R_{ligand} is independently selected from a structure as shown by formula (201), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



(201)

;

wherein * represents a conjugation site of the ligand on the sense strand or the antisense strand;

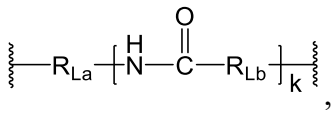
j is selected from 1, 2, 3 and 4;

each Z is selected from hydroxy and sulfydryl;

each p is selected from 1, 2 and 3;

each q is selected from 1, 2 and 3;

each R_2 is independently selected from H, any optionally substituted C_{1-6} alkyl and optionally substituted C_{1-6} alkoxy;

each L is selected from optionally substituted C_{2-20} alkylene and 

, wherein R_{La} and R_{Lb} are independently selected from any optionally substituted C_{1-10} alkylene, and k is selected from 1, 2, 3, 4 and 5; and

each Y is selected from O, S and NH;

optionally, j is selected from 1, 2 or 3;

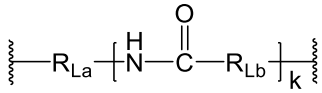
optionally, j is 3;

optionally, Z is hydroxy;

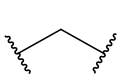
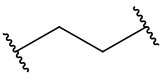
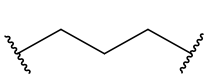
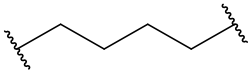
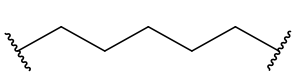
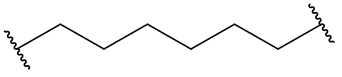
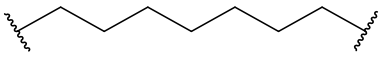
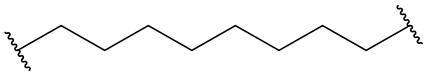
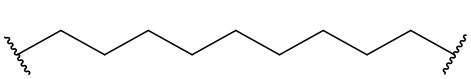
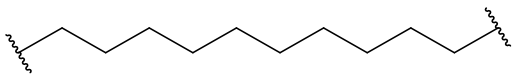
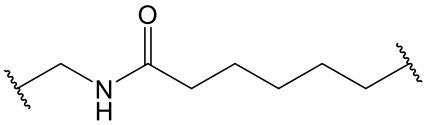
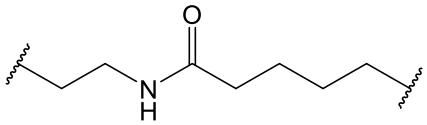
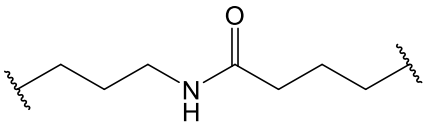
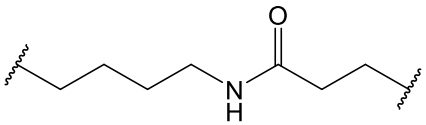
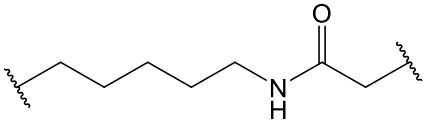
optionally, p is 1;

optionally, q is 1;

optionally, R_2 is H;

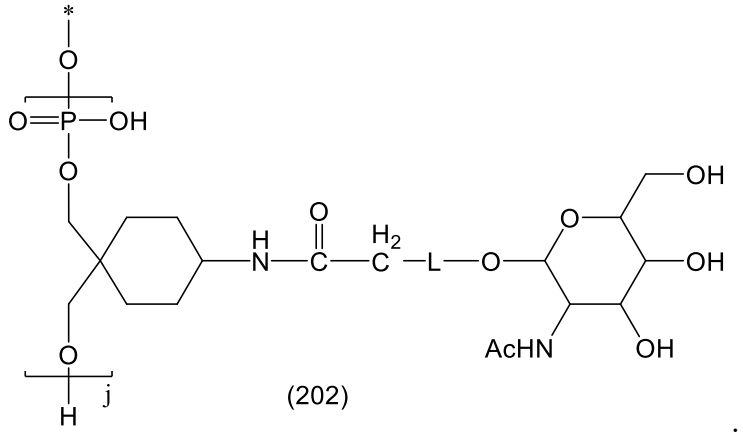
optionally, each L is selected from optionally substituted C_{2-10} alkylene and , wherein R_{La} and R_{Lb} are independently selected from any optionally substituted C_{1-10} alkylene, and k is selected from 1, 2 and 3;

optionally, k is 1;

optionally, each L is selected from , , , , , , , , , , , , , , and ; and

optionally, Y is O.

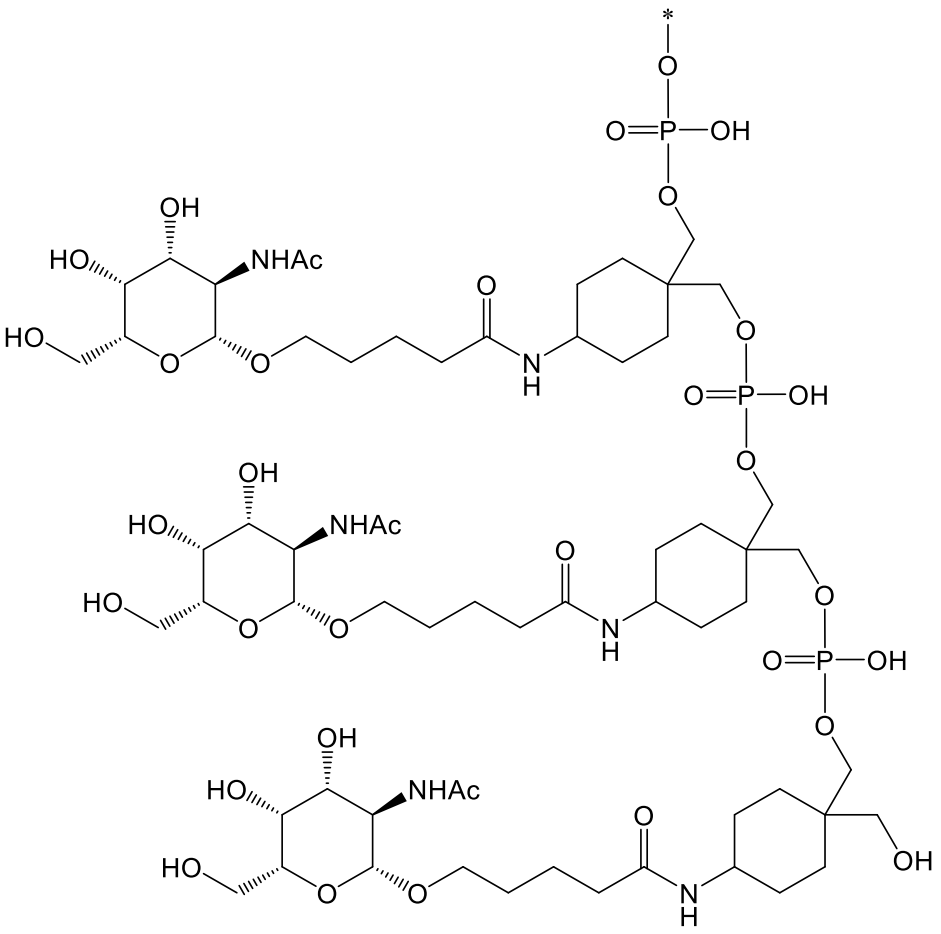
12. The conjugate according to claim 11, wherein each R_{ligand} is independently selected from a structure as shown by formula (202), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



(202)

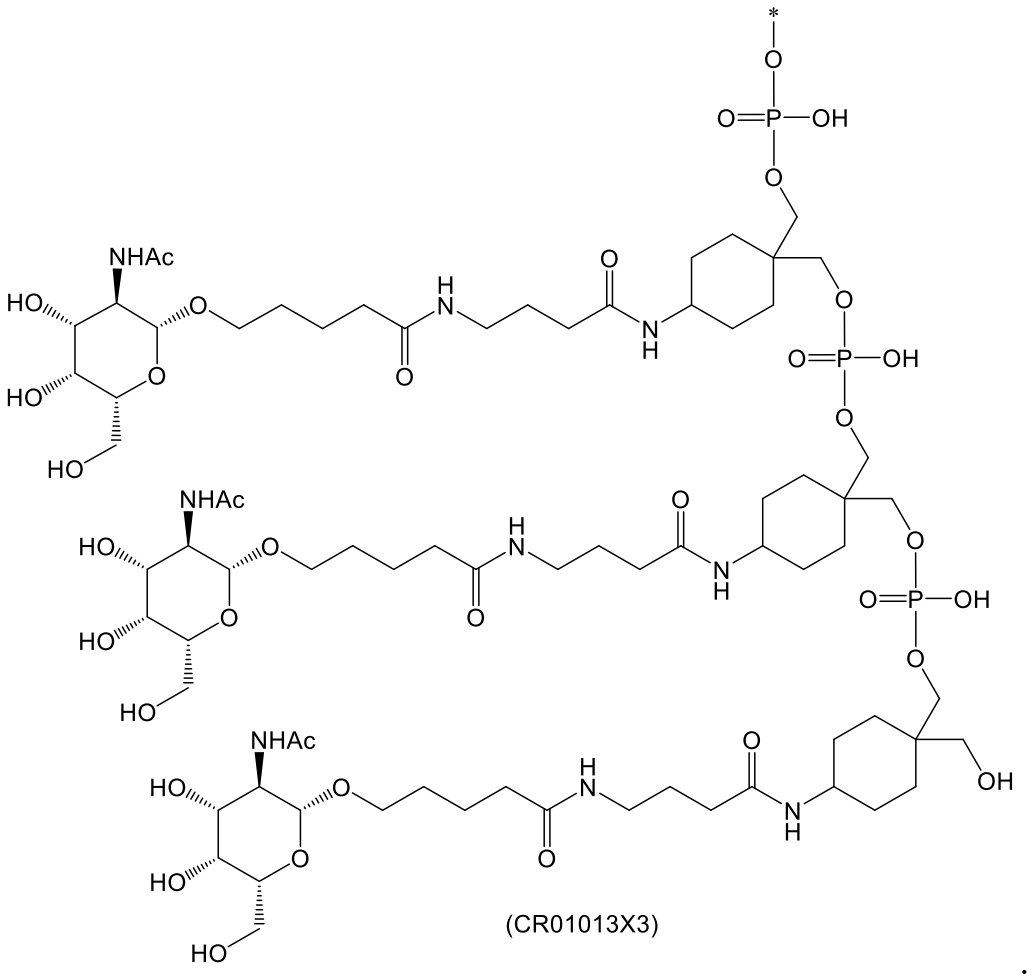
.

13. The conjugate according to any one of claims 9 to12, wherein each R_{ligand} is independently selected from a structure as shown by formula (CR01008×3), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



(CR01008X3)

alternatively, each R_{ligand} is independently selected from a structure as shown by formula (CR01013×3), a pharmaceutically acceptable salt thereof and a steroisomer thereof:



14. The conjugate according to claim 13, wherein the conjugate comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID No.892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID No.914
RZ002033	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RZ002034	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002036	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002037	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUm	SEQ ID NO: 889_(CR01008	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGm	SEQ ID NO: 909

	Um_(CR01008×3)	×3)	sUmsAm	
RZ002038	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002039	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAfUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 909
RZ002040	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002041	CmsGmsAmAmGmCmUfCfAfUfGmA(moe)AmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 889_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002042	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002043	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAfUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 911
RZ002050	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RZ002051	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002053	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002054	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002055	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002056	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAfAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 913
RZ002057	CmsAmsGmAmG(moe)AmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 893_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002058	CmsAmsGmAmGmAmAfAfUfUfCmT(moe)AmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 894_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002059	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002060	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAfAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 915
RZ002066	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 916
RZ002067	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAfGmCmAmAfT(moe)UfCmUmCmsCmsUm	SEQ ID NO: 917
RZ002068	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_	SEQ ID NO: 897_(CR01008	UmsUfsUmGmUmAfUmGmAmAmGfCmAmAfT(moe)UfCmUmCm	SEQ ID NO: 918

	(CR01008×3)	×3)	sCmsUm	
RZ00 2069	GmsAmsGmAmA(moe)UmUfGf CfUfUmCmAmUmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 898_(CR01008 ×3)	UmsUfsUmGmUmAfUmGmAmA fGmCmAmAfT(moe)UfCmUmCm sCmsUm	SEQ ID NO: 917
RZ00 2070	GmsAmsGmAmAmUmUfGfCfUf UmC(moe)AmUmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 899_(CR01008 ×3)	UmsUfsUmGmUmAfUmGmAmA fGmCmAmAfT(moe)UfCmUmCm sCmsUm	SEQ ID NO: 917
RZ00 2071	GmsAmsGmAmAmUmUfGfCfUf UmCmA(moe)UmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 900_(CR01008 ×3)	UmsUfsUmGmUmAfUmGmAmA fGmCmAmAfT(moe)UfCmUmCm sCmsUm	SEQ ID NO: 917
RZ00 2072	GmsAmsGmAmAmUmUfGfCfUf UmCmAmUmAmCmAmA(moe) Am_(CR01008×3)	SEQ ID NO: 901_(CR01008 ×3)	UmsUfsUmGmUmAfUmGmAmA fGmCmAmAfT(moe)UfCmUmCm sCmsUm	SEQ ID NO: 917
RZ00 2073	GmsAmsGmAmA(moe)UmUfGf CfUfUmCmAmUmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 898_(CR01008 ×3)	UmsUfsUmGmUmAfUmG(moe)A mAfGmCmAmAfUmUfCmUmCm sCmsUm	SEQ ID NO: 919
RZ00 2074	GmsAmsGmAmAmUmUfGfCfUf UmC(moe)AmUmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 899_(CR01008 ×3)	UmsUfsUmGmUmAfUmG(moe)A mAfGmCmAmAfUmUfCmUmCm sCmsUm	SEQ ID NO: 919
RZ00 2075	GmsAmsGmAmAmUmUfGfCfUf UmCmA(moe)UmAmCmAmAm Am_(CR01008×3)	SEQ ID NO: 900_(CR01008 ×3)	UmsUfsUmGmUmAfUmG(moe)A mAfGmCmAmAfUmUfCmUmCm sCmsUm	SEQ ID NO: 919
RZ00 2076	GmsAmsGmAmAmUmUfGfCfUf UmCmAmUmAmCmAmA(moe) Am_(CR01008×3)	SEQ ID NO: 901_(CR01008 ×3)	UmsUfsUmGmUmAfUmG(moe)A mAfGmCmAmAfUmUfCmUmCm sCmsUm	SEQ ID NO: 919
RZ00 2082	CmsAmsAmCmUmCmAfCfCfUf GmUmAmAmUmAmAmAmUm_ (CR01008×3)	SEQ ID NO: 902_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCfAm GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 920
RZ00 2083	CmsAmsAmCmUmCmAfCfCfUf GmUmAmAmUmAmAmAmUm_ (CR01008×3)	SEQ ID NO: 902_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmAf GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 921
RZ00 2084	CmsAmsAmCmUmCmAfCfCfUf GmUmAmAmUmAmAmAmUm_ (CR01008×3)	SEQ ID NO: 902_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmA mGfGmUmGfA(moe)GfUmUmG msAmsUm	SEQ ID NO: 922
RZ00 2085	CmsAmsAmCmT(moe)CmAfCfC fUfGmUmAmAmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 903_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmAf GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 921
RZ00 2086	CmsAmsAmCmUmCmAfCfCfUf GmT(moe)AmAmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 904_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmAf GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 921
RZ00 2087	CmsAmsAmCmUmCmAfCfCfUf GmUmA(moe)AmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 905_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmAf GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 921
RZ00 2088	CmsAmsAmCmUmCmAfCfCfUf GmUmAmAmUmAmAmA(moe) Um_(CR01008×3)	SEQ ID NO: 906_(CR01008 ×3)	AmsUfsUmUmAmUfUmAmCmAf GmGmUmGfA(moe)GfUmUmGm sAmsUm	SEQ ID NO: 921
RZ00 2089	CmsAmsAmCmT(moe)CmAfCfC fUfGmUmAmAmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 903_(CR01008 ×3)	AmsUfsUmUmAmUfUmA(moe)C mAfGmGmUmGfAmGfUmUmG msAmsUm	SEQ ID NO: 923
RZ00 2090	CmsAmsAmCmUmCmAfCfCfUf GmT(moe)AmAmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 904_(CR01008 ×3)	AmsUfsUmUmAmUfUmA(moe)C mAfGmGmUmGfAmGfUmUmG msAmsUm	SEQ ID NO: 923
RZ00 2091	CmsAmsAmCmUmCmAfCfCfUf GmUmA(moe)AmUmAmAmAm Um_(CR01008×3)	SEQ ID NO: 905_(CR01008 ×3)	AmsUfsUmUmAmUfUmA(moe)C mAfGmGmUmGfAmGfUmUmG msAmsUm	SEQ ID NO: 923
RZ00 2092	CmsAmsAmCmUmCmAfCfCfUf GmUmAmAmUmAmAmA(moe)	SEQ ID NO: 906_(CR01008	AmsUfsUmUmAmUfUmA(moe)C mAfGmGmUmGfAmGfUmUmG	SEQ ID NO: 923

	Um_(CR01008×3)	×3)	msAmsUm	
RZ002099	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002100	CmsGmsAmAmG(moe)CmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 888_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002101	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUfGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 910
RZ002102	CmsGmsAmAmGmCmUfCfAfUfGmAmA(moe)UmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 890_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002103	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmT(moe)Um_(CR01008×3)	SEQ ID NO: 891_(CR01008×3)	AmsAfsUmAmUmAfUmT(moe)CmAmUfGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 924
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002107	CmsAmsGmAmGmAmAfAfUfUfCmUmA(moe)CmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 895_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002108	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmA(moe)Um_(CR01008×3)	SEQ ID NO: 896_(CR01008×3)	AmsUfsGmUmAmGfUmA(moe)GmAmAfUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 925
RZ002112	CmsAmsAmCmUmCmAfCfCfUfGmUmA(moe)AmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 905_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGfGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 922
RZ002113	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmA(moe)Um_(CR01008×3)	SEQ ID NO: 906_(CR01008×3)	AmsUfsUmUmAmUfUmA(moe)CmAmGfGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 926
RZ002115	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RZ002116	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RZ002117	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RZ002118	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RZ002119	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 931
RZ002120	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RZ002121	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RZ002122	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RZ002123	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_	SEQ ID NO: 902_(CR01008	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsA	SEQ ID NO: 935

	(CR01008×3)	×3)	msUm	
RZ002124	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RZ002125	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RZ002126	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RZ002130	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RZ002131	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RZ002132	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RZ002133	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RZ002134	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

;

optionally, the conjugate comprises one or more pairs of:

Pair	Sense strand (5'-3')		Antisense strand (5'-3')	
RZ002033	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 908
RZ002050	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 912
RZ002082	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 920
RZ002106	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAfUmUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 914
RZ002115	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfC(moe)UfCmUmGmsUmsAm	SEQ ID NO: 927
RZ002116	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 928
RZ002117	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 929
RZ002118	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUmAmGmUfAmGfA(moe)AfUmUmUmsCmsUm	SEQ ID NO: 930
RZ002119	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_	SEQ ID NO: 887_(CR01008	AmsAfsUmAmUmAfUmUmCfAmUmGmAmGfCmUfUmCmGmsUm	SEQ ID NO: 931

	(CR01008×3)	×3)	sAm	
RZ002120	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfCmUfUmCmGmsUmsAm	SEQ ID NO: 932
RZ002121	CmsGmsAmAmGmCmUfCfAfUfGmAmAmUmAmUmAmUmUm_(CR01008×3)	SEQ ID NO: 887_(CR01008×3)	AmsAfsUmAmUmAfUmUmCmAmUmGfAmGfC(moe)UfUmCmGmsUmsAm	SEQ ID NO: 933
RZ002122	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCfAmGmGmUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 934
RZ002123	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfAmGfUmUmGmsAmsUm	SEQ ID NO: 935
RZ002124	CmsAmsAmCmUmCmAfCfCfUfGmUmAmAmUmAmAmAmUm_(CR01008×3)	SEQ ID NO: 902_(CR01008×3)	AmsUfsUmUmAmUfUmAmCmAmGmGfUmGfA(moe)GfUmUmGmsAmsUm	SEQ ID NO: 936
RZ002125	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGfAmAmUmUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 937
RZ002126	CmsAmsGmAmGmAmAfAfUfUfCmUmAmCmUmAmCmAmUm_(CR01008×3)	SEQ ID NO: 892_(CR01008×3)	AmsUfsGmUmAmGfUmAmGmAmAmUfUmUfCmUfCmUmGmsUmsAm	SEQ ID NO: 938
RZ002130	AmsAmsAmUmUmCmUfAfCfUfAmCmAmUmCmUmAmUmAm_(CR01008×3)	SEQ ID NO: 907_(CR01008×3)	UmsAfsUmAmGmAfUmGmUfAmGmUmAmGfAmAfUmUmUmsCmsUm	SEQ ID NO: 939
RZ002131	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 940
RZ002132	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfUmUfCmUmCmsCmsUm	SEQ ID NO: 941
RZ002133	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAfAmGmCmAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 942
RZ002134	GmsAmsGmAmAmUmUfGfCfUfUmCmAmUmAmCmAmAmAm_(CR01008×3)	SEQ ID NO: 897_(CR01008×3)	UmsUfsUmGmUmAfUmGmAmAmGmCfAmAfU(moe)UfCmUmCmsCmsUm	SEQ ID NO: 943

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15. Use of the double-stranded oligonucleotide according to any one of claims 1 to 8 or the conjugate according to any one of claims 9 to 14, in the manufacture of a medicament for ameliorating, preventing and/or treating a disease or disorder mediated by C3 gene;

optionally, the disease or disorder mediated by C3 gene is selected from: IgA nephropathy, atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulopathy, lupus nephritis, and membranous nephropathy.