CLAIMS

What is claimed is:

1. A double-stranded oligonucleotide, comprising a sense strand and an antisense strand, each having 17 to 35 nucleotides, wherein each nucleotide is a modified or unmodified nucleotide; the sense strand and the antisense strand are at least partially reversely complementary to form a double-stranded region, and the double-stranded region comprises a nucleotide with sterically bulky modification and/or a nucleotide with disubstitution modification, wherein

the double-stranded region is as represented by following Formula (I):

SS: 5'- $(N)_{a'}$ - $(X)_{p'}$ - $(N)_{b'}$ - $(X)_{q'}$ - $(N)_{c'}$ - $(X)_{r'}$ - $(N)_{d'}$ -3'

AS: 3' - $(N)_a$ - $(X)_p$ - $(N)_b$ - $(X)_q$ - $(N)_c$ -5' (I).

wherein SS represents the sense strand, and AS represents the antisense strand;

each X independently represents a nucleotide in which 2'-hydroxyl group of ribose is substituted with a sterically bulky group, or a nucleotide in which 2'-position is substituted with disubstituent,

wherein the sterically bulky group is independently selected from 2'-$(O)_{m1}(CH_2)_n(O)_{m2}R_1$, wherein each of m1 and m2 is independently 0 or 1, and n is an integer selected from 0 to 6,

wherein R_1 is substituted or unsubstituted C_1-C_6 alkyl or -$Si(R_2)_3$, wherein each R_2 is independently selected from substituted or unsubstituted C_1-C_6 alkyl or C_1-C_6 alkoxy, wherein the substitution comprises one or more substituents selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl group, amino group, cycloalkyl having up to 6 carbon atoms, aryl having up to 12 carbon atoms, and heteroaryl having up to 12 carbon atoms,

wherein each substituent in the disubstitution is independently selected from C_1-C_6 alkyl or halogen;

each N independently represents a modified or unmodified nucleotide, wherein when N represents a modified nucleotide, 2'-position of ribose thereof is modified and is not X, and each N is a nucleotide with modification independently selected from one or more of the following: 2'-O-alkyl, 2'-alkyl, 2'-substituted alkyl, 2'-halo, 2'-deoxy, or is a nucleotide analog, wherein the alkyl has 1-6 carbon atoms, and the nucleotide analog is selected from one or more of ENA, BNA, LNA, GNA and UNA;

each of a, a', p, p', b, b', q, q', c, c', r', and d' independently represents the number of nucleotides, wherein a' is an integer selected from 3 to 8; p' is an integer selected from 0 to 3; b' is an integer selected from 4 to 13; q' is an integer selected from 0 to 4; c' is an integer selected from 3 to 9; r' is an integer selected from 0 to 3; d' is an integer selected from 0 to 9; a is an integer selected from 4 to 7; p is an integer selected from 0 to 1; b is an integer selected from 4 to 8; q is an integer selected from 0 to 4; and c is an integer selected from 6 to 10; and

p', q', r', p and q are not simultaneously 0, and $0 \leq q'+r' \leq 4$.

2. The double-stranded oligonucleotide according to claim 1, wherein each X is a nucleotide with modification independently selected from 2'-$O(CH_2)_nOR_1$ or 2'-R_3-2'-R_4, wherein n is 1 or 2, R_1 is substituted or unsubstituted C_1-C_6 alkyl, or -$Si(R_2)_3$, and

each of R_3 and R_4 is independently selected from C_1-C_6 alkyl or halogen.

3. The double-stranded oligonucleotide according to claim 1 or 2, wherein each N is independently selected from nucleotide with 2'-OMe modification, nucleotide with 2'-F modification, nucleotide with 2'-H modification, or unmodified nucleotide;

optionally, each X is a nucleotide with modification independently selected from 2'-O-methoxyethyl, 2'-O-TBDMS, 2'-O-TOM, or 2'-O-CH_2-O-R_5, wherein R_5 is unsubstituted or substituted C_1-C_3 alkyl; optionally, the substituent is independently selected from one or more of halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, and amino group; and

optionally, the halogen is fluorine.

4. The double-stranded oligonucleotide according to any one of claims 1-3, wherein in a direction from 5'-end to 3'-end, at least one of nucleotides at positions 8, 9, 10 and 15 of the antisense strand of the Formula (I) is a modified nucleotide X, and/or a modified nucleotide X is present or absent in the sense strand;

optionally, when the sense strand comprises the modified nucleotide X, at least one nucleotide X is located at a site opposite to any of positions 2, 8 and 15 of the antisense strand;

optionally, the modified nucleotide X is located at at least one of positions 10 and 15 of the antisense strand;

optionally, each X is a nucleotide with modification independently selected from 2'-O-methoxyethyl, 2'-O-TBDMS, 2'-O-TOM, 2'-O-CH_2-O-CH_2-CH_3, or 2'-O-CH_2-O-CH_2-CF_3.

5. The double-stranded oligonucleotide according to any one of claims 1-4, wherein

q'+c'+r'+d'=9, and 0≤q'+r'≤4;

optionally, when p=0, a=5-7;

optionally, when p=1, in a direction from 5'-end to 3'-end, X is located at position 15 of the antisense strand;

optionally, when q=0, b+c=14;

optionally, in a direction from the 5'-end to the 3'-end, at least one X in (X)p' is located at a site of the sense strand opposite to position 15 of the antisense strand;

optionally, when p'=1, in the direction from the 5'-end to the 3'-end, X in (X)p' is located at a site opposite to position 15 of the antisense strand;

optionally, in the direction from the 5'-end to the 3'-end, the first four nucleotides of (N)b' on the sense strand comprise at least two fluoro-modified nucleotides;

optionally, q' is 0-2;

optionally, q' is 0 or 1;

optionally, when r'=1 and q'=1, b' and c' are 5, and d' is 1;

optionally, when p'=0, a'=6;

optionally, when p'=0, a'=8;

optionally, when q' and r' are not simultaneously 0, in the direction from the 5'-end to the 3'-end, at least one X on the sense strand is located at a position opposite to positions 1-8 of the antisense strand; and

optionally, d'=1-9.

6. The double-stranded oligonucleotide according to any one of claims 1-5, wherein

a' is an integer selected from 3 to 8; p' is an integer selected from 0 to 2; b' is an integer selected from 4 to 12; q' is an integer selected from 0 to 2; c' is an integer selected from 3 to 8; r' is an integer selected from 0 to 2; d' is an integer selected from 1 to 9; a is an integer selected from 4 to 7; p is an integer selected from 0 or 1; b is an integer selected from 4 to 8; q is an integer selected from 0 to 2; and c is an integer selected from 6 to 10;

optionally, each of (N)a and (N)b comprises at least one fluoro-modified nucleotide, and (N)c comprises at least two fluoro-modified nucleotides;

optionally, q'+c'+r'+d'=9, and 0≤q'+r'≤4; and

optionally, counting from 5'-end, the first four nucleotides of (N)b' comprise at least two fluoro-modified nucleotides.

7. The double-stranded oligonucleotide according to any one of claims 1-6, wherein

a' is an integer selected from 3 to 8; p' is 0 or 1; b' is an integer selected from 4 to 13; q' is 0 or 1; c' is an integer selected from 3 to 9; r' is 0 or 1; d' is an integer selected from 1 to 8; a is an integer selected from 4 to 7; p is 1; b is an integer selected from 4 to 8; q is selected from 0 or 1; and c is an integer selected from 6 to 10;

optionally, (N)a comprises at least one fluoro-modified nucleotide, and counting from 5'-end, position 16 of the antisense strand is a fluoro-modified nucleotide;

optionally, (N)b comprises at least one fluoro-modified nucleotide, and counting from the 5'-end, position 14 of the antisense strand is a fluoro-modified nucleotide;

optionally, (N)c comprises at least two fluoro-modified nucleotides, and counting from the 5'-end, positions 2 and 6 of the antisense strand are both fluoro-modified nucleotides;

optionally, q'+c'+r'+d'=9, and 0≤q'+r'≤2;

optionally, the sense strand comprises at least one X at a position opposite to a seed region of the antisense strand, wherein the seed region of the antisense strand is locatd at positions 1-8, counting from the 5'-end; and

optionally, counting from the 5'-end, the first four nucleotides of (N)b' are located at sites opposite to positions 10-13 of the antisense strand, and the first four nucleotides comprise at least two fluoro-modified nucleotides.

8. The double-stranded oligonucleotide according to any one of claims 1-7, wherein counting from 5'-end, X in Formula (I) is located at any of positions 8-10 and 15 of the antisense strand;

optionally, X in the sense strand is located at a position opposite to any of positions 2, 8 and 15 of the antisense strand; and

optionally, counting from the 5'-end, X is located at position 15 of the antisense strand, and the antisense strand comprises at least one fluoro modification at position 9 or position 12, and/or a position of the sense strand opposite to position 10 of the antisense strand comprises a fluoro modification.

9. The double-stranded oligonucleotide according to any one of claims 1-8, wherein in addition to the double-stranded region, the double-stranded oligonucleotide further comprises one or more overhang regions, wherein the overhang region has a length of 1-6 nucleotides.

10. The double-stranded oligonucleotide according to claim 9, wherein the double-stranded oligonucleotide comprising the overhang region is represented by following Formula (II):

SS: 5'-$(T)_{t1}$- $(N)_{a'}$ - $(X)_{p'}$ - $(N)_{b'}$ - $(X)_{q'}$ - $(N)_{c'}$ - $(X)_{r'}$ - $(N)_{d'}$ -$(T)_{t2}$-3'

AS: 3'-$(T)_{t1}$- $(N)_a$ - $(X)_p$ - $(N)_b$ - $(X)_q$ - $(N)_c$ -$(T)_{t2}$-5' (II),

wherein T represents a nucleotide of the overhang, each of t1 and t2 is an integer independently selected from 0 to 6, and cannot be simultaneously 0; and remaining substituents are as defined for Formula (I);

optionally, each nucleotide T of the overhang is independently a modified or unmodified nucleotide, wherein the modified nucleotide is selected from one or more of 2'-O-alkyl, 2'-alkyl, 2'-substituted alkyl, 2'-halogen, 2'-deoxy, abasic nucleotide, and inverted nucleotide.

11. The double-stranded oligonucleotide according to any one of claims 1-8, wherein the antisense strand of the double-stranded oligonucleotide comprises a nucleotide overhang at 3'-end, and the overhang comprises 1-3 nucleotides; and the double-stranded oligonucleotide molecule is represented by following Formula (IIa):

SS: 5'-$(N)_{a'}$ - $(X)_{p'}$ - $(N)_{b'}$ - $(X)_{q'}$ - $(N)_{c'}$ - $(X)_{r'}$ - $(N)_{d'}$ -3'

AS: 3'-$(T)_{t1}$- $(N)_a$ - $(X)_p$ - $(N)_b$ - $(X)_q$ - $(N)_c$ -5' (IIa),

wherein t1 is an integer selected from 1 to 3.

12. The double-stranded oligonucleotide according to any one of claims 9-11, wherein the overhang region further comprises a phosphorothioate modification.

13. The double-stranded oligonucleotide according to any one of claims 1-12, wherein each strand of the double-stranded oligonucleotide comprises 17-35 nucleotides;

optionally, each strand comprises 17-23 nucleotides;

optionally, each strand comprises 17-21 nucleotides;

optionally, each strand comprises 17-29 nucleotides;

optionally, each strand comprises 19-25 nucleotides;

optionally, each strand comprises 19-23 nucleotides;

optionally, each strand comprises 19-21 nucleotides; and

optionally, each strand comprises 21-23 nucleotides.

14. The double-stranded oligonucleotide according to any one of claims 1-11, wherein the double-stranded oligonucleotide has at least one of features as follows:

optionally, the sense strand comprises at least one nucleotide X; and counting from 5'-end, at least one X is located at a position opposite to any of position 15, position 8 and position 2 of the antisense strand;

optionally, counting from the 5'-end, four nucleotides on the sense strand located at positions opposite to positions 10-13 of the antisense strand comprise at least two fluoro-modified nucleotides;

optionally, counting from the 5'-end, position 2, position 6, position 14 and position 16 on the antisense strand are all fluoro-modified nucleotides;

optionally, counting from the 5'-end, at least one of position 8, position 9, position 10 and position 15 on the antisense strand is nucleotide X;

optionally, counting from the 5'-end, the antisense strand comprises at least one X at a position opposite to positions 1-8 on the antisense strand; and

optionally, counting from the 5'-end, position 15 on the antisense strand is nucleotide X,

optionally, the nucleotide X is a nucleotide with modification independently selected from 2'-O-MOE, 2'-O-TBDMS, 2'-O-TOM, 2'-O-CH_2-O-CH_2-CH_3, and 2'-O-CH_2-O-CH_2-CF_3; and

optionally, each of the sense strand and the antisense strand comprises at least one phosphorothioate group, and the phosphorothioate group is located in a terminal region of each single strand.

15. The double-stranded oligonucleotide according to claim 11, wherein an overhang $(T)_{t1}$ of the AS strand comprises at least one nucleotide with substitution of 2'-F-2'-Me.

16. The double-stranded oligonucleotide according to claim 1 or 2, wherein the double-stranded oligonucleotide further comprises at least one ligand;

optionally, the ligand comprises liver-targeting ligands and non-liver-targeting ligands;

optionally, the ligand is ASGPR ligand; and

optionally, the ASGPR ligand comprises GalNAc attached by a branched linker or a derivative thereof.

17. A double-stranded oligonucleotide, comprising a sense strand and an antisense strand, each having 17 to 35 nucleotides, wherein each nucleotide is a modified or unmodified nucleotide, the sense strand and the antisense strand are at least partially reversely complementary to form a double-stranded region, wherein the double-stranded oligonucleotide comprises at least one nucleotide with 2'- disubstitution modification, and each substituent in the 2'- disubstitution is independently selected from methyl or fluoro, wherein

when the double-stranded region of the double-stranded oligonucleotide comprises a nucleotide with 2'-disubstitution modification, the nucleotide with 2'-disubstitution modification is selected from 2'-difluoro substituted nucleotides; or, when the double-stranded oligonucleotide comprises a nucleotide modified with 2'-bisubstituent at positions outside the double-stranded region, the nucleotide with 2'-disubstitution modification is selected from nucleotides with substitution of 2'-F-2'-Me.

18. The double-stranded oligonucleotide according to any one of claims 1-17, having one or more of features as follows:

(1) when the double-stranded oligonucleotide comprises a 2'-difluoro substituted nucleotide, the 2'-difluoro substituted nucleotide is located at at least one of positions 7, 8, 9, and 10 of the sense strand counting from a 5'-end;

optionally, the 2'-difluoro substituted nucleotide is located at at least two or at least three of positions 7, 8, 9 and 10 of the sense strand counting from the 5'-end;

(2) when the double-stranded oligonucleotide comprises a 2'-difluoro substituted nucleotide, the 2'-difluoro substituted nucleotide is located at at least one of positions 2, 4, 6, 8, 9, 10, 12, 14 and 16 of the antisense strand counting from the 5'-end;

optionally, the 2'-difluoro substituted nucleotide is located at at least two of positions 2, 4, 6, 8, 9, 10, 12, 14 and 16 of the antisense strand counting from the 5'-end;

(3) when the double-stranded oligonucleotide comprises a nucleotide with substitution of 2'-F-2'-Me, the nucleotide with substitution of 2'-F-2'-Me is located at a position outside the double-stranded region of the oligonucleotide; and

(4) when the double-stranded oligonucleotide comprises a nucleotide with substitution of 2'-F-2'-Me, the nucleotide with substitution of 2'-F-2'-Me is located at an overhang at 3'-end of the antisense strand.

19. An oligonucleotide conjugate, comprising the double-stranded oligonucleotide according to any one of claims 1-18, and a conjugating group conjugated to the double-stranded oligonucleotide; and

optionally, the conjugating group comprises a pharmaceutically acceptable targeting group and/or a delivery assisting group.

20. A pharmaceutical composition, comprising the double-stranded oligonucleotide according to any one of claims 1-18 or the oligonucleotide conjugate according to claim 19.

21. Use of the double-stranded oligonucleotide according to any one of claims 1-18, the oligonucleotide conjugate according to claim 19, or the pharmaceutical composition according to claim 20 in the preparation of a medicament for treating and/or preventing diseases or conditions associated with level of mRNA expressed by a target gene.