CLAIMS

1. An oligonucleotide for inhibiting hepatitis B virus (HBV) or a pharmaceutically acceptable salt thereof, wherein the oligonucleotide comprises a sense strand (SS) and an antisense strand (AS), wherein,

the nucleotide sequence of the SS comprises a sequence shown in SEQ ID NO: 1 or a fragment thereof; and

the nucleotide sequence of the AS comprises a sequence shown in SEQ ID NO: 3 or a fragment thereof.

2. The oligonucleotide or the pharmaceutically acceptable salt thereof according to claim 1, wherein

preferably, the AS is further subjected to a modification, and the modification is selected from one or more of a 2'-methoxyethyl modification, a 2'-methoxy (m) modification, a 2'-deoxy-2'-fluoro (f) modification, a phosphorothioate group (s) modification, an adenosine-2' phosphate (A-2'-5') modification, a uridine-2' phosphate (U-2'-5') modification, a guanosine-2' phosphate (G-2'-5') modification, a guanosine-glycol nucleic acid (Ggn) modification, an adenosine-glycol nucleic acid (Agn) modification, an N-(2,3-dihydroxypropyl)-3,5-bis(trifluoromethyl)benzamide (GNF-BX) modification, or a 5'-phosphate mimic modification;

preferably, the modification is selected from one or more of a 2'-methoxyethyl modification, an adenosine-2' phosphate (A-2'-5') modification, a uridine-2' phosphate (U-2'-5') modification, a guanosine-2' phosphate (G-2'-5') modification, a guanosine-glycol nucleic acid (Ggn) modification, an adenosine-glycol nucleic acid (Agn) modification, an N-(2,3-dihydroxypropyl)-3,5-bis(trifluoromethyl)benzamide (GNF-BX) modification, or a 5'-phosphate mimic modification;

preferably, the modification is a combination of either a guanosine-glycol

nucleic acid (Ggn) modification or an adenosine-2’ phosphate (A-2’-5’) modification with a 5’-phosphate mimic modification;

preferably, the modification is located at any of nucleotides at positions 1 to 8 starting from the 5’ terminus of the AS; and

preferably, the modified AS comprises a nucleotide sequence shown in any of SEQ ID NOs: 4-35 or a fragment thereof.

3. The oligonucleotide or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein the 5’-phosphate mimic is selected from one or more of 5’-oxymethylphosphonate, 5’-vinylphosphonic acid (Vp), 5’-vinylphosphonate-2’-N-acetyl, or 5’-malonylphosphonate, and is more preferably one or more of 5’-vinylphosphonic acid (Vp) or 5’-vinylphosphonate-2’-N-acetyl, and is more preferably 5’-vinylphosphonic acid (Vp); and

preferably, the 5’-phosphate mimic is modified at the 5’ terminus of the AS.

4. The oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein the oligonucleotide comprises at least one modified internucleotide linkage; and

preferably, the at least one modified internucleotide linkage is a phosphorothioate linkage.

5. The oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein the oligonucleotide comprises a combination of SS and AS selected from the group consisting of:

(1) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 3;

(2) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 4;

(3) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 5;

(4) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 6;

(5) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 7;

(6) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 8;

(7) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 9;

(8) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 10;

(9) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 11;

(10) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 12;

(11) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 13;

(12) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 14;

(13) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 15;

(14) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 16;

(15) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 17;

(16) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 18;

(17) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 19;

(18) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 20;

(19) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 21;

(20) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 22;

(21) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 23;

(22) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 24;

(23) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 25;

(24) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 26;

(25) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 27;

(26) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 28;

(27) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 29;

(28) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 30;

(29) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 31;

(30) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 32;

(31) the SS shown in SEQ ID NO: 2 and the AS shown in SEQ ID NO: 33;

(32) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 34; and

(33) the SS shown in SEQ ID NO: 1 and the AS shown in SEQ ID NO: 35.

6. The oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands;

preferably, the targeting ligand is conjugated to the 3' terminus of the SS of the oligonucleotide;

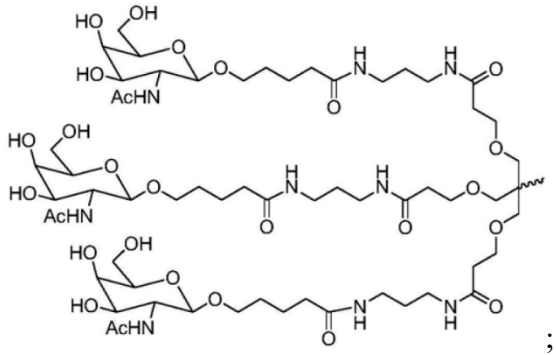
preferably, the targeting ligand comprises a carbohydrate, an amino sugar, cholesterol, a polypeptide, or a lipid;

preferably, the targeting ligand comprises the amino sugar;

preferably, the targeting ligand comprises an N-acetylgalactosamine (GalNAc) moiety;

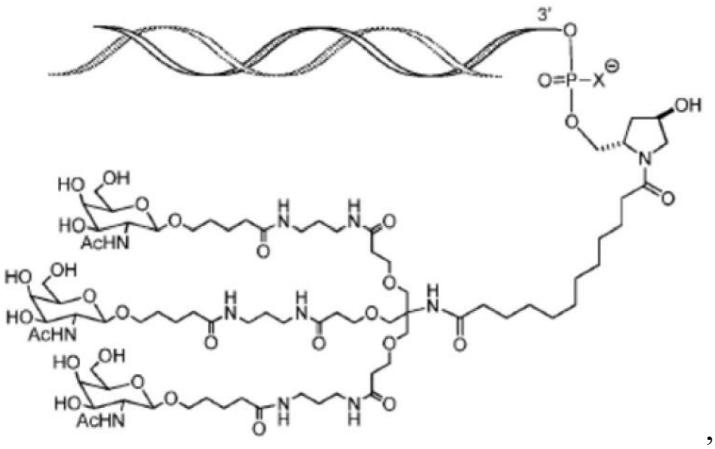
preferably, the GalNAc moiety is a monovalent GalNAc moiety, a divalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety;

preferably, the targeting ligand has the following structure:



; and

preferably, the targeting ligand is conjugated to the 3' terminus of the SS of the oligonucleotide through a linker to produce the following conjugate:



,

wherein X can be selected from S or O.

7. The oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein the oligonucleotide comprises a combination of SS and AS selected from the group consisting of:

(1) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 3;

(2) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 4;

(3) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 27;

(4) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 28;

(5) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 29;

(6) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 30;

(7) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 31;

(8) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 32;

(9) the SS shown in SEQ ID NO: 37 and the AS shown in SEQ ID NO: 39;

(10) the SS shown in SEQ ID NO: 38 and the AS shown in SEQ ID NO: 33;

(11) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 34; and

(12) the SS shown in SEQ ID NO: 36 and the AS shown in SEQ ID NO: 35.

8. A composition, comprising the oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, and optionally a pharmaceutically acceptable carrier.

9. Use of the oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 or the composition according to claim 8 in the manufacture of a medicament for treating HBV infection or hepatitis B and/or HBV-hepatitis D virus (HDV) coinfection;

preferably, the HBV infection is chronic HBV infection; and

preferably, the hepatitis B is chronic hepatitis B (CHB).

10. The oligonucleotide or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 or the composition according to claim 8, for use in the treatment of HBV infection or hepatitis B and/or HBV-HDV coinfection;

preferably, the HBV infection is chronic HBV infection; and

preferably, the hepatitis B is CHB.