SUMMARY

In one aspect, there is provided an antisense oligonucleotide selected from the group of:

(i) TcAACtttcactTcAG

(ii) TCaACtttcacttcAG

(iii) TcAACtttcacttcAG

(iv) TCAActttcacttCaGT

(v) TcAActttcacttCAGT

(vi) TcAactttcacttCAGT

wherein capital letters represent beta-D-oxy LNA nucleosides; lowercase letters represent DNA nucleosides; all cytosine LNA nucleosides are 5-methyl cytosine; and all internucleoside linkages are phosphorothioate internucleoside linkages.

In another aspect, there is provided a conjugate compound comprising the antisense oligonucleotide as defined herein and a conjugate moiety attached to said antisense oligonucleotide.

In another aspect, there is provided a pharmaceutically acceptable salt of the antisense oligonucleotide as defined herein or the conjugate compound as defined herein.

In another aspect, there is provided a pharmaceutically acceptable sodium salt of the antisense oligonucleotide as defined herein or the conjugate compound as defined herein.

In another aspect, there is provided a pharmaceutically acceptable potassium salt of the antisense oligonucleotide as defined herein or the conjugate compound as defined herein.

In another aspect, there is provided a pharmaceutical composition comprising the antisense oligonucleotide as defined herein, or the conjugate compound as defined herein or the pharmaceutically acceptable salt as defined herein, and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

In another aspect, there is provided an in vitro method for modulating PAPD5 and PAPD7 expression in a target cell which is expressing PAPD5 and PAPD7, said method comprising administering the antisense oligonucleotide as defined herein, the conjugate compound as defined herein or the pharmaceutically acceptable salt as defined herein to said target cell in an effective amount.

In another aspect, there is provided the antisense oligonucleotide as defined herein, the conjugate compound as defined herein or the pharmaceutically acceptable salt as defined herein; or the pharmaceutical composition as defined herein for use to treat HBV infection on a subject.

In another aspect, there is provided the antisense oligonucleotide as defined herein, the conjugate compound as defined herein or the pharmaceutically acceptable salt as defined herein; or the pharmaceutical composition as defined herein for use to treat chronic HBV infection in a subject.

In another aspect, there is provided the antisense oligonucleotide as defined herein, the conjugate compound as defined herein or the pharmaceutically acceptable salt as defined herein; or the pharmaceutical composition as defined herein, for use to reduce the infectiousness of a HBV-infected subject.

In another aspect, there is provided use of the antisense oligonucleotide as defined herein, the conjugate compound as defined herein, the pharmaceutically acceptable salt as defined herein in the manufacture of a medicament for treating HBV infection in a subject.

In another aspect, there is provided use of the antisense oligonucleotide as defined herein, the conjugate compound as defined herein, the pharmaceutically acceptable salt of as defined herein, in the manufacture of a medicament for treating chronic HBV infection in a subject.

In another aspect, there is provided use of the antisense oligonucleotide as defined herein, the conjugate compound as defined herein, the pharmaceutically acceptable salt as defined herein, in the manufacture of a medicament for reducing the infectiousness of a HBV-infected subject.

CLAIMS

1. An antisense oligonucleotide selected from the group of:

   (i) TcAACtttcactTcAG
   (ii) TCaACtttcacttcAG
   (iii) TcAACtttcacttcAG
   (iv) TCAActttcacttCaGT
   (v) TcAActttcacttCAGT
   (vi) TcAactttcacttCAGT

   wherein capital letters represent beta-D-oxy LNA nucleosides; lowercase letters represent DNA nucleosides; all cytosine LNA nucleosides are 5-methyl cytosine; and all internucleoside linkages are phosphorothioate internucleoside linkages.

2. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TcAACtttcactTcAG or a pharmaceutically acceptable salt thereof.

3. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TCaACtttcacttcAG or a pharmaceutically acceptable salt thereof.

4. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TcAACtttcacttcAG or a pharmaceutically acceptable salt thereof.

5. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TCAActttcacttCaGT or a pharmaceutically acceptable salt thereof.

6. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TcAActttcacttCAGT or a pharmaceutically acceptable salt thereof.

7. The antisense oligonucleotide of claim 1, wherein the antisense oligonucleotide is TcAactttcacttCAGT or a pharmaceutically acceptable salt thereof.

8. A conjugate compound comprising the antisense oligonucleotide of any one of claims 1 to 7 and a conjugate moiety attached to said antisense oligonucleotide.

9. The conjugate compound of claim 8, wherein the conjugate moiety is capable of binding to an asialoglycoprotein receptor.

10. The conjugate compound of claim 9, wherein the conjugate moiety is a trivalent N-acetyl-galactosamine (GalNAc) moiety.

11. The conjugate compound of any one of claims 8 to 10, wherein the conjugate moiety is covalently attached to said antisense oligonucleotide.

12. The conjugate compound of any one of claims 8 to 11, wherein a linker is positioned between the antisense oligonucleotide and the conjugate moiety.

13. The conjugate compound of claim 12, wherein the linker is a physiologically labile linker.

14. The conjugate compound of claim 13, wherein the physiologically labile linker is a S1 nuclease susceptible linker.

15. The conjugate compound of claim 13 or claim 14 wherein the physiologically labile linker is a phosphodiester linked cytidine-adenosine dinucleotide with three consecutive phosphodiester linkages.

16. The conjugate compound of any one of claims 13 to 15, wherein a C6 amino alkyl group is positioned between the conjugate moiety and the physiologically labile linker.

17. The conjugate compound of claim 16, wherein the conjugate moiety is capable of binding to an asialoglycoprotein receptor and wherein the conjugate moiety is a tri-valent N-acetyl-galactosamine (GalNAc) moiety; wherein the conjugate moiety is covalently attached to said antisense oligonucleotide; wherein a phosphodiester linked cytidine-adenosine dinucleotide with three consecutive phosphodiester linkages is positioned between the antisense oligonucleotide and the conjugate moiety; and wherein a C6 amino alkyl group is positioned between the conjugate moiety and the phosphodiester linked cytidine-adenosine dinucleotide with three consecutive phosphodiester linkages.

18. The conjugate compound of any one of claims 8 to 17, that has a formula selected from the group of:

(i) GN2-C6$_o$c$_o$a$_o$TcAACtttcactTcAG;

(ii) GN2-C6$_o$c$_o$a$_o$TCaACtttcacttcAG;

(iii) GN2-C6$_o$c$_o$a$_o$TcAACtttcacttcAG;

(iv) GN2-C6$_o$c$_o$a$_o$TCAActttcacttCaGT;

(v) GN2-C6$_o$c$_o$a$_o$TcAActttcacttCAGT; and

(vi) GN2-C6$_o$c$_o$a$_o$TcAactttcacttCAGT

wherein capital letters represent beta-D-oxy LNA nucleosides; all cytosine LNA nucleosides are 5-methyl cytosine; lowercase letters represent DNA nucleosides; subscript o represents a phosphodiester nucleoside linkage; and all other internucleoside linkages are phosphorothioate internucleoside linkages;

wherein C6 represents an amino alkyl group with 6 carbons; and

wherein GN2 represents a trivalent GalNAc cluster shown in Figure 2;

wherein the wavy bond line in Figure 2 indicates the site of conjugation of the trivalent GalNAc cluster to the C6 amino alkyl group.

19. A pharmaceutically acceptable salt of the antisense oligonucleotide of any one of claims 1 to 7 or the conjugate compound of any one of claims 8 to 18.

20. A pharmaceutically acceptable sodium salt of the antisense oligonucleotide of any one of claims 1 to 7 or the conjugate compound of any one of claims 8 to 18.

21. A pharmaceutically acceptable potassium salt of the antisense oligonucleotide of any one of claims 1 to 7 or the conjugate compound of any one of claims 8 to 18.

22. A pharmaceutical composition comprising the antisense oligonucleotide of any one of claims 1 to 7, or the conjugate compound of any one of claims 8 to 18 or the pharmaceutically acceptable salt of any one of claims 19 to 21, and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

23. The pharmaceutical composition of claim 22 wherein the pharmaceutically acceptable diluent is sterile phosphate buffered saline.

24. An in vitro method for modulating PAPD5 and PAPD7 expression in a target cell which is expressing PAPD5 and PAPD7, said method comprising administering the antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18 or the pharmaceutically acceptable salt of any one of claims 19 to 21 to said target cell in an effective amount.

25. The antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18 or the pharmaceutically acceptable salt of any one of claims 19 to 21; or the pharmaceutical composition of claim 22 or 23 for use to treat HBV infection on a subject.

26. The antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18 or the pharmaceutically acceptable salt of any one of claims 19 to 21; or the pharmaceutical composition of claim 22 or 23 for use to treat chronic HBV infection in a subject.

27. The antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18 or the pharmaceutically acceptable salt of any one of claims 19 to 21; or the pharmaceutical composition of claim 22 or 23, for use to reduce the infectiousness of a HBV-infected subject.

28. Use of the antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18, the pharmaceutically acceptable salt of any one of claims 19 to 21 in the manufacture of a medicament for treating HBV infection in a subject.

29. Use of the antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18, the pharmaceutically acceptable salt of any one of claims 19 to 21, in the manufacture of a medicament for treating chronic HBV infection in a subject.

30. Use of the antisense oligonucleotide of any one of claims 1 to 7, the conjugate compound of any one of claims 8 to 18, the pharmaceutically acceptable salt of any one of claims 19 to 21, in the manufacture of a medicament for reducing the infectiousness of a HBV-infected subject.