Figure 8: Representation of the ability of the oligonucleotides, tested in example 4, to reduce the expression of PAPD5 in HeLa cell cultures. Each oligonucleotide is represented by a dot indicating its location on the PAPD5 mRNA by chromosomal position. The oligonucleotide concentrations were 5 and 25 microM as indicated in the right hand side each plot.

Figure 9: Representation of the ability of the oligonucleotides, tested in example 5, to reduce the expression of PAPD7 in HeLa cell cultures. Each oligonucleotide is represented by a dot indicating its location on the PAPD7 mRNA by chromosomal position. The oligonucleotide concentrations were 5 and 25 microM as indicated in the right hand side each plot.

Figure 10: Representation of the inhibition of HBsAg in HBV infected HepaRG cells with combinations oligonucleotides targeting PAPD5 and PAPD7 (20 µM each) compared to the inhibition obtained using a single oligonucleotide (20 µM) present in the combination. The assay was conducted with gymnosis.

Figure 11: Representation of the inhibition of HBsAg in HBV infected HepaRG cells with combinations oligonucleotides targeting PAPD5 and PAPD7 (500 nM each) compared to the inhibition obtained using a single oligonucleotide (500 nM) from the combination. The assay was conducted with transfection.

SUMMARY

The present disclosure relates to a composition comprising a nucleic acid molecule for use in the treatment and/or prevention of Hepatitis B virus infection, wherein said nucleic acid molecule inhibits expression and/or activity of PAPD5. In particular a composition comprising a combined preparation of a nucleic acid molecule inhibits expression and/or activity of PAPD5 and another nucleic acid molecule inhibits expression and/or activity of PAPD7 for use in the treatment and/or prevention of Hepatitis B virus infection.

In one aspect, the present disclosure relates to a use of a composition comprising a nucleic acid molecule which directly inhibits expression and/or activity of PAP associated domain containing 5 (PAPD5) in the manufacture of a medicament for the treatment of Hepatitis B virus infection.

The present disclosure further relates to nucleic acid molecules that inhibit expression and/or activity of PAPD7. In particular single stranded antisense, siRNA and shRNA molecules.

~~A further aspect of the present disclosure relates to a nucleic acid molecule which consists of a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is 100% complementary to a PAPD7 target nucleic acid and the nucleic acid molecule is capable of reducing expression of PAPD7.~~

The present disclosure further relates to single stranded antisense oligonucleotides that inhibit expression and/or activity of PAPD5. In particular modified antisense oligonucleotides comprising 2'sugar modified oligonucleotide and phosphorothioate internucleoside linkages.

~~A further aspect of the present disclosure relates to a single stranded antisense oligonucleotide which consists of a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is 100% complementary to a PAPD5 target nucleic acid and the antisense oligonucleotide is capable of reducing expression of PAPD5.~~

The present disclosure further relates to conjugates of nucleic acid molecules of the disclosure, combined preparations of nucleic acid molecules capable of inhibiting expression and/or activity of both PAPD5 and PAPD7 and pharmaceutical compositions comprising the molecules of the disclosure.

~~A further aspect of the present disclosure relates to a conjugate comprising the antisense oligonucleotide or nucleic acid molecule of the disclosure, and at least one conjugate moiety covalently attached to said oligonucleotide.~~

~~A further aspect of the present disclosure relates to a combined preparation comprising~~

~~a. a nucleic acid molecule which inhibits expression and/or activity of PAPD5; and~~

~~b. a nucleic acid molecule which inhibits expression and/or activity of PAPD7;~~

~~wherein the nucleic acid molecule is selected from the disclosure or the conjugate of the disclosure.~~

~~A further aspect of the present disclosure relates to a pharmaceutical composition comprising the antisense oligonucleotide or nucleic acid molecule of the disclosure, or the conjugate of the disclosure, or the combined preparation of the disclosure.~~

The present disclosure further relates to a method for identifying a compound or composition that prevents, ameliorates and/or inhibits a hepatitis B virus (HBV) infection, comprising:

CLAIMS

1. A use of a composition comprising a nucleic acid molecule which directly inhibits expression and/or activity of PAP associated domain containing 5 (PAPD5) in the manufacture of a medicament for the treatment of Hepatitis B virus infection.

2. The use of claim 1, wherein said composition is a combined preparation comprising:
   a. a nucleic acid molecule which directly inhibits expression and/or activity PAPD5; and
   b. a nucleic acid molecule which directly inhibits expression and/or activity of PAP associated domain containing 7 (PAPD7).

3. The use of claim 1 or 2, wherein the nucleic acid molecules independently are selected from the group consisting of:
   a. a single stranded antisense oligonucleotide;
   b. a siRNA molecule;
   c. a shRNA molecule; and
   d. a genome editing machinery, comprising:
      i. a site-specific DNA nuclease or a polynucleotide encoding a site-specific DNA nuclease; and
      ii. a guide RNA or a polynucleotide encoding a guide RNA.

4. The use of claim 2 or 3, wherein the nucleic acid molecules are selected from:
   a. a single stranded antisense oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 80% complementarity to PAPD5 target nucleic acid and which capable of reducing expression of PAPD5; and
   b. a single stranded antisense oligonucleotide comprising a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 80% complementarity to a PAPD7 target nucleic acid and which is capable of reducing expression of PAPD7.

5. The use of any one of claims 1 to 4, wherein the composition reduces secretion of HBsAg, HBeAg and/or inhibits production of intracellular HBV mRNA or HBV DNA.

6. The use of any one of claims 1 to 5, wherein the composition inhibits development of chronic HBV infection and/or reduces the infectiousness of a HBV infected person.

7. A method for identifying a compound or composition that ameliorates and/or directly inhibits a hepatitis B virus (HBV) infection, comprising:
   a. contacting a test compound or composition with a cell expressing PAPD5 and/or PAPD7;
   b. measuring the expression and/or activity of PAPD5 and/or PAPD7 in the presence and absence of said test compound or composition; and
   c. identifying a compound or composition that reduces the expression and/or activity of PAPD5 and/or PAPD7 as a compound that ameliorates and/or inhibits a HBV infection.

8. The method of claim 7, wherein the test compound is a library of nucleic acid molecules and step c) identifies nucleic acid molecules that reduce PAPD5 or PAPD7 mRNA expression by at least 60%.

9. The method of claim 7, wherein the test composition is a combined preparation of a nucleic acid molecule capable of reducing PAPD5 and a nucleic acid molecule capable of reducing PAPD7.

10. The method of any one of claims 7 to 9, wherein the compound that inhibits propagation of HBV inhibits secretion of HBV surface antigen (HBsAg), and/or inhibits secretion of HBV envelope antigen (HBeAg), and/or inhibits production of intracellular HBV mRNA.

11. ~~A~~ The use according to claim 1 wherein the nucleic acid molecule is a single stranded antisense oligonucleotide which comprises or consists of a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is 100% complementary to a PAPD5 target nucleic acid and the antisense oligonucleotide is capable of reducing expression of PAPD5.

12. ~~A~~ The use according to claim 2 wherein the nucleic acid molecule is a nucleic acid molecule which comprises or consists of a contiguous nucleotide sequence of 10 to 30 nucleotides in length wherein the contiguous nucleotide sequence is 100% complementary to a PAPD7 target nucleic acid and the nucleic acid molecule is capable of reducing expression of PAPD7.

13. The ~~nucleic acid molecule of~~use according to claim 12, wherein the nucleic acid molecule is a single stranded antisense oligonucleotide.

14. The ~~antisense oligonucleotide or nucleic acid molecule of~~use according to any one of claims 11 to 13, ~~comprising~~ wherein the nucleic acid molecule comprises one or more 2' sugar modified nucleoside(s).

15. The ~~antisense oligonucleotide or nucleic acid molecule of~~use according to claim 14, wherein the one or more 2' sugar modified nucleoside is independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.

16. The ~~antisense oligonucleotide or nucleic acid molecule of~~use according to claim 14 or 15, wherein the one or more 2' sugar modified nucleoside is a LNA nucleoside.

17. The ~~antisense oligonucleotide or nucleic acid molecule of~~use according to any one of claims 11 to 16, wherein the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

18. The ~~antisense oligonucleotide of~~use according to any one of claims 11 or 13 to 17, wherein the ~~oligonucleotide~~ nucleic acid molecule is a gapmer of formula 5'-F-G-F'-3', where region F and F' independently comprise 1 - 7 2' sugar modified nucleosides and G is a region between 6 and 16 nucleosides which are capable of recruiting RNaseH.

19. ~~A conjugate comprising the antisense oligonucleotide or nucleic acid molecule~~The use according to any one of claims 11 to 18, wherein the nucleic acid molecule is a conjugate comprising ~~and~~ at least one conjugate moiety covalently attached to ~~said oligonucleotide~~the nucleic acid molecule.

20. ~~A~~ The use according to any one of claims 11 to 19, wherein the nucleic acid molecule is comprised within a composition which is a combined preparation comprising
    a. a nucleic acid molecule which inhibits expression and/or activity of PAPD5; and
    b. a nucleic acid molecule which inhibits expression and/or activity of PAPD7.~~;~~

    ~~wherein the nucleic acid molecule is selected from any one of the claims 11 to 18 or the conjugate of claim 19.~~

21. ~~A~~ The use according to any one of claims 11 to 20, wherein the nucleic acid molecule is comprised within a pharmaceutical composition ~~comprising the antisense oligonucleotide or nucleic acid molecule according to any one of claims 11 to 18, or the conjugate of claim 19, or the combined preparation of claim 20~~.