

In WO 2017/066712 down regulation of PAPD5 in relation to the treatment and diagnosis of telomere diseases has been described. Five shRNA structures for this purpose have been described.

To our knowledge the expression of PAPD5 or PAPD7 has never been associated with HBV infection, nor has modified single stranded antisense oligonucleotides been made against these targets.

OBJECTIVE OF THE INVENTION

Thus, the technical problem underlying the present invention is the identification and provision of ameliorated means and methods for treating and/or preventing a HBV infection.

The technical problem is solved by the provision of the embodiments described herein and characterized in the claims.

SUMMARY

In one aspect, there is provided 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 PAP associated domain containing 5 (PAPD5).

In another aspect, there is provided a method for identifying a compound or composition that prevents, ameliorates and/or 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 prevents, ameliorates and/or inhibits a HBV infection.

In another aspect, there is provided 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% complementarity to a PAPD5 target nucleic acid and the antisense oligonucleotide is capable of reducing expression of PAPD5.

In another aspect, there is provided 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% complementarity to a PAPD7 target nucleic acid and the nucleic acid molecule is capable of reducing expression of PAPD7.

In another aspect, there is provided a conjugate comprising the antisense oligonucleotide or nucleic acid molecule as defined herein, and at least one conjugate moiety covalently attached to said oligonucleotide.

In another aspect, there is provided 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.

In another aspect, there is provided a pharmaceutical composition comprising the antisense

- 5 oligonucleotide or nucleic acid molecule as defined herein, or the conjugate as defined herein, or the combined preparation as defined herein.

BRIEF DESCRIPTION OF THE FIGURES

The Figures show:

- 10 **Figure 1:** Pictures from 1-by-1 experiment with HBX129653/HBX129654 chemical probes and the 3 prey fragments.

Figure 2: Pictures from 1-by-1 experiment with HBX129653/HBX129654 chemical probes and PAPD5/7 full length proteins.

Figure 3: Pictures from competition assay using HBX129653 (DHQ) and MOL653/654 for competition

- 15 **Figure 4:** Pictures from competition assay using HBX129654 (THP) and MOL653/654 for competition

Figure 5: Pictures from competition assay using HBX129653 (DHQ) and INACT653/INACT654 for competition. MOL653 was included as positive control.

- 20 **Figure 6:** Pictures from competition assay using HBX129654 (THP) and INACT653/INACT654 for competition. MOL653 was included as positive control.

- 25 **Figure 7: (A)** SiRNA knock-down (KD) of PAPD5 and PAPD7 in HBV-infected dHepaRG leads to reduction in HBV expression. Differentiated HepaRG cells were infected with HBV and treated with siRNA against either PAPD5, PAPD7 or both (25nM each) one day prior to HBV infection and on day 4 post infection. Supernatant were harvested on day 11, levels of HBsAg and HBeAg secreted in the supernatant were measured by ELISA and normalized to non-treated control. Cell toxicity and inhibition of gene expression was measured subsequently and also normalized to the non-treated control. **(B)** The same experiment as described in (A) was performed, with the exception that only the level of HBsAg secreted in the supernatant was measured.