

HBV infected cell. The enhanced antisense oligonucleotides targeting FUBP1 or the conjugate thereof can be used in the treatment and/or prevention of an HBV infection, or in the treatment of cancer.

SUMMARY

The disclosure relates to antisense oligonucleotides, or conjugates thereof, which target a FUBP1 (Far upstream element-binding protein 1) nucleic acid, such as a mammalian FUBP1 nucleic acid, and which are capable of inhibiting the expression of said nucleic acid in a cell expressing said nucleic acid, and their use in medicine. Said antisense oligonucleotides are complementary to a mammalian FUBP1 nucleic acid, such as human FUBP1.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is complementary to, such as fully complementary to a region from nucleotides 16184 to 16205 of the human FUBP1 pre-mRNA (as illustrated in SEQ ID NO: 1).

Also, the disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is complementary to, such as fully complementary to a region from nucleotides 30536-30553 of the human FUBP1 pre-mRNA (as illustrated in SEQ ID NO: 1).

In some examples, the antisense oligonucleotide or the contiguous nucleotide sequence is complementary to, such as fully complementary to a region from nucleotides 16184 to 16200 of SEQ ID NO: 1.

In some examples, the antisense oligonucleotide or the contiguous nucleotide sequence is complementary to, such as fully complementary to a region from nucleotides 16186 to 16203 of SEQ ID NO: 1.

In some examples, the antisense oligonucleotide or the contiguous nucleotide sequence is complementary to, such as fully complementary to a region from nucleotides 30536-30553 of SEQ ID NO: 1.

In some examples, the antisense oligonucleotide or the contiguous nucleotide sequence is complementary to, such as fully complementary to a region from nucleotides 16188 to 16205 of SEQ ID NO: 1. In some examples, the antisense oligonucleotide or the contiguous nucleotide sequence is complementary to, such as fully complementary to a region from nucleotides 16189 to 16205 of SEQ ID NO: 1.

The antisense oligonucleotide of the disclosure is typically 12 – 30, such as 12 to 22, such as 16 to 20 nucleotides in length, and comprises a contiguous nucleotide sequence of at least 12 nucleotides, such as of 13, 14, 15, 16, 17 or 18 nucleotides, which is complementary to, such as fully complementary to a region of the human FUBP1 pre-mRNA (as illustrated in SEQ ID NO: 1), selected from a region from nucleotides 16184-16205, 16184-16200, 16186-16203, 16188-16205, 16189-16205 and 30536-30553 of SEQ ID NO: 1.

The disclosure provides for an antisense oligonucleotide, 12-22 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 12 – 22 nucleotides in length, wherein the contiguous nucleotide sequence is complementary, such as fully complementary, to SEQ ID NO 10.

The disclosure provides for an antisense oligonucleotide, 12-20 nucleotides in length (such as 15, 16, 17, or 18 nucleotides in length), wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 12 – 18 nucleotides in length (such as 15, 16, 17, or 18 nucleotides in length), wherein the contiguous nucleotide sequence is complementary, such as fully complementary, to SEQ ID NO 11.

The disclosure provides for an antisense oligonucleotide, 12-20 nucleotides in length (such as 15, 16, 17, or 18 nucleotides in length), wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 12 – 18 nucleotides in length (such as 15, 16, 17, or 18 nucleotides in length), wherein the contiguous nucleotide sequence is complementary, such as fully complementary, to SEQ ID NO 19.

The disclosure provides for an antisense oligonucleotide 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length, wherein the contiguous nucleotide sequence is 100% identical to a sequence selected from the group consisting of SEQ ID NOs: 6, 7, 8, 9 and 18; or at least 14 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length, wherein the contiguous nucleotide sequence is 100% identical to a sequence selected from the group consisting of SEQ ID NOs: 6, 7, 8, 9 and 18, or at least 15 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length, wherein the contiguous

nucleotide sequence is 100% identical to a sequence selected from the group consisting of SEQ ID NOs: 6, 7, 8, 9 and 18, or at least 16 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence, which is 100% identical to a sequence selected from the group consisting of SEQ ID NOs: 6, 7, 8, 9 and 18, or 14, 15, 16, or 17 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide, which comprises (or consists of) a contiguous nucleotide sequence selected from the group consisting of SEQ ID NOs: 6, 7, 8, 9 and 18.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is 100% identical to SEQ ID NO: 6 (CTTATGCTTTTTATGGT), or 14, 15 or 16 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is 100% identical to SEQ ID NO: 7 (CTTATGCTTTTTATGGTT), or 14, 15, 16 or 17 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is 100% identical to SEQ ID NO: 8 (GCTTTTTATGGTTTCAC), or 14, 15 or 16 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is 100% identical to SEQ ID NO: 9 (TATGCTTTTTATGGTTTC), or 14, 15, 16 or 17 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide, which comprises a contiguous nucleotide sequence, which is 100% identical to SEQ ID NO: 18 (ACCAATTTTCATTTCTAC), or 14, 15, 16 or 17 contiguous nucleotides thereof.

The disclosure provides for an antisense oligonucleotide selected from

CTTatGctttttatgGT (SEQ ID NO: 6, Compound ID No 6_1),
CTTaTgctttttatgGT (SEQ ID NO: 6, Compound ID No 6_2),
CTtATgctttttatgGTT (SEQ ID NO: 7, Compound ID No 7_1),
CTtAtgctttttatgGTT (SEQ ID NO: 7, Compound ID No 7_2),
CTtAtgctttttatGgTT (SEQ ID NO: 7, Compound ID No 7_3),

CTtAtgctttttatGGTT (SEQ ID NO: 7, Compound ID No 7_4),
GcttTttatggtTtCAC (SEQ ID NO: 8, Compound ID No 8_1),
TATgcTttttatggtTTC (SEQ ID NO: 9, Compound ID No 9_1), and
AcCAAttttcatttCtAC (SEQ ID NO: 18, Compound ID No 18_1)

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

In one aspect, the present disclosure provides an antisense oligonucleotide selected from the group of antisense oligonucleotides consisting of

CTtAtgctttttatGgTT (SEQ ID NO: 7),
AcCAAttttcatttCtAC (SEQ ID NO: 18),
CTTatGctttttatgGT (SEQ ID NO: 6),
CTTaTgctttttatgGT (SEQ ID NO: 6),
CTtATgctttttatgGTT (SEQ ID NO: 7),
CTtAtgctttttatgGTT (SEQ ID NO: 7),
CTtAtgctttttatGGTT (SEQ ID NO: 7),
GcttTttatggtTtCAC (SEQ ID NO: 8), and
TATgcTttttatggtTTC (SEQ ID NO: 9),

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

The present disclosure also provides for a pharmaceutically acceptable salt of the antisense oligonucleotide of the present disclosure.

The disclosure provides for an antisense oligonucleotide selected from the group listed in Table 1, or a pharmaceutically acceptable salt thereof.

Table 1. Compound Table (Exemplary antisense oligonucleotides of the present disclosure) – HELM Annotation Format

SEQ ID Number	Compound ID Number #	HELM Annotation Written 5' – 3'.	Comprised by conjugate shown in Fig.
6	6_1	{[LR]([5meC])[sP].[LR](T)[sP].[LR](T)[sP].[dR](A)[sP].[dR](T)[sP].[LR](G)[sP].[dR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](G)[sP].[LR](G)[sP].[LR](T)}	1
6	6_2	{[LR]([5meC])[sP].[LR](T)[sP].[LR](T)[sP].[dR](A)[sP].[LR](T)[sP].[dR](G)[sP].[dR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](G)[sP].[LR](G)[sP].[LR](T)}	2
7	7_1	{[LR]([5meC])[sP].[LR](T)[sP].[dR](T)[sP].[LR](A)[sP].[LR](T)[sP].[dR](G)[sP].[dR](C)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](G)[sP].[LR](G)[sP].[LR](T)[sP].[LR](T)}	3

[dR](G) is a DNA guanine nucleoside,
[dR](T) is a DNA thymine nucleoside,
[dR](A) is a DNA adenine nucleoside,
[dR](C) is a DNA cytosine nucleoside,
[sP] is a phosphorothioate internucleoside linkage,
P is a phosphodiester internucleoside linkage.

The disclosure thus provides for an antisense oligonucleotide selected from the group consisting of compound ID Nos # 6_1, 6_2, 7_1, 7_2, 7_3, 7_4; 8_1 and 9_1.

The disclosure further provides for an antisense oligonucleotide with compound ID No: 18_1.

In an example, the antisense oligonucleotide is not an antisense oligonucleotide compound ID Nos 53_1 or 54_1 as disclosed in WO 2019/193165 (see also Table 7 in the Examples section).

In an example, the antisense oligonucleotide is not an antisense oligonucleotide compound ID Nos 78_1 and 79_1 as disclosed in WO 2019/193165 (see also Table 7 in the Examples section).

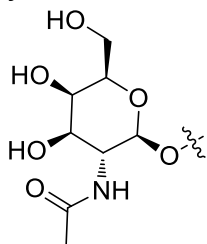
In another aspect, the present disclosure further provides a conjugate comprising the antisense oligonucleotide of the present disclosure, and at least one conjugate moiety covalently attached to said antisense oligonucleotide.

In some examples, the conjugate moiety is capable of binding to the asialoglycoprotein receptor, such as the human asialoglycoprotein receptor. For example, the conjugate moiety may comprise at least one asialoglycoprotein receptor-targeting moiety selected from group consisting of galactose, galactosamine, N-formyl-galactosamine, N-acetylgalactosamine, N-propionyl-galactosamine, N-n-butanoyl-galactosamine and N-isobutanoylgalactosamine.

In some examples, the asialoglycoprotein receptor-targeting moiety is N-acetylgalactosamine (GalNAc). Thus, the antisense oligonucleotide of the present disclosure may be conjugated to at least one conjugate moiety comprising at least one N-Acetylgalactosamine (GalNAc) moiety, such as at least one conjugate moiety comprising at least one N-Acetylgalactosamine (GalNAc) moiety as described below. According to one example of the disclosure, the conjugate moiety is a GalNAc residue R as described hereinunder.

In some examples, the conjugate moiety is an at least trivalent, such as a divalent, trivalent or tetravalent GalNAc residue R. Preferably the conjugate moiety is a trivalent GalNAc residue R.

The term “trivalent GalNAc residue” as used herein refers to a residue comprising three N-Acetylgalactosamine moieties, i.e. preferably three moieties of formula



The conjugate moiety or the GalNAc residue R, respectively, and the antisense oligonucleotide may be linked together via a linker L, such as a biocleavable linker L. Thus, the conjugate compound may comprise a linker L, which is positioned between the antisense oligonucleotide and the conjugate moiety or GalNAc residue R, respectively.

In some examples, the linker L comprises between 1 and 10 linked nucleosides, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 linked nucleosides, such as between 2 and 6 linked nucleosides, such as between 2 and 5 linked nucleosides, such as between 2 and 4 linked nucleosides. In some examples, the linker comprises two linked nucleotides. Thus, the nucleosides may be DNA nucleosides. Typically, the nucleosides are linked via phosphodiester internucleoside linkages. Moreover, the linker L may be linked to the antisense compound via a phosphodiester internucleoside linkage.

Exemplary conjugates are provided in Table 2 (in HELM Annotation format) as well as in Fig. 1 to 8, Fig. 8.1 and Fig. 10.

In another aspect, the present disclosure provides a conjugate selected from the group of conjugates shown in Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8 and Fig. 8.1.

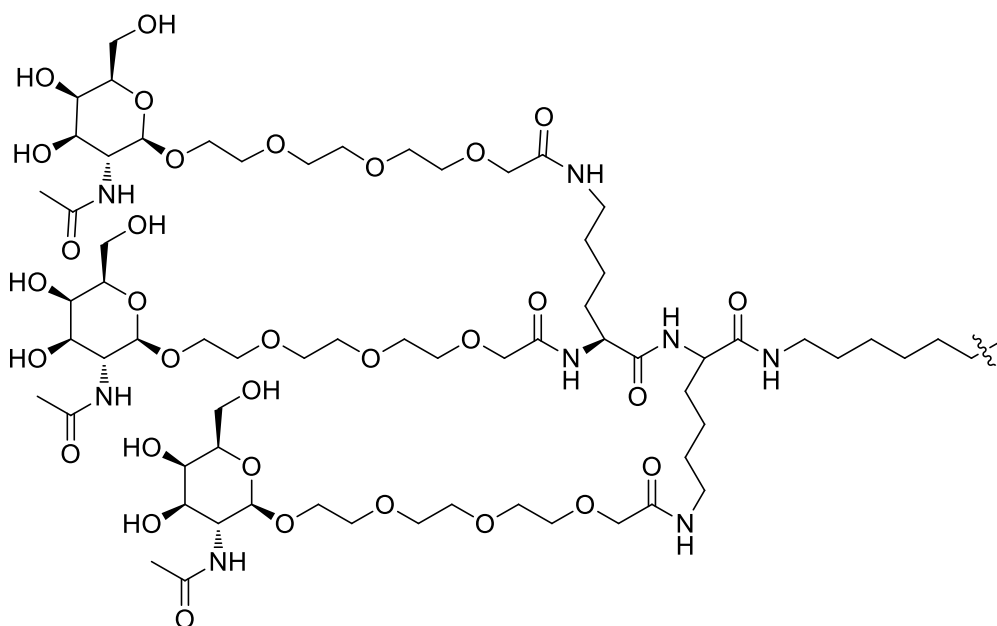
The disclosure provides for a conjugate selected from the group of conjugates listed in Table 2, or a pharmaceutically acceptable salt thereof.

Table 2. Compound Table (Exemplary conjugates of the present disclosure) – HELM Annotation Format (for the annotation on the HELM annotation, see explanations for Table 1).

SEQ ID Number	Oligo Compound ID Number # (acc. to Table 1 above)	HELM Annotation Written 5' – 3'.	Exemplary compound – see Figure

		.[dR](T)[sP].[dR](A)[sP].[dR](T)[sP].[dR](G)[sP].[dR](G)[sP].[dR](T)[sP].[LR](T)[sP].[LR](T)[sP].[LR]([5meC])}	
18	18_1	{[5gn2c6]}P.[dR](C)P.[dR](A)P.[LR](A)[sP].[dR](C)[sP].[LR]([5meC])[sP].[LR](A)[sP].[LR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](C)[sP].[dR](A)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[dR](T)[sP].[LR]([5meC])[sP].[dR](T)[sP].[LR](A)[sP].[LR]([5meC])}	8.1

In the above Table, [5gn2c6] is a GalNAc residue R having the formula:



It is to be understood that R as shown in the figure above and as used in the above table is a mixture of the two stereoisomers shown in Fig. 9D1 and 9D2.

According to a further example of the disclosure, R as shown in the figure above and as used in the above table is the stereoisomer as shown in to Fig 9D1.

According to a further example of the disclosure R as shown in the figure above and as used in the above table is the stereoisomer as shown in Fig 9D1. The structures of the conjugates provided in Table 2 are shown in Figures 1 to 8, and 8.1.

The disclosure provides for the conjugate of Figure 1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 6_1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 2, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 6_2, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 3, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 7_1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 4, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 7_2, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 5, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 7_3, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 6, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 7_4, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 7, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 8_1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 8, or a pharmaceutically acceptable salt thereof.

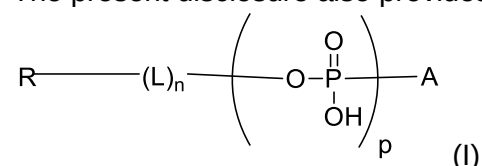
The disclosure provides for the antisense oligonucleotide of Compound ID Number 9_1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the antisense oligonucleotide of Compound ID Number 18_1, or a pharmaceutically acceptable salt thereof.

The disclosure provides for the conjugate of Figure 8.1, or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure provides a pharmaceutically acceptable salt of the oligonucleotide as described herein, or the conjugate as described herein.

The compound of formula (I)

The present disclosure also provides for compounds of the following formula (I)



wherein

n is 0 or 1

p is 0 or 1

with the proviso that in case n is 1, p is preferably 1,

and with the proviso that in case n is 0 and p is 0, R is preferably H,

L is a linker, preferably L is a linker comprising or consisting of 2-10 nucleosides, such as 2-5 nucleosides,

R is a GalNAc residue, preferably a trivalent GalNAc residue,

and A is an antisense oligonucleotide residue according to the present disclosure.

The term “antisense oligonucleotide residue” refers to an antisense oligonucleotide according to the present disclosure which is attached via its 5' end to residue R via $-(\text{L})_n-(\text{O}-\text{P}(=\text{O})(-\text{OH})-)_p-$, such as an antisense oligonucleotide as shown in Table 6. Preferred antisense oligonucleotide residues are depicted in Fig. 1A, 2A, 3A, 4A, 5A, 6A, 7A and 8A. A further preferred antisense oligonucleotide residue is depicted in Fig. 8.1A.

The GalNAc residue R

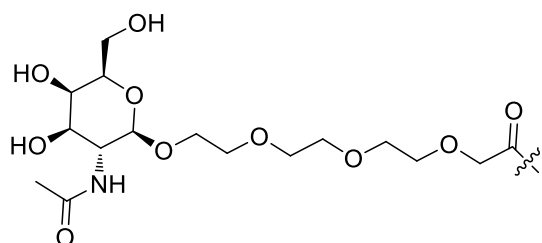
R is a GalNAc residue, preferably a trivalent GalNAc residue. The term “GalNAc residue” as used herein refers to a residue comprising at least one N-Acetylgalactosamine (GalNAc) moiety, i.e. at least one moiety of formula

The term “alkyl-oxy-alkyl” groups refers to at least two alkyl groups linked via an oxygen, preferably to ethyl-oxy-ethyl groups, such as $-(CH_2-O)_x-$ groups with integer x preferably being in the range of from 2 to 20, more preferably in the range of from 2 to 6, such as 2, 3, 4, 5 or 6, more preferably x is 3 or 5.

According to an example of the disclosure, the GalNAc building block (L^a) is selected from the group of the following structures (L^a).

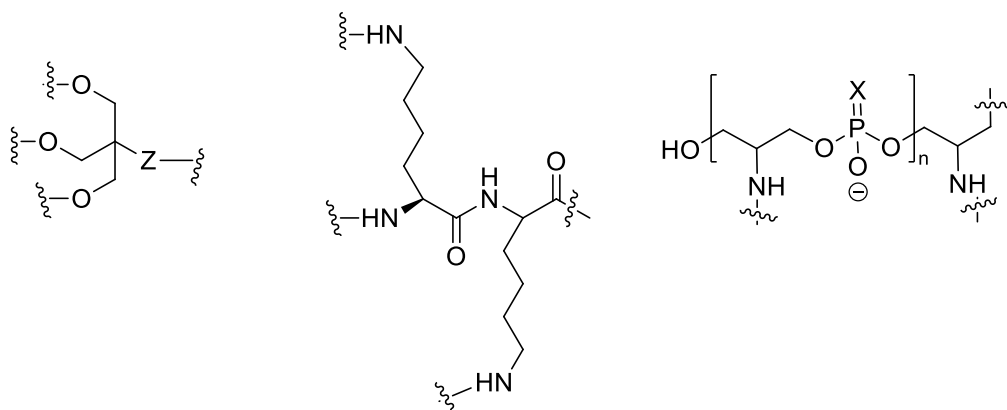
If more than one residue (L^a) is present in a GalNAc residue, such as the three residues in the trivalent GalNAc residue, then all residues are preferably the same.

Most preferably, L^a has the structure



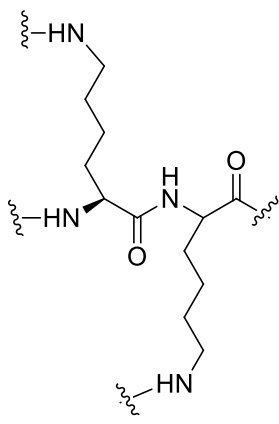
In case, the conjugate moiety R comprises multiple, such as preferably three, GalNAc moieties, R comprises besides the GalNAc building blocks (L^a), a multivalent, preferably a tetravalent, building block (L^b), to which the building blocks (L^a) are preferably being attached, to the antisense oligonucleotide residue A via $-(L)_n-(O-P(=O)(-OH)-)_p-$.

L^b is preferably selected from one of the following structures:



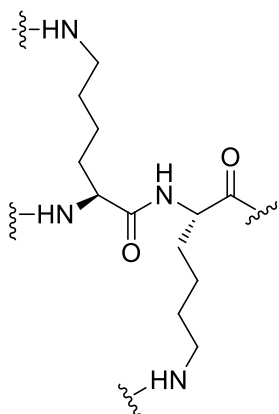
with X being O or S , and with Z being O or NH , and wherein n is of from 1 to 4, preferably 2 or 3, more preferably 2.

More preferably, L^b has the structure

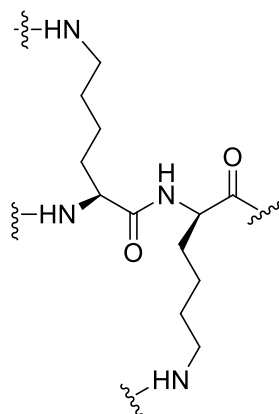


It is to be understood that, L^b has either the structure L^{b*} or the structure L^{b**} or is a mixture thereof.

According to a preferred example L^b is a mixture of L^{b*} and L^{b**} :

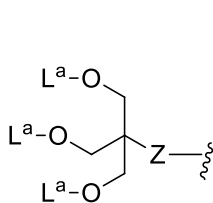
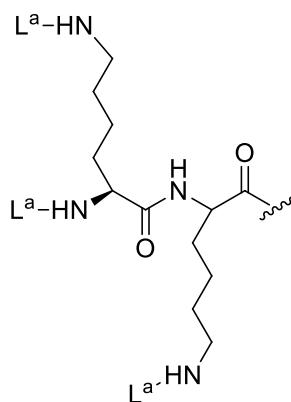
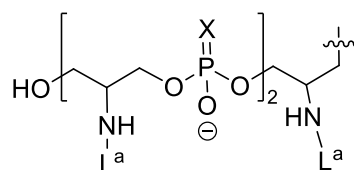


(L^{b*})



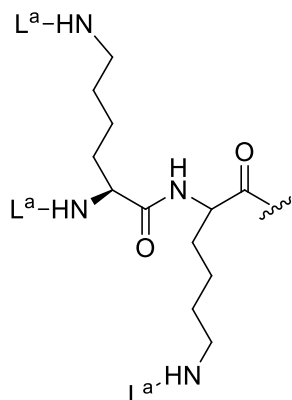
(L^{b**})

Thus, the conjugate moiety R preferably comprises a structure $(L^a)_3-L^b$, more preferably R comprises one of the following structures

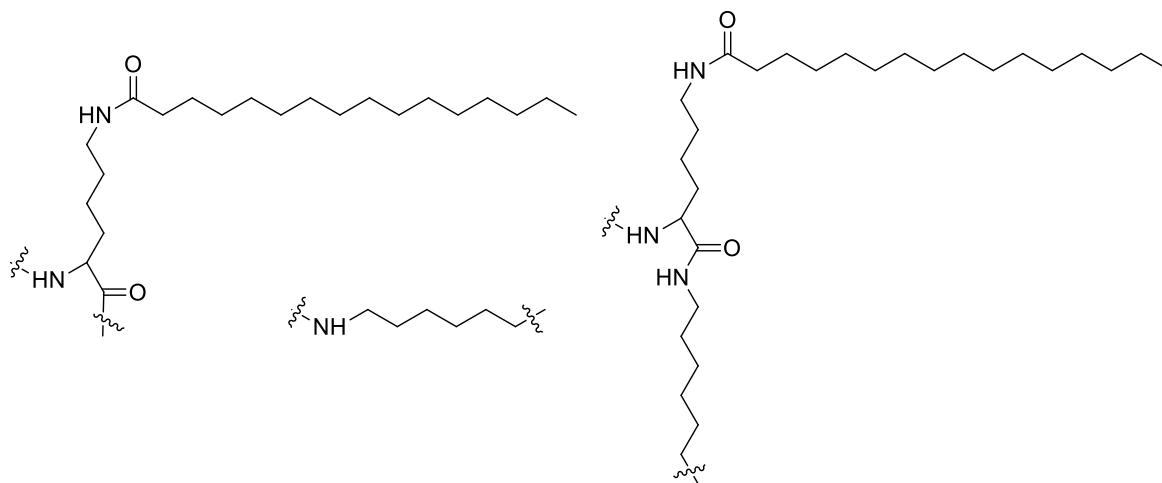


Depending on the structure of L^b , L^c is selected from the group consisting of alkyl, alkyl-oxy-alkyl, amino-alkyl (-NH-alkyl-), amino-alkyl-oxy-alkyl, unnatural amino acid residues, and natural amino acid residues. According to one example of the disclosure, L^c is a substituted or unsubstituted lysine group.

According to one example of the disclosure, R is $(L^a)_3-L^b-(L^c)_c$ with $c = 1$ and $(L^a)_3-L^b$ is

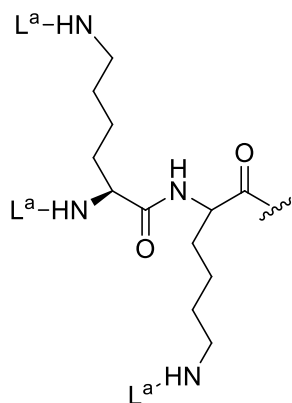


L^c is preferably an amino-alkyl group or an amino acid, such as a substituted or unsubstituted lysine group, in particular L^c is e.g. selected from the group consisting of



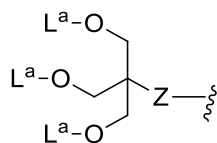
with the amino group being attached to the carbonyl group of L^b thereby forming an amide bond. Preferred residues R according to this example are depicted in Fig. 9A1, 9A2; 9C1, 9C2, 9D1, 9D2. Thus, according to one example of the disclosure, R is selected from the group consisting of the residues depicted in Fig. 9A1, 9A2; 9C1, 9C2, 9D1 and 9D2.

According to a further example of the disclosure, R has the structure $(L^a)_3-L^b-(L^c)_c$ with c being 0, and wherein $(L^a)_3-L^b$ is



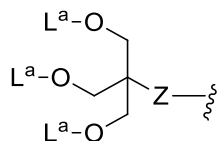
Preferred residues R according to this example of the disclosure are depicted in Fig. 9B1 and 9B2.

According to a further example of the disclosure, R has the structure $(L^a)_3-L^b-(L^c)_c$ with $(L^a)_3-L^b$ being

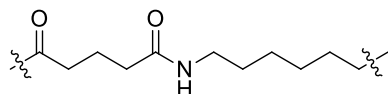


and with Z being O. In this case, c is preferably 1 and L^c is preferably an alkyl group, more preferably a C3 to C6 alkyl group, more preferably a propyl group, most preferably a n-propyl group. Preferred residues R according to this example are depicted in Fig. 9E1, 9F1, 9G1 and 9H1. Thus, according to one example of the disclosure, R is selected from the group consisting of the residues depicted in Fig. 9E1, 9F1, 9G1 and 9H1

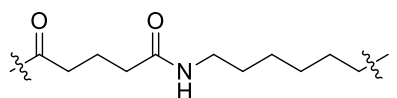
According to a further example of the disclosure, R has the structure $(L^a)_3-L^b-(L^c)_c$ with $(L^a)_3-L^b$ being



and with Z being NH. In this case c is preferably 1 and L^c is preferably an alkyl group, a namino acid comprising group or a group having the following structure:

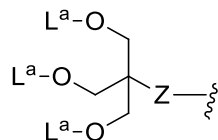


In particular, in this case L^c is



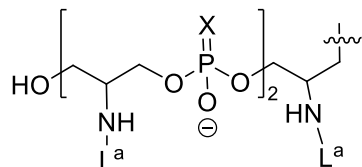
A preferred residue R according to this example of the disclosure is depicted in Fig. 9J1.

According to a further example of the disclosure, R has the structure $(L^a)_3-L^b-(L^c)_c$ with $(L^a)_3-L^b$ being



and with Z being NH and c being 0. A preferred residue R according to this example of the disclosure is depicted in Fig. 9I1.

According to one example of the disclosure, R is $(L^a)_3-L^b-(L^c)_c$ with $c = 0$ and wherein $(L^a)_3-L^b$ is



Preferred residues R according to this example of the disclosure are depicted in Fig. 9L1 and 9L2.

Thus, R is preferably selected from the residues depicted in Fig. 9A1, 9A2; 9C1, 9C2, 9D1, 9D2, 9E1, 9F1, 9G1, 9H1, 9I1, 9J1, 9L1 9L2, and mixtures thereof, such as stereoisomeric mixtures of 9A1 and 9A2; of 9C1 and 9C2 or of 9D1 and 9D2, more preferably R is selected from the residues depicted in 9D1, 9D2 and a mixture thereof, more preferably R is a mixture of the residues depicted in 9D1 and 9D2, such as a mixture having a molar ratio of 9D1 to 9D2 in the range of from 10: 90 to 90:10, such as in the range of from 30:70 to 70:30, such as in the range of from 45:55 to 55:45 .

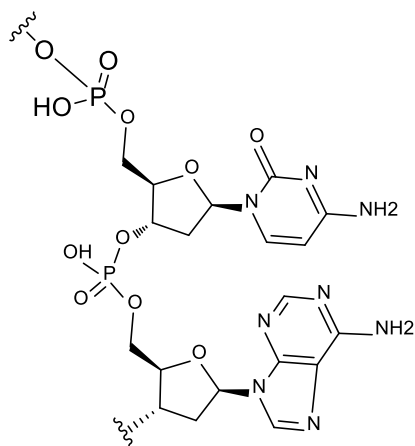
Thus, compound (I) is preferably selected from the compounds depicted in Fig. 10A1, 10A2; 10C1, 10C2, 10D1, 10D2, 10E1, 10F1, 10G1, 10H1, 10I1, 10J1, 10L1, 10L2 and mixtures thereof, such as stereoisomeric mixtures of 10A1 and 10A2; of 10C1 and 10C2 or of 10D1 and 10D2, depicted in 10D1, 10D2, and mixtures thereof, more preferably compound (I) is a mixture of the compounds depicted in 10D1 and 10D2, such as a mixture having a molar ratio of 10D1 to 10 D2 in the range of from 10: 90 to 90:10, such as in the range of from 30:70 to 70:30, such as in the range of from 45:55 to 55:45 .

The linker L

In the above formula, L is a linker as defined herein, preferably L is a linker comprising or consisting of 2-10 nucleosides, such as 2-5 nucleosides, such as 2 nucleosides, wherein optionally the nucleosides are phosphodiester linked nucleosides.

As the linker L comprises between 1 and 10 linked nucleosides, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 linked nucleosides, such as between 2 and 6 linked nucleosides, such as between 2 and 5 linked nucleosides, such as between 2 and 4 linked nucleosides. In some examples, the linker comprises two linked nucleotides. Thus, the nucleosides may be DNA nucleosides. Typically, the nucleosides are linked via phosphodiester internucleoside linkages. Moreover, the linker L may be linked to the antisense compound via a phosphodiester internucleoside linkage. Further, the linker L is linked to conjugate moiety R via a suitable function group, such as eg, via an amide, an amine, an ether, an ester, a phosphodiester (-O-P(=O)(-OH)-O-) or thiophosphodiester (-O-P(=S)(-OH)-O-) linkage. It is to be understood that L may optionally additionally comprise alkyl groups or alkyl-oxy-alkyl groups between the nucleosides and the functional group linking L to R. In this case, the nucleosides are preferably linked via a phosphodiester bond to the alkyl groups or alkyl-oxy-alkyl group which in turn is linked to R via a suitable function group, such as eg, via an amide, an amine, an ether, an ester, a phosphodiester (-O-P(=O)(-OH)-O-) or thiophosphodiester (-O-P(=S)(-OH)-O-) bond

According to a preferred example L is

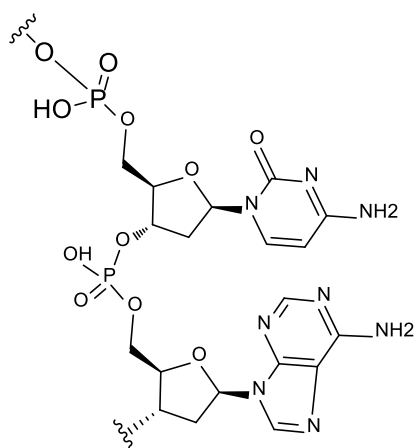


The antisense (A) oligonucleotide residue

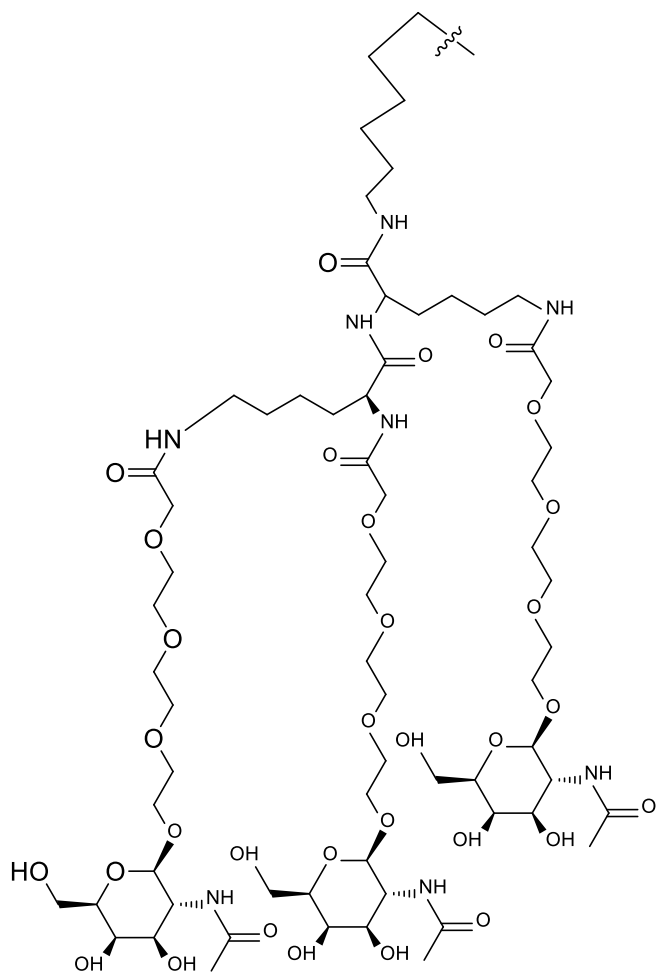
A is an antisense oligonucleotide residue according to the present disclosure, such an antisense oligonucleotide shown in Table 6, being attached via its 5'prime end to R via $-(L)_n-(O-P(=O)(-OH)-)_p$. Preferably, A is an antisense oligonucleotide residue selected from the residues depicted in Fig. 1A, 2A, 3A, 4A, 5A, 6A, 7A and 8A or depicted in Fig. 1A, 2A 3A, 4A, 5A, 6A, 7A, 8A and 8.1A.

According to a further example of the disclosure, A is the antisense oligonucleotide residue depicted in Fig. 8.1A.

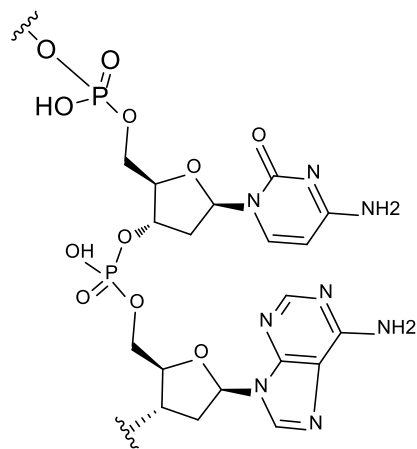
Thus, compound (I) is preferably selected from the compounds depicted in Fig. 10A1, 10A2; 10C1, 10C2, 10D1, 10D2, 10E1, 10F1, 10G1, 10H1, 10I1, 10J1, 10L1 10L2, and mixtures thereof, such as stereoismeric mixtures of 10A1 and 10A2; of 10C1 and 10C2 or of 10D1 and 10D2, more preferably compound (I) is selected from the compounds depicted in 10D1 and 10D2, and a mixture thereof, more preferably compound (I) is a mixture of compound 10D1 and 10D2, preferably with A being selected from the antisense oligonucleotide shown in Table 6, preferably with A being an antisense oligonucleotide residue selected from the residues depicted in Fig. 1A, 2A 3A, 4A, 5A, 6A, 7A and 8A. and with L is a linker comprising or consisting of 2-10 nucleosides, such as 2-5 nucleosides, such as 2 nucleosides, wherein optionally the nucleosides are phosphodiester linked nucleosides, more preferably wherein L is



In a further example, R is a residue having the structure (I)



L is a linker as defined herein, preferably L is a linker comprising or consisting of 2-10 nucleosides, such as 2-5 nucleosides, such as 2 nucleosides, wherein optionally the nucleosides are phosphodiester linked nucleosides, more preferably L is



and

A is an antisense oligonucleotide according to the present disclosure, such as an antisense oligonucleotide shown in Table 6.

According to one example of the disclosure, A is an antisense oligonucleotide residue selected from the residues depicted in Fig. 1A, 2A 3A, 4A, 5A, 6A, 7A and 8A or depicted in Fig. 1A, 2A 3A, 4A, 5A, 6A, 7A 8A, and 8.1A.

According to a further example of the disclosure, A is the antisense oligonucleotide residue depicted in Fig. 8.1A.

The disclosure provides pharmaceutical compositions comprising the antisense oligonucleotide of the disclosure or the conjugate of the present disclosure, and a pharmaceutically acceptable diluents, carriers, salts and/or adjuvants.

The disclosure provides for a pharmaceutically acceptable salt of the antisense oligonucleotide of the disclosure or the conjugate thereof. In some examples, the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a potassium salt and an ammonium salt.

The disclosure provides for a pharmaceutical solution of the antisense oligonucleotide of the disclosure or the conjugate thereof, wherein the pharmaceutical solution comprises the antisense oligonucleotide of the disclosure or the conjugate thereof and a pharmaceutically acceptable solvent, such as phosphate buffered saline. Alternative, the solvent is water or a sodium chloride solution.

The disclosure provides for the antisense oligonucleotide of the disclosure or the conjugate thereof in solid powdered form, such as in the form of a lyophilized powder.

The disclosure provides for a pharmaceutically acceptable salt of the antisense oligonucleotide of the disclosure or the conjugate thereof.

The disclosure provides for a pharmaceutically acceptable salt of the antisense oligonucleotide according to the disclosure, or the conjugate of the disclosure, wherein the pharmaceutically acceptable salt is a sodium salt. Alternatively, the salt is a potassium salt.

The disclosure provides for a pharmaceutical composition comprising the antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the salt of the disclosure and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the antisense oligonucleotide of the disclosure, the conjugate of the disclosure, or the pharmaceutically acceptable salt of the disclosure, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

The disclosure provides for a method for inhibiting FUBP1 expression in a target cell, which is expressing FUBP1, said method comprising administering an antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the salt of the disclosure, or the composition of the disclosure in an effective amount to said cell. The method may be an *in vivo* method or an *in vitro* method.

In another aspect, the present disclosure provides an *in vitro* method for modulating FUBP1 expression in a target cell which is expressing FUBP1, said method comprising administering the antisense oligonucleotide of the disclosure, the conjugate of the disclosure, the pharmaceutically acceptable salt of the disclosure, or the pharmaceutical composition of the disclosure in an effective amount to said cell.

The disclosure provides for a method for treating and/or preventing an HBV infection in a subject such as a human, comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the salt of the disclosure, or the composition of the disclosure, such as to treat and/or prevent a disease selected from the group consisting of HBV infection, such as chronic HBV infection and proliferative diseases such as cancer, in particular hepatocellular carcinoma.

The antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the salt of the disclosure, or the pharmaceutical composition of the disclosure, is for the use in the treatment and/or prevention of an HBV infection, such as a chronic HBV infection.

The disclosure provides the antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the pharmaceutical composition, or the salt of the disclosure for use in medicine. In another aspect, the present disclosure provides the antisense oligonucleotide of the disclosure, the conjugate of the disclosure, the pharmaceutically acceptable salt of the disclosure, or the pharmaceutical composition of the disclosure for use in medicine. In another aspect, the present disclosure provides the antisense oligonucleotide of the disclosure, the conjugate of the disclosure, the pharmaceutically acceptable salt of the disclosure, or the pharmaceutical composition of the disclosure for use in the treatment or prevention of hepatitis B virus (HBV) infection and/or cancer. The disclosure provides methods for inhibition of FUBP1 expression in a target cell, which is expressing FUBP1, by administering an antisense oligonucleotide of the disclosure, or conjugate of the disclosure in an effective amount to said cell. The disclosure

provides methods for *in vivo* or *in vitro* method for inhibition of FUBP1 expression in a target cell, which is expressing FUBP1, by administering an antisense oligonucleotide, or the conjugate of the disclosure in an effective amount to said cell. The cell may for example be a human cell, such as a liver cell, such as a hepatocyte. In one example, the cell is a hepatocellular carcinoma cell.

The disclosure provides methods for reducing cccDNA in an HBV infected cell, by administering an antisense oligonucleotide of the disclosure, or conjugate of the disclosure in an effective amount to said cell.

The disclosure provides methods for *in vivo* or *in vitro* method for reducing cccDNA in an HBV infected cell, by administering an antisense oligonucleotide of the disclosure, or the conjugate of the disclosure in an effective amount to said cell.

The disclosure provides methods for treating and/or preventing a disease selected from the group consisting of HBV infection, such as chronic HBV infection and proliferative diseases such as cancer, in particular hepatocellular carcinoma.

The disclosure provides the antisense oligonucleotide, or the conjugate of the disclosure, or the pharmaceutical composition of the disclosure, for use in the manufacture of a medicament for the treatment and/or prevention of a disease selected from the group consisting of HBV infection, such as chronic HBV infection and proliferative diseases such as cancer, in particular hepatocellular carcinoma.

In another aspect, the present disclosure provides use of the antisense oligonucleotide of the disclosure, the conjugate of the disclosure, the pharmaceutically acceptable salt of the disclosure, or the pharmaceutical composition of the disclosure, in the preparation of a medicament for treatment or prevention of a hepatitis B virus (HBV) infection and/or cancer.

The disclosure provides the antisense oligonucleotide, or the conjugate of the disclosure, or the pharmaceutical composition of the disclosure, for use in the manufacture of an antiviral drug.

The disclosure provides the antisense oligonucleotide, or the conjugate of the disclosure, or the pharmaceutical composition of the disclosure, for use in the manufacture of an antitumor drug.

The disclosure provides for the antisense oligonucleotide of the disclosure, or the conjugate of the disclosure, or the pharmaceutical composition of the disclosure, for use in the treatment and/or prevention of a disease selected from the group consisting of HBV infection, such as chronic HBV infection and proliferative diseases such as cancer, in particular hepatocellular carcinoma.

CLAIMS

1. An antisense oligonucleotide selected from the group of antisense oligonucleotides consisting of
CTtAtgcttttatGgTT (SEQ ID NO: 7),
AcCAAttttcatttCtAC (SEQ ID NO: 18),
CTTatGcttttatgGT (SEQ ID NO: 6),
CTTaTgcttttatgGT (SEQ ID NO: 6),
CTtATgcttttatgGTT (SEQ ID NO: 7),
CTtAtgcttttatgGTT (SEQ ID NO: 7),
CTtAtgcttttatGGTT (SEQ ID NO: 7),
GcttTttatggtTtCAC (SEQ ID NO: 8), and
TATgcTtttatggtTTC (SEQ ID NO: 9),
wherein capital letters are beta-D-oxy LNA nucleosides, lowercase letters are DNA nucleosides,
all LNA C are 5-methyl cytosine, and all internucleoside linkages are phosphorothioate
internucleoside linkages.
2. A conjugate comprising the antisense oligonucleotide of claim 1, and at least one conjugate
moiety covalently attached to said antisense oligonucleotide.
3. The conjugate of claim 2, wherein the at least one conjugate moiety is capable of binding to the
asialoglycoprotein receptor.
4. The conjugate of claims 2 or 3, wherein the conjugate moiety is selected from one of the trivalent
GalNAc moieties in FIG. 9.
5. The conjugate of claim 4, wherein the conjugate moiety is the trivalent GalNAc moiety in Figure
9D1, or 9D2 or a mixture thereof.
6. The conjugate of any one of claims 1 to 5, comprising a linker positioned between the antisense
oligonucleotide and the conjugate moiety.
7. The conjugate of claim 6, wherein the linker comprises or consists of 2 to 5 consecutive
phosphodiester linked nucleosides.

8. A conjugate selected from the group of conjugates shown in Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8 and Fig. 8.1.
9. A pharmaceutically acceptable salt of the oligonucleotide of claim 1, or the conjugate according to any one of claims 2 to 8.
10. A pharmaceutical composition comprising the antisense oligonucleotide of claim 1, the conjugate of any one of claims 2 to 8, or the pharmaceutically acceptable salt of claim 9, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
11. An *in vitro* method for modulating FUBP1 expression in a target cell which is expressing FUBP1, said method comprising administering the antisense oligonucleotide of claim 1, the conjugate of any one of claims 2 to 8, the pharmaceutically acceptable salt of claim 9, or the pharmaceutical composition of claim 10 in an effective amount to said cell.
12. The antisense oligonucleotide of claim 1, the conjugate of any one of claims 2 to 8, the pharmaceutically acceptable salt of claim 9, or the pharmaceutical composition of claim 10 for use in medicine.
13. The antisense oligonucleotide of claim 1, the conjugate of any one of claims 2 to 8, the pharmaceutically acceptable salt of claim 9, or the pharmaceutical composition of claim 10 for use in the treatment or prevention of hepatitis B virus (HBV) infection and/or cancer.
14. Use of the antisense oligonucleotide of claim 1, the conjugate of any one of claims 2 to 8, the pharmaceutically acceptable salt of claim 9, or the pharmaceutical composition of claim 10, in the preparation of a medicament for treatment or prevention of a hepatitis B virus (HBV) infection and/or cancer.
15. The antisense oligonucleotide, conjugate, pharmaceutical composition, or the pharmaceutically acceptable salt for use of claim 13, or the use of claim 14, wherein the disease is hepatitis B virus (HBV) infection, such as chronic HBV infection.
16. The antisense oligonucleotide, conjugate, pharmaceutical composition, or the pharmaceutically acceptable salt for use of claim 13, or the use of claim 14, wherein the disease is cancer, such as hepatocellular carcinoma.