(LdT), and adefovir are also used, but for nucleoside/nucleotide therapies in general, the emergence of resistance limits therapeutic efficacy.

US 8,598,334 and WO 2012/145697 mention the use of antisense oligonucleotides to target HBV.

The control of viral infection needs a tight surveillance of the host innate immune system which could respond within minutes to hours after infection to impact on the initial growth of the virus and limit the development of a chronic and persistent infection. Despite the available current treatments based on IFN and nucleos(t)ide analogues, the Hepatitis B virus (HBV) infection remains a major health problem worldwide which concerns an estimated 350 million chronic carriers who have a higher risk of liver cirrhosis and hepatocellular carcinoma.

There is a need for new anti-viral therapies, in particular anti-HBV therapies. There is also a need to have a therapeutic strategy that enables one to target different types of HBV genotypes.

SUMMARY

The present disclosure relates to oligomer conjugates, uses thereof, methods using same, that are suitable for use in medicine, such as the treatment of a viral disorder.

In particular, the present disclosure provides an oligomer or an oligomer conjugate – that is suitable for use in the treatment of a viral disorder - wherein said oligomer or said oligomer of the oligomer conjugate is capable of modulating a target sequence of Hepatitis B Virus (HBV), preferably HBx or HBsAg of HBV. In certain embodiments a carrier component is conjugated to the oligomer.

In one aspect, the present disclosure provides an oligomer conjugate comprising (a) at least one first oligomer of 10 to 20 nucleotides in length and is 100% complementary to a sequence from positions 1530 to 1598 of SEQ ID NO:3; and (b) a carrier component comprising an asialoglycoprotein receptor (ASGP-R) targeting moiety or a cholesterol conjugate moiety.

The disclosure provides an oligomer or an oligomer conjugate as herein defined wherein the oligomer or oligomer component of the oligomer conjugate comprises at least 6, preferably at least 7, preferably at least 8, preferably at least 9, preferably at least 10 units, preferably at least 11 units, preferably at least 12 units, preferably at least 13 units, preferably at least 14 units, preferably at least 15 units, preferably at least 16 units that are at least 80% identical, preferably at least 85% identical, preferably at least 90% identical, preferably at least 91% identical, preferably at least 92% identical, preferably at least 93% identical, preferably at least 94% identical, preferably at least 95% identical, preferably at least 96% identical, preferably at least 97% identical, preferably at least 98% identical, preferably at least 99% identical, preferably identical to a region corresponding to a HBV HBx gene or HBsAg gene or to

the reverse complement of a target region of a nucleic acid which encodes a HBV HBx or HBV HBsAg.

The disclosure provides an oligomer or an oligomer conjugate as herein defined wherein the oligomer or oligomer component of the oligomer conjugate comprises at least 6, preferably at least 7, preferably at least 8, preferably at least 9, preferably at least 10 units that are identical

to a region corresponding to a HBV HBx gene or HBsAg gene or to the reverse complement of a target region of a nucleic acid which encodes a HBV HBx or HBV HBsAg.

For certain embodiments, the disclosure provides an oligomer or an oligomer conjugate as herein defined wherein the oligomer or oligomer component of the oligomer conjugate comprises less than 20 units, such as less than 19 units, such as less than 18 units, such as less than 17 units, such as 16 or less units.

For certain embodiments, the disclosure provides an oligomer or an oligomer conjugate as herein defined wherein the oligomer or oligomer component of the oligomer conjugate comprises 15 units or 16 units.

The disclosure provides a conjugate comprising the oligomer according to the disclosure, and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said oligomer.

The disclosure provides a pharmaceutical composition comprising the oligomer or the conjugate according to the disclosure, and a pharmaceutically acceptable diluent (such as water or saline), carrier, salt or adjuvant. In another aspect, the present disclosure provides for a pharmaceutical composition comprising an oligomer conjugate according to the disclosure; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

The disclosure provides the oligomer or the conjugate according to the disclosure for use as a medicament, such as for the treatment of a viral disorder. In another aspect, the present disclosure provides for the oligomer conjugate according to the disclosure or the pharmaceutical composition according to the disclosure for use in the treatment of a viral disorder in the liver, wherein said oligomer conjugate is to be administered subcutaneously.

The disclosure provides the use of an oligomer or the conjugate according to the disclosure for the manufacture of a medicament for the treatment of a viral disorder. In another aspect, the present disclosure provides for use of the oligomer conjugate according to the disclosure or the pharmaceutical composition according to the disclosure in the manufacture of a medicament for the treatment of a viral disorder in the liver, wherein said oligomer conjugate is to be administered subcutaneously.

The disclosure provides a method of treating a viral disorder, said method comprising administering an effective amount of, an oligomer, an oligomer conjugate or a pharmaceutical composition according to the disclosure, to an animal suffering from, or likely to suffer from a viral disorder (such as an animal suffering from or susceptible to the disease or disorder).

The disclosure provides a method of treating a viral disorder, said method comprising administering an effective amount of, an oligomer, an oligomer conjugate or a pharmaceutical

composition according to the disclosure, to a non-human animal suffering from, or likely to suffer from a viral disorder (such as a non-human animal suffering from or susceptible to the disease or disorder).

The disclosure provides a method of treating a viral disorder, said method comprising administering an effective amount of, an oligomer, an oligomer conjugate or a pharmaceutical composition according to the disclosure, to a human patient suffering from, or likely to suffer from a viral disorder (such as a human patient suffering from or susceptible to the disease or disorder).

Also disclosed are methods of treating an animal (a non-human animal or a human) suspected of having, or susceptible to, a disease or condition, associated with expression, or over-expression of HBx or HBsAg by administering to the non-human animal or human a therapeutically or prophylactically effective amount of one or more of the oligomers, conjugates or pharmaceutical compositions of the disclosure. Further, methods of using oligomers for the inhibition of expression of HBx or HBsAg, and for treatment of diseases associated with activity of HBx or HBsAg are provided.

The disclosure further provides a pharmaceutical system comprising a pharmaceutical composition according to the disclosure and an additional pharmaceutical entity/therapeutic entity. The additional pharmaceutical entity may be an oligomer or oligomer conjugate according to the present disclosure. The additional pharmaceutical entity may be an oligomer or oligomer conjugate capable of modulating a target sequence in HBV which is not within HBx or HBsAg. For example, at least one oligomer or oligomer conjugate may be capable of modulating a target sequence within the gene or mRNA for HBV HBsAg, HBeAg, or DNA polymerase. In another aspect, the present disclosure provides use of the oligomer conjugate according to the present disclosure or the pharmaceutical composition according to the present disclosure for modulating a target sequence of Hepatitis B Virus (HBV).

In one embodiment, a plurality of oligomers or conjugates according to the disclosure are administered to a subject in need of treatment. The oligomers or conjugates may administered with additional pharmaceutical/therapeutic agents.

In one embodiment, the disease or disorder or condition is associated with overexpression of HBx or HBsAg.

The disclosure provides for methods for modulating the expression of HBx or HBsAg in a cell or a tissue, the method comprising the step of contacting the cell or tissue, *in vitro* or *in vivo*, with an effective amount of one or more oligomers, conjugates, or pharmaceutical compositions thereof, to effect modulation of expression of HBx or HBsAg.

The disclosure provides for methods of inhibiting (*e.g.,* by down-regulating) the expression of HBx in a cell or a tissue, the method comprising the step of contacting the cell or tissue, *in vitro* or *in vivo*, with an effective amount of one or more oligomers, conjugates, or pharmaceutical compositions thereof, to effect down-regulation of expression of HBx or HBsAg.

The disclosure provides for a method for the inhibition of HBx or HBsAg in a cell which is expressing HBx or HBsAg, said method comprising administering an oligomer, or a conjugate according to the invention to said cell so as to affect the inhibition of HBx or HBsAg in said cell.

Further provided are methods of down-regulating the expression of HBx or HBsAg in cells or tissues comprising contacting said cells or tissues, *in vitro* or *in vivo*, with an effective amount of one or more of the oligomers, oligomer conjugates or compositions of the disclosure.

Features of the present disclosure are now provided.

The present disclosure provides an oligomer conjugate for use in the treatment of a viral disorder, wherein said oligomer conjugate comprises:

a) at least one first oligomer region capable of modulating a target sequence of Hepatitis B Virus (HBV), preferably HBx or HBsAg of HBV, to treat said viral disorder; and

b) a carrier component. Preferably, for delivering said first oligomer to the liver.

The present disclosure provides an oligomer conjugate suitable for the treatment of a viral disorder, wherein said oligomer conjugate comprises:

a) at least one first oligomer region capable of modulating a target sequence of Hepatitis B Virus (HBV), preferably HBx or HBsAg of HBV, to treat said viral disorder; and

b) a carrier component. Preferably, for delivering said first oligomer to the liver.

The present disclosure provides a composition suitable for the treatment of a viral disorder, wherein said composition comprises an oligomer conjugate and at least one additional different oligonucleotide; wherein said oligomer conjugate comprises:

a) at least one first oligomer region capable of modulating a target sequence of Hepatitis B Virus (HBV), preferably HBx or HBsAg of HBV, to treat said viral disorder; and

b) a carrier component. Preferably, for delivering said first oligomer to the liver.

The present disclosure provides an oligomer or the oligomer component of the oligomer conjugate that hybridize to a target sequence selected from the group consisting of any one or more of positions: 1530 to 1598; 1264-1278 and 670 to 706 of SEQ ID NO: 3.

The present disclosure provides an oligomer based on a core motif selected from the group consisting of any one or more of:

GCGTAAAGAGAGG (SEQ ID NO: 13);
GCGTAAAGAGAGGT (SEQ ID NO: 11);
AGCGAAGTGCACACG (SEQ ID NO: 20);
AGGTGAAGCGAAGTG (SEQ ID NO: 26);
AGCGAAGTGCACACGG (SEQ ID NO 18);
CGAACCACTGAACA (SEQ ID NO: 7);
GAACCACTGAACAAA (SEQ ID NO 4);
CGAACCACTGAACAAA (SEQ ID NO 5);
CGAACCACTGAACAA (SEQ ID NO 6);
CGAACCACTGAAC (SEQ ID NO 8)
CCGCAGTATGGATCG (SEQ ID NO 9)
CGCAGTATGGATC (SEQ ID NO: 10);
CGCGTAAAGAGAGGT (SEQ ID NO 12);

AGAAGGCACAGACGG (SEQ ID NO 14);
GAGAAGGCACAGACGG (SEQ ID NO 15)
GAAGTGCACACGG (SEQ ID NO 16);
GCGAAGTGCACACGG (SEQ ID NO 17);
CGAAGTGCACACG (SEQ ID NO 19);
AGGTGAAGCGAAGT (SEQ ID NO 27); and
TAGTAAACTGAGCCA (SEQ ID NO: 834),

which is capable of modulating a target sequence in HBx or HBsAg of HBV to treat a viral disorder.

The present disclosure provides a composition suitable for the treatment of a viral disorder, wherein said composition comprises an oligomer and at least one additional different oligonucleotide; wherein said oligomer comprises at least one first oligomer region capable of modulating a target sequence of Hepatitis B Virus (HBV), preferably HBx or HBsAg of HBV, to treat said viral disorder.

The present disclosure provides a method for treating a viral disorder, said method comprising administering to a subject in need of treatment an effective amount of an oligomer conjugate according to the disclosure.

The present disclosure provides a method for treating a viral disorder, said method comprising administering to a subject in need of treatment an effective amount of a composition according to the disclosure.

The present disclosure provides a method for treating a viral disorder, said method comprising administering to a subject in need of treatment an effective amount of an oligomer according to the disclosure.

The present disclosure provides a pharmaceutical composition comprising an oligomer conjugate according to the disclosure; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

The present disclosure provides a pharmaceutical composition comprising a composition according to the disclosure; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

The present disclosure provides a pharmaceutical composition comprising an oligomer according to the disclosure; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

The present disclosure provides a pharmaceutical system comprising a pharmaceutical composition according to the disclosure and an additional pharmaceutical entity.

The present disclosure provides a motif selected from the group consisting of any one or more of:

GCGTAAAGAGAGG (SEQ ID NO: 13);
GCGTAAAGAGAGGT (SEQ ID NO: 11);
AGCGAAGTGCACACG (SEQ ID NO: 20);
AGGTGAAGCGAAGTG (SEQ ID NO: 26);
AGCGAAGTGCACACGG (SEQ ID NO 18);

for constructing an oligomer conjugate according to the disclosure.

The present disclosure provides a motif selected from the group consisting of any one or more of:NO: 13) GCGTAAAGAGAGGT (SEQ ID NO: 11) and CGCGTAAAGAGAGGT (SEQ ID NO 12) for constructing a composition according to the disclosure.

The present disclosure provides a motif selected from the group consisting of any one or more of:AGCGAAGTGCACACG (SEQ ID NO: 20); AGGTGAAGCGAAGTG (SEQ ID NO: 26); AGCGAAGTGCACACGG (SEQ ID NO 18); GAAGTGCACACGG (SEQ ID NO 16); GCGAAGTGCACACGG (SEQ ID NO 17); CGAAGTGCACACG (SEQ ID NO 19) and AGGTGAAGCGAAGT (SEQ ID NO 27) for constructing an oligomer according to the disclosure.

The present disclosure provides a method of manufacturing an oligomer conjugate according to the disclosure, comprising conjugating one or more oligomers according to the disclosure with a carrier component according to the disclosure.

The present disclosure provides a method of manufacturing a composition according to the disclosure, comprising admixing an oligomer conjugate according to the disclosure with a pharmaceutically acceptable diluents, carriers, salts or adjuvants.

BRIEF DESCRIPTION OF FIGURES

Figure 1: Presents a scheme for a LNA oligomer GalNAc conjugation step.

Figure 2: Presents examples of a cholesterol or mono-GalNAc carrier components including a C6 linker moiety (region E) which is used to link the carrier component to the oligomer (region A or to a physiologically labile linker region PL, such as a PO linker). The wavy line represents the covalent link to the oligomer or region PL.

Figure 3: Presents examples of tri-GalNAc carrier components. Conjuagtes 1 – 4 illustrate 4 suitable GalNAc carrier components, and conjugates 1a – 4a refer to the same carrier components with an additional C6 linker moiety (region E) which is used to link the carrier

component to the oligomer (region A or to a physiologically labile linker, region PL, such as a PO linker). The wavy line represents the covalent link to the oligomer or region PL.

Figure 4: Presents examples of oligomer conjugates with trivalent GalNAc carrier components.

CLAIMS

1. An oligomer conjugate comprising:
   a) at least one first oligomer of 10 to 20 nucleotides in length and is 100% complementary to a sequence from positions 1530 to 1598 of SEQ ID NO:3; and
   b) a carrier component comprising an asialoglycoprotein receptor (ASGP-R) targeting moiety or a cholesterol conjugate moiety.

2. The oligomer conjugate of claim 1, wherein the first oligomer is 100% complementary to a sequence from positions 1530 to 1544 or 1551-1566 of SEQ ID NO:3.

3. The oligomer conjugate of claim 1 or 2, wherein said first oligomer comprises a 2'-deoxyribonucleotide gap region flanked on each side by a wing, wherein each wing independently comprises one or more LNA units.

4. The oligomer conjugate of any one of claims 1 to **Error! Reference source not found.**, wherein said carrier component is a GalNAc cluster comprising two to four terminal GalNAc moieties, a PEG spacer linking each GalNAc moiety to a branch point group.

5. The oligomer conjugate of claim 4, wherein the GalNAc cluster is a trivalent GalNAc selected from the group consisting of Conj 1, 2, 1a or 2a.

6. The oligomer conjugate of any one of claims 1 to 5, wherein said carrier component is GalNAc2 (Figure 3).

7. The oligomer conjugate of any one of claims 1 to 6, wherein the carrier component is linked to the first oligomer by way of a PO linker comprising two, three, four or five phosphodiester linked DNA or RNA nucleosides.

8. The oligomer conjugate of claim 7, wherein the PO linker consists of the dinucleotide sequence CA.

9. The oligomer conjugate of any one of claims 1 to 8, wherein said first oligomer comprises a sequence selected from the group consisting of any one or more of:

GCGTAAAGAGAGG (SEQ ID NO: 13);

GCGTAAAGAGAGGT (SEQ ID NO: 11);

CGCGTAAAGAGAGGT (SEQ ID NO 12);

AGAAGGCACAGACGG (SEQ ID NO 14);

GAGAAGGCACAGACGG (SEQ ID NO 15);

AGCGAAGTGCACACGG (SEQ ID NO 18);

GAAGTGCACACGG (SEQ ID NO 16);

GCGAAGTGCACACGG (SEQ ID NO 17);

AGCGAAGTGCACACG (SEQ ID NO: 20);

CGAAGTGCACACG (SEQ ID NO 19);

AGGTGAAGCGAAGTG (SEQ ID NO: 26); and

AGGTGAAGCGAAGT (SEQ ID NO 27).

10. The oligomer conjugate of any one of claims 1 to 9, wherein said first oligomer comprises a sequence selected from the group consisting of:

GCGTAAAGAGAGG (SEQ ID NO: 13);

GCGTAAAGAGAGGT (SEQ ID NO: 11);

CGCGTAAAGAGAGGT (SEQ ID NO 12);

AGAAGGCACAGACGG (SEQ ID NO 14); and

GAGAAGGCACAGACGG (SEQ ID NO 15).

11. The oligomer conjugate of any one of claims 1 to 9, wherein said first oligomer consists of a sequence selected from the group consisting of:

GCGtaaagagaGG(SEQ ID NO: 303);

GCGtaaagagaGGT(SEQ ID NO: 301);

GCGtaaagagAGG (SEQ ID NO: 618);
CGCgtaaagagaGGT (SEQ ID NO: 302);
AGAaggcacagaCGG (SEQ ID NO: 304);
GAGaaggcacagaCGG (SEQ ID NO: 305);
GAAgtgcacacGG (SEQ ID NO: 306);
GCGaagtgcacaCGG (SEQ ID NO: 307);
GAAgtgcacaCGG (SEQ ID NO: 628);
AGCgaagtgcacaCGG (SEQ ID NO: 308);
CGAagtgcacaCG (SEQ ID NO: 309);
AGCgaagtgcacACG (SEQ ID NO: 310);
AGGtgaagcgaagTGC (SEQ ID NO: 315);
AGGtgaagcgaaGTG (SEQ ID NO: 316);
AGGtgaagcgaAGT (SEQ ID NO: 317); and
AGgtgaagcgaAGTG (SEQ ID NO: 668),

wherein uppercase letters denote LNA units and lower case letters denote DNA units.

12. The oligomer conjugate of any one of claims 1 to 10, wherein said first oligomer consists of a sequence selected from the group consisting of:

GCGtaaagagaGG (SEQ ID NO: 303)

GCGtaaagagaGGT(SEQ ID NO: 301);

GCGtaaagagAGG (SEQ ID NO: 618);

CGCgtaaagagaGGT (SEQ ID NO: 302);

AGAaggcacagaCGG (SEQ ID NO: 304); and

GAGaaggcacagaCGG (SEQ ID NO: 305),

wherein uppercase letters denote LNA units and lower case letters denote DNA units.

13. The oligomer conjugate of any one of claims 1 to 12, selected from the group consisting of:

5'- GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$a$_S$**G$_S$G**-3' (SEQ ID NO: 815)

5'- GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$a$_S$**G$_S$G$_S$T**-3' (SEQ ID NO: 814)

5'-GN2-C6 ca**G$_S$** ^{m}**C$_S$**G$_S$t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$**A$_S$G$_S$G**-3' (SEQ ID NO: 825)

5'- GN2-C6 ca**A$_S$G$_S$** ^{m}**C$_S$**g$_S$a$_S$a$_S$g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$**A$_S$** ^{m}**C$_S$G**-3' (SEQ ID NO: 808)

5'-GN2-C6 ca**A$_S$G$_S$**g$_S$t$_S$g$_S$a$_S$a$_S$g$_S$ ^{m}c$_S$g$_S$a$_S$**A$_S$G$_S$T$_S$G**-3' (SEQ ID NO: 826)

5'- GN2-C6 ca**A$_S$G$_S$** ^{m}**C$_S$**g$_S$a$_S$a$_S$g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 807)

5'- GN2-C6 ca**G$_S$A$_S$A$_S$**c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$a$_S$c$_S$**A$_S$A$_S$A**-3' (SEQ ID NO: 799)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$a$_S$c$_S$**A$_S$A$_S$A**-3' (SEQ ID NO: 800)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$a$_S$ ^{m}**C$_S$A$_S$A**-3' (SEQ ID NO: 801)

5'- GN2-C6 ca ^{m}**C$_S$** ^{m}**C$_S$G$_S$**c$_S$a$_S$g$_S$t$_S$a$_S$t$_S$g$_S$g$_S$a$_S$**T$_S$** ^{m}**C$_S$G**-3' (SEQ ID NO: 802)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$** ^{m}**C$_S$**g$_S$t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$a$_S$**G$_S$G$_S$T**-3' (SEQ ID NO: 803)

5'- GN2-C6 ca**A$_S$G$_S$A$_S$**a$_S$g$_S$g$_S$c$_S$a$_S$c$_S$a$_S$g$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 804)

5'- GN2-C6 ca**G$_S$A$_S$G$_S$**a$_S$a$_S$g$_S$g$_S$c$_S$a$_S$c$_S$a$_S$g$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 805)

5'- GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**a$_S$a$_S$g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 806)

5'- GN2-C6 ca**A$_S$G$_S$G$_S$**t$_S$g$_S$a$_S$a$_S$g$_S$ ^{m}c$_S$g$_S$a$_S$a$_S$g$_S$**T$_S$G$_S$** ^{m}**C**-3' (SEQ ID NO: 809)

5'- GN2-C6 ca**A$_S$G$_S$G$_S$**t$_S$g$_S$a$_S$a$_S$g$_S$ ^{m}c$_S$g$_S$a$_S$a$_S$**G$_S$T$_S$G**-3' (SEQ ID NO: 810)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$**A$_S$** ^{m}**C$_S$A**-3' (SEQ ID NO: 811)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$**A$_S$** ^{m}**C**-3' (SEQ ID NO: 812)

5'- GN2-C6 ca ^{m}**C$_S$G$_S$** ^{m}**C$_S$**a$_S$g$_S$t$_S$a$_S$t$_S$g$_S$g$_S$a$_S$**T$_S$** ^{m}**C**-3' (SEQ ID NO: 813)

5'- GN2-C6 ca**G$_S$A$_S$A$_S$**g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$a$_S$ ^{m}c$_S$**G$_S$G**-3' (SEQ ID NO: 816)

5'-GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$a$_S$ ^{m}**C$_S$G**-3' (SEQ ID NO: 817)

5'-GN2-C6 ca**A$_S$G$_S$G$_S$**t$_S$g$_S$a$_S$a$_S$g$_S$ ^{m}c$_S$g$_S$a$_S$**A$_S$G$_S$T**-3' (SEQ ID NO: 818)

5'-GN2-C6 ca**G$_S$A$_S$A$_S$**c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$a$_S$ ^{m}**C$_S$A$_S$A$_S$A**-3' (SEQ ID NO: 819)

5'-GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$A$_S$**c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$a$_S$a$_S$c$_S$**A$_S$A$_S$A**-3' (SEQ ID NO: 820)

5'-GN2-C6 ca**G$_S$A$_S$A$_S$**g$_S$t$_S$g$_S$c$_S$a$_S$c$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 821)

5'-GN2-C6 ca**T$_S$A$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$c$_S$t$_S$g$_S$a$_S$g$_S$ ^{m}**C$_S$** ^{m}**C$_S$A$_S$**3' (SEQ ID NO: 822)

5'-GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$**A$_S$A$_S$** ^{m}**C**-3' (SEQ ID NO: 823), and

5'-GN2-C6 ca ^{m}**C$_S$G$_S$A$_S$**a$_S$c$_S$c$_S$a$_S$c$_S$t$_S$g$_S$**A$_S$A$_S$** ^{m}**C$_S$A**-3' (SEQ ID NO: 824),

wherein uppercase letters denote beta-D-oxy-LNA units; lowercase letters denote DNA units; the subscript "s" denotes a phosphorothioate linkage; superscript m denotes a a DNA or beta-D-oxy-LNA unit containing a 5-methylcytosine base; GN2-C6 denotes a GalNAc2 carrier component with a C6 linker.

14. The oligomer conjugate of any one of claims 1 to 13, selected from the group consisting of:

5'- GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$a$_S$**G$_S$G**-3' (SEQ ID NO: 815)

5'- GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$a$_S$**G$_S$G$_S$T**-3' (SEQ ID NO: 814)

5'-GN2-C6 ca**G$_S$** ^{m}**C$_S$G$_S$**t$_S$a$_S$a$_S$a$_S$g$_S$a$_S$g$_S$**A$_S$G$_S$G**-3' (SEQ ID NO: 825)

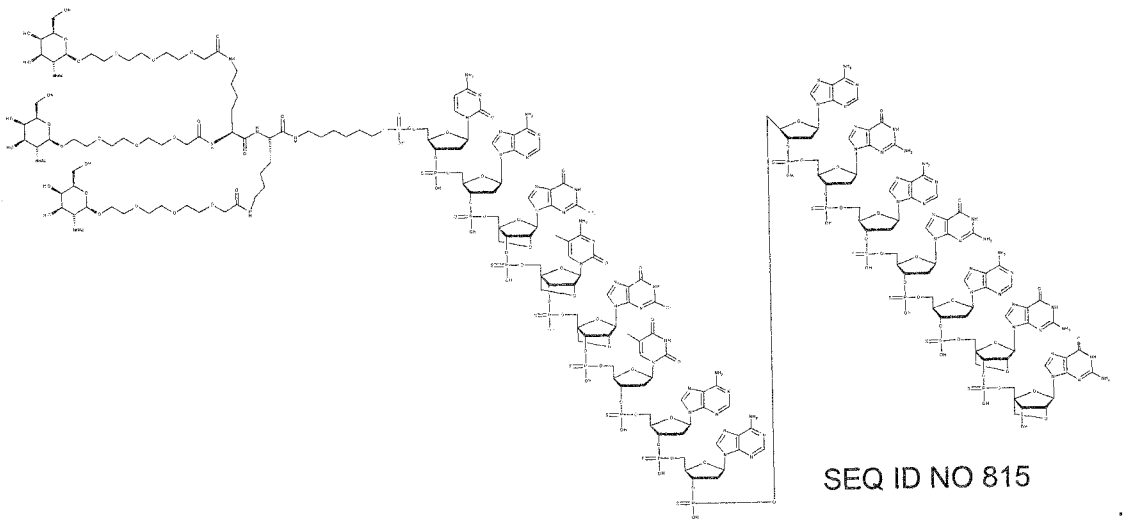
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5'- GN2-C6 ca**A$_S$G$_S$A$_S$**a$_S$g$_S$g$_S$c$_S$a$_S$c$_S$a$_S$g$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 804), and

5'- GN2-C6 ca**G$_S$A$_S$G$_S$**a$_S$a$_S$g$_S$g$_S$c$_S$a$_S$c$_S$a$_S$g$_S$a$_S$ ^{m}**C$_S$G$_S$G**-3' (SEQ ID NO: 805)

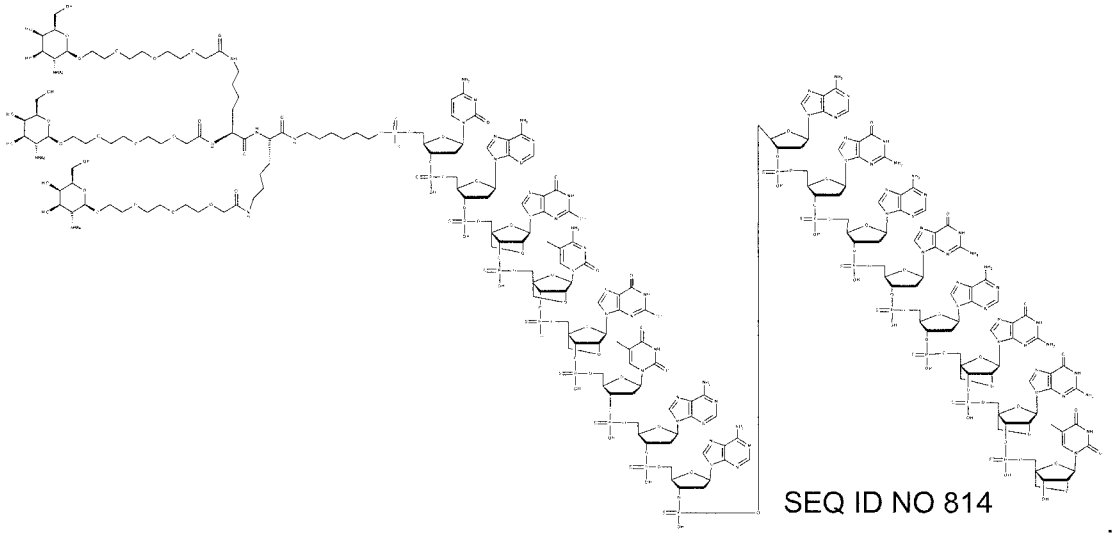
wherein uppercase letters denote beta-D-oxy-LNA units; lowercase letters denote DNA units; the subscript "s" denotes a phosphorothioate linkage; superscript m denotes a DNA or beta-D-oxy-LNA unit containing a 5-methylcytosine base; GN2-C6 denotes a GalNAc2 carrier component with a C6 linker.

15. The oligomer conjugate of any one of claims 1 to 14, wherein the oligomer conjugate has the following structure:

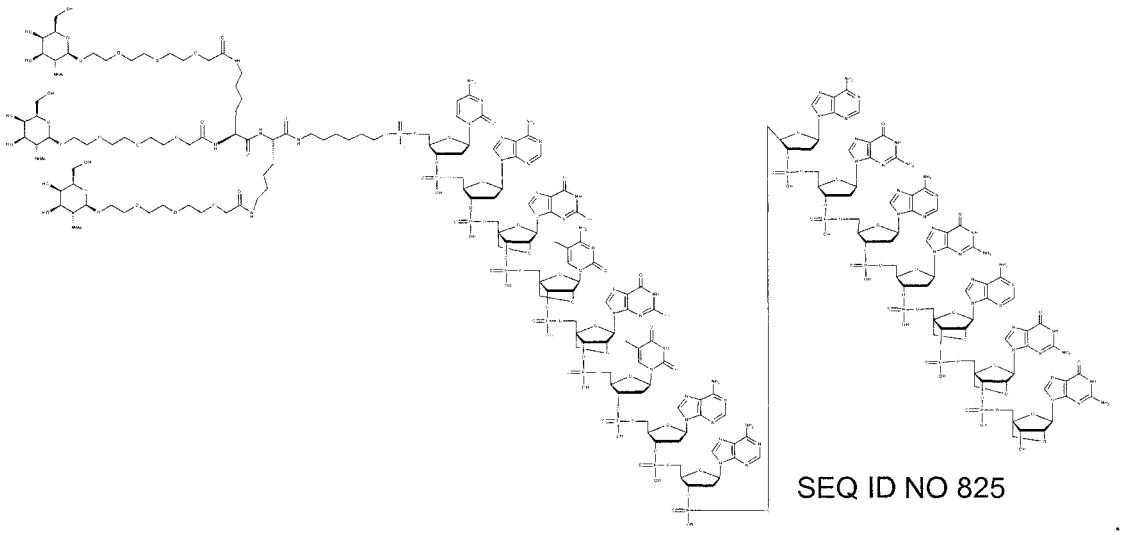


SEQ ID NO 815

16. The oligomer conjugate of any one of claims 1 to 14, wherein the oligomer conjugate has the following structure:



17. The oligomer conjugate of any one of claims 1 to 14, wherein the oligomer conjugate has the following structure:



18. A pharmaceutical composition comprising an oligomer conjugate according to any one of claims 1 to 17; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

19. The oligomer conjugate as defined in any one of claims 1 to 17 or the pharmaceutical composition of claim 18 for use in the treatment of a viral disorder in the liver, wherein said oligomer conjugate is to be administered subcutaneously.

20. Use of the oligomer conjugate as defined in any one of claims 1 to 17 or the pharmaceutical composition of claim 19 for modulating a target sequence of Hepatitis B Virus (HBV).

21. Use of the oligomer conjugate as defined in any one of claims 1 to 17 or the pharmaceutical composition of claim 18 in the manufacture of a medicament for the treatment of a viral disorder in the liver, wherein said oligomer conjugate is to be administered subcutaneously.