(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 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); and

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)

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.

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 an oligomer conjugate for use in the treatment of a viral disorder in the liver, wherein said oligomer conjugate according to the disclosure.

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 in the manufacture of a medicament for the treatment of a viral disorder in the liver.

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

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 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.

CLAIMS

1. An oligomer conjugate selected from the group consisting of:

5'- GN2-C6 caG_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 caG_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 caG_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); and

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)

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.

2. The oligomer conjugate of claim 1, selected from the group consisting of:

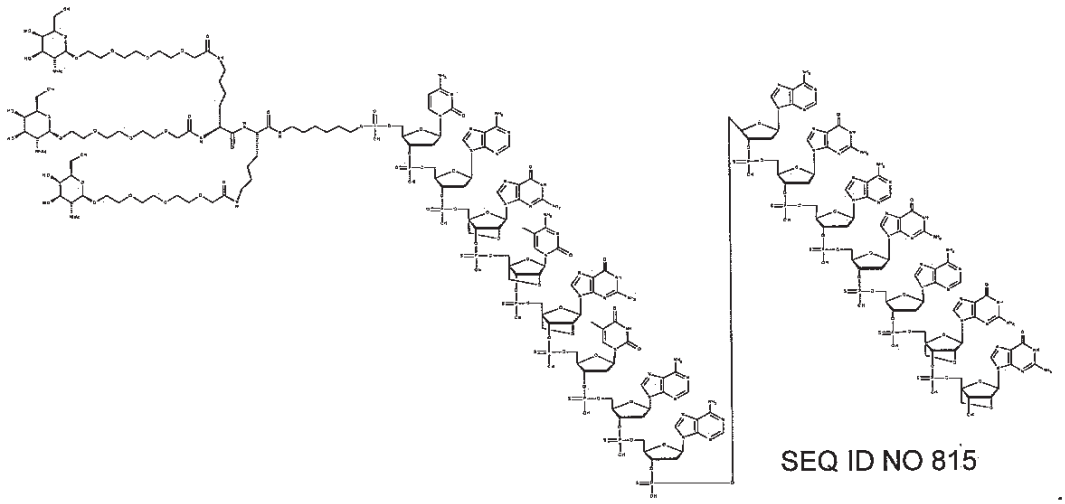
5'- GN2-C6 ca$G_s{}^mC_sG_st_sa_sa_sa_sg_sa_sg_sa_sG_sG$-3' (SEQ ID NO: 815)

5'- GN2-C6 ca$G_s{}^mC_sG_st_sa_sa_sa_sg_sa_sg_sa_sG_sG_sT$-3' (SEQ ID NO: 814); and

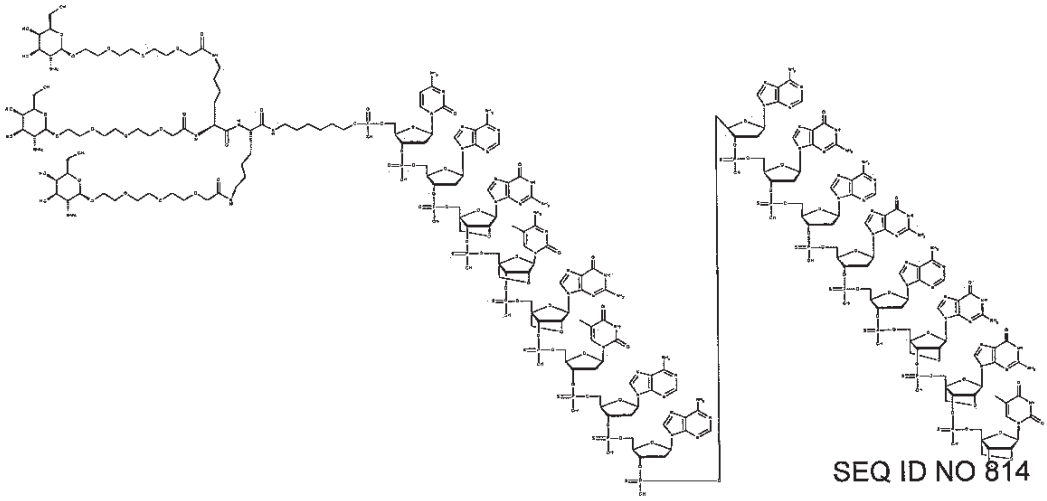
5'-GN2-C6 ca$G_s{}^mC_sG_st_sa_sa_sa_sg_sa_sg_sA_sG_sG$-3' (SEQ ID NO: 825)

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.

3. The oligomer conjugate of claim 1, wherein the oligomer conjugate has the following structure:

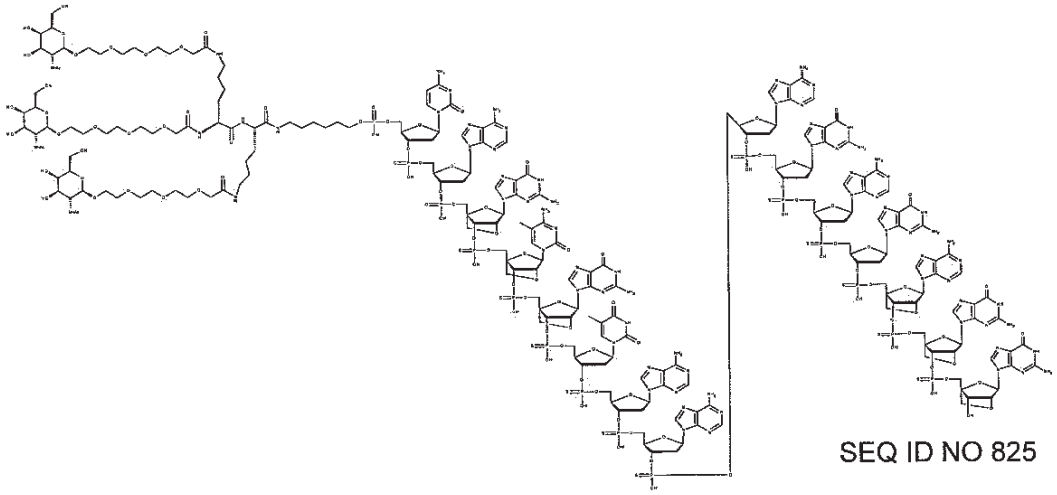


4. The oligomer conjugate of claim 1, wherein the oligomer conjugate has the following structure:



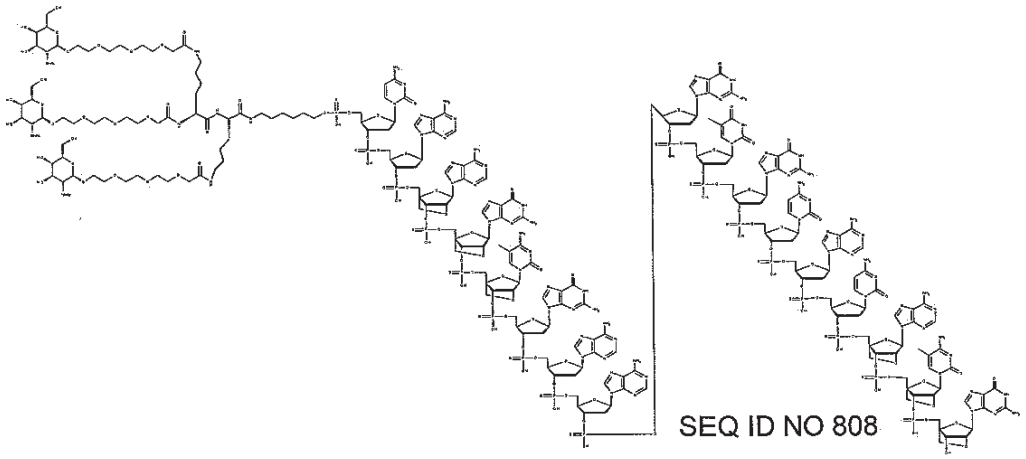
SEQ ID NO 814

5. The oligomer conjugate of claim 1, wherein the oligomer conjugate has the following structure:

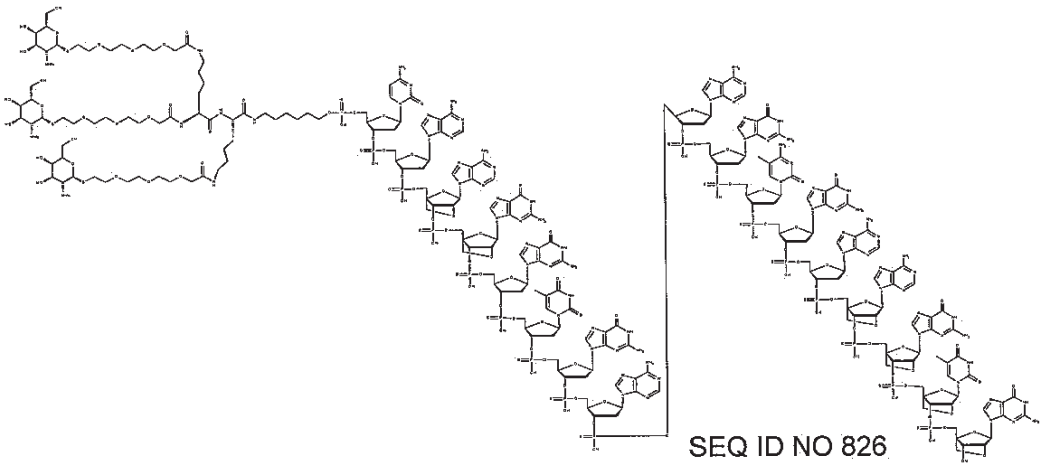


SEQ ID NO 825

6. The oligomer conjugate of claim 1, where the oligomer conjugate has the following structure:



7. The oligomer conjugate of claim 1, where the oligomer conjugate has the following structure:



8. A pharmaceutical composition comprising an oligomer conjugate according to any one of claims 1 to 7; and one or more pharmaceutically acceptable diluents, carriers, salts or adjuvants.

9. An oligomer conjugate for use in the treatment of a viral disorder in the liver, wherein said oligomer conjugate is defined in any one of claims 1 to 7.

10. The oligomer conjugate for use in the treatment of claim 9, wherein the oligomer conjugate is for subcutaneous administration.

11. Use of the oligomer conjugate as defined in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of a viral disorder in the liver.

12. The use of the oligomer of claim 11, wherein the medicament is to be administered subcutaneously.