CLAIMS

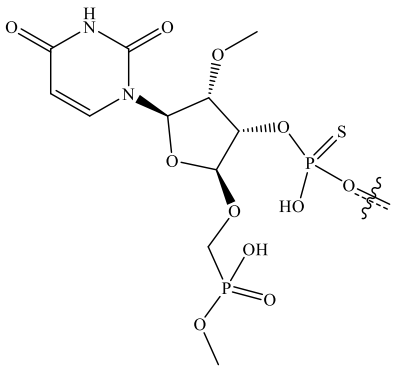
What is claimed is:

1. An oligonucleotide comprising a sense strand forming a duplex region with an antisense strand, wherein:

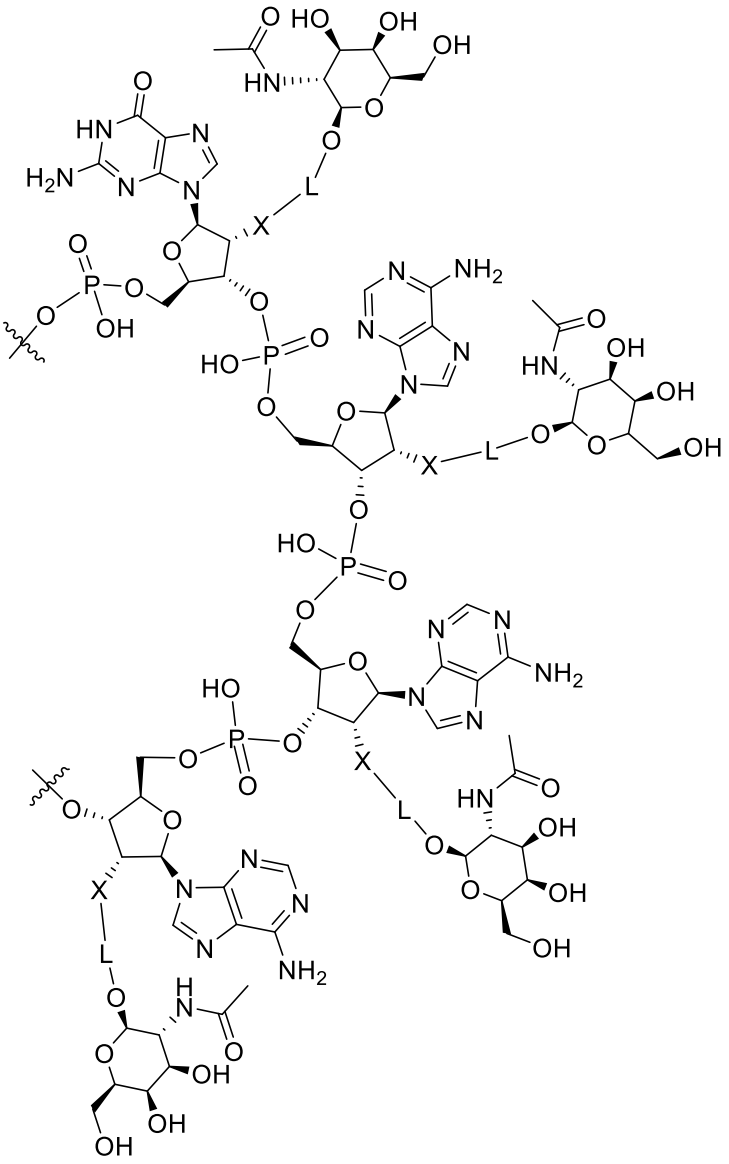
the sense strand consists of a sequence as set forth in GACAAAAAUCCUCACAAUAAGCAGCCGAAAGGCUGC (SEQ ID NO: 8) and comprising 2′-fluoro modified nucleotides at positions 3, 8-10, 12, 13, and 17, 2′-O-methyl modified nucleotides at positions 1, 2, 4-7, 11, 14-16, 18-26, and 31-36, and a phosphorothioate linkage between the nucleotides at positions 1 and 2, wherein each of the nucleotides of the -GAAA- sequence on the sense strand is conjugated to a monovalent GalNac moiety; and

the antisense strand consists of a sequence as set forth in UUAUUGUGAGGAUUUUUGUCGG (SEQ ID NO: 5.1) and comprising 2′-fluoro modified nucleotides at positions 2, 3, 5, 7, 8, 10, 12, 14, 16, and 19, 2′-O-methyl modified nucleotides at positions 1, 4, 6, 9, 11, 13, 15, 17, 18, and 20-22, and phosphorothioate linkages between nucleotides at positions 1 and 2, between nucleotides at positions 2 and 3, between nucleotides at positions 3 and 4, between nucleotides at positions 20 and 21, and between nucleotides at positions 21 and 22, wherein the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a methoxy phosphonate (MOP).

2. The oligonucleotide of claim 1, wherein the 5’-nucleotide of the antisense strand has the following structure:



3. The oligonucleotide of claim 1 or 2, wherein the –GAAA– motif comprises the structure:



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wherein:

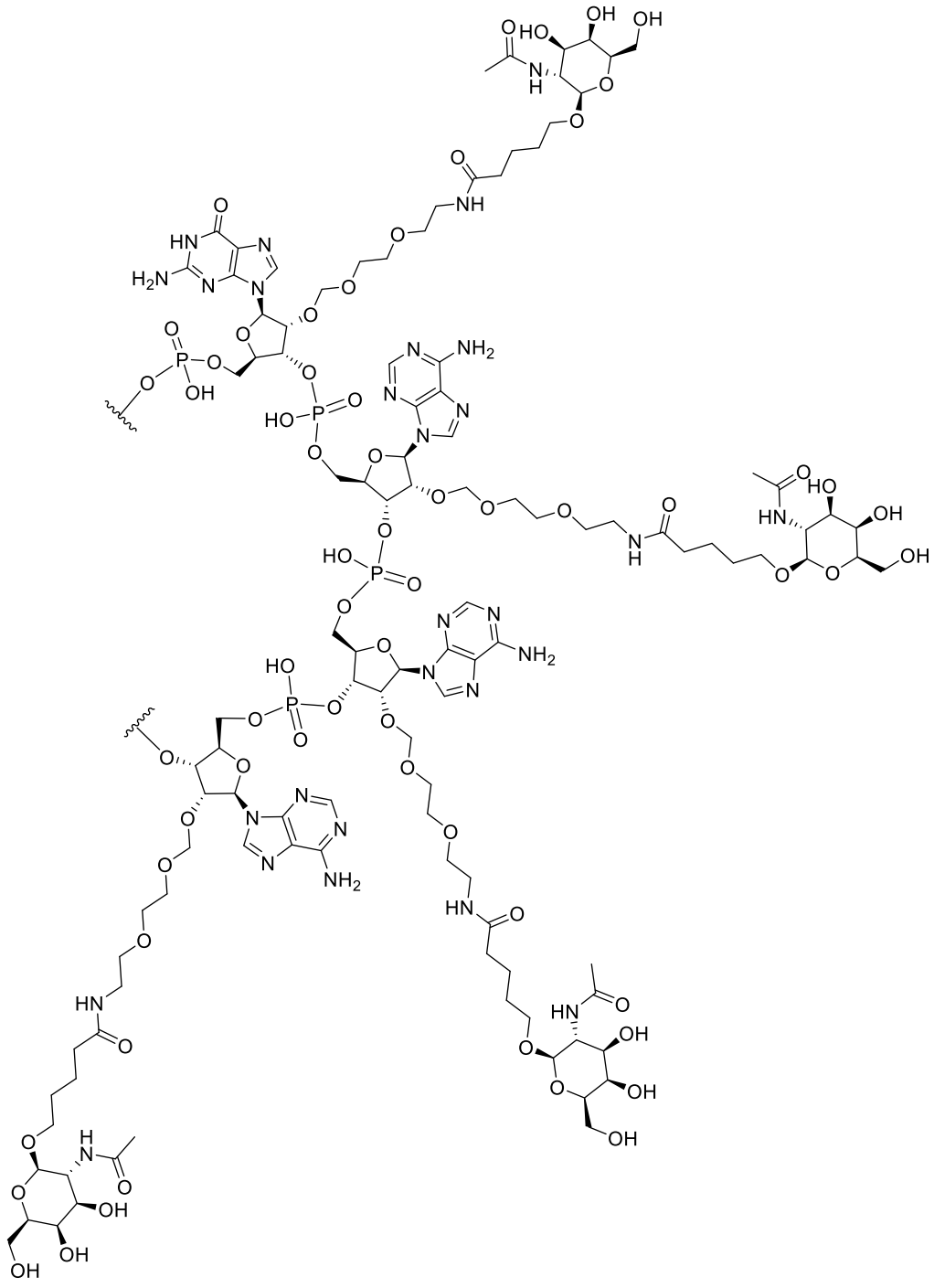
L represents a bond, click chemistry handle, or a linker of 1 to 20, inclusive, consecutive, covalently bonded atoms in length, selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, and combinations thereof; and

X is a O or S.

4. The oligonucleotide of claim 3, wherein L is an acetal linker.

5. The oligonucleotide of claim 3 or 4, wherein X is O.

6. The oligonucleotide of any one of claims 1 to 5, wherein the –GAAA– sequence comprises the structure:



7. A composition comprising the oligonucleotide of any one of claims 1 to 6.

8. The composition of claim 7 comprising a counterion.

9. The composition of claim 7 or claim 8 comprising a pharmaceutically acceptable carrier.

10. The composition of any one of claims 7 to 9 comprising an excipient.

11. The composition of any one of claims 7 to 10 comprising phosphate-buffered saline solution.

12. An *in vitro* method of reducing expression of hepatitis B virus (HBV) surface antigen (HBsAg) in a cell, the method comprising delivering to the cell the oligonucleotide of any one of claims 1 to 6.

13. The method of claim 12, wherein the cell is a hepatocyte.

14. Use of the oligonucleotide according to any one of claims 1 to 6, or the composition according to any one of claims 7 to 11, in the manufacture of a medicament for treating HBV infection in a subject.

15. The use of claim 14, wherein the oligonucleotide or composition is to be administered subcutaneously to the subject.

16. The use of claim 14, wherein the oligonucleotide or composition is to be administered intravenously to the subject.

17. The use of claim 16, wherein the medicament comprises a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier is a solvent or dispersion medium containing water.