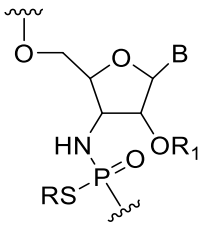
Claims

1. ~~1.~~ A chimeric antisense oligonucleotide represented by Formula (A): 5'X—Y—Z 3' (A), wherein X—Y—Z is a chimeric oligonucleotide comprising a sequence of 18 to 22 nucleosides, optionally conjugated at the 5' and/or 3' end to a ligand targeting group; X is a domain comprising a sequence of modified nucleosides that is 3-10 nucleosides in length; Z is a domain comprising a sequence of modified nucleosides that is 3-10 nucleosides in length; and Y is a domain comprising a sequence of 2 to 10 2'-deoxy-nucleosides linked through thiophosphate intersubunit linkages, wherein each modified nucleoside in the X domain and each modified nucleoside in the Z domain are nucleosides of Formula (1)



wherein R is H or a positively charged counter ion, B is a nucleobase, R_1 is ~~—(~~(~~CR'2)2OCR'3~~ or ~~OEt~~ Et, and R' is independently in each instance H or F; and wherein said chimeric antisense oligonucleotide is complementary to a sequence of the hepatitis B virus (HBV) genome.

~~2.~~

2. The chimeric antisense oligonucleotide of claim ~~1,~~1, wherein R is H, R_1 is ~~—(~~(~~CR'2)2OCR'3~~, and each R' is H.

~~3.~~

3. The chimeric antisense oligonucleotide of claim ~~1,~~1, wherein the X domain and the Z domain each comprise a sequence of modified nucleosides that is 4~~-6~~ to 8 nucleosides in length.

~~4.~~

4. The chimeric antisense oligonucleotide of claim ~~1,~~1, wherein R_1 is ~~-OEt.~~

~~5. -~~Et.

5. The chimeric antisense oligonucleotide of claim ~~1,~~1, wherein R_1 is ~~-(-~~$(CH_2)_2OCH_3$.~~-~~

~~6.~~

6. The chimeric antisense oligonucleotide of claim ~~1,~~1, wherein the Y domain sequence comprises 5 to 10 2'-deoxy-nucleosides.

~~7.~~

7. The chimeric antisense oligonucleotide of claim ~~6,~~6, wherein the Y domain comprises ~~a nucleobase sequence of GGTGAAG(5m)CGA (SEQ ID NO: 576).~~

~~8. ~~10 2'-deoxy-nucleosides.

8. The chimeric antisense oligonucleotide of claim ~~6,~~1, wherein the X domain and the Z domain each comprise a sequence of modified nucleosides that is 5 nucleosides in length~~.~~

~~9. The oligonucleotide of claim 1, wherein the ligand targeting group comprises a GalNAc moiety.~~

~~10. A pharmaceutical composition comprising an oligonucleotide of claim 1 and a pharmaceutically acceptable excipient.~~, and wherein the Y domain sequence comprises 10 2'-deoxy-nucleosides.

9. The chimeric antisense oligonucleotide of claim 1, wherein the ligand targeting group comprises a GalNAc moiety.

10. A pharmaceutical composition comprising the chimeric antisense oligonucleotide of claim 1 and a pharmaceutically acceptable excipient.

11. The chimeric antisense oligonucleotide of claim 1, wherein B is selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine, 2,6-diaminopurine, and 5-methyluracil.