

Claims

1. A double stranded short interfering nucleic acid (siNA) comprising: (a) a sense strand comprising 19-21 nucleotides in a nucleic acid sequence that is at least 80% identical to SEQ ID NO: 40, wherein 15 or more of the nucleotides are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, and wherein at least 11 of the modified nucleotides are a 2'-O-methyl nucleotide and at least 4 of the modified nucleotides are a 2'-fluoro nucleotide; and (b) an antisense strand comprising 19-21 nucleotides in a nucleic acid sequence that is at least 80% complementary to SEQ ID NO: 40, wherein 15 or more of the nucleotides are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, and wherein at least 11 of the modified nucleotides are a 2'-O-methyl nucleotide and 4 to 6 of the modified nucleotides are a 2'-fluoro nucleotide.
2. The double stranded siNA of claim 1, wherein: (a) the nucleotide(s) at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, or 19 from the 5' end of the sense strand is a 2'-fluoro nucleotide; and (b) the nucleotide(s) at position 2, 5, 6, 8, 10, 14, 16, 17, or 18 from the 5' end of the antisense strand is a 2'-fluoro nucleotide.
3. The double stranded siNA of claim 1, wherein the sense strand comprises SEQ ID NO: 438 or SEQ ID NO: 435, and the antisense strand comprises any one of SEQ ID NOs: 501-519, SEQ ID NO: 537, SEQ ID NO: 538, or SEQ ID NO: 539.
4. The double stranded siNA of claim 1, wherein the sense strand comprises SEQ ID NO: 438, and the antisense strand comprises any one of SEQ ID NO: 501, SEQ ID NO: 537, SEQ ID NO: 538, or SEQ ID NO: 539.
5. A short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a nucleic acid sequence consisting of SEQ ID NO: 438 or SEQ ID NO: 435, and (b) an antisense strand comprising a nucleic acid sequence consisting of any one of SEQ ID NO: 501, SEQ ID NO: 505, SEQ ID NO: 506, SEQ ID NO: 537, SEQ ID NO: 538, and SEQ ID NO: 539.
6. The double stranded siNA of claim 4, wherein the sense strand comprises SEQ ID NO: 438 and the antisense comprises SEQ ID NO: 501.
7. The double stranded siNA of claim 4, wherein the sense strand comprises SEQ ID NO: 438 and the antisense comprises any one of SEQ ID NO: 537-539.
8. A double stranded short interfering nucleic acid (siNA) comprising:

(a) a sense strand of

(SEQ ID NO: 438)

5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-
ps2-GalNAc-3'

and an antisense strand of

(SEQ ID NO: 501)

5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCfCmAfCmCmAmCpsm
GpsmA-3';

(b) a sense strand of

(SEQ ID NO: 438)

5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-
ps2-GalNAc-3'

and an antisense strand of

(SEQ ID NO: 521)

5'-mApsfUpsmUmGmAfGmAfGfAmAmGmUmCfCmAfCmCmAmCpsm
GpsmA-3';

(c) a sense strand of

(SEQ ID NO: 438)

5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-
ps2-GalNAc-3'

and an antisense strand of

(SEQ ID NO: 522)

5'-mApsfUpsmUmGfAmGmAfGmAmAmGmUmCfCmAfCmCmAmCpsm
GpsmA-3';

(d) a sense strand of

(SEQ ID NO: 438)

5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-
p-ps2-GalNAc-3'

and an antisense strand of

(SEQ ID NO: 537)

5'-mApsf4PpsmUmGmAfGmAmGmAmGmUmCfCmAfCmCmAmCp
smGpsmA-3';

(e) a sense strand of

(SEQ ID NO: 438)

5'-mGpsmUpsmGmGfUmGfGfAfcUmUmCmUmCmUmCmAmAmU-
p-ps2-GalNAc-3'

and an antisense strand of

(SEQ ID NO: 538)

5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCf2PmAfCmCmAmCp
smGpsmA-3';
or

(f) a sense strand of

(SEQ ID NO: 438)

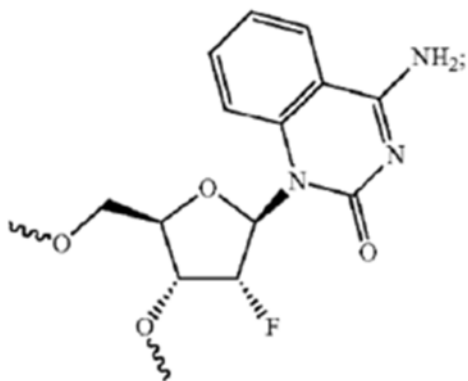
5'-mGpsmUpsmGmGfUmGfGfAfcUmUmCmUmCmUmCmAmAmU-p-
ps2-GalNAc-3'

and an antisense strand of

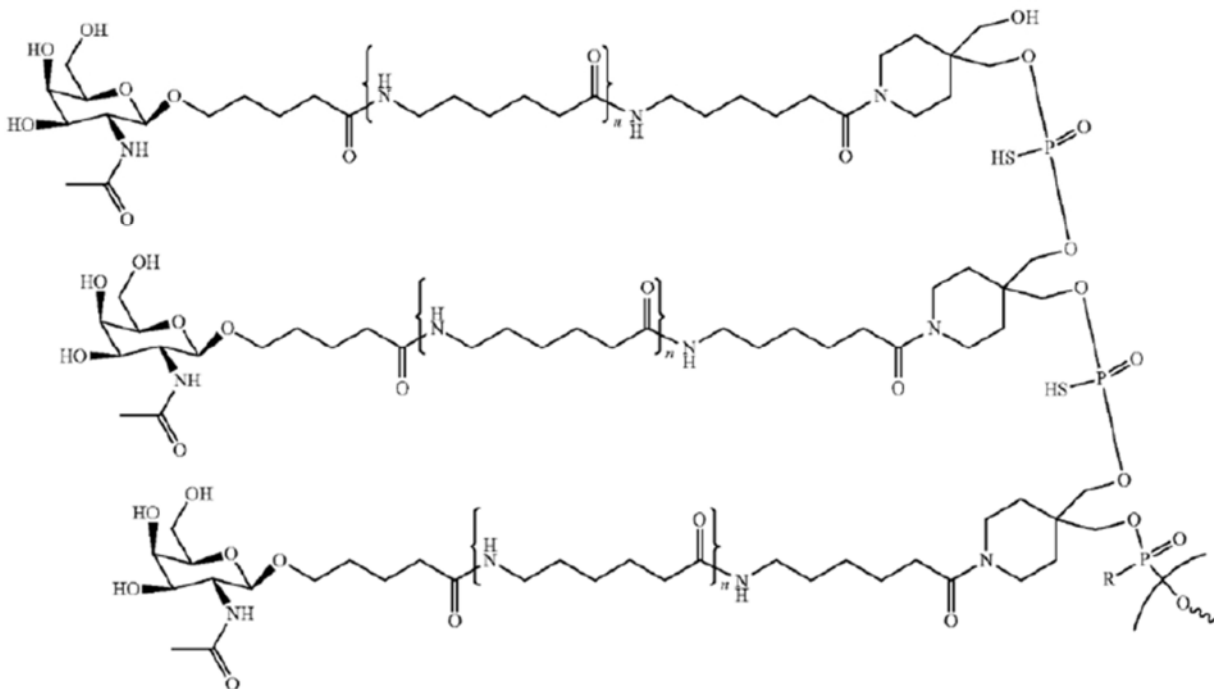
(SEQ ID NO: 539)

5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCfCmAfXmCmAmCpsm
GpsmA-3',

wherein fX is



wherein Ga1NAc comprises a structure of Formula (VII):



wherein n is 1, and R is OH.

9. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCfCmAfCmCmAmCpsmGpsmA-3' (SEQ ID NO: 501).

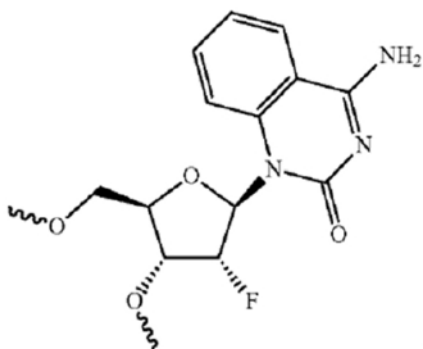
10. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc-3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsfUpsmUmGmAfGmAfGfAmAmGmUmCfCmAfCmCmAmCpsmGpsmA-3' (SEQ ID NO: 521).

11. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc-3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsfUpsmUmGfAmGmAfGmAmAmGmUmCfCmAfCmAmCpsmGpsmA-3' (SEQ ID NO: 522).

12. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc-3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsf4PpsmUmGmAfGmAmGmAmAmGmUmCfCmAfCmCmAmCpsmGpsmA-3' (SEQ ID NO: 537).

13. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmAmAmU-p-ps2-GalNAc-3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCf2PmAfCmCmAmCpsmGpsmA-3'(SEQ ID NO: 538).

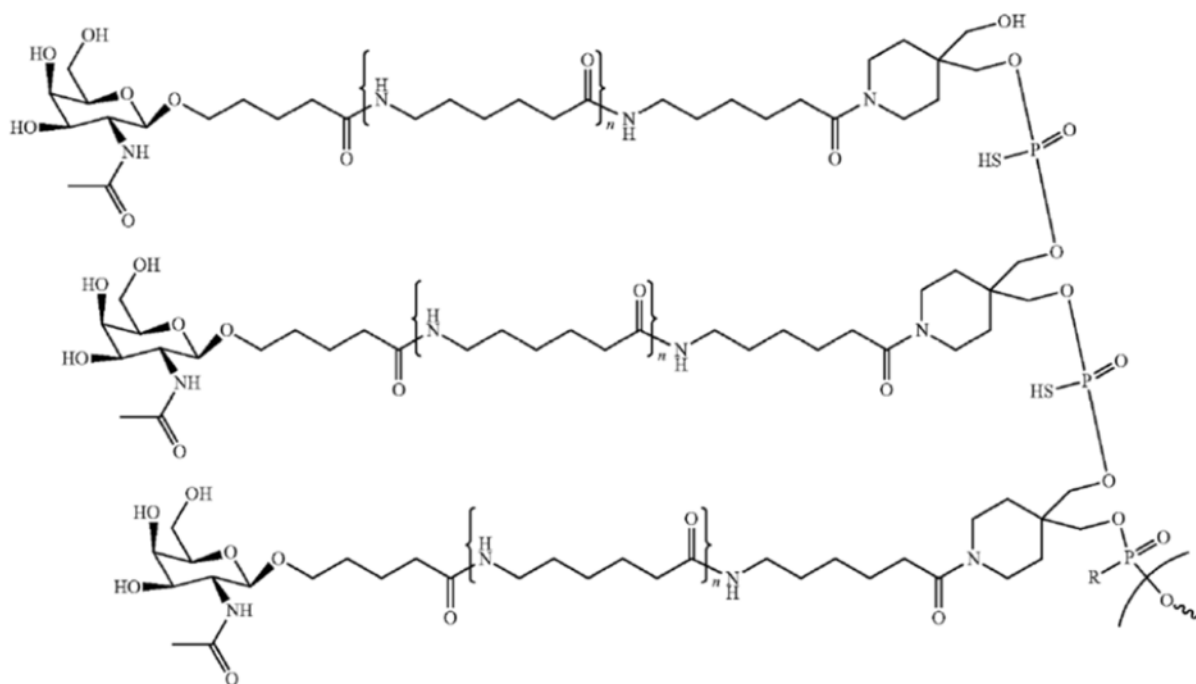
14. The double stranded siNA of claim 8, comprising a sense strand of 5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc-3' (SEQ ID NO: 438) and an antisense strand of 5'-mApsfUpsmUmGmAfGmAmGmAmAmGmUmCfCmAfXmCmAmCpsmGpsmA-3'(SEQ ID NO: 539), wherein fX is



15. The double stranded siNA of claim 4 further comprising a galactosamine attached to the sense strand.

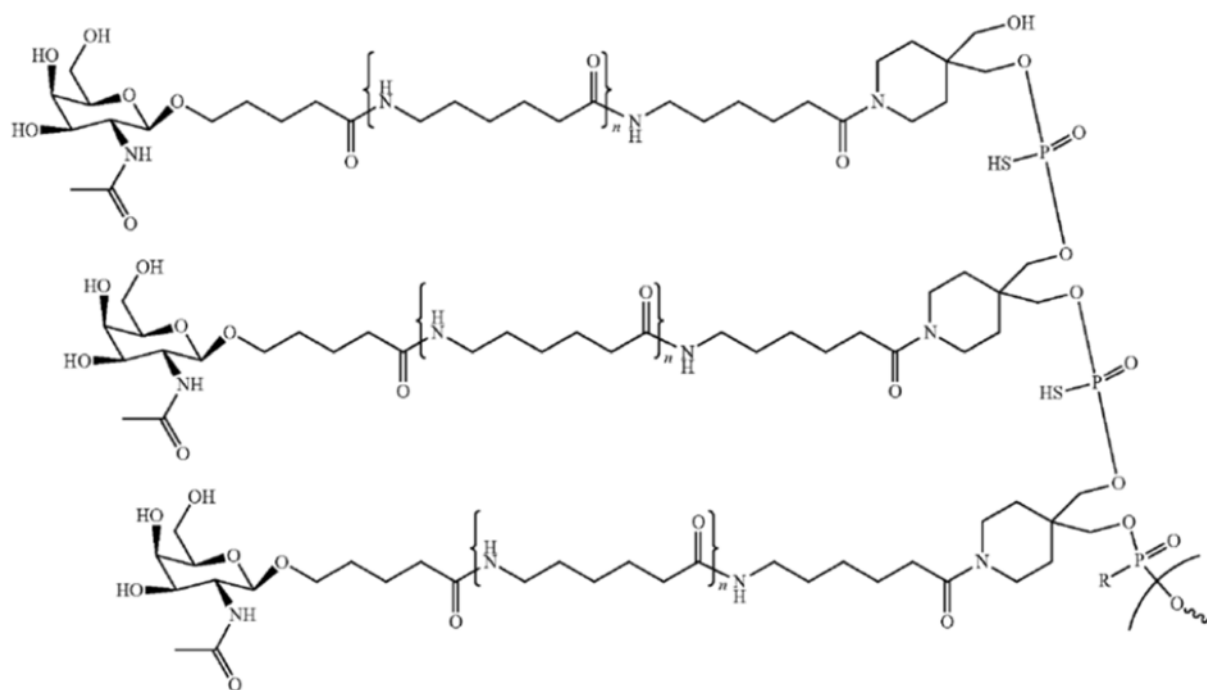
16. The double stranded siNA of claim 4 further comprising a Nacetyl galactosamine (GalNAc) attached to the 3' of the sense strand.

17. The double stranded siNA of claim 16, wherein the GalNAc comprises a structure of Formula (VII):



wherein n is 1, and R is OH.

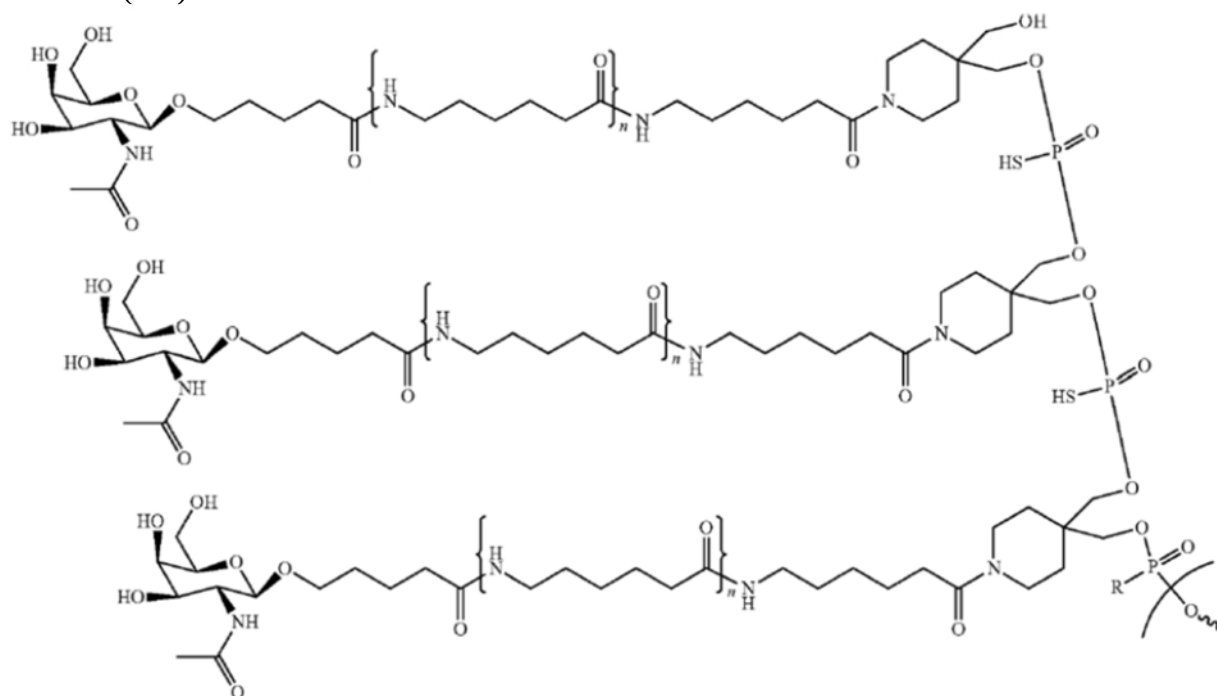
18. The siNA molecule of claim 5 further comprising a galactosamine attached to the sense strand.
19. The siNA molecule of claim 5 further comprising a N-acetylgalactosamine (Ga1NAc) attached to the 3' of the sense strand.
20. The siNA molecule of claim 19, wherein the Ga1NAc comprises a structure of Formula (VII):



wherein n is 1, and R is OH.

21. The double stranded siNA of claim 6 further comprising a Nacetylgalactosamine (Ga1NAc) attached to the 3' of the sense strand.

22. The double stranded siNA of claim 21, wherein the Ga1NAc comprises a structure of Formula (VII):



wherein n is 1, and R is OH.