Each $n_p$ and $n_q$ independently represents an overhang nucleotide sequence comprising 0-6 nucleotides; each n and n' represents an overhang nucleotide; and p and q are each independently 0-6.

In ~~another aspect, the~~ disclosure also relates to a dsRNA agent capable of inhibiting the expression of a target gene. The dsRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 30 nucleotides. The sense strand contains at least two motifs of three identical modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site within the strand and at least one of the motifs occurs at another portion of the strand that is separated from the motif at the cleavage site by at least one nucleotide. The antisense strand contains at least one motif of three identical modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site within the strand and at least one of the motifs occurs at another portion of the strand that is separated from the motif at or near cleavage site by at least one nucleotide. The modification in the motif occurring at or near the cleavage site in the sense strand is different than the modification in the motif occurring at or near the cleavage site in the antisense strand.

In ~~another aspect, the invention~~ disclosure also relates to a dsRNA agent capable of inhibiting the expression of a target gene. The dsRNA agent comprises a sense strand and an antisense strand, each strand having 14 to 30 nucleotides. The sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site in the strand. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

~~In another aspect, the disclosure relates to a double-stranded RNAi agent capable of inhibiting the expression of a target gene, comprising a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, one of said motifs occurring at or near the cleavage site in the strand; and wherein the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides, one of said motifs occuring at or near the cleavage site.~~

10. The double-stranded RNAi agent of claim 1, wherein the duplex region is 17-30 nucleotide pairs in length.

11. The double-stranded RNAi agent of claim 10, wherein the duplex region is 17-19 nucleotide pairs in length.

12. The double-stranded RNAi agent of claim 10, wherein the duplex region is 27-30 nucleotide pairs in length.

13. The double-stranded RNAi agent of claim 1, wherein each strand has 17-30 nucleotides.

14. The double-stranded RNAi agent of claim 1, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2'-deoxy, and combinations thereof.

15. The double-stranded RNAi agent of claim 14, wherein the nucleotides are modified with either 2'-$OCH_3$ or 2'-F.

16. The double-stranded RNAi agent of claim 1, further comprising at least one ligand.

17. The double-stranded RNAi agent of claim 16, wherein the ligand is a one or more GalNAc ~~derivatives~~ attached through a bivalent or trivalent branched linker.

18. The double-stranded RNAi agent of claim 1, wherein the modifications on the nucleotides are selected from the group consisting of 2'-O-methyl nucleotide, 2′-deoxyfluoro nucleotide, 2'-O-N-methylacetamido (2'-O-NMA) nucleotide, a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleotide, 2'-O-aminopropyl (2'-O-AP) nucleotide, 2'-ara-F, and combinations thereof.

19. The double-stranded RNAi agent of claim ~~14~~16, wherein the ligand is attached to the 3' end of the sense strand.

20. The double-stranded RNAi agent of claim 1, further comprising at least one phosphorothioate or methylphosphonate internucleotide linkage.

21. The double-stranded RNAi agent of claim 1, wherein the nucleotide at the 1 position of the 5'-end of the duplex in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT.

22. The double-stranded RNAi agent of claim 1, wherein the base pair at the 1 position of the 5'-end of the duplex is an AU base pair.

23. The double-stranded RNAi agent of claim 1, wherein the Y nucleotides contain a 2'-fluoro modification.

24. The double-stranded RNAi agent of claim 1, wherein the Y' nucleotides contain a 2'-O-methyl modification.

~~25. A double-stranded RNAi agent capable of inhibiting the expression of a target gene, comprising a sense strand and an antisense strand, each strand having 14 to 30 nucleotides,~~

~~wherein the sense strand contains at least two motifs of three identical modifications on three consecutive nucleotides, one of said motifs occurring at the cleavage site in the strand and at least one of said motifs occurring at another portion of the strand that is separated from the motif at the cleavage site by at least one nucleotide; and~~

~~wherein the antisense strand contains at least first motif of three identical modifications on three consecutive nucleotides, one of said motifs occurring at or near the cleavage site in the strand and a second moitif occurring at another portion of the strand that is separated from the first motif by at least one nucleotide;~~

wherein the modification in the motif occurring at the cleavage site in the sense strand is different than the modification in the motif occurring at or near the cleavage site in the antisense strand.

26. The double-stranded RNAi agent of claim 25, wherein at least one of the nucleotides occurring at the cleavage site in the sense strand forms a base pair with one of the nucleotides in the motif occurring at or near the cleavage site in the antisense strand.

27. The double-stranded RNAi agent of claim 25, wherein the duplex has 17-30 nucleotides.

28. The double-stranded RNAi agent of claim 25, wherein the duplex has 17-19 nucleotides.

29. The double-stranded RNAi agent of claim 25, wherein each strand has 17-23 nucleotides.

30. The double-stranded RNAi agent of claim 25, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C-allyl, 2′-fluoro, 2'-deoxy, and combinations thereof.

31. The double-stranded RNAi agent of claim 30, wherein the modifications on the nucleotide are 2'-$OCH_3$ or 2'-F.

32. The double-stranded RNAi agent of claim 31, further comprising a ligand attached to the 3'-end of the sense strand.

33. A double-stranded RNAi agent capable of inhibiting the expression of a target gene, comprising a sense strand and an antisense strand, each strand having 14 to 30 nucleotides,

wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, one of said motifs occurring at or near the cleavage site in the strand; and

wherein the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides, one of said motifs occuring at or near the cleavage site.

34. The double-stranded RNAi agent of claim 33, wherein the sense strand comprises one or more motifs of three identical modifications on three consecutive nucleotides, said motifs occurring at another portion of the strand that is separated from the three 2'-F modifications at the cleavage site by at least one nucleotide.

35. The double-stranded RNAi agent of claim 33, wherein the antisense strand comprises one or more motifs of three identical modifications on three consecutive nucleotides, said motifs occurring at another portion of the strand that is separated from the three 2'-O-methyl modifications by at least one nucleotide.

36. The double-stranded RNAi agent of claim 33, wherein at least one of the nucleotides having a 2'-F modification forms a base pair with one of the nucleotides having a 2'-O-methyl modification.

37. The double-stranded RNAi agent of claim 33, wherein the duplex is 17-30 nucleotide pairs in length.

38. The double-stranded RNAi agent of claim 33, wherein the duplex is 17-19 nucleotide pairs in length.

39. The double-stranded RNAi agent of claim 33, wherein each strand has 17-23 nucleotides.

~~40. The double-stranded RNAi agent of claim 33, further comprising a ligand attached to the 3' end of the sense strand.~~

~~41~~25. A pharmaceutical composition comprising the double-stranded RNAi agent according to any one of the preceding claims alone or in combination with a pharmaceutically acceptable carrier or excipient.

~~42~~26. A double-stranded RNAi agent according to any one of ~~the preceding~~ claims 1 to 24 for use in inhibiting the expression of a target gene.

~~43~~27. The double-stranded RNAi agent of claim ~~42~~26, wherein the double-stranded RNAi agent is formulated for administration through subcutaneous or intravenous administration.

~~44~~28. A dsRNA agent for use in delivering a polynucleotide to a specific target in a subject, the dsRNA agent being represented by formula (III):

sense: 5' $n_p$ -$N_a$ -(X X X) $_i$-$N_b$ -Y Y Y -$N_b$ -(Z Z Z)$_j$ -$N_a$ - $n_q$ 3'

antisense: 3' $n_p'$-$N_a'$-(X'X'X')$_k$-$N_b'$-Y'Y'Y'-$N_b'$-(Z'Z'Z')$_l$-$N_a'$- $n_q'$ 5'

(III)

wherein:

i, j, k, and l are each independently 0 or 1;

p and q are each independently 0-6;

each $N_a$ and $N_a'$ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotideseach $N_b$ and $N_b'$ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each $n_p$, $n_p'$, $n_q$ and $n_q'$ independently represents an overhang nucleotide sequence comprising 0-6 nucleotide sequence; and

XXX, YYY, ZZZ, X'X'X', Y'Y'Y', and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides; and

wherein the modifications on $N_b$ is different than the modification on Y and the modification on $N_b$' is different than the modification on Y'.

~~45~~29. The dsRNA agent of claim ~~44~~28, wherein said dsRNA agent is formulated for administration by an administration means comprising intramuscular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, intravenous, subcutaneous, cerebrospinal, or combinations thereof.

~~46~~30. A dsRNA agent according to claim 1 for use in delivering a polynucleotide to a specific target of a subject, the dsRNA agent being formulated for subcutaneous administration.