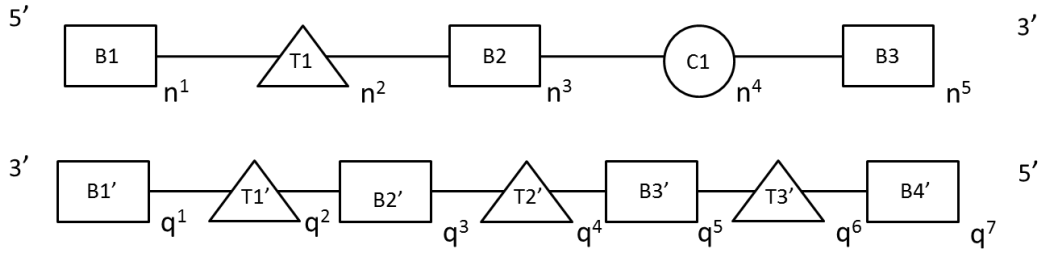
We claim:

1. A double-stranded RNA (dsRNA) agent capable of inhibiting the expression of a target gene, the dsRNA agent comprising a sense strand and an antisense strand, each strand having 14 to 40 nucleotides, wherein the dsRNA agent is represented by formula (I):



(I),

wherein:

B2 and B3 each represent a nucleotide containing a 2'-OMe modification;

B1, B1', B2', B3', and B4' each independently represent a nucleotide containing a modification selected from the group consisting of 2'-OMe and 2'-F;

C1 is a glycol hexane placed at a site opposite to the seed region (positions 2-8) of the antisense strand;

T1, T1', T2', and T3' each independently represent a 2'-F modification;

n^2 is 3 nucleotides in length;

T1' is at position 14 from the 5'-end from the antisense strand, and q^2 is 1;

T3' is at position 2 from the 5'-end of the antisense strand, and q^6 and q^7 are each 1

each n^1, n^3, and q^1 is independently 4-15 nucleotide(s) in length;

each n^5 and q^3 is independently 1-6 nucleotide(s) in length;

q^5 is independently 0-10 nucleotide(s) in length; and

each n^4 and q^4 is independently 0-3 nucleotide(s) in length,

wherein,

(a) the sense strand comprises one or more blocks of phosphorothioate linkages; and,

(b) one of the T1 nucleotides (i) is at a site of the sense strand opposite to position 11 of the 5'-end of the antisense strand, or, (ii) at position 11 of the sense strand by factoring from the 5' end of the sense strand.

2. The dsRNA agent of claim 1, wherein C1 is at a site opposite to positions 5-8 of the 5’-end of the antisense strand.

3. The dsRNA agent of claim 2, wherein C1 is at position 14-17 of the 5’-end of the sense strand, and n^4 is 1.

4. The dsRNA agent of claim 1, wherein T2’ is positions 6-10 from the 5’ end of the antisense strand, and q^4 is 1.

5. The dsRNA agent of claim 1, wherein B1, B2, B3, B1’, B2’, B3’, and B4’ each contain 2’-OMe modifications.

6. The dsRNA agent of claim 1, wherein n^4 is 0.

7. The dsRNA agent of claim 1, wherein the sense strand and/or antisense strand comprises one or more blocks of phosphorothioate or methylphosphonate internucleotide linkages.

8. The dsRNA agent of claim 7, wherein the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages.

9. The dsRNA agent of claim 7, wherein the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 14, 15, 16, 17, or 18 phosphate internucleotide linkages.

10. The dsRNA agent of claim 9, wherein the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 16-18 phosphate internucleotide linkages.

11. The dsRNA agent of claim 1, wherein the sense strand has 19-22 nucleotides, and the antisense strand has 19-25 nucleotides .

12. The dsRNA agent of claim 1, wherein the sense strand has 21 nucleotides, and the antisense strand has 23 nucleotides.

13. The dsRNA agent of claim 1, wherein the dsRNA agent has a 3’ and/or 5’ overhang(s) of 1-10 nucleotides in length.

14. The dsRNA agent of claim 1, wherein the dsRNA agent has a 3’ overhang at the 3’-end of the antisense strand, and a blunt end at the 5’-end of the antisense strand.

15. The dsRNA agent of claim 1, wherein the dsRNA agent has a 5’ overhang at the 5’-end of the sense strand.

16. The dsRNA agent of claim 1, wherein the nucleotide at position 1 of the 5’-end of the antisense strand in the duplex is selected from the group consisting of A, dA, dU, U, and dT.

17. The dsRNA agent of claim 1, wherein at least one of the first, second, and third base pair from the 5’-end of the antisense strand is an AU base pair.

18. The dsRNA agent of claim 1, further comprising at least one ASGPR ligand.

19. The dsRNA agent of claim 18, wherein the one or more ligands improves nuclease resistance of the dsRNA agent.

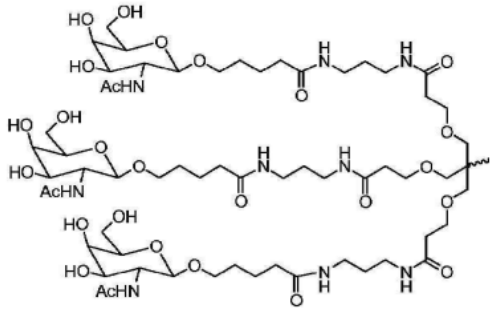
20. The dsRNA agent of claim 18 comprising the one or more ASGPR ligands.

21. The dsRNA agent of claim 20, wherein the ASGPR ligand is attached to the 5’ end or 3’ end of the sense strand.

22. The dsRNA agent of claim 21, wherein the ASGPR ligand is attached to the 3’ end of the sense strand.

23. The dsRNA agent of claim 21, wherein the ASGPR ligand is one or more GalNAc derivatives attached to the 3’ end of the sense strand.

24. The dsRNA agent of claim 23, wherein the ASGPR ligand is as follows:



25. The dsRNA agent of claim 1, wherein the dsRNA agent has a blunt end at the 5’ end of the antisense strand.

26. The dsRNA agent of claim 1, wherein the antisense strand contains four 2’-F modifications at positions 2, 6, 14, and 16 of the antisense strand from the 5’ end of the antisense strand.

27. The dsRNA agent of claim 1, wherein the antisense strand contains six 2’-F modifications at positions 2, 6, 8-9, 14, and 16 of the antisense strand from 5’-end of the antisense strand.

28. The dsRNA agent of claim 1, wherein at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand can be chosen independently from the group consisting of: A:U, G:U, I:C, and mismatched pairs.

29. The dsRNA agent of claim 1, wherein formula (I) further comprises a 5'-vinyl phosphonate (VP).

30. The dsRNA agent of claim 1, wherein formula (I) further comprises a 2'-deoxythymidine linked via a phosphorodithioate (PS_2) linkage at the 5'-end of the antisense strand or sense strand.

31. The dsRNA agent of claim 1, wherein B3' is 2-OMe.

32. The dsRNA agent of claim 1, having a duplex area of a pair of nucleotides 19 to 21 in length.

33. The dsRNA agent of claim 1, having two blunt ends at both ends of the dsRNA duplex.

34. A pharmaceutical composition comprising the dsRNA agent according to any one of claims 1-33 alone or in combination with a pharmaceutically acceptable carrier or excipient.

35. Use of a pharmaceutical composition in the manufacture of a medicament for inhibiting the expression of a target gene, wherein the dsRNA agent according to any one of claims 1-33 is to be administered in an amount sufficient to inhibit expression of the target gene.

36. The use of claim 35, wherein the dsRNA agent is to be administered through subcutaneous or intravenous administration.

37. Use of a pharmaceutical composition in the manufacture of a medicament for delivering polynucleotide to specific target in a subject, wherein the dsRNA agent according to any one of claims 1-33 is to be administered to the subject.

38. The use of claim 37, wherein said administering step is carried out by an administration means comprising intramuscular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, intravenous, subcutaneous, cerebrospinal, or combinations thereof.

39. Use of a pharmaceutical composition in the manufacture of a medicament for delivering a polynucleotide to specific target of a subject, wherein a dsRNA agent according to any one of claims 1-33 is to be delivered by subcutaneous administration into the subject, such that the polynucleotide is delivered into specific target of the subject.

40. A pharmaceutical composition comprising the dsRNA agent according to any one of claims 1-33 for use in therapy.