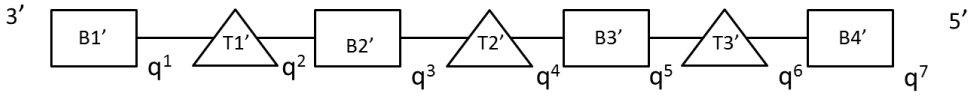
We claim:

1. A double-stranded RNA (dsRNA) agent capable of inhibiting the expression of a target gene, comprising an antisense strand sequence complementary to at least one portion of a mRNA corresponding to the target gene, having 19, 20, 21, 22, 23, 24, or 25 nucleotides in length and being represented by formula (Ia):



(Ia)

wherein:

B1', B2', B3', and B4' each independently represent a nucleotide containing a modification selected from the group consisting of 2'-Oalkyl, 2'-substituted alkoxy, 2'-substituted alkyl, 2'-halo, ENA, and BNA/LNA;

T1', T2', and T3' each independently represent a nucleotide comprising a chemical modification selected from the group consisting of DNA, RNA, LNA, 2'-F, and 2'-F-5'-methyl;

q^1 is independently 4 to 15 nucleotides in length;

q^3 or q^7 is independently 1-6 nucleotide(s) in length;

q^2 or q^6 is independently 1-3 nucleotide(s) in length;

q^4 is independently 0-3 nucleotide(s) in length; and

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

wherein:

the antisense strand has 2′-F modifications, and wherein the 2′-F modifications on the antisense strand consist of four, and only four, 2′-F modifications or six, and only six, 2′-F modifications.

2. The dsRNA agent of claim 1, wherein T1' and T3' are separated by 11 nucleotides in length.

3. The dsRNA agent of claim 1, wherein T1' is at position 14 from the 5' end of the antisense strand, and q^2 is 1.

4. The dsRNA agent of claim 1, wherein T3' is at position 2 from the 5' end of the antisense strand, and q^6 is 1.

5. 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.

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

7. The dsRNA agent of claim 1, wherein the antisense strand comprises two blocks of two phosphorothioate or methylphosphonate internucleotide linkages separated by 16-18 phosphate internucleotide linkages.

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

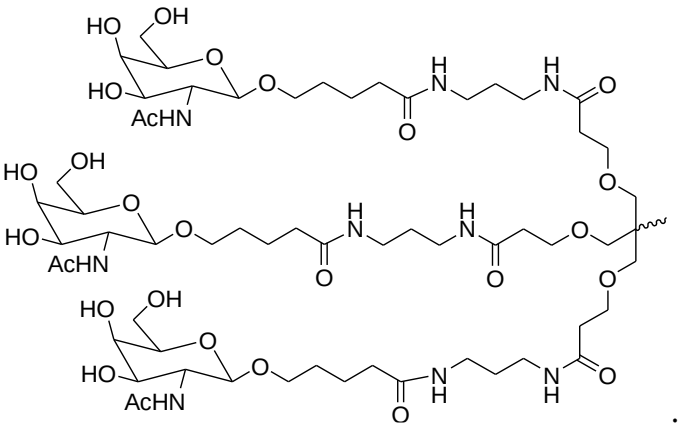
9. The dsRNA agent of claim 1, wherein the nucleotide at position 1 of the 5'-end of the antisense strand in the duplex is selected from the group consisting of A, dA, dU, U, and dT.

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

11. The dsRNA agent of claim 10, wherein the ASGPR ligand is attached to the 3' end of the sense strand.

12. The dsRNA agent of claim 10, wherein the ASGPR ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

13. The dsRNA agent of claim 12, wherein the ASGPR ligand is:



14. The dsRNA agent of claim 1, wherein formula (Ia) further comprises a 5′-vinyl phosphonate (VP).

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

16. A pharmaceutical composition comprising the dsRNA agent according to claim 1 in combination with a pharmaceutically acceptable carrier or excipient.

17. The dsRNA agent of claim 1 for use in therapy, wherein the dsRNA agent is to be administered in an amount sufficient to inhibit the expression of a target gene.

18. The dsRNA agent for use of claim 17, wherein the dsRNA agent is to be administered through subcutaneous or intravenous administration.

19. The dsRNA agent of claim 1 for use in therapy, wherein the dsRNA agent is to be administered for delivering polynucleotide to a specific target in a subject.

20. The dsRNA agent for use of claim 19, wherein the dsRNA agent is to be administered by an administration means comprising intramuscular, intrabronchial, intrapleural, intraperitoneal, intraarterial, lymphatic, intravenous, subcutaneous, cerebrospinal, or combinations thereof.

21. The dsRNA agent of claim 1 for use in therapy, wherein the dsRNA agent is to be administered subcutaneously into a subject, such that a polynucleotide is delivered to a specific target of the subject.

22. The dsRNA agent of claim 1, wherein the 2′-F modifications on the antisense strand consist of four 2′-F modifications.

23. The dsRNA agent of claim 22, wherein the four 2′-F modifications are at positions 2, 6, 14, and 16 from the 5′-end of the antisense strand.

24. The dsRNA agent of claim 1, wherein the 2′-F modifications on the antisense strand consist of six 2′-F modifications.

25. The dsRNA agent of claim 24, wherein the six 2′-F modifications are at positions 2, 6, 8-9, 14, and 16 from the 5′-end of the antisense strand.