WHAT IS CLAIMED IS:

1. A double-stranded nucleic acid inhibitor molecule, comprising:

a sense strand comprising 15-43 nucleotides and having a first region (R1) and a second region (R2);

an antisense strand comprising 18-35 nucleotides and a 5′- and 3′-end, wherein the antisense strand has a single stranded overhang of 6-10 nucleotides at the 3′-end and wherein the sense strand and antisense strand are separate strands;

a first duplex (D1) formed by the first region of the sense strand and the antisense strand, wherein the first duplex has a length of 8-29 base pairs;

wherein the second region of the sense strand comprises a first subregion (S1), a second subregion (S2) and a single stranded loop that joins the first and second subregions, wherein the first and second subregions form a second duplex (D2); and

wherein the second duplex has a length of 6 base pairs and does not contain a T_m-increasing nucleotide or has a length of 1-5 base pairs and comprises at least one T_m-increasing nucleotide.

2. The double-stranded nucleic acid inhibitor molecule of claim 1, wherein:

a) the sense strand has 15-30 nucleotides; the antisense strand has 20 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 10-14 base pairs;

b) the sense strand has 16-31 nucleotides; the antisense strand has 21 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 11-15 base pairs;

c) the sense strand has 17-32 nucleotides; the antisense strand has 22 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 12-16 base pairs;

d) the sense strand has 18-33 nucleotides; the antisense strand has 23 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 13-17 base pairs;

e) the sense strand has 19-34 nucleotides; the antisense strand has 24 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 14-18 base pairs;

f) the sense strand has 20-35 nucleotides; the antisense strand has 25 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 15-19 base pairs;

g) the sense strand has 21-36 nucleotides; the antisense strand has 26 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 16-20 base pairs;

h) the sense strand has 22-37 nucleotides; the antisense strand has 27 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 17-21 base pairs;

i) the sense strand has 23-38 nucleotides; the antisense strand has 28 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 18-22 base pairs;

j) the sense strand has 24-39 nucleotides; the antisense strand has 29 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 19-23 base pairs;

k) the sense strand has 25-40 nucleotides; the antisense strand has 30 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 20-24 base pairs;

l) the sense strand has 26-41 nucleotides; the antisense strand has 31 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 21-25 base pairs;

m) the sense strand has 27-42 nucleotides; the antisense strand has 32 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 22-26 base pairs; or

n) the sense strand has 28-43 nucleotides; the antisense strand has 33 nucleotides and the single-stranded overhang of 6-10 nucleotides at the 3′-end; and the first duplex has a length of 23-27 base pairs.

3. The double-stranded nucleic acid inhibitor molecule of claim 1 or 2, wherein the antisense strand has 20-24, 21-23, or 22 nucleotides, wherein the 3′-end of the antisense strand has a single-stranded overhang of 7-9 nucleotides, wherein the first duplex has a length of 12-16 base pairs, and wherein the loop is a tetraloop or a triloop.

4. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein at least one nucleotide in the antisense strand is modified with a 2′-F and wherein the at least one nucleotide in the antisense strand that is modified with the 2′-F is flanked by a phosphorous-containing internucleotide linkage other than a phosphodiester linkage.

5. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein nucleotide 14 of the antisense strand is modified with a 2′-F and is linked to nucleotides 13 and 15 of the antisense strand by the phosphorous-containing internucleotide linkage other than the phosphodiester linkage and/or wherein nucleotide 2 of the antisense strand is modified with a 2′-F and is linked to nucleotides 1 and 3 of the antisense strand by the phosphorous-containing internucleotide linkage other than the phosphodiester linkage.

6. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the antisense strand contains at least two nucleotides modified with a 2′-F that are flanked by the phosphorous-containing internucleotide linkage other than the phosphodiester linkage, and wherein the phosphorous-containing internucleotide linkage is a phosphorothioate linkage.

7. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the nucleotide in region 1 of the sense strand that base pairs with nucleotide 6 of the antisense strand is a T_m-increasing nucleotide and/or the nucleotide in region 1 of the sense strand that base pairs with nucleotide 5 of the antisense strand is a T_m-increasing nucleotide.

8. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein none of the nucleotides in region 1 of the sense strand that base pair with nucleotides 1-4 of the antisense strand is a T_m-increasing nucleotide.

9. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the second duplex has a length of 1-3 base pairs and contains at

least one T_m-increasing nucleotide, and wherein the second duplex contains 2-10 T_m-increasing nucleotides and has a length of 1-5 base pairs or wherein the second duplex contains 2-6 T_m-increasing nucleotides and has a length of 1-3 base pairs.

10. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the sense strand is between 16-33 nucleotides in length, the antisense strand is between 21-23 nucleotides in length, the first duplex has a length of 12-17 base pairs, and the second duplex has a length of 1-3 base pairs and contains at least one T_m-increasing nucleotide.

11. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the first region of the sense strand is 12-16 nucleotides in length and the second region of the sense strand is 5-10 nucleotides in length;

wherein the first duplex formed by the first region of the sense strand and the antisense strand has a length of 12-16 base pairs;

wherein the second duplex formed by the first and second nucleic acids of the second region of the sense strand has a length of 3 base pairs, 2 base pairs, or 1 base pair and contains at least one T_m-increasing nucleotide; and

wherein the antisense strand is 22 nucleotides in length and has the single-stranded overhang of 6-10 nucleotides at its 3′-end.

12. The double-stranded nucleic acid inhibitor molecule of claim 11, wherein the second region of the sense strand is 5 or 6 nucleotides in length and the second duplex has a length of 1 base pair.

13. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the second duplex comprises at least two T_m-increasing nucleotides.

14. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the tetraloop is an RNA tetraloop selected from UNCG, GNRA, CUUG, A/UGNN, GGUG, RNYA, or AGNN or a DNA tetraloop selected from d(GNAB), d(CNNG), or d(TNCG).

15. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the tetraloop has the sequence GAAA, and wherein the triloop has the sequence GAA.

16. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the T_m-increasing nucleotide is selected from the group consisting of a bicyclic nucleotide, a tricyclic nucleotide, a G-clamp and analogues thereof, a hexitol nucleotide, and a modified nucleotide, wherein the modified nucleotide is a 5-bromo-uracil, a 5-iodo-uracil, 5- propynyl-modified pyrimidine, a 2-amino adenine, a 2-thio uridine, 5 Me-thio uridine, or a pseudo uridine.

17. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the T_m-increasing nucleotide is a bicyclic nucleotide, wherein the bicyclic nucleotide comprises a first ring, wherein the first ring is a furanosyl and a bridge that connects the 2'-carbon and the 4'-carbon of the furanosyl to form a second ring, and wherein the bridge that connects the 2′-carbon and the 4′-carbon of the furanosyl is selected from the group consisting of:

    a) 4′-CH_2-O-N(R)-2′ and 4′-CH_2-N(R)-O-2′, wherein R is H, C_1-C_{12} alkyl, or a protecting group, including, for example, 4′-CH_2-NH-O-2′ (also known as BNA^{NC}) or 4′-CH_2-N(CH_3)-O-2′ (also known as BNA^{NC}[NMe]);

    b) 4′-CH_2-2′; 4′-(CH_2)$_2$-2′; 4′-(CH_2)$_3$-2′; 4′-(CH_2)-O-2′ (also known as LNA); 4′-(CH_2)-S-2′; 4′-(CH_2)$_2$-O-2′ (also known as ENA); 4′-CH(CH_3)-O-2′ (also known as cEt); and 4′-CH(CH_2OCH_3)-O-2′ (also known as cMOE), and analogs thereof;

    c) 4′-C(CH_3)(CH_3)-O-2′ and analogs thereof;

    d) 4′-CH_2-N(OCH_3)-2′ and analogs thereof;

    e) 4′-CH_2-O-N(CH_3)-2′ and analogs thereof;

    f) 4′-CH_2-C(H)(CH_3)-2′ and analogs thereof; and

    g) 4′-CH_2-C(=CH_2)-2′ and analogs thereof.

18. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the tetraloop comprises one, two, three, or four ligand conjugated nucleotides or the triloop comprises one, two or three conjugated nucleotides, wherein the ligand is a GalNAc, and wherein the GalNAc is conjugated to the nucleotide at the 2′-postion of the sugar moiety.

19. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, further comprising a 5′-phosphate mimic at the 5′-terminus of the sense strand and/or the antisense strand.

20. The double-stranded nucleic acid inhibitor molecule of any of the preceding claims, wherein the double-stranded the nucleic acid inhibitor molecule is formulated with a lipid nanoparticle, wherein the lipid nanoparticle comprises core lipids and envelope lipids, wherein the core lipids comprise a first cationic lipid and a first pegylated lipid and wherein the envelope lipids comprise a second cationic lipid, a neutral lipid, a sterol, and a second pegylated lipid, and wherein the first cationic lipid is DL-048, the first pegylated lipid is DSG-MPEG, the second cationic lipid is DL-103, the neutral lipid is DSPC, the sterol is cholesterol, and the second pegylated lipid is DSPE-MPEG.

21. A composition comprising a therapeutically effective amount of the double-stranded nucleic acid inhibitor molecule of any one of the preceding claims and an excipient, and wherein the excipient is a pharmaceutically-acceptable excipient.

22. Use of an oligonucleotide, or a pharmaceutical composition comprising the oligonucleotide, of any of the preceding claims in the manufacture of a medicament for reducing expression of a target gene in a subject, wherein the target gene is a structural gene, a housekeeping gene, a gene that encodes a transcription factor, a gene that encodes a motility factor, a gene that encodes a cell cycle factor, a gene that encodes a cell cycle inhibitor, a gene that encodes an enzyme, a gene that encodes a growth factor, a gene that encodes a cytokine, or a gene that encodes a tumor suppressor.