

EP 1423406 Maintained Claims

1. A chemically modified short interfering nucleic acid (siNA) molecule that down-regulates expression of a target gene by RNA interference (RNAi), wherein:
 - a. the siNA comprises a sense strand and a separate antisense strand wherein said antisense strand comprises a sequence that is complementary to RNA of the target gene and wherein the sense strand comprises a nucleotide sequence that is complementary to the antisense strand,
 - b. each strand of the nucleic acid molecule is independently 18 to 24 nucleotides in length and the siNA duplex comprises 17 to 23 base pairs;
 - c. 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically modified with 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides, with one or more phosphorothiate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.
2. The siNA molecule of claim 1, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends.
3. The siNA molecule of claim 2, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides, wherein pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
4. The siNA molecule of any previous claim, wherein said terminal cap moiety is an inverted deoxybasic moiety.
5. The siNA molecule of claim 2, wherein pyrimidine nucleotides of the said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides, and wherein the purine nucleotides in the antisense region are 2'-O-methyl purine nucleotides.
6. The siNA molecule of claim 2, wherein purine nucleotides present in said antisense region are 2'-deoxy purine nucleotides and wherein the pyrimidine nucleotides present in said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
7. The siNA molecule of any one of claims 2, 5 and 6, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.
8. The siNA molecule of claim 2, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.
9. The siNA molecule of claim 2, wherein 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule.
10. The siNA molecule of claim 2, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoding the target gene or a portion thereof.
11. The siNA molecule of claim 2, wherein purine nucleotides in the sense region are purine ribonucleotides, and wherein pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro

pyrimidine nucleotides and wherein the sense fragment includes a terminal cap moiety at the 5' and 3' ends.

12. The siNA molecule of claim 2, wherein the purine nucleotides in the sense region are purine ribonucleotides, and wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides and wherein the sense fragment includes a terminal cap moiety at the 5' and 3' ends.
13. A composition comprising the nucleic acid molecule of any previous claim and a pharmaceutically acceptable carrier or diluents.