MODIFIED ANTIMIR-138 OLIGONUCLEOTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of Singapore patent application No. 10201404535S, filed 31 July 2014, the contents of it being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to biochemistry in particular biomarkers. In particular, the present invention relates to oligonucleotides that can regulate the expression of biomarker miR-138, pharmaceutical compositions and methods of using the biomarkers thereof.

BACKGROUND OF THE INVENTION

[0003] MicroRNAs (miRNAs) are endogenous small noncoding RNAs that regulate various physiological pathways such as cellular differentiation and proliferation via gene silencing. The microRNAs are thought to contribute to the initiation, progression and eventual metastasis of various proliferative diseases. For example, dysregulation of the expression of a miRNA may lead to aberrant expression of its target proteins, resulting in an altered phenotype in a cell. Impaired miRNA regulatory network is known to be one of the key mechanisms in the pathogenesis of proliferative diseases such as cancer. Thus, there is a need to provide molecules that have the potential to influence the expression of miRNA.

SUMMARY OF THE INVENTION

[0004] In one aspect, there is provided an oligonucleotide comprising at least one locked nucleic acid (LNA), wherein the oligonucleotide is substantially complementary to a nucleotide sequence of miR-138, and wherein the oligonucleotide reduces or inhibits the activity of one or more miR-138.

[0005] In another aspect, there is provided a pharmaceutical composition comprising an effective amount of the oligonucleotide as described herein, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier or diluent.

[0006] Also described herein is a method of treating a proliferative disease in a subject in need thereof comprising administering the oligonucleotide as described herein to the subject.

[0007] In another aspect, there is provided a use of an oligonucleotide as described herein in the manufacture of a medicament for treating proliferative disease in a subject in need thereof.

[0008] Also described herein is a method of reducing or inhibiting the activity of miR-138 in a cell comprising contacting the cell with the oligonucleotide as described herein.

15. The oligonucleotide of claim 14, wherein the modification comprises adding 2'-*O*-deoxy, 2'-*O*-methyl, 2'-*O*-alkyl, 2'-halo, or 2'-fluoro to the 2-hydroxyl group of the ribose moiety of a non-locked nucleic acid.

16. The oligonucleotide of any one of claims 1 to 15, comprising the sequence 5'-CGGCCUGAUTCACAACACCAGCU-3' (SEQ ID NO: 2; antimRNA-138) and 5'-CGGCCUGAUUCACAACACCAGCU-3' (SEQ ID NO: 3; antimRNA-138), wherein SEQ ID NO: 2 and SEQ ID NO: 3, independently, comprises at least one locked nucleic acid.

17. The oligonucleotide of claim 16, wherein the locked nucleic acids are at positions 3, 5, 8, 10, 12, 15, 17, 19 and 21 of SEQ ID NO: 2, wherein position 1 of SEQ ID NO: 2 is the 5' end terminus and position 23 of SEQ ID NO: 2 is the 3' end terminus.

18. The oligonucleotide of claim 17, wherein the phosphorothioate links are independently selected from positions 1 to 5 or 19 to 23 of SEQ ID NO: 2.

19. The oligonucleotide of claim 18, wherein the phosphorothioate links are at positions 1, 2, 3, 20, 21, and 23 of SEQ ID NO: 2.

20. The oligonucleotide of claim 19, wherein the modification is a 2'-O-methylation at positions 1, 2, 4, 6, 7, 9, 11, 13, 14, 16, 18, 20, 22, 23 of SEQ ID NO: 2.

21. The oligonucleotide of any one of claims 1 to 20, comprising one or more of the sequence selected from the group consisting of 5'-mC*mG*G*mCCmUmGA mUTmCAmCmAAmC AmCCmA*G*mC*mU-3' (SEQ ID NO: 13), 5'-mC*mG*G*mCmCTmGmATmUmCAmCmAAmCmACmCmA*G*mC*mU-3' (SEQ ID NO: 12), and 5'-mC*mG*mG*mCmCTmGAmUTmCAmCAmACmACmCmA*mG*mC*mU-3' (SEQ ID NO: 10), wherein m is a 2'-*O*-methylation, * is a phosphorothioate linkage and underlined nucleotides represent a locked nucleic acid modification.

22. The oligonucleotide of any one of claims 1 to 10, comprising the sequence 5'-A*C*AACACCAG*C*-3' (SEQ ID NO: 5), wherein * is a phosphorothioate linkage and underlined nucleotides represent a locked nucleic acid modification.

23. A pharmaceutical composition comprising an effective amount of the oligonucleotide of any one of claims 1 to 22, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier or diluent.

24. Use of an oligonucleotide as claimed in any one of claims 1 to 22 in the manufacture of a medicament for treating a proliferative disease in a subject in need thereof.

25. The use of claim 24, wherein the proliferative disease is a benign tumor or cancer.

26. The use of claim 25, wherein the cancer is selected from the group consisting of malignant glioma and breast cancer.