MICRORNA COMPOUNDS AND METHODS FOR MODULATING MIR-21 ACTIVITY

FIELD OF INVENTION

Provided herein are methods and compositions for the modulation of miR-21 activity.

DESCRIPTION OF RELATED ART

MicroRNAs (microRNAs), also known as "mature microRNA" are small (approximately 18-24 nucleotides in length), non-coding RNA molecules encoded in the genomes of plants and animals. In certain instances, highly conserved, endogenously expressed microRNAs regulate the expression of genes by binding to the 3'-untranslated regions (3'-UTR) of specific mRNAs. More than 1000 different microRNAs have been identified in plants and animals. Certain mature microRNAs appear to originate from long endogenous primary microRNA transcripts (also known as pri-microRNAs, pri-mirs, pri-miRs or pri-pre-microRNAs) that are often hundreds of nucleotides in length (Lee, et al., EMBO J., 2002, 21(17), 4663-4670).

Functional analyses of microRNAs have revealed that these small non-coding RNAs contribute to different physiological processes in animals, including developmental timing, organogenesis, differentiation, patterning, embryogenesis, growth control and programmed cell death. Examples of particular processes in which microRNAs participate include stem cell differentiation, neurogenesis, angiogenesis, hematopoiesis, and exocytosis (reviewed by Alvarez-Garcia and Miska, Development, 2005, 132, 4653-4662).

SUMMARY

Provided herein are compounds comprising a modified oligonucleotide, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 and wherein the modified oligonucleotide has a nucleoside pattern described herein.

Provided herein are methods for inhibiting the activity of miR-21 comprising contacting a cell with a compound described herein. In certain embodiments, the cell is *in vivo*. In certain embodiments, the cell is *in vitro*.

Provided herein are methods for treating a disease associated with miR-21 comprising administering to a subject having a disease associated with miR-21 a compound described herein. In certain embodiments, the subject is a human. In certain embodiments, the subject is a canine.

The compounds described herein are provided for use in therapy.

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of ~~8 to~~21 or 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is

complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least ~~8~~ 21 contiguous nucleosides of the following nucleoside pattern III in the 5' to 3' orientation:

$$(R)_X\text{-}N^B\text{-}N^Q\text{-}N^Q\text{-}N^B\text{-}(N^Q\text{-}N^Q\text{-}N^Q\text{-}N^B)_3\text{-}N^Y\text{-}N^Z$$

wherein each R is a non-bicyclic nucleoside; X is from 1 to 4; each N^B is a bicyclic nucleoside; each N^Q is a non-bicyclic nucleoside; N^Y is a ~~modified nucleoside or an unmodified~~bicyclic nucleoside; and each N^Z is a modified nucleoside.

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of ~~8 to~~18 or 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 18 contiguous nucleosides of the following nucleoside pattern IV in the 5' to 3' orientation:

$$N^M\text{-}N^B\text{-}N^Q\text{-}N^Q\text{-}N^B\text{-}(N^Q\text{-}N^Q\text{-}N^Q\text{-}N^B)_3\text{-}N^Y\text{-}N^Z$$

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside; each N^B is a bicyclic nucleoside; each N^Q is a non-bicyclic nucleoside; N^Y is a ~~modified nucleoside or an unmodified~~bicyclic nucleoside; and N^Z is a modified nucleoside.

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of ~~8~~ 10 to 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least ~~8~~ 10 contiguous nucleosides of the following nucleoside pattern V in the 5' to 3' orientation:

$$N^M\text{-}N^B\text{-}(N^Q\text{-}N^Q\text{-}N^B\text{-}N^B)_4\text{-}N^Z$$

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside; each N^B is a bicyclic nucleoside; each N^Q is a non-bicyclic nucleoside; and N^Z is a modified nucleoside.

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of ~~8~~ 11 to 15 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1), and wherein the modified oligonucleotide comprises at least ~~8~~ 11 contiguous nucleosides of the following nucleoside pattern VI in the 5' to 3' orientation:

$$N^Q\text{-}N^B\text{-}N^B\text{-}N^Q\text{-}(N^B\text{-}N^B\text{-}N^Q\text{-}N^Q)_2\text{-}N^B\text{-}N^Q\text{-}N^B$$

wherein each N^Q is a non-bicyclic nucleoside; and each N^B is a bicyclic nucleoside.

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of ~~8 to~~18 or 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1), and wherein the modified oligonucleotide comprises at least 18 contiguous nucleosides of the following nucleoside pattern VII in the 5' to 3' orientation:

$$N^M\text{-}(N^B\text{-}N^M\text{-}N^M)_2\text{-}N^M\text{-}(N^B\text{-}N^Q\text{-}N^Q\text{-}N^Q)_2\text{-}N^B\text{-}N^B\text{-}N^Z$$

wherein each N^M is a modified nucleoside that is not a bicyclic nucleoside; each N^B is a bicyclic nucleoside; each N^Q is a non-bicyclic nucleoside; and N^Z is a modified nucleoside.

In certain embodiments of any of the compounds provided herein, the modified oligonucleotide comprises at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least

independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and N^Z is an S-cEt nucleoside. In certain embodiments of nucleoside pattern VII, each N^M is a 2'-O-methoxyethyl nucleoside; each N^B is an S-cEt nucleoside; each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and N^Z is 2'-O-methoxyethyl nucleoside. In certain embodiments of nucleoside pattern VII, the modified oligonucleotide has the structure:

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_SU_SA_S$ (SEQ ID NO: 3).

In one aspect, there is provided a compound comprising a modified oligonucleotide consisting of 8 to 22 linked nucleosides, wherein the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19 contiguous nucleosides of a structure selected from the structures in Table 1. In one aspect, there is provided a compound comprising a modified oligonucleotide having a structure selected from the structures in Table 1. In one aspect, there is provided a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier.

In certain embodiments of any of the compounds provided herein, at least one internucleoside linkage is a modified internucleoside linkage. In certain embodiments of any of the compounds provided herein, each internucleoside linkage is a modified internucleoside linkage. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain embodiments of any of the compounds provided herein, at least one nucleoside comprises a modified nucleobase. In certain embodiments of any of the compounds provided herein, at least one cytosine is a 5-methyl cytosine. In certain embodiments of any of the compounds provided herein, each cytosine is a 5-methylcytosine. In certain embodiments of any of the compounds provided herein, the cytosine at position two of the modified oligonucleotide is a 5-methylcytosine.

In certain embodiments of any of the compounds provided herein, the modified oligonucleotide has the nucleobase sequence of a sequence selected from SEQ ID NOs: 3 to 10, wherein each T in the sequence is independently selected from T and U.

In certain embodiments of any of the compounds provided herein, the modified oligonucleotide has 0, 1, 2, or 3 mismatches with respect to the nucleobase sequence of miR-21. In certain embodiments of any of the compounds provided herein, the modified oligonucleotide has 0, 1, or 2 mismatches with respect to the nucleobase sequence of miR-21. In certain such embodiments, the modified oligonucleotide has 0 mismatches with respect to the nucleobase sequence of miR-21. In certain embodiments, the modified oligonucleotide has 1 mismatch with respect to the nucleobase sequence of miR-21. In certain embodiments, the modified oligonucleotide has 2 mismatches with respect to the nucleobase sequence of miR-21.

In one aspect, there is provided a method of inhibiting the activity of miR-21 comprising contacting a cell with a compound as described herein, wherein the cell is *in vitro*.

What is claimed is:

1. A compound comprising a modified oligonucleotide consisting of 21 or 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 21 contiguous nucleosides of the following nucleoside pattern III in the 5' to 3' orientation:

$(R)_X$-N^B-N^Q-N^Q-N^B-$(N^Q$-N^Q-N^Q-$N^B)_3$-N^Y-N^Z

wherein each R is a non-bicyclic nucleoside; X is from 1 to 4;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside;

N^Y is a bicyclic nucleoside; and

each N^Z is a modified nucleoside.

2. A compound comprising a modified oligonucleotide consisting of 18 or 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 18 contiguous nucleosides of the following nucleoside pattern IV in the 5' to 3' orientation:

N^M-N^B-N^Q-N^Q-N^B-$(N^Q$-N^Q-N^Q-$N^B)_3$-N^Y-N^Z

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside;

N^Y is a bicyclic nucleoside; and

N^Z is a modified nucleoside.

3. A compound comprising a modified oligonucleotide consisting of 10 to 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 10 contiguous nucleosides of the following nucleoside pattern V in the 5' to 3' orientation:

N^M-N^B-$(N^Q$-N^Q-N^B-$N^B)_4$-N^Z

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside; and

N^Z is a modified nucleoside.

4. A compound comprising a modified oligonucleotide consisting of 11 to 15 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 11 contiguous nucleosides of the following nucleoside pattern VI in the 5' to 3' orientation:

N^Q-N^B-N^B-N^Q-(N^B-N^B-N^Q-N^Q)$_2$-N^B-N^Q-N^B

wherein each N^Q is a non-bicyclic nucleoside; and

each N^B is a bicyclic nucleoside.

5. A compound comprising a modified oligonucleotide consisting of 18 or 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 18 contiguous nucleosides of the following nucleoside pattern VII in the 5' to 3' orientation:

N^M-(N^B-N^M-N^M)$_2$-N^M-(N^B-N^Q-N^Q-N^Q)$_2$-N^B-N^B-N^Z

wherein each N^M is a modified nucleoside that is not a bicyclic nucleoside;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside; and

N^Z is a modified nucleoside.

6. The compound of any one of the preceding claims, wherein each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside.
7. The compound of any one of the preceding claims, wherein each bicyclic nucleoside is an S-cEt nucleoside.
8. The compound of any one of claims 1 to 6, wherein each bicyclic nucleoside is an LNA nucleoside.
9. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, a 2'-O-methyl, and a 2'-O-methoxyethyl nucleoside.
10. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside and a 2'-O-methoxyethyl nucleoside.
11. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is a β-D-deoxyribonucleoside.
12. The compound of any one of claims 1 to 8 wherein each non-bicyclic nucleoside is a 2'-O-methoxyethyl nucleoside.
13. The compound of claim 2 wherein:

N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside;

N^Y is an S-cEt nucleoside; and

N^Z is an S-cEt nucleoside.

14. The compound of claim 2 wherein:

N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a β-D-deoxyribonucleoside and a 2'-O-methoxyethyl nucleoside;

N^Y is an S-cEt nucleoside; and

N^Z is an S-cEt nucleoside.

15. The compound of any one of claims 1, 2, and 14 having the structure:

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_STA_S$ (SEQ ID NO: 3); or

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_SU_SA_S$ (SEQ ID NO: 3).

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; and nucleosides followed by a subscript "S" are S-cEt nucleosides.

16. The compound of claim 3 wherein:

N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and

N^Z is a 2'-O-methoxyethyl nucleoside.

17. The compound of claim 3 or 16 having the structure:

$A_EC_SATC_SA_SGTC_SU_SGAU_SA_SAGC_SUSA_E$ (SEQ ID NO: 8);

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; and nucleosides followed by a subscript "S" are S-cEt nucleosides.

18. The compound of claim 4 wherein:

a. each N^B is an S-cEt nucleoside; and

each N^Q is a 2'-O-methoxyethyl nucleoside; or

b. each N^B is an S-cEt nucleoside; and

each N^Q is a β-D-deoxyribonucleoside.

19. The compound of claim 4 or claim 18 having the structure:

$^{Me}C_EA_SA_ST_EC_SU_SA_EA_EU_SA_SA_EG_EC_ST_EA_S$ (SEQ ID NO: 7);

wherein nucleosides followed by a subscript "E" are 2'-MOE nucleosides; nucleosides followed by a subscript "S" are S-cEt nucleosides; and ^{Me}C is 5-methyl cytosine.

20. The compound of claim 5, wherein:

a. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is selected from an S-cEt nucleoside and a 2'-O-methoxyethyl nucleoside;

b. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and

N^Z is an S-cEt nucleoside;

c. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is an S-cEt nucleoside; or

d. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is a 2'-O-methoxyethyl nucleoside.

21. The compound of claim 5 or 20 having the structure:

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_SU_SA_S$ (SEQ ID NO: 3).

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; and nucleosides followed by a subscript "S" are S-cEt nucleosides.

22. The compound of any one of the preceding claims, wherein the modified oligonucleotide comprises at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, or 22 contiguous nucleosides of nucleoside pattern III, IV, V, VI, or VII.

23. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to the nucleobase sequence of miR-21 (SEQ ID NO: 1).

24. The compound of any one of the preceding claims, wherein the modified oligonucleotide consists of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides of nucleoside pattern III, IV, V, VI, or VII.

25. The compound of any one of the preceding claims, wherein at least one internucleoside linkage is a modified internucleoside linkage, or wherein each internucleoside linkage is a modified internucleoside linkage, and wherein the modified internucleoside linkage is optionally a phosphorothioate internucleoside linkage.
26. The compound of any one of the preceding claims, wherein at least one cytosine is a 5-methyl cytosine, or wherein each cytosine is a 5-methylcytosine.
27. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is selected from SEQ ID NOs: 3 to 10, wherein each T is independently selected from T and U.
28. The compound of any one of the preceding claims, wherein the modified oligonucleotide has 0, 1, 2, or 3 mismatches with respect to the nucleobase sequence of miR-21.
29. The compound of claim 28, wherein the modified oligonucleotide has 0 mismatches with respect to the nucleobase sequence of miR-21.
30. The compound of claim 28, wherein the modified oligonucleotide has 1 mismatch with respect to the nucleobase sequence of miR-21.
31. The compound of claim 28, wherein the modified oligonucleotide has 2 mismatches with respect to the nucleobase sequence of miR-21.
32. A compound comprising a modified oligonucleotide consisting of 8 to 22 linked nucleosides, wherein the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, or at least 19 contiguous nucleosides of a structure selected from the structures in Table 1.
33. A compound comprising a modified oligonucleotide having a structure selected from the structures in Table 1.
34. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable carrier.
35. A method of inhibiting the activity of miR-21 comprising contacting a cell with a compound of any of claims 1 to 34, wherein the cell is *in vitro*.
36. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for inhibiting the activity of miR-21 in a cell.
37. The method of claim 35 or use of claim 36 wherein the cell is a fibroblast cell, a hyperproliferative cell, a keratinocyte, or a hypoxic cell.
38. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for decreasing collagen expression in a cell.

39. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for treating, preventing or delaying the onset of a disease associated with miR-21 in a subject having a disease associated with miR-21.
40. The use of claim 39, wherein the disease is fibrosis.
41. The use of claim 40, wherein the fibrosis is selected from kidney fibrosis, lung fibrosis, liver fibrosis, cardiac fibrosis, skin fibrosis, age-related fibrosis, spleen fibrosis, scleroderma, and post-transplant fibrosis.
42. The use of claim 41, wherein:
    a. the kidney fibrosis is present in a subject having a disease selected from glomerulosclerosis, tubulointerstitial fibrosis, IgA nephropathy, interstitial fibrosis/tubular atrophy; chronic kidney damage, glomerular disease, glomerulonephritis, Alport Syndrome, diabetes mellitus, idiopathy focal segmental glomerulosclerosis, membranous nephropathy, collapsing glomerulopathy, chronic recurrent kidney infection, and end stage renal disease;
    b. the kidney fibrosis results from acute or repetitive trauma to the kidney;
    c. the liver fibrosis is present in a subject having a disease selected from chronic liver injury, hepatitis infection, non-alcoholic steatohepatitis, and cirrhosis; the pulmonary fibrosis is idiopathic pulmonary fibrosis; and/or

the subject has chronic obstructive pulmonary disease.

43. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for treating a fibroproliferative disorder in a subject.
44. The method of claim 35 or method or use of claim 37 or use of any one of claims 36 and 38 to 43, wherein a subject having elevated miR-21 expression in one or more tissues is to be selected.
45. The use of any one of claims 39 to 43 or method or use of claim 44 wherein the subject is in need of improved organ function, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function.
46. The use of any one of claims 39 to 43 or method or use of claims 44 or 45 wherein the medicament improves organ function in the subject, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function.
47. The use of any one of claims 39 to 43 or method or use of any one of claims 44 to 46, wherein at least one therapeutic agent is to be administered, wherein said therapeutic agent is to be selected from an anti-inflammatory agent, an immunosuppressive agent, an anti-diabetic agent, digoxin, a vasodilator, an angiotensin II converting enzyme (ACE) inhibitors, an angiotensin II receptor blockers (ARB), a calcium channel blocker, an isosorbide dinitrate, a hydralazine, a nitrate, a

hydralazine, a beta-blocker, a natriuretic peptides, a heparinoid, and a connective tissue growth factor inhibitor.

48. The use of claim 39, wherein the disease is cancer.
49. The use of claim 48, wherein the cancer is liver cancer, breast cancer, bladder cancer, prostate cancer, colon cancer, lung cancer, brain cancer, hematological cancer, pancreatic cancer, head and neck cancer, cancer of the tongue, stomach cancer, skin cancer, or thyroid cancer.
50. The use of claim 48 or claim 49, wherein at least one additional anti-cancer therapy is to be administered to the subject.
51. The use of any one of claims 39 to 43 and 48 to 50 or method or use of any one of claims 44 to 47, wherein the subject is a human.
52. The method of claim 35 or use of any one of claims 36, 38 to 43 and 48 to 50 or method or use of any one of claims 37, 44 to 47 and 51, wherein the compound is present as a pharmaceutical composition.
53. A compound of any one of claims 1 to 34 for use in therapy.
54. A compound of any of claims 1 to 34 for use in the treatment of fibrosis.
55. A compound of any of claims 1 to 34 for use in the treatment and/or prevention of impaired kidney function or end stage renal disease in a subject.
56. A compound of any of claims 1 to 34 for use in promoting wound healing.
57. A compound of any of claims 1 to 34 for use in treating cancer.
58. A compound of any of claims 1 to 34 for use in preventing and/or delaying the onset of metastasis.
59. A compound of any of claims 1 to 34 for use in treating cardiac disease.
60. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament.
61. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for treating fibrosis.
62. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for promoting wound healing.
63. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for treating cancer.
64. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for preventing and/or delaying the onset of metastasis.
65. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for preventing and/or delaying the onset of impaired kidney function or end stage renal disease.

What is claimed is:

1. A compound comprising a modified oligonucleotide consisting of 8 to 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following nucleoside pattern III in the 5' to 3' orientation:

$(R)_X$-N^B-N^Q-N^Q-N^B-$(N^Q$-N^Q-N^Q-$N^B)_3$-N^Y-N^Z

wherein each R is a non-bicyclic nucleoside; X is from 1 to 4;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside;

N^Y is a modified nucleoside or an unmodified nucleoside; and

each N^Z is a modified nucleoside.

2. A compound comprising a modified oligonucleotide consisting of 8 to 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following nucleoside pattern IV in the 5' to 3' orientation:

N^M-N^B-N^Q-N^Q-N^B-$(N^Q$-N^Q-N^Q-$N^B)_3$-N^Y-N^Z

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside;

N^Y is a modified nucleoside or an unmodified nucleoside; and

N^Z is a modified nucleoside.

3. A compound comprising a modified oligonucleotide consisting of 8 to 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following nucleoside pattern V in the 5' to 3' orientation:

N^M-N^B-$(N^Q$-N^Q-N^B-$N^B)_4$-N^Z

wherein N^M is a modified nucleoside that is not a bicyclic nucleoside;

each N^B is a bicyclic nucleoside;

each N^Q is a non-bicyclic nucleoside; and

N^Z is a modified nucleoside.

4. A compound comprising a modified oligonucleotide consisting of 8 to 15 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following nucleoside pattern VI in the 5' to 3' orientation:

N^Q-N^B-N^B-N^Q-$(N^B$-N^B-N^Q-$N^Q)_2$-N^B-N^Q-N^B

wherein each N^Q is a non-bicyclic nucleoside; and

each N^B is a bicyclic nucleoside.

5. A compound comprising a modified oligonucleotide consisting of 8 to 19 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following nucleoside pattern VII in the 5' to 3' orientation:

N^M-(N^B-N^M-N^M)$_2$-N^M-(N^B-N^Q-N^Q-N^Q)$_2$-N^B-N^B-N^Z

wherein each N^M is a modified nucleoside that is not a bicyclic nucleoside;
each N^B is a bicyclic nucleoside;
each N^Q is a non-bicyclic nucleoside; and
N^Z is a modified nucleoside.

6. The compound of any one of the preceding claims, wherein each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside.
7. The compound of any one of the preceding claims, wherein each bicyclic nucleoside is an S-cEt nucleoside.
8. The compound of any one of claims 1 to 6, wherein each bicyclic nucleoside is an LNA nucleoside.
9. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, a 2'-O-methyl, and a 2'-O-methoxyethyl nucleoside.
10. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside and a 2'-O-methoxyethyl nucleoside.
11. The compound of any one of the preceding claims, wherein each non-bicyclic nucleoside is a β-D-deoxyribonucleoside.
12. The compound of any one of claims 1 to 8 wherein each non-bicyclic nucleoside is a 2'-O-methoxyethyl nucleoside.
13. The compound of claim 1 wherein:
    a. each R is a 2'-O-methoxyethyl nucleoside; X is 1;
    each N^B is an S-cEt nucleoside;
    each N^Q is a β-D-deoxyribonucleoside;
    N^Y is a β-D-deoxyribonucleoside; and
    N^Z is a 2'-O-methoxyethyl nucleoside;
    b. each R is a 2'-O-methoxyethyl nucleoside; X is 1;
    each N^B is an S-cEt nucleoside;
    each N^Q is a β-D-deoxyribonucleoside;
    N^Y is a β-D-deoxyribonucleoside; and
    N^Z is an S-cEt nucleoside; or

c. each R is a 2'-O-methoxyethyl nucleoside; X is 1;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
N^Y is an S-cEt nucleoside; and
N^Z is an S-cEt nucleoside.

14. The compound of claim 1 wherein:
each R is a 2'-O-methoxyethyl nucleoside; X is 1;
each N^B is an S-cEt nucleoside;
each N^Q is independently selected from a β-D-deoxyribonucleoside and a 2'-O-methoxyethyl nucleoside;
N^Y is selected from an S-cEt nucleoside and a β-D-deoxyribonucleoside; and
N^Z is an S-cEt nucleoside.

15. The compound of claim 2 wherein:
a. N^M is a 2'-O-methoxyethyl nucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
N^Y is a β-D-deoxyribonucleoside;
N^Z is a 2'-O-methoxyethyl nucleoside; and
b. N^M is a 2'-O-methoxyethyl nucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
N^Y is a β-D-deoxyribonucleoside; and
N^Z is an S-cEt nucleoside;
c. N^M is a 2'-O-methoxyethyl nucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
N^Y is an S-cEt nucleoside; and
N^Z is an S-cEt nucleoside.

16. The compound of claim 2 wherein:
N^M is a 2'-O-methoxyethyl nucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is independently selected from a β-D-deoxyribonucleoside and a 2'-O-methoxyethyl nucleoside;
N^Y is selected from an S-cEt nucleoside and a β-D-deoxyribonucleoside; and
N^Z is an S-cEt nucleoside.

17. The compound of any one of claims 1, 2, 14, and 16 having the structure:

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_STA_S$ (SEQ ID NO: 3); or

$A_EC_SA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_SU_SA_S$ (SEQ ID NO: 3).

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; and nucleosides followed by a subscript "S" are S-cEt nucleosides.

18. The compound of claim 3 wherein:

N^M is a 2'-O-methoxycthyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and

N^Z is a 2'-O-methoxyethyl nucleoside.

19. The compound of claim 3 having the structure:

$A_EC_SATC_SA_SGTC_SU_SGAU_SA_SAGC_SUSA_E$ (SEQ ID NO: 8);

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; and nucleosides followed by a subscript "S" are S-cEt nucleosides.

20. The compound of claim 4 wherein:

a. each N^B is an S-cEt nucleoside; and

each N^Q is a 2'-O-methoxyethyl nucleoside; or

b. each N^B is an S-cEt nucleoside; and

each N^Q is a β-D-deoxyribonucleoside.

21. The compound of claim 4 or claim 20 having the structure:

$^{Me}C_EA_SA_ST_EC_SU_SA_EA_EU_SA_SA_EG_EC_ST_EA_S$ (SEQ ID NO: 7);

wherein nucleosides followed by a subscript "E" are 2'-MOE nucleosides; nucleosides followed by a subscript "S" are S-cEt nucleosides; and ^{Me}C is 5-methyl cytosine.

22. The compound of claim 5, wherein:

a. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is selected from an S-cEt nucleoside and a 2'-O-methoxyethyl nucleoside;

b. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and

N^Z is an S-cEt nucleoside;

c. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is an S-cEt nucleoside; or

d. each N^M is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is independently selected from a 2'-O-methyl nucleoside and a β-D-deoxyribonucleoside; and

N^Z is a 2'-O-methoxyethyl nucleoside.

23. The compound of any one of the preceding claims, wherein the modified oligonucleotide comprises at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, or 22 contiguous nucleosides of nucleoside pattern III, IV, V, VI, or VII.
24. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to the nucleobase sequence of miR-21 (SEQ ID NO: 1).
25. The compound of any one of the preceding claims, wherein the modified oligonucleotide consists of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides of nucleoside pattern III, IV, V, VI, or VII.
26. The compound of any one of the preceding claims, wherein at least one internucleoside linkage is a modified internucleoside linkage, or wherein each internucleoside linkage is a modified internucleoside linkage, and wherein the modified internucleoside linkage is optionally a phosphorothioate internucleoside linkage.
27. The compound of any one of the preceding claims, wherein at least one cytosine is a 5-methyl cytosine, or wherein each cytosine is a 5-methylcytosine.
28. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is selected from SEQ ID NOs: 3 to 10, wherein each T is idependently selected from T and U.
29. The compound of any one of the preceding claims, wherein the modified oligonucleotide has 0, 1, 2, or 3 mismatches with respect to the nucleobase sequence of miR-21.
30. The compound of claim 29, wherein the modified oligonucleotide has 0 mismatches with respect to the nucleobase sequence of miR-21.
31. The compound of claim 29, wherein the modified oligonucleotide has 1 mismatch with respect to the nucleobase sequence of miR-21.
32. The compound of claim 29, wherein the modified oligonucleotide has 2 mismatches with respect to the nucleobase sequence of miR-21.

33. A compound comprising a modified oligonucleotide consisting of 8 to 22 linked nucleosides, wherein the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, atl east 17, at least 18, or at least 19 contiguous nucleosides of a structure selected from the structures in Table 1.
34. A compound comprising a modified oligonucleotide having a structure selected from the structures in Table 1.
35. A method of inhibiting the activity of miR-21 comprising contacting a cell with a compound of any of claims 1 to 34, wherein the cell is *in vitro*.
36. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for inhibiting the activity of miR-21 in a cell.
37. The method of claim 35 or use of claim 36 wherein the cell is a fibroblast cell, a hyperproliferative cell, a keratinocyte, or a hypoxic cell.
38. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for decreasing collagen expression in a cell.
39. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for treating, preventing or delaying the onset of a disease associated with miR-21 in a subject having a disease associated with miR-21.
40. The use of claim 39, wherein the disease is fibrosis.
41. The use of claim 40, wherein the fibrosis is selected from kidney fibrosis, lung fibrosis, liver fibrosis, cardiac fibrosis, skin fibrosis, age-related fibrosis, spleen fibrosis, scleroderma, and post-transplant fibrosis.
42. The use of claim 41, wherein:
    a. the kidney fibrosis is present in a subject having a disease selected from glomerulosclerosis, tubulointerstitial fibrosis, IgA nephropathy, interstitial fibrosis/tubular atrophy; chronic kidney damage, glomerular disease, glomerulonephritis, Alport Syndrome, diabetes mellitus, idiopathy focal segmental glomerulosclerosis, membranous nephropathy, collapsing glomerulopathy, chronic recurrent kidney infection, and end stage renal disease;
    b. the kidney fibrosis results from acute or repetitive trauma to the kidney;
    c. the liver fibrosis is present in a subject having a disease selected from chronic liver injury, hepatitis infection, non-alcoholic steatohepatitis, and cirrhosis; the pulmonary fibrosis is idiopathic pulmonary fibrosis; and/or
    d. the subject has chronic obstructive pulmonary disease.

43. Use of a compound of any of claims 1 to 34 in the manufacture of a medicament for treating a fibroproliferative disorder in a subject.
44. The method of claim 35 or method or use of claim 37 or use of any one of claims 36 and 38 to 43, wherein a subject having elevated miR-21 expression in one or more tissues is to be selected.

45. The useof any one of claims 39 to 43 or method or use of claim 44 wherein the subject is in need of improved organ function, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function.
46. The useof any one of claims 39 to 43 or method or use of claims 44 or 45 wherein the medicament improves organ function in the subject, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function.
47. The useof any one of claims 39 to 43 or method or use of any one of claims 44 to 46, wherein at least one therapeutic agent is to be administered, wherein said therapeutic agent is to be selected from an anti-inflammatory agent, an immunosuppressive agent, an anti-diabetic agent, digoxin, a vasodilator, an angiotensin II converting enzyme (ACE) inhibitors, an angiotensin II receptor blockers (ARB), a calcium channel blocker, an isosorbide dinitrate, a hydralazine, a nitrate, a hydralazine, a beta-blocker, a natriuretic peptides, a heparinoid, and a connective tissue growth factor inhibitor.
48. The useof claim 39, wherein the disease is cancer.
49. The useof claim 48, wherein the cancer is liver cancer, breast cancer, bladder cancer, prostate cancer, colon cancer, lung cancer, brain cancer, hematological cancer, pancreatic cancer, head and neck cancer, cancer of the tongue, stomach cancer, skin cancer, or thyroid cancer.
50. The useof claim 48 or claim 49, wherein at least one additional anti-cancer therapy is to be administered to the subject.
51. The useof any one of claims 39 to 43 and 48 to 50 or method or use of any one of claims 44 to 47, wherein the subject is a human.
52. The method of claim 35 or use of any one of claims 36, 38 to 43 and 48 to 50 or method or use of any one of claims 37, 44 to 47 and 51, wherein the compound is present as a pharmaceutical composition.
53. A compound of any one of claims 1 to 34 for use in therapy.
54. A compound of any of claims 1 to 34 for use in the treatment of fibrosis.
55. A compound of any of claims 1 to 34 for use in the treatment and/or prevention of impaired kidney function or end stage renal disease in a subject.
56. A compound of any of claims 1 to 34 for use in promoting wound healing.
57. A compound of any of claims 1 to 34 for use in treating cancer.
58. A compound of any of claims 1 to 34 for use in preventing and/or delaying the onset of metastasis.
59. A compound of any of claims 1 to 34 for use in treating cardiac disease.
60. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament.
61. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for treating fibrosis.
62. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for promoting wound healing.

63. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for treating cancer.
64. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for preventing and/or delaying the onset of metastasis.
65. Use of a compound of any one of claims 1 to 34 for the preparation of a medicament for preventing and/or delaying the onset of impaired kidney function or end stage renal disease.