MICRORNA COMPOUNDS AND METHODS FOR MODULATING MIR-21 ACTIVITY

This application claims the benefit of priority to U.S. Provisional Application Nos. 61/478,767, filed April 25, 2011, and 61/565,779, filed December 1, 2011, which are incorporated herein by reference in their entireties for any purpose.

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 OF INVENTION

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 examples, the cell is *in vivo*. In certain examples, 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 examples, the animal is a human.

The compounds described herein are provided for use in therapy.

Provided herein are compounds 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 I in the 5' to 3' orientation:

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

wherein each R is, independently, a non-bicyclic nucleoside; X is from 1 to 4; each N^B is, independently, a bicyclic nucleoside; each N^Q is, independently, a non-bicyclic nucleoside; and each N^Z is, independently, a modified nucleoside.

Provided herein are compounds 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 II in the 5' to 3' orientation:

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

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

In one aspect, the present invention provides a compound comprising a modified oligonucleotide complementary to miR-21 (SEQ ID NO: 1), wherein the modified oligonucleotide consists of 19 contiguous nucleosides of the following nucleoside pattern II in the 5' to 3' orientation:

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

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

each N^B is, independently, a bicyclic nucleoside;

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

N^Z is, independently, a modified nucleoside, and wherein

(i) each bicyclic nucleoside comprises a non-methylated nucleobase, or

(ii) no more than two non-bicyclic nucleosides are 2'-O-methoxyethyl nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside; and wherein each internucleoside linkage is a phosphorothioate linkage; and

wherein the modified oligonucleotide has the nucleobase sequence of SEQ ID NO: 3.

Provided herein are compounds 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 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 nucleoside; and each N^Z is a modified nucleoside.

Provided herein are compounds 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:

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

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 nucleoside; and N^Z is a modified nucleoside.

Provided herein are compounds 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:

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

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 certain examplesof nucleoside pattern I or III, X is 1, X is 2, X is 3, or X is 4.

In certain examplesof 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 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 I, II, III, IV or V. In certain examplesof any of the compounds provided herein, 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 I, II, III, IV or V.

In another aspect, the present invention provides acompound comprising a modified oligonucleotide consisting of at least 16 contiguous nucleotides of the structure:

$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$,

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, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

In yet another aspect, the present invention provides amodified oligonucleotide having the structure:

$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$,

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; and wherein each internucleoside linkage is a phosphorothioate linkage.

In certain examplesof any of the compounds provided herein, the nucleobase sequence of the modified oligonucleotide is at least 90% complementary is at least 95% complementary, or is 100% complementary to the nucleobase sequence of miR-21 (SEQ ID NO: 1).

In certain examplesof any of the compounds provided herein, the nucleobase at position 1 of miR-21 is paired with the first nucleobase at the 3'-terminus of the modified oligonucleotide.

In certain examplesof any of the compounds provided herein, each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside.

In certain examplesof any of the compounds provided herein, at least two non-bicyclic nucleosides comprise sugar moieties that are different from one another. In certain examplesof any of the compounds provided herein, each non-bicyclic nucleoside has the same type of sugar moiety.

In certain examplesof any of the compounds provided herein, each bicyclic nucleoside is a cEt nucleoside. In certain examples, the cEt nucleoside is an S-cEt nucleoside. In certain examples, the cEt nucleoside is an R-cEt nucleoside. In certain examplesof any of the compounds provided herein, each bicyclic nucleoside is an LNA nucleoside.

In certain examplesof any of the compounds provided herein, each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, a β-D-ribonucleoside, 2'-O-methyl nucleoside, a 2'-O-methoxyethyl nucleoside, and a 2'-fluoronucleoside. In certain examplesof any of the compounds provided herien, each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, and a 2'-O-methoxyethyl nucleoside. In certain examplesof any of the compounds provided herein, each non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain examplesof any of the compounds provided herein, each non-bicyclic nucleoside is a 2'-O-methoxyethyl nucleoside.

In certain examplesof any of the compounds provided herein, each bicyclic nucleoside comprises a non-methylated nucleobase.

In certain examplesof any of the compounds provided herein, no more than two non-bicyclic nucleosides are 2'-O-methoxyethyl nucleosides. In certain such examples, each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

In certain examplesof any of the compounds provided herein, the 5'-most and the 3'-most non-bicyclic nucleosides are 2'-O-methoxyethyl nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain examplesof any of the compounds provided herein, two non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

In certain examplesof nucleoside pattern I or III, each nucleoside of R is a 2'-O-methoxyethyl nucleoside. In certain examplesof nucleoside pattern I or III, three nucleosides of R are 2'-O-methoxyethyl nucleosides and one nucleoside of R is a β-D-deoxyribonucleoside.

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

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

In certain examplesof nucleoside pattern I, R consists of four linked nucleosides N^{R1}-N^{R2}-N^{R3}-N^{R4}, where N^{R1} is a 2'-O-methoxyethyl nucleoside and each of N^{R2}-N^{R3}-N^{R4} is a β-D-deoxyribonucleoside; 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. In certain examplesof nucleoside pattern I, 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; and N^{Z} is a 2'-O-methoxyethyl nucleoside. In certain examplesof nucleoside pattern I, each R is a 2'-O-methoxyethyl nucleoside; X is 1; each N^{B} is an S-cEt nucleoside; each N^{Q} is a 2'-O-methoxyethyl nucleoside; and N^{Z} is a 2'-O-methoxyethyl nucleoside. In certain examplesof nucleoside pattern I, 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; and N^{Z} is an S-cEt nucleoside. In certain examplesof nucleoside pattern I, each R is a 2'-O-methoxyethyl nucleoside; X is 1; each N^{B} is an LNA nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; and N^{Z} is a 2'-O-methoxyethyl nucleoside. In certain examplesof nucleoside pattern I, each R is a 2'-O-methoxyethyl nucleoside; X is 1; each N^{B} is an LNA nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; and N^{Z} is an LNA nucleoside.

In certain examplesof nucleoside pattern II, 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. In certain examplesof nucleoside pattern II, N^{M} is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside; each N^Q is a 2'-O-methoxyethyl nucleoside; and N^Z is a 2'-O-methoxyethyl nucleosid. In certain examplesof nucleoside pattern I, N^M is a 2'-O-methoxyethyl nucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; each N is a β-D-deoxyribonucleoside; and N^Z is an S-cEt nucleoside. In certain examplesof nucleoside pattern II, N^M is a 2'-O-methoxyethyl nucleoside; each N^B is an LNA nucleoside; each N^Q is a β-D-deoxyribonucleoside; and N^Z is a 2'-O-methoxyethyl nucleoside. In certain examplesof nucleoside pattern II, N^M is a 2'-O-methoxyethyl nucleoside; each N^B is an LNA nucleoside; each N^Q is a β-D-deoxyribonucleoside; and N^Z is an LNA nucleoside.

In certain examplesof nucleoside pattern III, 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. In certain examplesof nucleoside pattern III, 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. In certain examplesof nucleoside pattern III, 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.

In certain examplesof nucleoside pattern IV, 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. In certain examplesof nucleoside pattern IV, 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. In certain examplesof nucleoside pattern IV, 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.

In certain examplesof nucleoside pattern V, 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.

In certain examplesof any of the compounds provided herein, the modified oligonucleotide has the nucleobase sequence of SEQ ID NO: 3, wherein each T in the sequence is independently selected from T and U. In certain examplesof any of the compounds provided herein, the modified oligonucleotide has the nucleobase sequence of SEQ ID NO: 4, wherein each T in the sequence is independently selected from T and U.

Provided herein are methods for inhibiting the activity of miR-21 comprising contacting a cell with a compound provided herein. In certain examples, the cell is is *in vivo*. In certain examples, the cell is *in vitro*. In certain examples, the cell is a fibroblast cell, a hyperproliferative cell, a keratinocyte, or a hypoxic cell. In certain examples, the fibroblast cell is a hyperproliferative fibroblast cell.

Provided herein are methods for decreasing collagen expression in a cell comprising contacting a cell with a compound provided herein.

Provided herein are methods to treat, prevent, or delay the onset of a disease associated with miR-21, comprising administering to a subject having such a disease any of the compounds provided herein.

In certain examples, the disease is fibrosis. In certain examplesthe fibrosis is kidney fibrosis, lung fibrosis, liver fibrosis, cardiac fibrosis, skin fibrosis, age-related fibrosis, spleen fibrosis, scleroderma, or post-transplant fibrosis.

In certain examples, the fibrosis is kidney fibrosis and 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, diabetes mellitus, idiopathy focal segmental glomerulosclerosis, membranous nephropathy, collapsing glomerulopathy, chronic recurrent kidney infection, and end stage renal disease. In certain examples, the kidney fibrosis results from acute or repetitive trauma to the kidney.

In certain examples, the fibrosis is liver fibrosis and is present in a subject having a disease selected from chronic liver injury, hepatitis infection, non-alcoholic steatohepatitis, and cirrhosis.

In certain examples, the pulmonary fibrosis is idiopathic pulmonary fibrosis, or the subject has chronic obstructive pulmonary disease.

In certain examples, disease is an inflammatory disease.

Provided herein are methods of promoting wound healing in a subject comprising administering to a subject having an acute or chronic wound any of the compounds provided herein. In certain examples, the chronic wound is an acute or chronic surgical wound, a penetrating wound, an avulsion injury, a crushing injury, a shearing injury, a burn injury, a laceration, a bite wound, an arterial ulcer, a venous ulcer, a pressure ulcer, or a diabetic ulcer. In certain examples, the compound is administered topically to the wound.

Provided herein are methods to treat a fibroproliferative disorder in a subject comprising administering to the subject any of the compounds provided herein.

Any of the methods provided herein may comprise selecting a subject having elevated miR-21 expression in one or more tissues.

In certain examples, administering any of the compounds provided herein to a subject reduces collagen expression.

In certain examples, a subject is in need of improved organ function, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function. In certain examples, the administering of any of the compounds provided herein improves organ function in the subject, wherein the organ function is selected from cardiac function, pulmonary function, liver function, and kidney function.

Any of the methods provided herein comprises evaluating kidney function in a subject, which may include measuring blood urea nitrogen in the blood of the subject; measuring creatinine in the blood of the subject; measuring creatinine clearance in the subject; measuring proteinuria in the subject; measuring albumin:Cr ratio in the subject; and/or measuring urinary output in the subject.

Any of the methods provided herein may comprise evaluating liver function in a subject, which may include measuring alanine aminotransferase levels in the blood of the subject; measuring aspartate aminotransferase levels in the blood of the subject; measuring bilirubin levels in the blood of the subject; measuring albumin levels in the blood of the subject; measuring prothrombin time in the subject; measuring ascites in the subject; and/or measuring encephalopathy in the subject.

Any of the methods provided herein may comprise evaluating lung function in a subject, which may include measuring vital capacity in the subject; measuring forced vital capacity in the subject; measuring forced expiratory volume in one second in the subject; measuring peak expiratory flow rate in the subject; measuring forced expiratory flow in the subject; measuring maximal voluntary ventilation in the subject; determining the ratio of forced expiratory volume in one second to forced vital capacity in the subject; measuring ventilation/perfusion ratio in the subject; measuring nitrogen washout in the subject; and/or measuring absolute volume of air in one or more lungs of a subject.

Any of the methods provided herein may comprise evaluating cardiac function in a subject, which may include measuring cardiac output in the subject; measuring stroke volume in the subject; measuring mean systolic ejection rate in the subject; measuring systolic blood pressure in the subject; measuring left ventricular ejection fraction in the subject; determining stroke index in the subject; determining cardiac index in the subject; measuring left ventricular percent fractional shortening in the subject; measuring mean velocity of circumferential fiber shortening in the subject; measuring left ventricular inflow velocity pattern in the subject; measuring pulmonary venous flow velocity pattern in the subject; and/ormeasuring peak early diastolic velocity of the mitral annulus of the subject.

Any of the methods provided herein may comprise administering to a subject at least one therapeutic agent 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. In certain examples, the anti-inflammatory agent is a non-steroidal anti-inflammatory agent, wherein the non-steroidal anti-inflammatory agent is optionally selected from ibuprofen, a COX-1 inhibitor and a COX-2 inhibitor. In certain examples, the immunosuppressive agent is selected from a corticosteroid, cyclophosphamide, and mycophenolate mofetil. In certain examples, anti-inflammatory agent is a corticosteroid,

wherein the corticosteroid is optionally prednisone. In certain examples, the angiotensin II converting enzyme (ACE) inhibitors is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril. In certain examples, the angiotensin II receptor blockers (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan.

In certain examples, a disease is cancer. In certain examples, 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. In certain examples, the liver cancer is hepatocellular carcinoma. In certain examples, the brain cancer is glioblastoma multiforme. In certain examples, the hematological cancer is acute myelogenous leukemia, acute lymphocytic leukemia, acute monocytic leukemia, multiple myeloma, chronic lymphotic leukemia, chronic myeloid leukemia, hodgkin's lymphoma, or non-hodgkin's lymphoma.

In certain examples, the methods provided herein comprise administering at least one additional anti-cancer therapy to the subject. In certain examples, the anti-cancer therapy is a DNA damaging agent, a proliferation inhibitor, an anti-folate, a growth factor receptor inhibitor, an anti-angiogenic agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a growth factor inhibitor, a cytotoxic agent, radiation therapy, or surgical resection of a tumor. In certain examples, the DNA damaging agent is 1,3-bis(2-chloroethyl) -1-nitrosourea, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, daunorubicin, doxorubicin, epirubicin, etoposide, idarubicin, ifosfamide, irinotecan, lomustine, mechlorethamine, melphalan, mitomycin C, mitoxantrone, oxaliplatin, temozolomide, or topotecan. In certain examples, the anti-folate is methotrexate, aminopterin, thymidylate synthase, serine hydroxymethyltransferase, folyilpolyglutamyl synthetase, g-glutamyl hydrolase, glycinamide-ribonucleotide transformylase, leucovorin, amino-imidazole-carboxamide-ribonucleotide transformylase, 5-fluorouracil, or a folate transporter. In certain examples, the growth factor receptor inhibitor is erlotinib, or gefitinib. In certain examples, the angiogenesis inhibitor is bevacizumab, thalidomide, carboxyamidotriazole, TNP-470, CM101, IFN-α, platelet factor-4, suramin, SU5416, thrombospondin, a VEGFR antagonist, cartilage-derived angiogenesis inhibitory factor, a matrix metalloproteinase inhibitor, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, prolactin, or linomide. In certain examples, the kinase inhibitor is bevacizumab, BIBW 2992, cetuximab, imatinib, trastuzumab, gefitinib, ranibizumab, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, panitumumab, vandetanib, E7080, pazopanib, mubritinib, or fostamatinib.

In certain examples, the administering to a subject having cancer results in reduction of tumor size and/ or tumor number. In certain examples, the administering to a subject having cancer prevents or delays an increase in tumor size and/or tumor number. In certain examples,

the administering to a subject having cancer prevents or slows metastatic progression. In certain examples, the administering to a subject having cancer extends overall survival time and/or progression-free survival of the subject. In certain examples, the methods provided herein comprise selecting a subject having elevated serum alpha-fetoprotein and/or elevated serum des-gamma-carboxyprothrombin. In certain examples, the methods provided herein comprise reducing serum alpha-fetoprotein and/or serum des-gamma-carboxyprothrombin. In certain examples, the methods provided herein comprise selecting an animal having abnormal liver function.

In any of the methods provided herein, subject is a human.

In any of the methods provided herien, the compound is present as a pharmaceutical composition.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the compound described herein or the modified oligonucleotide described herein and a pharmaceutically acceptable carrier.

Any of the compounds provided herein may be foruse in therapy. Any of the compounds provided herein may be for use in the treatment of fibrosis. Any of the compounds provided herein may be foruse in promoting wound healing. Any of the compounds provided herein may be for use in treating cancer. Any of the compounds provided herien may be for use in preventing and/or delaying the onset of metastatis.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein in the manufacture of a medicament for inhibiting the activity of miR-21 in a cell, wherein the medicament is to be contacted to a cell.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein in the manufacture of a medicament for decreasing collagen expression in a cell, wherein the medicament is to be contacted to a cell.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide of described herein 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, wherein the medicament is to be adiministered into the subject having a disease associated with miR-21.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide of described herein in the manufacture of a medicament for treating a fibroproliferative disorder in a subject, wherein the medicament is to be administered into the subject.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in therapy.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in the treatment of fibrosis.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in promoting wound healing.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in treating cancer.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in preventing and/or delaying the onset of metastasis.

Any of the compounds provided herein may be for use in treating cardiac disease.

In yet another aspect, the present invention provides a compound described herein or the modified oligonucleotide described herein, for use in treating cardiac disease.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein for the preparation of a medicament.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein for the preparation of a medicament for treating fibrosis.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein for the preparation of a medicament for promoting wound healing.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein for the preparation of a medicament for treating cancer.

In yet another aspect, the present invention provides use of a compound described herein or the modified oligonucleotide described herein for the preparation of a medicament for preventing and/or delaying the onset of metastasis.

Any of the compounds provided herein may be for use in the preparation of a medicament. Any of the compounds provided herein may be for use in the preparation of a medicament for treating fibrosis. Any of the compounds provided herein may be for use in the preparation of a medicament for promoting wound healing. Any of the compounds provided herein may be for use in the preparation of a medicament for treating cancer. Any of the compounds provided herein may be for use in the preparation of a medicament for preventing and/or delaying the onset of metastasis.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows urinary albumin to creatinine ratio (ACR, μgAlb/mgCr) in ischemic reperfusion/nephrectomy (IR/Nx) model mice administered anti-miR21 compounds, as described in Example 5.

Figure 2 shows (A) collagen 1A1 and (B) collagen 3A1 expression in kidneys of UUO model mice administered anti-miR21 compounds, as described in Example 6.

DETAILED DESCRIPTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the arts to which the invention belongs. Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and