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 ~~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 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.

~~Provided herein are~~In one aspect, there is provided a 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 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~~In one aspect, there is provided a 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.

In one aspect, there is provided a ~~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 one aspect, there is provided a ~~Provided herein are~~ compounds 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:

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

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

In one aspect, there is provided a ~~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 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:

$A_ECsA_ET_EC_SA_EG_ET_EC_STGAU_SAAGC_SU_SA_S$ (SEQ ID NO: 3).

In ~~certain embodiments,~~one aspect, there is provided a compound comprisinges 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 ~~certain embodiments,~~one aspect, there is provided a compound comprisinges a modified oligonucleotide having a structure selected from the structures in Table 1.

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*.

In one aspect, there is provided the use of a compound as described herein in the manufacture of a medicament for inhibiting the activity of miR-21 in a cell.

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

a keratinocyte, or a fibrocyte. In certain embodiments, the cell is a hyperproliferative cell or a hypoxic cell. In certain embodiments, the fibroblast cell is a hyperproliferative fibroblast cell.

Provided herein are methods of inhibiting the activity of miR-21 comprising contacting a cell with with any of the compounds described herein. In certain embodiments, the cell is *in vivo*. In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is a fibroblast cell, a hyperproliferative cell, a keratinocyte, or a hypoxic cell.

In one aspect, there is provided the use of a compound as described herein in the manufacture of a medicament for decreasing collagen expression in a cell.

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

In one aspect, there is provided the use of a compound as described herein in the manufacture of a medicament for treating, preventing or delaying the onset of a disease associated with miR-21in a subject having a disease associated with miR-21.

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

In certain embodiments, the fibrosis is kidney fibrosis and is present in a subject having a disease or condition selected from glomerulosclerosis, tubulointerstitial fibrosis, IgA nephropathy, interstitial fibrosis/tubular atrophy; chronic kidney damage, chronic kidney disease,, glomerular disease, glomerulonephritis, diabetes mellitus, idiopathy focal segmental glomerulosclerosis, membranous nephropathy, collapsing glomerulopathy, chronic recurrent kidney infection, chronic kidney disease following acute kidney injury (AKI), kidney damage following exposure to environmental toxin and/or natural product, and end stage renal disease. In certain embodiments, the kidney fibrosis results from acute or repetitive trauma to the kidney.

In certain embodiments, the fibrosis is liver fibrosis and is present in a subject having a disease selected from chronic liver injury, hepatitis infection (such as hepatitis B infection and/or hepatitis C infection), non-alcoholic steatohepatitis, alcoholic liver disease, liver damage following exposure to environmental toxin and/or natural product, and cirrhosis.

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

In certain embodiments, 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 embodiments, 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 embodiments, the compound is administered topically to the wound.

In one aspect, there is provided the use of a compound as described herein in the manufacture of a medicament for treating a fibroproliferative disorder in a subject.

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 embodiments, administering any of the compounds provided herein to a subject reduces collagen expression.

In certain embodiments, 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 embodiments, 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:creatinine ratio in the subject; measuring urinary output in the subject; measuring inulin clearance in the urine of the subject; measuring urinary osmolarity in the subject; measuring urinary osmolality in the subject; measuring hematuria in the subject; measuring cystatin C in the blood and/or urine of the subject; and/or measuring neutrophil gelatinase-associated lipocalin (NGAL) in the blood or urine of 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; measuring encephalopathy in the subject; and/or measuring liver stiffness, for example, using transient elastography.

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;

In certain embodiments, the methods provided herein comprise administering at least one additional anti-cancer therapy to the subject. In certain embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the growth factor receptor inhibitor is erlotinib, or gefitinib. In certain embodiments, 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 embodiments, 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 embodiments, the administering to a subject having cancer results in reduction of tumor size and/ or tumor number. In certain embodiments, the administering to a subject having cancer prevents or delays an increase in tumor size and/or tumor number. In certain embodiments, the administering to a subject having cancer prevents or slows metastatic progression. In certain embodiments, the administering to a subject having cancer extends overall survival time and/or progression-free survival of the subject. In certain embodiments, the methods provided herein comprise selecting a subject_ having elevated serum alpha-fetoprotein and/or elevated serum des-gamma-carboxyprothrombin. In certain embodiments, the methods provided herein comprise reducing serum alpha-fetoprotein and/or serum des-gamma-carboxyprothrombin. In certain embodiments, the methods provided herein comprise selecting an animal having abnormal liver function.

In certain embodiments, a subject is a human. In certain embodiments, a subject is a canine.

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

~~Any of the~~In one aspect, there is provided a compounds ~~as provided~~ described herein ~~may be~~ for use in therapy. In one aspect, there is provided a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for use in the treatment of fibrosis. In one aspect, there is provided a ~~Any of the~~ compounds as ~~provided~~ described herein

~~may be~~ for use in promoting wound healing. In one aspect, there is provided a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for use in
treating cancer. In one aspect, there is provided a ~~Any of the~~ compounds as described ~~provided~~ herein ~~may be~~ for use in preventing and/or delaying
the onset of metastasis.
In one aspect, there is provided a compound as described herein for use in the treatment and/or prevention of impaired kidney function or end stage renal disease in a subject.

In one aspect, there is provided a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for use in treating cardiac disease.

In one aspect, there is provided the use of a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for ~~use in~~ the preparation of a medicament.
In one aspect, there is provided the use of a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for ~~use in~~ the preparation of a medicament for treating
fibrosis. In one aspect, there is provided the use of a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for ~~use in~~ the preparation of a medicament for
promoting wound healing. In one aspect, there is provided the use of a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for ~~use in~~ the preparation
of a medicament for treating cancer. In one aspect, there is provided the use of a ~~Any of the~~ compounds as ~~provided~~ described herein ~~may be~~ for ~~use in~~ the
preparation of a medicament for preventing and/or delaying the onset of metastasis.
In one aspect, there is provided the use of a compound as described herein for the preparation of a medicament for preventing and/or delaying the onset of impaired kidney function or end stage renal disease.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the change in (A) collagen 1A1 and (B) collagen 3A1 expression in kidneys of UUO model mice administered certain anti-miR-21 compounds, as described in Example 1.

Figure 2 shows the change in (A) collagen 1A1 and (B) collagen 3A1 expression in kidneys of UUO model mice administered certain anti-miR-21 compounds, as described in Example 1.

Figure 3 shows the change in (A) collagen 1A1 and (B) collagen 3A1 expression in kidneys of UUO model mice administered certain anti-miR-21 compounds, as described in Example 2.

Figure 4 shows (A) the change in collagen 1A1 expression, (B) the change in collagen 3A1 expression, and (C) the collagen area fraction in kidneys of unilateral IRI model mice administered certain anti-miR-21 compounds, as described in Example 3.

Figure 5 shows (A) urinary albumin to creatinine ratio in kidneys of IR/Nx model mice administered compound 36328 or a control compound, (B) urinary albumin to creatinine ratio in

kidneys of IR/Nx model mice administered compound 36284, and (C) urinary albumin to creatinine ratio in kidneys of IR/Nx model mice administered compound 25220, as described in Example 4.

Figure 6 shows (A) luciferase activity of anti-miR-21 compounds and (B) anti-proliferative effects of anti-miR-21 compounds in cultured cells, as described in Example 6.

Figure 7 shows the change in (A) collagen 1A1 and (B) collagen 3A1 expression in kidneys of UUO model mice administered certain anti-miR-21 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

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. The method of claim 35, wherein the cell is *in vivo* or 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. ~~A method of decreasing collagen expression in a cell comprising contacting a cell with~~ 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. ~~A method of treating, preventing or delaying the onset of a disease associated with miR-21 comprising administering to a subject having a disease associated with miR-21~~ 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 ~~method~~ of claim 39, wherein the disease is fibrosis.
41. The use ~~method~~ 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 ~~method~~ 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. ~~A method of treating a fibroproliferative disorder in a subject comprising administering to the subject~~ 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~~35~~ 38 to 43, ~~comprising selecting~~ wherein a subject having elevated miR-21 expression in one or more tissues is to be selected.

45. The use~~method~~ of any one of claims 39 to 4344 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~~method~~ of any one of claims 39 to 43 or method or use of claims 44 or 45 wherein the ~~administering~~ 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~~method~~ of any one of claims 39 to 43 or method or use of any one of claims 44 to 46, ~~comprising administering~~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~~method~~ of claim 39, wherein the disease is cancer.
49. The use~~method~~ 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~~method~~ of claim 48 or claim 49, ~~further comprising administering~~wherein at least one additional anti-cancer therapy is to be administered to the subject.
51. The use~~method~~ 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 ~~35 to 51~~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.