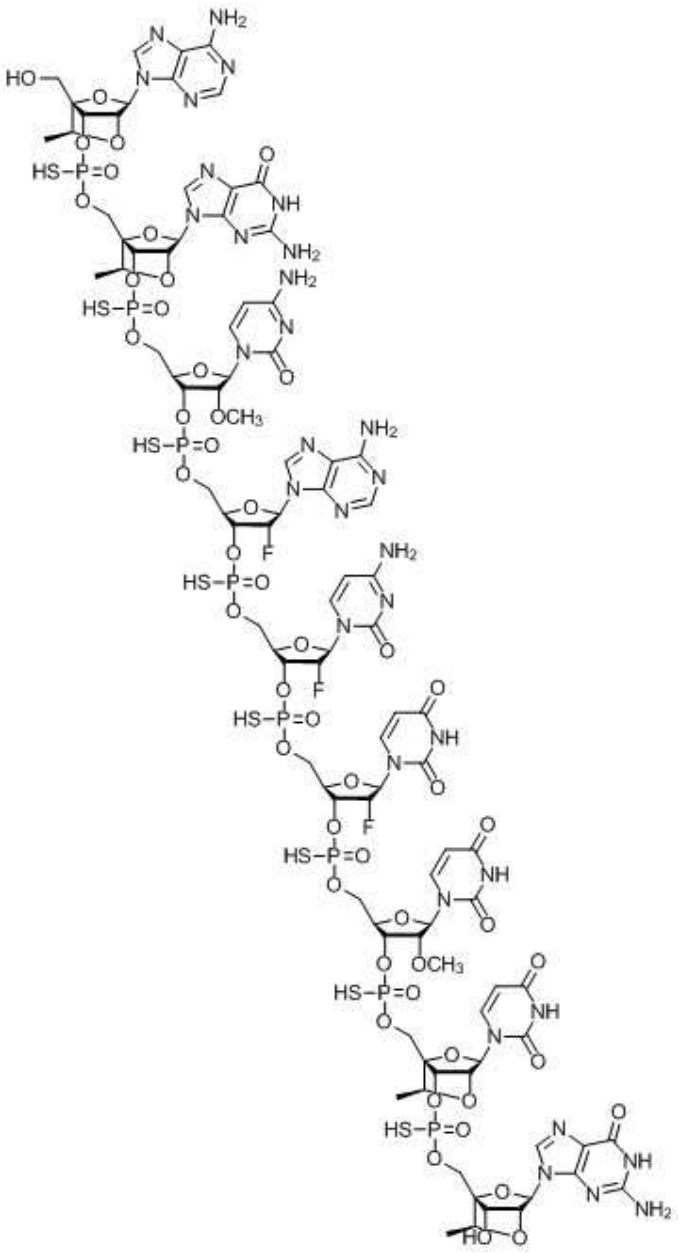
Claims

1. Use of a compound comprising a modified oligonucleotide consisting of 9 linked nucleosides in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the modified oligonucleotide has the following nucleoside pattern in the 5' to 3' orientation:

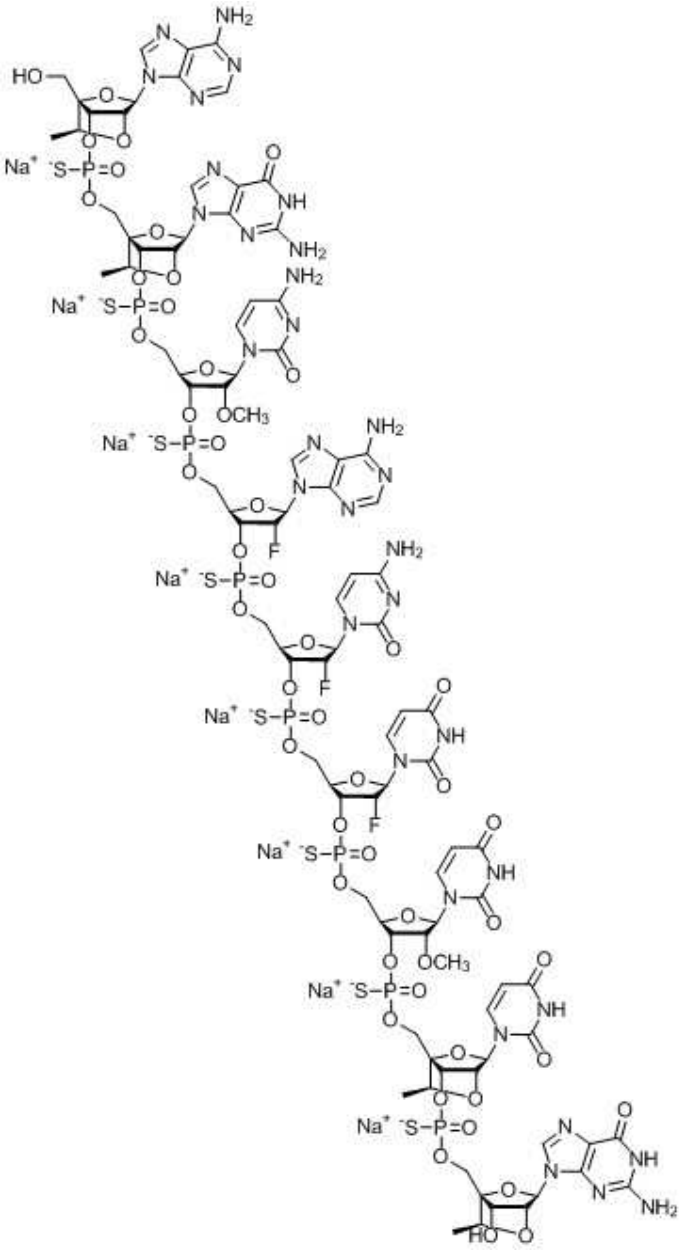
   $$N_SN_SN_MN_FN_FN_FN_MN_SN_S$$

   wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides, nucleosides followed by subscript "F" are 2'-fluoro nucleosides, nucleosides followed by subscript "S" are S-cEt nucleosides, and all linkages are phosphorothioate linkages;
   wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-CACUUU-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof, and wherein the compound is to be administered to a subject in need thereof .
2. The use of claim 1, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-GCACUUU-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine.
3. The use of claim 1 or 2, wherein the nucleobase sequence of the modified oligonucleotide is 5'-AGCACUUUG-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine.
4. The use of any one of claims 1 to 3, wherein the compound consists of the modified oligonucleotide or a pharmaceutically acceptable salt thereof.
5. The use of any one of claims 1 to 4, wherein the pharmaceutically acceptable salt is a sodium salt.
6. Use of a modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the compound is to be administered to a subject in need thereof.

7. The method of claim 6, wherein the modified oligonucleotide is a pharmaceutically acceptable salt of the structure.
8. The method of claim 7, wherein the modified oligonucleotide is a sodium salt of the structure.
9. Use of a modified oligonucleotide having the structure:



in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the modified oligonucleotide is to be administered to a subject in need thereof.

10. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the pharmaceutical composition comprises:
    a) a compound comprising a modified oligonucleotide consisting of 9 linked nucleosides, wherein the modified oligonucleotide has the following nucleoside pattern in the 5' to 3' orientation:

$$N_SN_SN_MN_FN_FN_FN_MN_SN_S$$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides, nucleosides followed by subscript "F" are 2'-fluoro nucleosides, nucleosides followed by subscript "S" are S-cEt nucleosides, and all linkages are phosphorothioate linkages; and

wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-CACUUU-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable diluent,

wherein the pharmaceutical composition is to be administered to a subject in need thereof.

11. The use of claim 10, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-GCACUUU-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine.

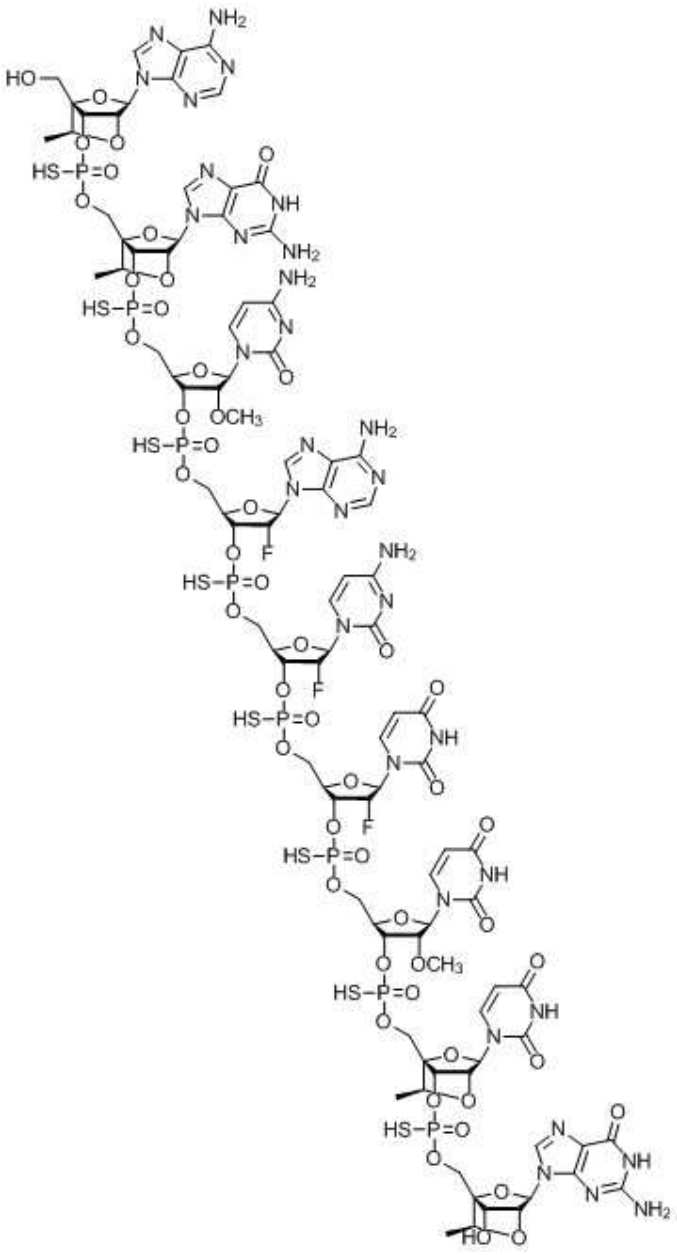
12. The use of claim 10, wherein the nucleobase sequence of the modified oligonucleotide is 5'-AGCACUUUG-3', wherein each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine.

13. The method of any one of claims 10 to 12, wherein the compound consists of the modified oligonucleotide or a pharmaceutically acceptable salt thereof.

14. The use of any one of claims 10 to 13, wherein the pharmaceutically acceptable salt is a sodium salt.

15. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the pharmaceutical composition comprises

a) a modified oligonucleotide having the structure:



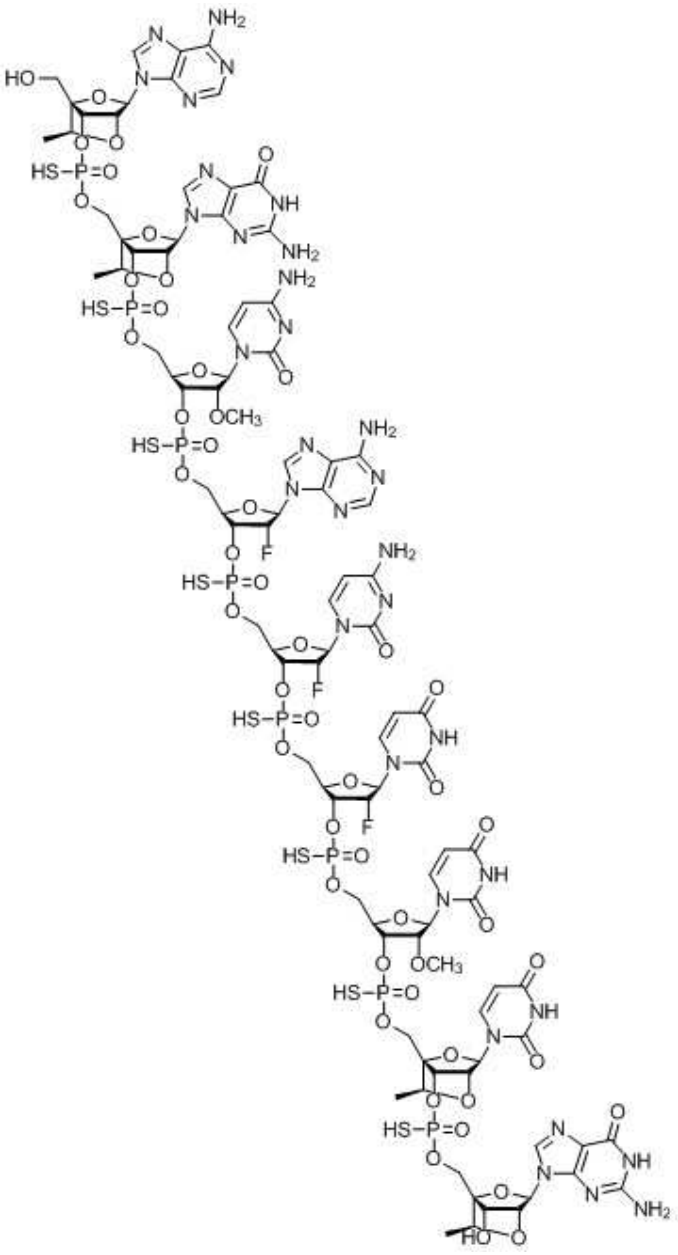
or a pharmaceutically acceptable salt thereof;

b) and a pharmaceutically acceptable diluent, and

wherein the pharmaceutical composition is to be administered to a subject in need thereof.

16. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the pharmaceutical composition consists essentially of:

a) a modified oligonucleotide having the structure:



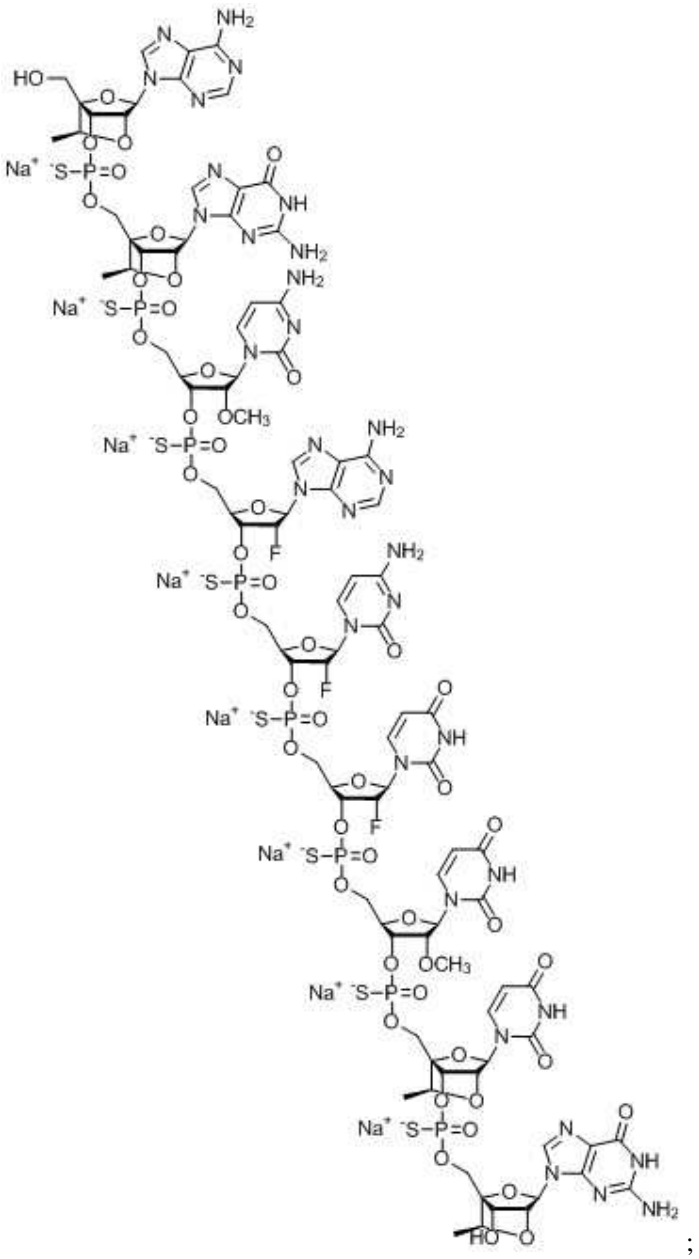
or a pharmaceutically acceptable salt thereof;

b) and a pharmaceutically acceptable diluent, and

wherein the pharmaceutical composition is to be administered to a subject in need thereof.

17. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the pharmaceutical composition comprises

a) a modified oligonucleotide having the structure:



;

b) and a pharmaceutically acceptable diluent, and

wherein the pharmaceutical composition is to be administered to a subject in need thereof.

18. The use of any one of claims 10 to 17, wherein the pharmaceutically acceptable diluent is a sterile aqueous solution.

19. The use of claim 18, wherein the sterile aqueous solution is a saline solution.

20. The use of any one of the preceding claims, wherein the subject has polycystic kidney disease.

21. The use of any one of the preceding claims, wherein the subject is suspected of having polycystic kidney disease.

22. The use of any one of the preceding claims wherein the subject has been diagnosed as having polycystic kidney.

23. The use of any one of the preceding claims wherein the subject was determined to have an increased level of miR-17 in the kidney, urine or blood of the subject.

24. The use of any one of the preceding claims, wherein the polycystic kidney disease is autosomal recessive polycystic kidney disease.

25. The use of any one of claims 1 to 23, wherein the polycystic kidney disease is autosomal dominant polycystic kidney disease.

26. The use of any one of the preceding claims, wherein the subject has a mutation selected from a mutation in the *PKD1* gene or a mutation in the *PKD2* gene.

27. The use of any one of the preceding claims, wherein the subject has increased total kidney volume.

28. The use of any one of the preceding claims, wherein the subject has hypertension.

29. The use of any one of the preceding claims, wherein the subject has impaired kidney function.

30. The use of any one of the preceding claims, wherein the subject is in need of improved kidney function.

31. The use of any one of the preceding claims, wherein the administration:

    a) improves kidney function in the subject;

    b) delays the worsening of kidney function in the subject;

    c) reduces total kidney volume in the subject;

    d) slows the increase in total kidney volume in the subject;

    e) inhibits cyst growth in the subject;

    f) slows the increase in cyst growth in the subject;

    g) reduces kidney pain in the subject;

    h) slows the increase in kidney pain in the subject;

    i) delays the onset of kidney pain in the subject;

    j) reduces hypertension in the subject;

    k) slows the worsening of hypertension in the subject;

    l) delays the onset of hypertension in the subject;

    m) reduces fibrosis in the kidney of the subject;

    n) slows the worsening of fibrosis in the kidney of the subject;

    o) delays the onset of end stage renal disease in the subject;

p) delays time to dialysis for the subject;

q) delays time to renal transplant for the subject; and/or

r) improves life expectancy of the subject.

32. The use of any one of the preceding claims, wherein the administration:

a) reduces albuminuria in the subject;

b) slows the worsening of albuminuria in the subject;

c) delays the onset of albuminuria in the subject;

d) reduces hematuria in the subject;

e) slows the worsening of hematuria in the subject;

f) delays the onset of hematuria in the subject;

g) reduces blood urea nitrogen level in the subject;

h) reduces serum creatinine level in the subject;

i) improves creatinine clearance in the subject;

j) reduces albumin:creatinine ratio in the subject;

k) improves glomerular filtration rate in the subject;

l) slows rate of decline of glomerular filtration rate in the subject;

m) reduces neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or

n) reduces kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

33. The use of one of the preceding claims, comprising:

a) measuring total kidney volume in the subject;

b) measuring hypertension in the subject;

c) measuring kidney pain in the subject;

d) measuring fibrosis in the kidney of the subject;

e) measuring blood urea nitrogen level in the subject;

f) measuring serum creatinine level in the subject;

g) measuring creatinine clearance in the subject;

h) measuring albuminuria in the subject;

i) measuring albumin:creatinine ratio in the subject;

j) measuring glomerular filtration rate in the subject;

k) measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or

l) measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

34. The use of any one of the preceding claims, wherein the administration reduces total kidney volume in the subject.

35. The use of any one of the preceding claims, wherein the administration slows the rate of increase of total kidney volume in the subject.

36. The use of any one of claims 27, 31, 33, 34, or 35, wherein the total kidney volume is height-adjusted total kidney volume.

37. The use of any one of the preceding claims, wherein the administration slows the rate of decline of glomerular filtration rate in the subject.

38. The use of any one of claims 32, 33, or 37, wherein the glomerular filtration rate is estimated glomerular filtration rate.

39. The use of claim 31, wherein the cyst is present in one or more kidneys in the subject.

40. The use of claim 31, wherein the cyst is present in the liver of the subject.

41. The use of any one of the preceding claims, comprising at least one additional therapy to be administered, wherein at least one additional therapy is an anti-hypertensive agent.

42. The use of any one of the preceding claims, comprising at least one additional therapy to be administered, wherein the additional therapy is selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a diuretic, a calcium channel blocker, a kinase inhibitor, an adrenergic receptor antagonist, a vasodilator, a benzodiazepine, a renin inhibitor, an aldosterone receptor antagonist, an endothelin receptor blocker, an mammalian target of rapamycin (mTOR) inhibitor, a hormone analogue, a vasopressin receptor 2 antagonist, an aldosterone receptor antagonist, dialysis, and kidney transplant.

43. The use of claim 42, wherein the angiotensin II converting enzyme (ACE) inhibitor is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril.

44. The use of claim 42, wherein the angiotensin II receptor blocker (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan.

45. The use of claim 42, wherein the vasopressin receptor 2 antagonist is tolvaptan.

46. The use of claim 42, wherein the aldosterone receptor antagonist is spironolactone.

47. The use of claim 42, wherein the kinase inhibitor is selected from bosutinib and KD019.

48. The use of claim 42, wherein the mTOR inhibitor is selected from everolimus, rapamycin, and sirolimus.

49. The use of claim 42, the hormone analogue is selected from somatostatin and adrenocorticotrophic hormone.

50. The use of any one of the preceding claims, comprising a therapeutically effective amount of the compound to be administered.

51. Use of a compound in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the compound comprises

a modified oligonucleotide consisting of 9 linked nucleosides, wherein the modified oligonucleotide has the following nucleoside pattern in the 5' to 3' orientation:

$N_SN_SN_MN_FN_FN_FN_FN_MN_SN_S$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides, nucleosides followed by subscript "F" are 2'-fluoro nucleosides, nucleosides followed by subscript "S" are S-cEt nucleosides, and all linkages are phosphorothioate linkages; and wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-CACUUU-3', wherein each C is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof; wherein the compound is to be administered to a selected subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria, and

wherein the subject, following the administration of the compound, experiences an improvement in one or more markers of polycystic kidney disease selected from:

i) total kidney volume;

ii) hypertension;

iii) glomerular filtration rate;

iv) kidney pain.

52. Use of a compound in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the compound comprises

a modified oligonucleotide consisting of 9 linked nucleosides, wherein the modified oligonucleotide has the following nucleoside pattern in the 5' to 3' orientation:

$N_SN_SN_MN_FN_FN_FN_FN_MN_SN_S$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides, nucleosides followed by subscript "F" are 2'-fluoro nucleosides, nucleosides followed by subscript "S" are S-cEt nucleosides, and all linkages are phosphorothioate linkages; and

wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-CACUUU-3', wherein each C is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof; wherein the compound is to be administered to a selected subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; wherein the subject has

i) increased kidney volume;

ii) hypertension;

iii) impaired glomerular filtration rate; and/or

iv) kidney pain, and

wherein the subject, following the administration of the compound, experiences an improvement in one or more markers of polycystic kidney disease selected from:

i) total kidney volume;

ii) hypertension;

iii) glomerular filtration rate;

iv) kidney pain.

53. The use of claim 51 or 52, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence 5'-GCACUUU-3', wherein each C is independently selected from a non-methylated cytosine and a 5-methylcytosine.

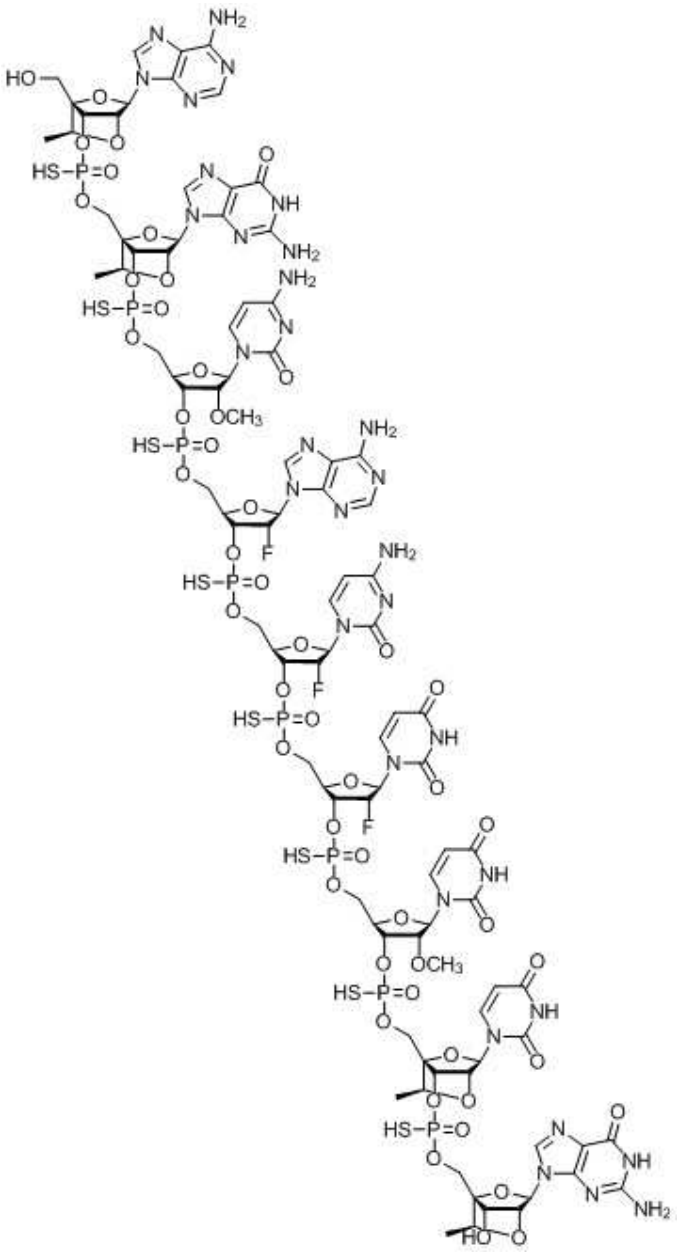
54. The use of claim 51 or 52, wherein the nucleobase sequence of the modified oligonucleotide is 5'-AGCACUUUG-3', wherein each C is independently selected from a non-methylated cytosine and a 5-methylcytosine.

55. The use of any one of claims 51 to 54, wherein the compound consists of the modified oligonucleotide or a pharmaceutically acceptable salt thereof.

56. The use of any one of claims 51 to 55, wherein the pharmaceutically acceptable salt is a sodium salt.

57. Use of a modified oligonucleotide in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein

the modified oligonucleotide has the structure:



or a pharmaceutically acceptable salt thereof; wherein the modified oligonucleotide is to be administered to a selected subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; and

wherein the subject, following the administration of the modified oligonucleotide, experiences an improvement in one or more markers of polycystic kidney disease selected from:

i) total kidney volume;

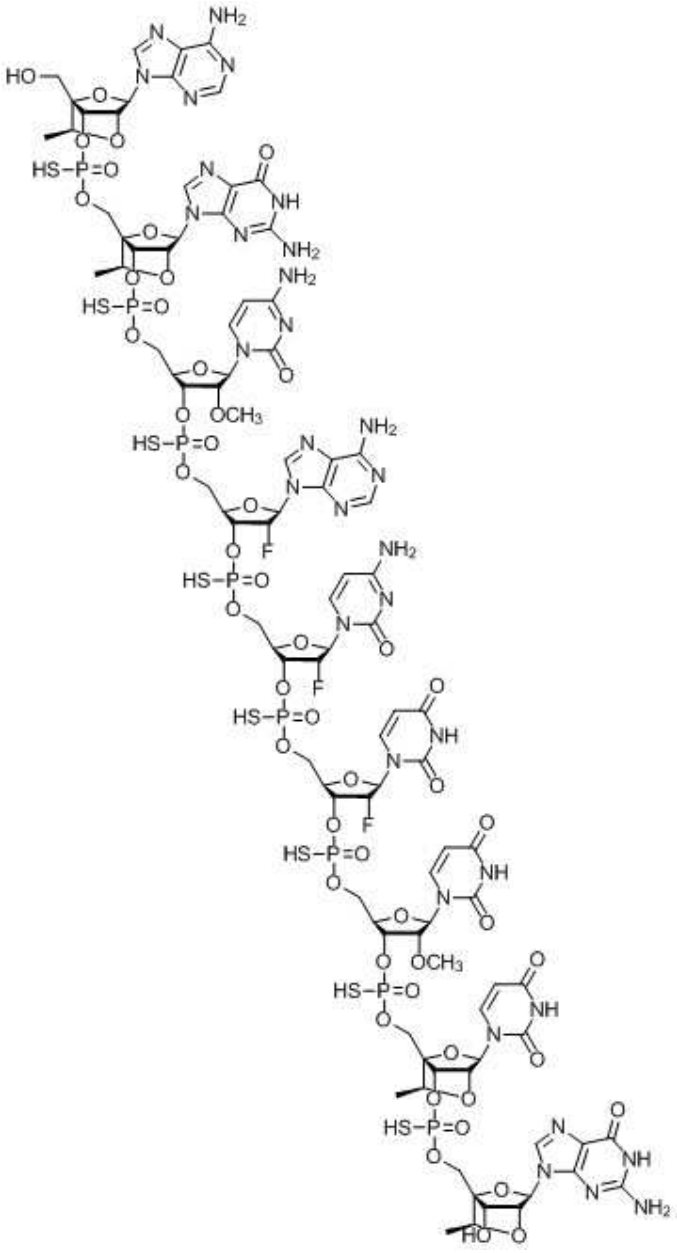
ii) hypertension;

iii) glomerular filtration rate; and/or

iv) kidney pain.

58. Use of a modified oligonucleotide in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the

modified oligonucleotide has the structure:



or a pharmaceutically acceptable salt thereof; wherein the modified oligonucleotide is to be administered to a subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; wherein the subject has

i) increased kidney volume;

ii) hypertension;

iii) impaired glomerular filtration rate; and/or

iv) kidney pain, and

wherein the subject, following the administering of the compound, experiences an improvement in one or more markers of polycystic kidney disease selected from:

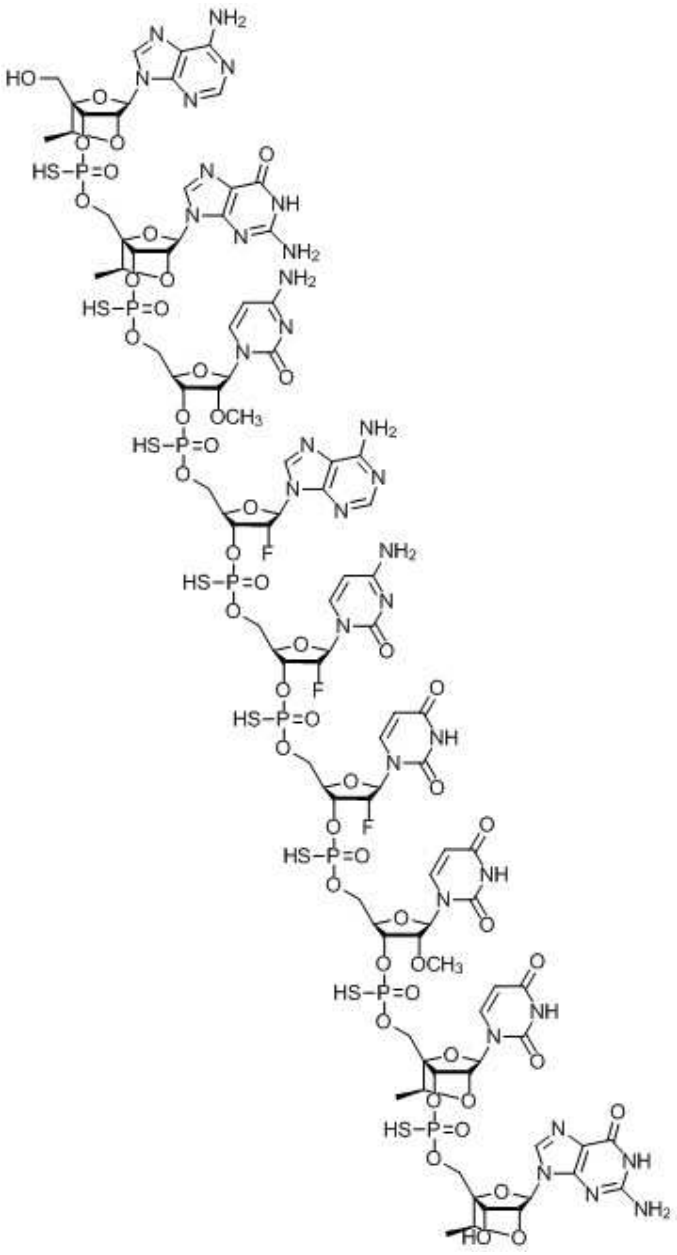
i) total kidney volume;

ii) hypertension;

iii) glomerular filtration rate; and/or

iv) kidney pain.

59. Use of a modified oligonucleotide in the manufacture of a medicament for the reduction of decline in kidney function over time in a subject with polycystic kidney disease, wherein the modified oligonucleotide has the structure:



or a pharmaceutically acceptable salt thereof; wherein the modified oligonucleotide is to be administered to a subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria, and

wherein the subject, following the administration of the modified oligonucleotide, experiences an improvement in one or more markers of kidney function selected from:

i) glomerular filtration rate;

ii) blood urea nitrogen level; and/or

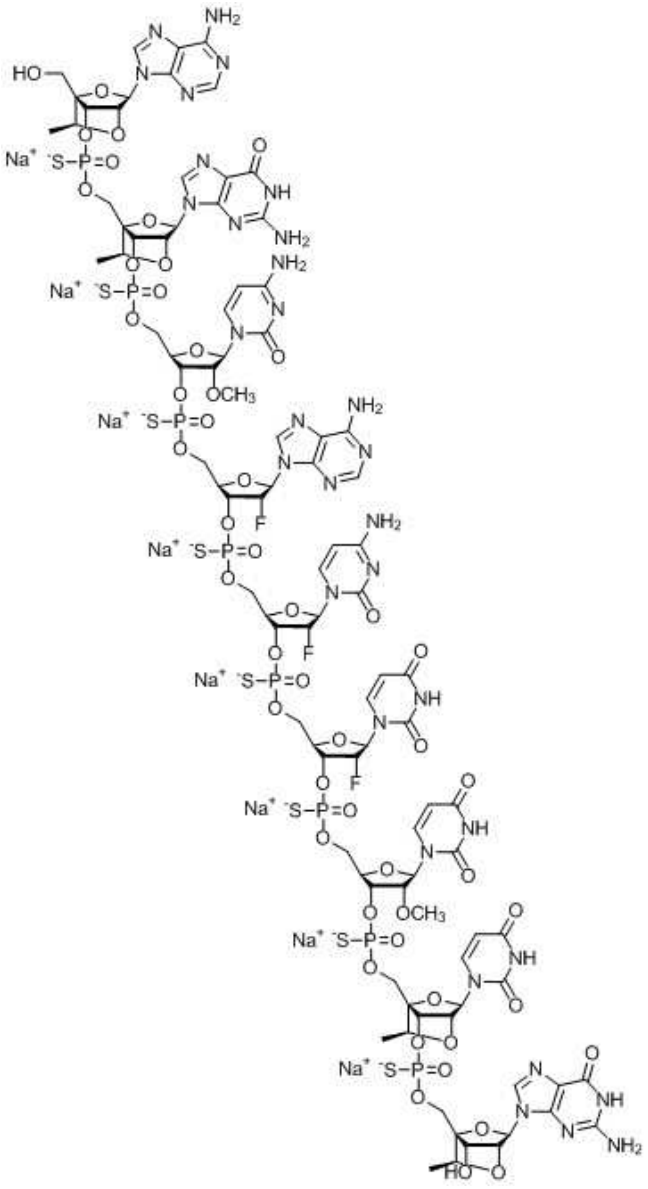
iii) serum creatinine level.

60. The use of any one of claims 57, 58, or 59, wherein the modified oligonucleotide is a pharmaceutically acceptable salt of the structure.

61. The use of claim 60, wherein the modified oligonucleotide is a sodium salt of the structure.

62. Use of a modified oligonucleotide in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the

modified oligonucleotide has the structure:



; wherein the modified oligonucleotide is to be administered to a subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; and

wherein the subject, following the administration of the modified oligonucleotide, experiences an improvement in one or more markers of polycystic kidney disease selected from:

i) total kidney volume;

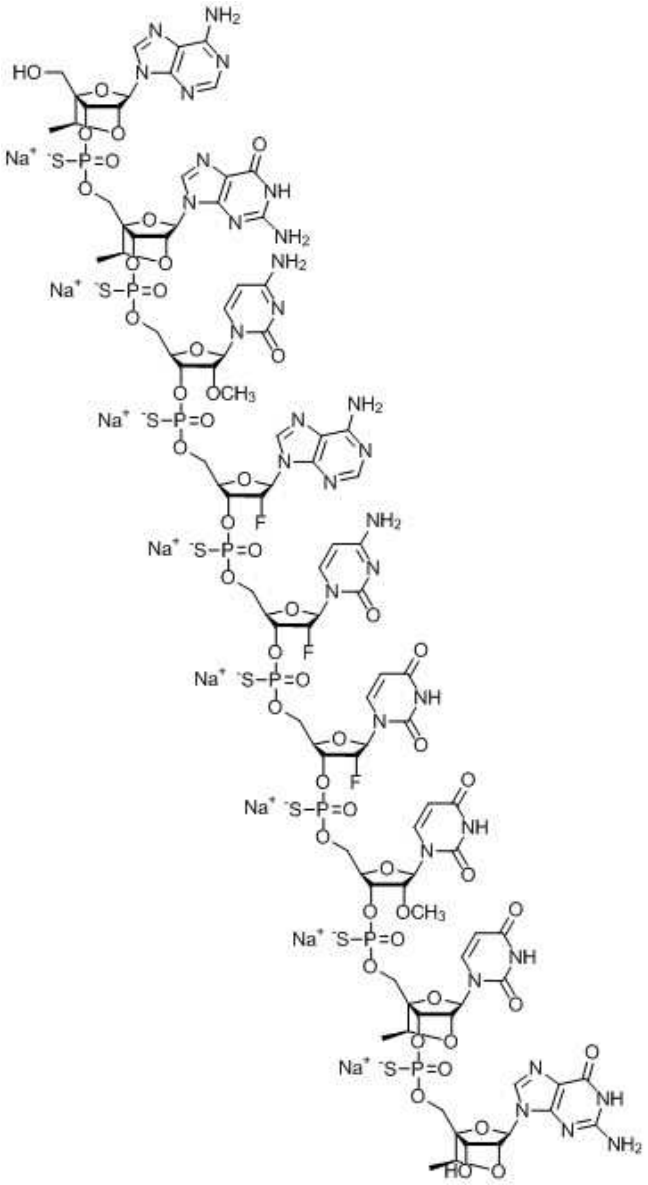
ii) hypertension;

iii) glomerular filtration rate; and/or

iv) kidney pain.

63. Use of a modified oligonucleotide in the manufacture of a medicament for the treatment of polycystic kidney disease, wherein the

modified oligonucleotide having the structure:



; wherein the modified oligonucleotide is to be administered to a selected subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; wherein the subject has

i) increased kidney volume;

ii) hypertension;

iii) impaired glomerular filtration rate; and/or

iv) kidney pain; and

wherein the subject, following the administration of the modified oligonucleotide, experiences an improvement in one or more markers of polycystic kidney disease selected from:

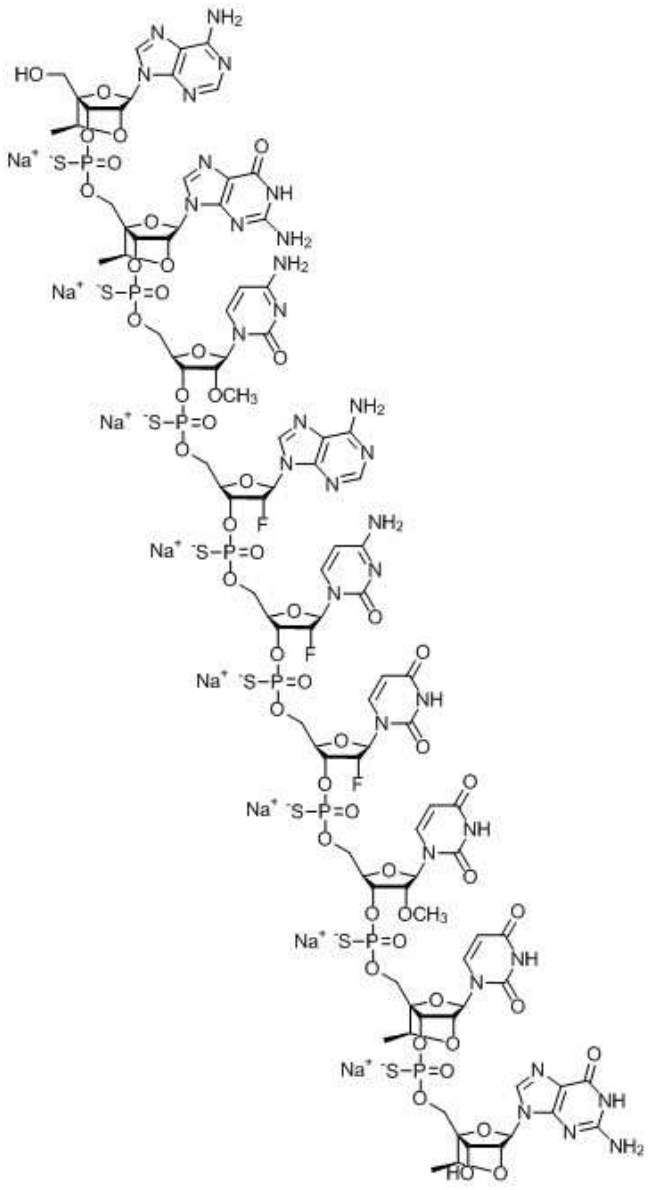
i) total kidney volume;

ii) hypertension;

iii) glomerular filtration rate; and/or

iv) kidney pain.

64. Use of a modified oligonucleotide in the manufacture of a medicament for the reduction of decline in kidney function over time, wherein the modified oligonucleotide has the structure:



; wherein the modified oligonucleotide is to be administered to a selected subject who has been diagnosed with polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; and

wherein the subject, following the administration of the modified oligonucleotide, experiences an improvement in one or more markers of kidney function selected from:

i) glomerular filtration rate;

ii) blood urea nitrogen level; and/or

iii) serum creatinine level.

65. The use of any one of claims 51 to 64, wherein the polycystic kidney disease is the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD).

66. The use of any one of claims 51 to 64, wherein the polycystic kidney disease is autosomal recessive polycystic kidney disease (ARPKD).

67. The use of any one of claims 1 to 64, wherein the polycystic kidney disease is nephronophthisis.
68. The use of any one of claims 1 to 64, wherein the subject has Joubert syndrome and related disorders (JSRD), Meckel syndrome (MKS), or Bardet-Biedl syndrome (BBS).
69. The use of any one of claims 1 to 68, wherein the subject is a human subject.
70. The use of any one of claims 1-14, 18-56, or 65-69, wherein each cytosine is a non-methylated cytosine.