METHODS AND COMPOSITIONS FOR TREATMENT OF POLYCYSTIC KIDNEY DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 63/253,933, filed October 8, 2021, which is incorporated by reference herein in its entirety for any purpose.

FIELD

[0002] Provided herein are compositions and methods for the treatment of polycystic kidney disease.

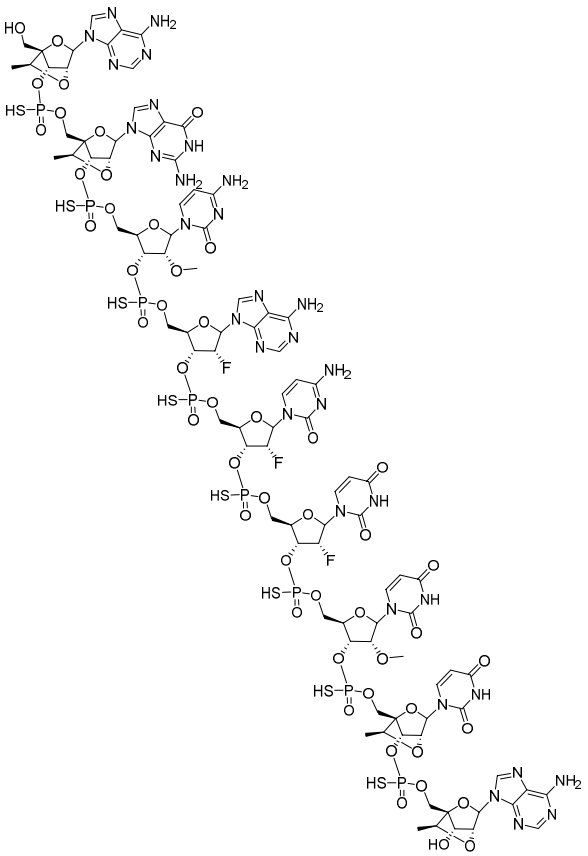
BACKGROUND

[0003] Polycystic kidney disease is characterized by the accumulation of numerous fluid-filled cysts in the kidney. These cysts are lined by a single layer of epithelial cells called the cyst epithelium. Over time, the cysts increase in size due to elevated cell proliferation and active secretion of fluid by the cyst epithelium. The enlarged cysts compress surrounding normal tissue, resulting in a decline of kidney function. The disease eventually progresses to end-stage renal disease, requiring dialysis or kidney transplant. At this stage, the cysts may be surrounded by areas of fibrosis containing atrophic tubules. Polycystic kidney disease can also cause cysts to develop in the liver and elsewhere in the body.

[0004] A number of genetic disorders can result in polycystic kidney disease (PKD). The various forms of PKD are distinguished by the manner of inheritance, for example, autosomal dominant or autosomal recessive inheritance; the involvement of organs and presentation of phenotypes outside of the kidney; the age of onset of end-stage renal disease, for example, at birth, in childhood or adulthood; and the underlying genetic mutation that is associated with the disease. *See*, for example, Kurschat et al., 2014, Nature Reviews Nephrology, 10: 687–699.

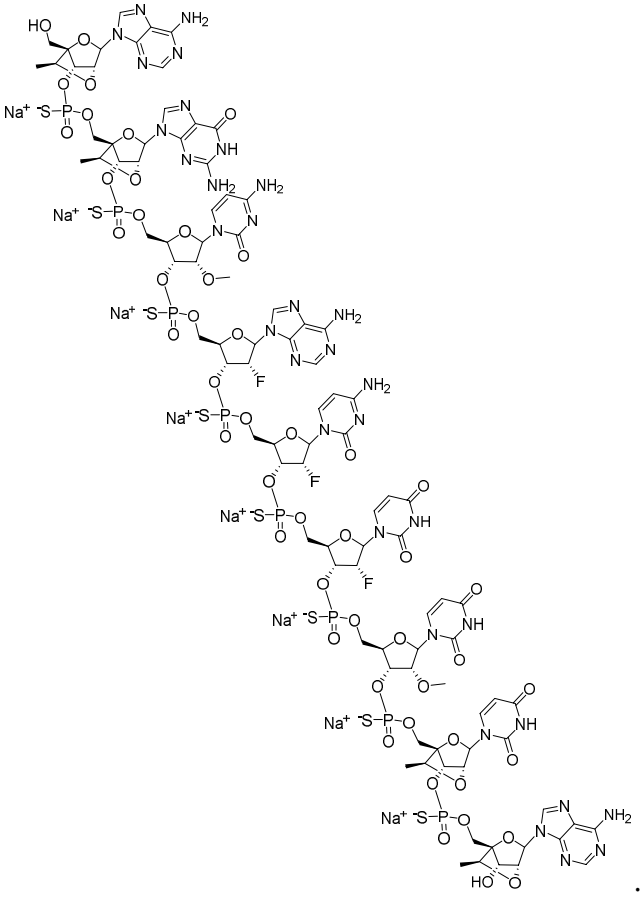
SUMMARY

[0004a] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

[0004b] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



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[0004c] In one aspect, the disclosure provides a pharmaceutical composition comprising a modified oligonucleotide of the disclosure and a pharmaceutically acceptable diluent.

[0004d] In one aspect, the disclosure provides a pharmaceutical composition comprising a modified oligonucleotide of the disclosure, which is a lyophilized composition.

[0004e] In one aspect, the disclosure provides the modified oligonucleotide of the disclosure or the pharmaceutical composition of the disclosure, for use in therapy.

[0004f] In one aspect, the disclosure provides a use of the modified oligonucleotide of the disclosure or the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating autosomal dominant polycystic kidney disease in a subject.

Example 1. A compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5' to 3' orientation:

$$(N'')_p\text{-}(N)_r\text{-}(N')_q$$

wherein each N" is, independently, a modified or unmodified nucleoside;

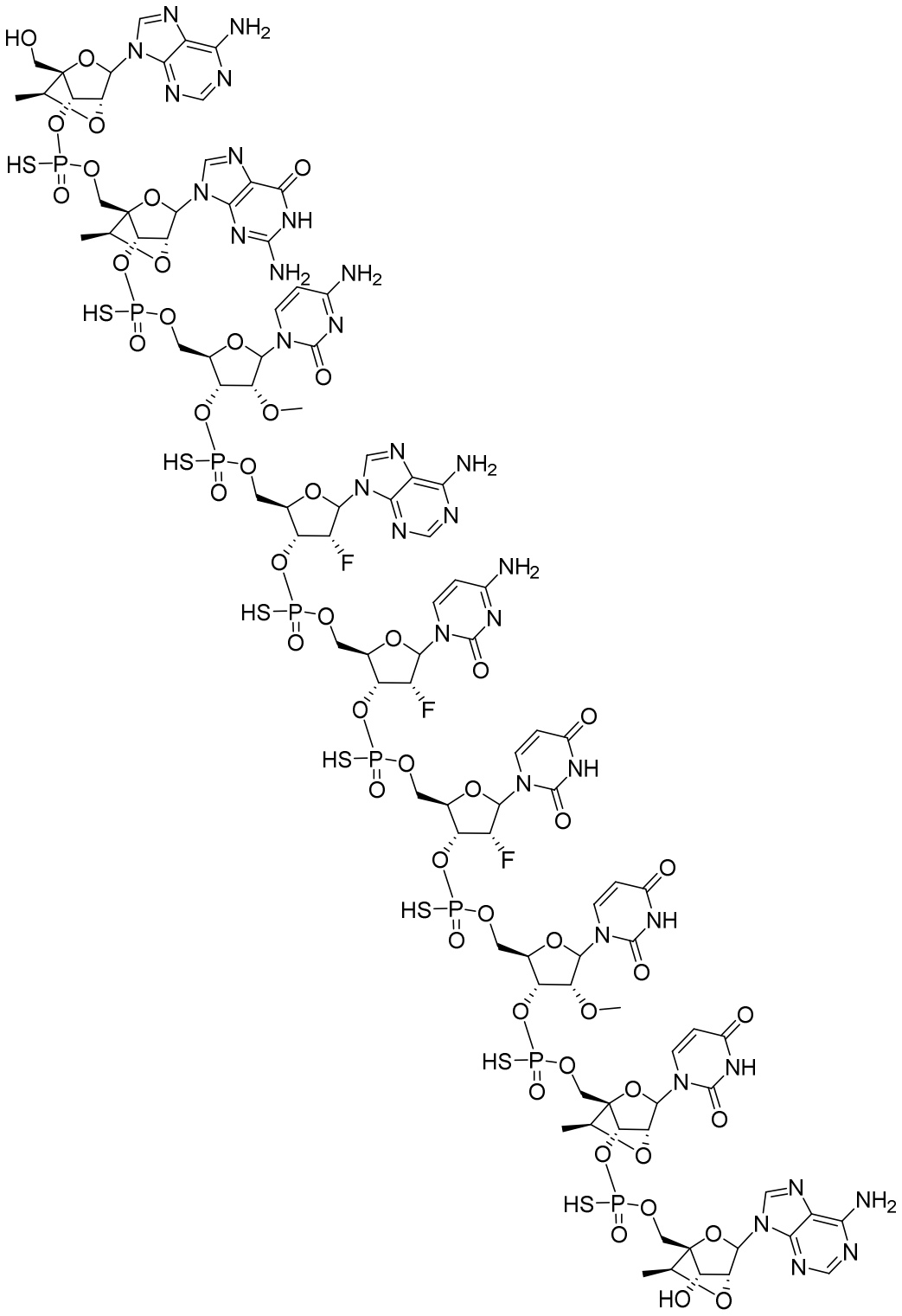
p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;

each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5'-AGCACUUU-3';

N' is a nucleoside comprising a modified sugar moiety;

What is claimed is:

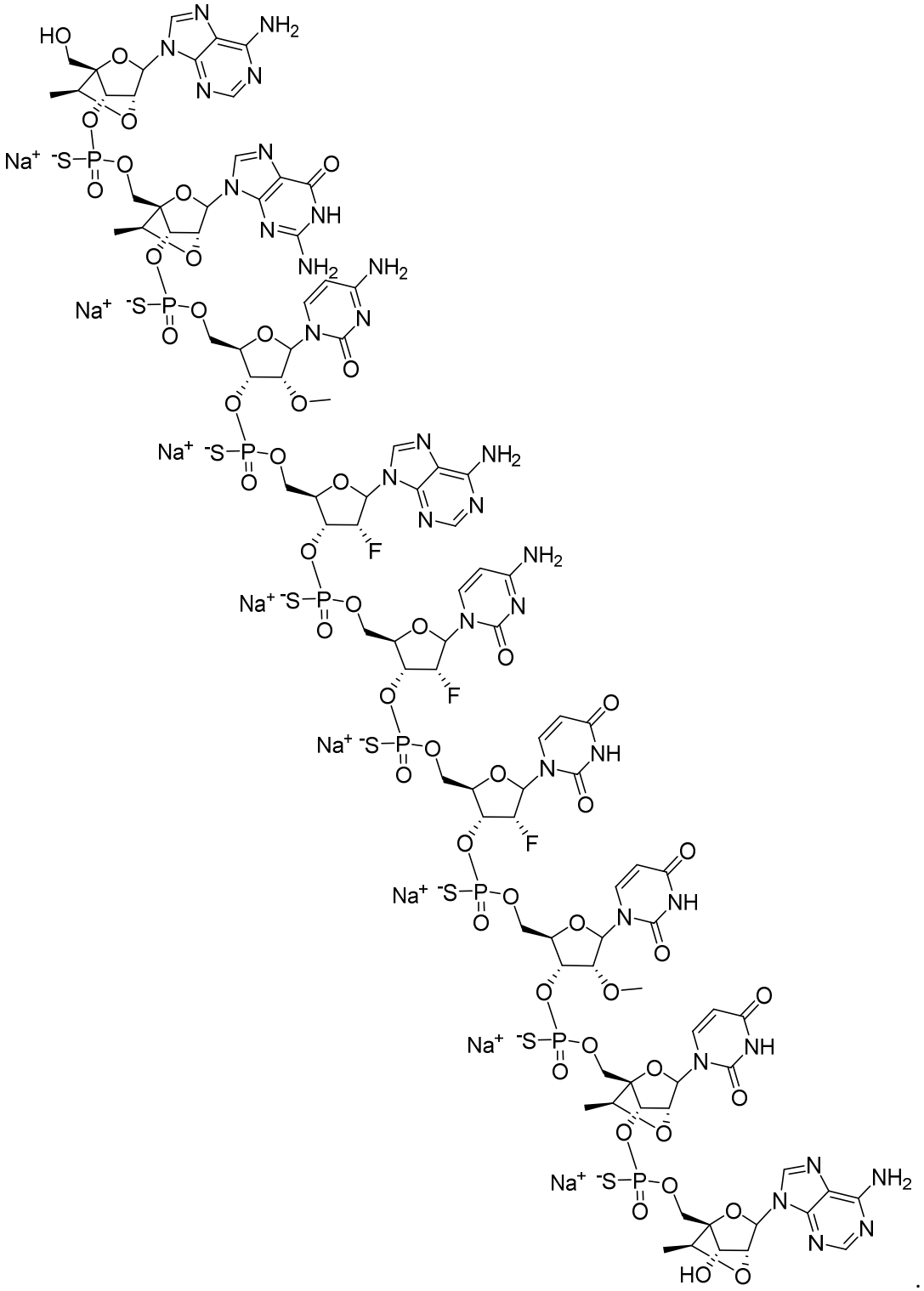
1. A modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

2. The modified oligonucleotide of claim 1, wherein the pharmaceutically acceptable salt is a sodium salt.

3. A modified oligonucleotide having the structure:



4. A pharmaceutical composition comprising a modified oligonucleotide of any one of claims 1 to 3 and a pharmaceutically acceptable diluent.

5. The pharmaceutical composition of claim 4, wherein the pharmaceutically acceptable diluent is a saline solution.

6. A pharmaceutical composition comprising a modified oligonucleotide of any one of claims 1 to 3, which is a lyophilized composition.

7. The modified oligonucleotide of any one of claims 1 to 3 or the pharmaceutical composition of claim 4 or claim 5, for use in therapy.

8. Use of the modified oligonucleotide of any one of claims 1 to 3 or the pharmaceutical composition of claim 4 or claim 5 in the manufacture of a medicament for treating autosomal dominant polycystic kidney disease in a subject.

9. The use of claim 8, wherein the subject has been diagnosed as having autosomal dominant polycystic kidney disease using clinical, histopathologic, and/or genetic criteria.

10. The use of claim 8 or claim 9, wherein the subject, prior to administration of the modified oligonucleotide or pharmaceutical composition, was determined to have a decreased level of polycystin-1 (PC1) and/or polycystin-2 (PC2) in the kidney, urine or blood of the subject.

11. The use of any one of claims 8 to 10, wherein the subject has a mutation selected from a mutation in the *PKD1* gene or a mutation in the *PKD2* gene.

12. The use of any one of claims 8 to 11, wherein the subject has hypertension and/or the subject has impaired kidney function.

13. The use of any one of claims 8 to 12, wherein administration of the medicament slows the rate of decline of glomerular filtration rate in the subject and/or increases glomerular filtration rate in the subject, optionally wherein the glomerular filtration rate is estimated glomerular filtration rate.

14. The use of any one of claims 8 to 13, wherein at least one additional therapy is to be administered, wherein at least one additional therapy is an anti-hypertensive agent.

15. The use of any one of claims 8 to 14, wherein at least one additional therapy 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, a glucosylceramide synthase inhibitor, an antihyperglycermic agent, dialysis, and kidney transplant is to be administered.

16. The use of claim 15, wherein the angiotensin II converting enzyme (ACE) inhibitor is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril.

17. The use of claim 15, wherein the angiotensin II receptor blocker (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan.

18. The use of claim 15, wherein the vasopressin receptor 2 antagonist is tolvaptan.

19. The use of claim 15, wherein the aldosterone receptor antagonist is spironolactone.

20. The use of claim 15, wherein the kinase inhibitor is selected from bosutinib and KD019.

21. The use of claim 15, wherein the mTOR inhibitor is selected from everolimus, rapamycin, and sirolimus.

22. The use of claim 15, wherein the hormone analogue is selected from somatostatin and adrenocorticotrophic hormone.

23. The use of claim 15, wherein the glucosylceramide synthase inhibitor is venglustat.

24. The use of claim 15, wherein the antihyperglycemic agent is metformin.