METHODS FOR TREATMENT OF ALPORT SYNDROME

FIELD OF INVENTION

Provided herein are methods and compositions for the treatment of Alport Syndrome.

DESCRIPTION OF RELATED ART

Type IV collagen, a major component of the basement membrane, is a family of six alpha chains: alpha-1 collagen (Type IV), alpha-2 collagen (Type IV), alpha-3 collagen (Type IV), alpha-4 collagen (Type IV), alpha-5 collagen (Type IV), and alpha-6 collagen (Type IV). The alpha-3, alpha-4 and alpha-6 chains of collagen IV are fundamental components of the collagen network of the glomerular basement membrane (GBM), which performs the critical function of filtration of blood by the kidney.

Alport Syndrome is an inherited form of kidney disease in which an abnormal type of glomerular basement membrane (GBM) is produced, leading to interstitial fibrosis, glomerular sclerosis and eventual loss of kidney function. The disease is also frequently characterized by hearing defects and ocular anomalies. Alport Syndrome is caused by a mutation in *Col4a3*, *Col4a4*, or *Col4a5*, which encode the alpha3(IV), alpha4(IV), and alpha5(IV) chains of type IV collagen, respectively. Mutations in the *Col4a5* gene on the X chromosome cause the X-linked form of Alport Syndrome, which accounts for 85% of all cases of the disease. An autosomal recessive form is due to inheritance of mutations in each copy of either *Col4a3* or *Col4a4*, each of which is located on chromosome 2. The rare autosomal dominant form is due to inheritance of a dominant-negative mutation in either the *Col4a3* or *Col4a4* gene. The X-linked form is more severe in males than in females, with most cases in males progressing to end-stage renal disease (ESRD) . The autosomal form is of similar severity in males and females. Most cases of the disease are due to an inherited mutation, but some cases are due to a de novo mutation in one of the *Col4aA* genes.

SUMMARY ~~OF INVENTION~~

Provided here are methods for treating Alport Syndrome comprising administering to a subject having or suspected of having Alport Syndrome a modified oligonucleotide consisting of 12 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21.

In one aspect, there is provided the use of a modified oligonucleotide consisting of 12 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21, in the manufacture of a medicament for treating Alport Syndrome in a subject having or suspected of having Alport Syndrome.

In certain embodiments, the subject has been diagnosed as having Alport Syndrome prior to administering the modified oligonucleotide. In certain embodiments, the subject, prior to administration of the modified oligonucleotide, was determined to have an increased level of miR-21 in the kidney tissue of the subject. In certain embodiments, the subject, prior to administration of the modified oligonucleotide, was determined to have an increased level of miR-21 in the urine or blood of the subject.

In any of the embodiments provided herein, administration of a modified oligonucleotide complementary to miR-21, to a subject having or suspected of having Alport Syndrome, may improve kidney function; delay the onset of end stage renal disease; delay time to dialysis; delay time to renal transplant; and/or improve life expectancy in the subject.

In any of the embodiments provided herein, administration of a modified oligonucleotide complementary to miR-21, to a subject having or suspected of having Alport Syndrome may reduce hematuria; delay the onset of hematuria; reduce proteinuria; delay the onset of proteinuria; reduce kidney fibrosis; slow further progression of fibrosis; and/or halt further progression of fibrosis.

In any of the embodiments provided herein, the subject may have a mutation selected from a mutation in the gene encoding the alpha 3 chain of type IV collagen, a mutation in the gene encoding the alpha 4 chain of type IV collagen, or a mutation in the gene encoding the alpha 5 chain of type IV collagen. In certain embodiments, the subject is male. In certain embodiments, the subject is female. In certain embodiments, the subject is identified as having hematuria, and/or proteinuria. In certain embodiments, the subject has reduced kidney function. In certain embodiments, the subject is in need of improved kidney function.

Any of the embodiments provided herein may comprise 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; and/or measuring glomerular filtration rate in the subject.

Any of the embodiments provided herein may comprise measuring N-acetyl-β-D-glucosaminidase (NAG) protein in the urine of the subject; measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject; measuring interleukin-18 (IL-18) protein in the urine of the subject; measuring monocyte chemoattractant protein (MCP1) levels in the urine of the subject; measuring connective tissue growth factor (CTGF) levels in the urine of the subject; measuring collagen IV (Col IV) fragments in the urine of the subject; measuring collagen III (Col III) fragments in the urine of the subject; and/or measuring podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin. Any of the embodiments provided herein may comprise measuring cystatin C protein in the blood of a subject; measuring β-trace protein (BTP) in the blood of a subject; and measuring 2-microglobulin (B2M) in the blood of a subject.

Any of the methods or uses provided herein may improve one or more markers of kidney function in the subject, selected from reduced blood urea nitrogen in the subject; reduced creatinine in the blood of the subject; improved creatinine clearance in the subject; reduced proteinuria in the subject; reduced albumin:creatinine ratio in the subject; and/or improved glomerular filtration rate in the subject. Any of

the methods or uses provided herein may improve one or more markers of kidney function in the subject, selected from reduced NAG in the urine of the subject; reduced NGAL in the urine of the subject; reduced KIM-1 in the urine of the subject; reduced IL-18 in the urine of the subject; reduced MCP1 in the urine of the subject; reduced CTGF in the urine of the subject; reduced collagen IV fragments in the urine of the subject; reduced collagen III fragments in the urine of the subject; and reduced podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin. Any of the methods or uses provided herein may improve one or more markers of kidney function selected from reduced cystatin C protein in the blood of a subject, reduced β-trace protein (BTP) in the blood of a subject, and reduced 2-microglobulin (B2M) in the blood of a subject.

In any of the embodiments provided herein, the proteinuria is albuminuria. The albuminuria may be high normal albuminuria, microalbuminuria, or macroalbuminuria.

In certain embodiments, the Alport Syndrome is the X-linked form of Alport Syndrome. In certain embodiments, the Alport Syndrome is the autosomal form of Alport Syndrome.

Any of the embodiments provided herein may comprise administering at least one additional therapy selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), an anti-hypertensive agent, a vitamin D analog, an oral phosphate binder, dialysis, and kidney transplant. In any of these embodiments, the angiotensin II converting enzyme (ACE) inhibitors is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril. In any of these embodiments, the angiotensin II receptor blockers (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan. In any of these embodiments, an ACE inhibitor is selected from cilazapril, perindopril, and trandolapril.

In certain embodiments, an ACE inhibitor is administered at a dose ranging from 0.5 to 1 $mg/m^2/day$, from 1 to 6 $mg/m^2/day$, from 1 to 2 $mg/m^2/day$, from 2 to 4 $mg/m^2/day$, or from 4 to 8 $mg/m^2/day$.

In certain embodiments, an ARB is administered at a dose ranging from 6.25 to 150 mg/m2/day. In any of these embodiments, an ARB is administered at a dose of 6.25 $mg/m^2/day$, 10 $mg/m^2/day$, 12.5 $mg/m^2/day$, 18.75 $mg/m^2/day$, 37.5 $mg/m^2/day$, 50 $mg/m^2/day$, or 150 $mg/m^2/day$.

In certain embodiments, the at least one additional therapy is an aldosterone antagonsist. In certain embodiments, an aldosterone antagonist is spironolactone. In certain embodiments, spironolactone is administered at a dose ranging from 10 to 35 mg daily. In certain embodiments, spironolactone is administered at a dose of 25 mg daily.

In any of the embodiments 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 any of the embodiments provided herein, the modified oligonucleotide consists of 8 to 30, 12 to 25, or 15 to 25 linked nucleosides. In any of the embodiments provided herein, the modified oligonucleotide consists of 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides. In any of the embodiments provided herein, the modified oligonucleotide consists of 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides.

In any of the embodiments provided herein, the modified oligonucleotide comprises at least one modified nucleoside. The modified nucleoside may be selected from an S-cEt nucleoside, a 2'-O-methoxyethyl nucleoside, and an LNA nucleoside. The modified oligonucleotide may comprise at least one modified internucleoside linkage. Each internucleoside linkage of the modified oligonucleotide may be a modified internucleoside linkage. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In one aspect, there is provided the use of a modified oligonucleotide of the structure 5'-$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$-3', where nucleosides not followed by a subscript indicate β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" indicate 2'-MOE nucleosides; nucleosides followed by a subscript "S" indicate S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage, in the manufacture of a medicament for treating Alport syndrome in a subject having or suspected of having Alport syndrome.

In any of the embodiments provided herein, the modified oligonucleotide may have the structure 5'-$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$-3', (SEQ ID NO: 3) where nucleosides not followed by a subscript indicate β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" indicate 2'-MOE nucleosides; nucleosides followed by a subscript "S" indicate S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

Provided herein is the use of a modified oligonucleotide consisting of 8 to 30, 12 to 25, or 15 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21, for the treatment of Alport Syndrome.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Anti-miR-21 improves kidney function of *Col4a3-/-mice*. Blood urea nitrogen (BUN) at 9 weeks (A) and urinary albumin/creatinine ratio at weeks 3, 5, 7 and 9 (B). * indicates statistical significance.

Figure 2. Anti-miR-21 prevents glomerulosclerosis in *Col4a3-/-* mice. Glomerulosclerosis was evaluated using semi-quantitative sclerosis scores ranging from 0 (no sclerosis) to 4 (complete sclerosis) (n=10).

Figure 3. Anti-miR-21 reduces fibrosis in *Col4a3-/-* mice. (A) Quantification of Picrosirius (Sirius) red-stained fibrosis in kidney (n=6) and (B) Quantitative PCR of *Col1a1* transcripts normalized to GAPDH (n=6). * indicates statistical significance.

What is claimed is:

1. A method of treating Alport Syndrome comprising administering to a subject having or suspected of having Alport Syndrome a modified oligonucleotide consisting of 12 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21.

2. The method of claim 1 wherein the subject has been diagnosed as having Alport Syndrome prior to administering the modified oligonucleotide.

3. The method of claim 1 wherein the subject, prior to administration of the modified oligonucleotide, was determined to have an increased level of miR-21 in the kidney, urine or blood of the subject.

4. The method of any of the above claims, wherein the administering:
    a. improves kidney function;
    b. delays the onset of end stage renal disease;
    c. delays time to dialysis;
    d. delays time to renal transplant; and/or
    e. improves life expectancy.

5. The method of any of the above claims, wherein the administering:
    a. reduces hematuria;
    b. delays the onset of hematuria;
    c. reduces proteinuria;
    d. delays the onset of proteinuria;
    e. reduces kidney fibrosis;
    f. slows further progression of fibrosis; and/or
    g. halts further progression of fibrosis.

6. The method of any of the above claims, wherein the subject has a mutation selected from a mutation in the gene encoding the alpha 3 chain of type IV collagen, a mutation in the gene encoding the alpha 4 chain of type IV collagen, or a mutation in the gene encoding the alpha 5 chain of type IV collagen.

7. The method of any of the above claims, wherein the subject is male.

8. The method of any of the above claims, wherein the subject is female.

9. The method of any of the above claims, wherein the subject is identified as having hematuria, and/or proteinuria.

10. The method of any of the above claims, wherein the subject has reduced kidney function.

11. The method of any of the above claims, wherein the subject is in need of improved kidney function.

12. The method of any of the above claims, comprising:
    a. measuring blood urea nitrogen in the blood of the subject;
    b. measuring creatinine in the blood of the subject;
    c. measuring creatinine clearance in the subject;
    d. measuring proteinuria in the subject;
    e. measuring albumin:creatinine ratio in the subject;
    f. measuring glomerular filtration rate in the subject;
    g. measuring cystatin C in the subject;
    h. measuring β-trace protein (BTP) in the blood of the subject;
    i. measuring 2-microglobulin in the blood of the subject;
    j. measuring N-acetyl-β-D-glucosaminidase (NAG) protein in the urine of the subject;
    k. measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject;
    l. measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject;
    m. measuring interleukin-18 (IL-18) protein in the urine of the subject;
    n. measuring monocyte chemoattractant protein (MCP1) levels in the urine of the subject;
    o. measuring connective tissue growth factor (CTGF) levels in the urine of the subject;
    p. measuring collagen IV fragments in the urine of the subject;
    q. measuring collagen III fragments in the urine of the subject; and/or
    r. measuring podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin.

13. The method of any of the above claims, wherein the administering improves one or more markers of kidney function in the subject, selected from:
    a. reduced blood urea nitrogen in the subject;
    b. reduced creatinine in the blood of the subject;

c. improved creatinine clearance in the subject;
d. reduced proteinuria in the subject;
e. reduced albumin:creatinine ratio in the subject;
f. improved glomerular filtration rate in the subject;
g. reduced cystatin C in the blood of the subject;
h. reduced β-trace protein (BTP) in the blood of the subject;
i. reduced 2-microglobulin (B2M) in the blood of a subject;
j. reduced NAG protein in the urine of the subject;
k. reduced NGAL protein in the urine of the subject;
l. reduced KIM-1 protein in the urine of the subject;
m. reduced IL-18 protein in the urine of the subject;
n. reduced monocyte chemoattractant protein (MCP1) levels in the urine of the subject;
o. reduced connective tissue growth factor (CTGF) levels in the urine of the subject;
p. reduced collagen IV fragments in the urine of the subject;
q. reduced collagen III fragments in the urine of the subject; and/or
r. reduced podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin.

14. The method of any of claims 5, 12, or 13, wherein the proteinuria is albuminuria.

15. The method of claim 14 wherein the albuminuria is high normal albuminuria, microalbuminuria, or macroalbuminuria.

16. The method of any of the above claims, wherein the Alport Syndrome is the X-linked form of Alport Syndrome.

17. The method of any of the above claims, wherein the Alport Syndrome is the autosomal form of Alport Syndrome.

18. The method of any of the above claims, comprising administering at least one additional therapy selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), an anti-hypertensive agent, a vitamin D analog, an oral phosphate binder, dialysis, and kidney transplant.

19. The method of claim 17 wherein the angiotensin II converting enzyme (ACE) inhibitors is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril.

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

21. The method of any of the above claims, wherein 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).

22. The method of any of the above claims, wherein the modified oligonucleotide consists of 15 to 25 linked nucleosides.

23. The method of any of the above claims, wherein the modified oligonucleotide consists of 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides.

24. The method of any of the above claims, wherein the modified oligonucleotide comprises at least one modified nucleoside.

25. The method of claim 21, wherein the modified nucleoside is selected from an S-cEt nucleoside, a 2'-O-methoxyethyl nucleoside, and an LNA nucleoside.

26. The method of any of the above claims, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

27. The method of any of the above claims, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

28. The method of claim 23 or 24, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

29. The method of any of the above claims, wherein the modified oligonucleotide has the structure 5'-$A_ECsATCsAGTCsTGAUsAAGCsTA_E$-3', where nucleosides not followed by a subscript indicate β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" indicate 2'-MOE nucleosides; nucleosides followed by a subscript "S" indicate S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

30. Use of a modified oligonucleotide consisting of 12 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21, for the treatment of Alport Syndrome.

What is claimed is:

1. Use of a modified oligonucleotide consisting of 12 to 25 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-21, in the manufacture of a medicament for treating Alport Syndrome in a subject having or suspected of having Alport Syndrome.

2. The use of claim 1 wherein the subject has been diagnosed as having Alport Syndrome prior to administration of the modified oligonucleotide.

3. The use of claim 1 wherein the subject, prior to administration of the modified oligonucleotide, was determined to have an increased level of miR-21 in the kidney, urine or blood of the subject.

4. The use of any of the above claims, wherein the administration :
    a. improves kidney function;
    b. delays the onset of end stage renal disease;
    c. delays time to dialysis;
    d. delays time to renal transplant; and/or
    e. improves life expectancy.

5. The use of any of the above claims, wherein the administration :
    a. reduces hematuria;
    b. delays the onset of hematuria;
    c. reduces proteinuria;
    d. delays the onset of proteinuria;
    e. reduces kidney fibrosis;
    f. slows further progression of fibrosis; and/or
    g. halts further progression of fibrosis.

6. The use of any of the above claims, wherein the subject has a mutation selected from a mutation in the gene encoding the alpha 3 chain of type IV collagen, a mutation in the gene encoding the alpha 4 chain of type IV collagen, or a mutation in the gene encoding the alpha 5 chain of type IV collagen.

7. The use of any of the above claims, wherein the subject is male.

8. The use of any of the above claims, wherein the subject is female.

9. The use of any of the above claims, wherein the subject is identified as having hematuria, and/or proteinuria.

10. The use of any of the above claims, wherein the subject has reduced kidney function.

11. The use of any of the above claims, wherein the subject is in need of improved kidney function.

12. The use of any of the above claims, comprising:
    a. measuring blood urea nitrogen in the blood of the subject;
    b. measuring creatinine in the blood of the subject;
    c. measuring creatinine clearance in the subject;
    d. measuring proteinuria in the subject;
    e. measuring albumin:creatinine ratio in the subject;
    f. measuring glomerular filtration rate in the subject;
    g. measuring cystatin C in the subject;
    h. measuring β-trace protein (BTP) in the blood of the subject;
    i. measuring 2-microglobulin in the blood of the subject;
    j. measuring N-acetyl-β-D-glucosaminidase (NAG) protein in the urine of the subject;
    k. measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject;
    l. measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject;
    m. measuring interleukin-18 (IL-18) protein in the urine of the subject;
    n. measuring monocyte chemoattractant protein (MCP1) levels in the urine of the subject;
    o. measuring connective tissue growth factor (CTGF) levels in the urine of the subject;
    p. measuring collagen IV fragments in the urine of the subject;
    q. measuring collagen III fragments in the urine of the subject; and/or
    r. measuring podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin.

13. The use of any of the above claims, wherein the administration improves one or more markers of kidney function in the subject, selected from:
    a. reduced blood urea nitrogen in the subject;
    b. reduced creatinine in the blood of the subject;
    c. improved creatinine clearance in the subject;
    d. reduced proteinuria in the subject;

e. reduced albumin:creatinine ratio in the subject;
f. improved glomerular filtration rate in the subject;
g. reduced cystatin C in the blood of the subject;
h. reduced β-trace protein (BTP) in the blood of the subject;
i. reduced 2-microglobulin (B2M) in the blood of a subject;
j. reduced NAG protein in the urine of the subject;
k. reduced NGAL protein in the urine of the subject;
l. reduced KIM-1 protein in the urine of the subject;
m. reduced IL-18 protein in the urine of the subject;
n. reduced monocyte chemoattractant protein (MCP1) levels in the urine of the subject;
o. reduced connective tissue growth factor (CTGF) levels in the urine of the subject;
p. reduced collagen IV fragments in the urine of the subject;
q. reduced collagen III fragments in the urine of the subject; and/or
r. reduced podocyte protein levels in the urine of the subject, wherein the podocyte protein is selected from nephrin and podocin.

14. The use of any of claims 5, 12, or 13, wherein the proteinuria is albuminuria.

15. The use of claim 14 wherein the albuminuria is high normal albuminuria, microalbuminuria, or macroalbuminuria.

16. The use of any of the above claims, wherein the Alport Syndrome is the X-linked form of Alport Syndrome.

17. The use of any of the above claims, wherein the Alport Syndrome is the autosomal form of Alport Syndrome.

18. The use of any of the above claims, wherein the medicament is to be administered with at least one additional therapy selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), an anti-hypertensive agent, a vitamin D analog, an oral phosphate binder, dialysis, and kidney transplant.

19. The use of claim 18 wherein the angiotensin II converting enzyme (ACE) inhibitors is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril.

20. The use of claim 18 wherein the angiotensin II receptor blockers (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan.

21. The use of any of the above claims, wherein 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).

22. The use of any of the above claims, wherein the modified oligonucleotide consists of 15 to 25 linked nucleosides.

23. The use of any of the above claims, wherein the modified oligonucleotide consists of 15, 16, 17, 18, 19, 20, 21, or 22 linked nucleosides.

24. The use of any of the above claims, wherein the modified oligonucleotide comprises at least one modified nucleoside.

25. The use of claim 21, wherein the modified nucleoside is selected from an S-cEt nucleoside, a 2'-O-methoxyethyl nucleoside, and an LNA nucleoside.

26. The use of any of the above claims, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

27. The use of any of the above claims, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

28. The use of claim 23 or 24, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

29. The use of any of the above claims, wherein the modified oligonucleotide has the structure 5'-$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$-3', where nucleosides not followed by a subscript indicate β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" indicate 2'-MOE nucleosides; nucleosides followed by a subscript "S" indicate S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

30. Use of a modified oligonucleotide of the structure 5'-$A_EC_SATC_SAGTC_STGAU_SAAGC_STA_E$-3', where nucleosides not followed by a subscript indicate β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" indicate 2'-MOE nucleosides; nucleosides followed by a subscript "S" indicate S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate

internucleoside linkage, in the manufacture of a medicament for treating Alport syndrome in a subject having or suspected of having Alport syndrome.