

these treatments are not always effective. Accordingly, there is a need in the art for alternative treatments for subjects having disorders associated with iron overload.

Summary of the Invention

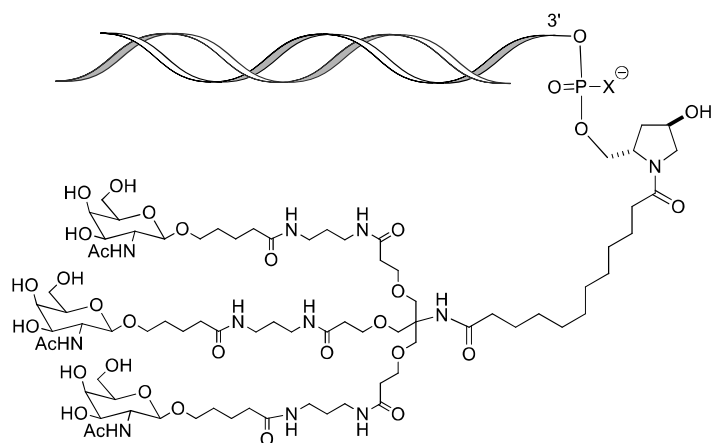
5 In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Transmembrane protease, serine 6 (TMPRSS6) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region, wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu-3' (SEQ ID NO:395) and the
10 nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcugsga -3' (SEQ ID NO:521), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and wherein the dsRNA agent is conjugated to a ligand.

15 In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Transmembrane protease, serine 6 (TMPRSS6) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu-3' (SEQ ID NO:395) and the antisense strand comprises the
20 nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcugsga -3' (SEQ ID NO:521), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and wherein the dsRNA agent is conjugated to a ligand.

In another aspect, provided herein is an isolated cell containing the dsRNA agent, or a
25 pharmaceutically acceptable salt thereof, as described herein.

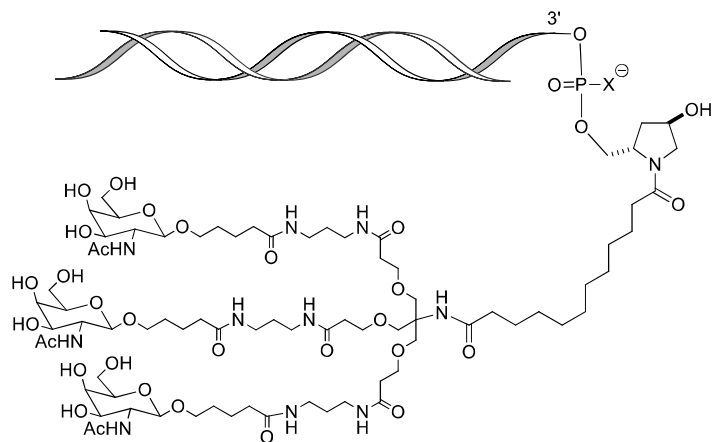
In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding Transmembrane protease, serine 6 (TMPRSS6) comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, and a pharmaceutically acceptable carrier.

30 In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand, forming a double stranded region of a dsRNA agent, wherein the sense strand comprises the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaaguL96-3' (SEQ ID NO:395) and the antisense strand comprises the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcugsga -3' (SEQ ID NO:521), wherein a, g, c
35 and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and wherein L96 is a ligand conjugated to the 3'-end of the sense strand as shown in the following schematic



, and wherein X is O.

In another aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region of a dsRNA agent, wherein the sense strand consists of the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaaguL96-3' (SEQ ID NO:395) and the antisense strand consists of the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and wherein L96 is a ligand conjugated to the 3'-end of the sense strand as shown in the following schematic



, and wherein X is O.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for inhibiting expression of a Transmembrane protease, serine 6 (TMPRSS6) gene in a cell.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a subject having a TMPRSS6-associated disorder.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein, as

described herein in the manufacture of a medicament for preventing at least one symptom in a subject having a TMPRSS6-associated disorder.

In another aspect, provided herein is a kit for performing a method of inhibiting expression of TMPRSS6 gene in a cell, comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein.

In another aspect, provided herein is a vial comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein.

In another aspect, provided herein is a syringe comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein.

In another aspect, provided herein is an RNA-induced silencing complex (RISC) comprising an antisense strand of the dsRNA agent, or a pharmaceutically acceptable salt thereof, wherein the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'-asdCsuudTadTuccadAaGfggcagcusgsa-3' (SEQ ID NO:521), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage.

In another aspect, provided herein is the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein for use in therapy.

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding Transmembrane protease, serine 6 (TMPRSS6). The TMPRSS6 gene may be within a cell, *e.g.*, a cell within a subject, such as a human subject. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of a TMPRSS6 gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of a TMPRSS6 gene, *e.g.*, a subject suffering or prone to suffering from a TMPRSS6-associated disorder, *e.g.*, an iron overload associated disorder and/or a disorder of ineffective erythropoiesis, such as thalassemia, *e.g.*, β -thalassemia, hemochromatosis, myelodysplastic syndromes (MDS), or polycythemia vera.

Accordingly, in an aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of Transmembrane protease, serine 6 (TMPRSS6) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding TMPRSS6, and wherein the region of complementarity comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.

In one embodiment, the dsRNA agent comprises a sense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the

nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising a contiguous nucleotide sequence which has at least 85%, *e.g.*, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, nucleotide sequence identity over its entire length to any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

5 In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequences of the antisense strands in
10 any one of Tables 2-7.

 In one embodiment, the dsRNA agent comprises a sense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by no more than two nucleotides from any one of the nucleotide sequences of the sense strands in any one of Tables 2-7 and an antisense strand comprising at least 15, *e.g.*, 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides differing by
15 no more than two nucleotides from any one of the nucleotide sequences of the antisense strands in any one of Tables 2-7.

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We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Transmembrane protease, serine 6 (TMPRSS6) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the nucleotide sequence of the sense strand differs by no more than 4 bases from the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu-3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and

wherein the dsRNA agent is conjugated to a ligand.

2. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1, wherein:

(i) the nucleotide sequence of the sense strand differs by no more than 3 bases from the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu-3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand differs by no more than 3 bases from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521);

(ii) the nucleotide sequence of the sense strand differs by no more than 2 bases from the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu -3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand differs by no more than 2 bases from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521);

(iii) the nucleotide sequence of the sense strand differs by no more than 1 base from the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu -3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand differs by no more than 1 base from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521);

(iv) the nucleotide sequence of the sense strand comprises the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu -3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand comprises the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521); or

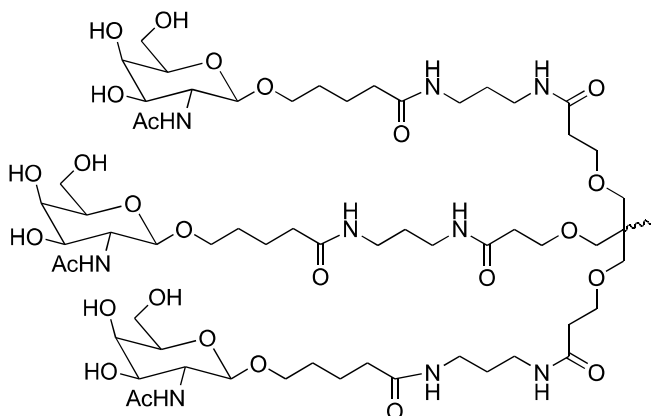
(v) the nucleotide sequence of the sense strand consists of the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu -3' (SEQ ID NO:395) and the nucleotide sequence of the antisense strand consists of the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521).

3. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 1 or 2, wherein:

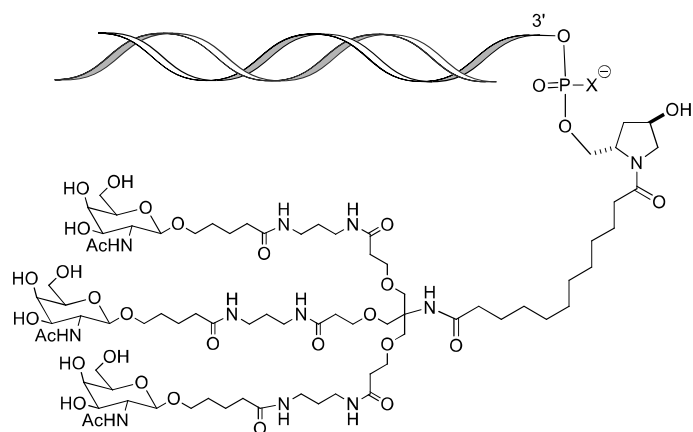
- (i) the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent;
- (ii) the ligand is an N-acetylgalactosamine (GalNAc) ligand;
- (iii) the ligand is a GalNAc ligand attached through a monovalent, bivalent, or trivalent linker;

and/or

- 5 (iv) the ligand is



- 10 4. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 3, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



, wherein X is O or S.

- 15 5. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 4, wherein X is O.

6. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Transmembrane protease, serine 6 (TMPRSS6) in a cell, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaagu-3' (SEQ ID NO:395) and the antisense strand comprises the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa -3' (SEQ ID NO:521),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and

wherein the dsRNA agent is conjugated to a ligand.

7. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-6, which is in a sodium salt form.

8. An isolated cell containing the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7.

9. A pharmaceutical composition for inhibiting expression of a gene encoding Transmembrane protease, serine 6 (TMPRSS6) comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7, and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is in an unbuffered solution, optionally wherein the unbuffered solution is saline or water.

11. The pharmaceutical composition of claim 9, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is in a buffer solution.

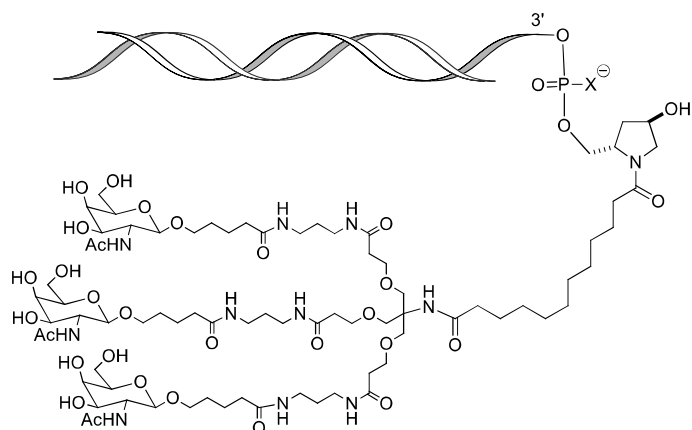
12. The pharmaceutical composition of claim 11, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof, optionally wherein the buffer solution is phosphate buffered saline (PBS).

13. A double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region of a dsRNA agent,

wherein the sense strand comprises the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaaguL96-3' (SEQ ID NO:395) and the antisense strand comprises the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcugsga -3' (SEQ ID NO:521),

5 wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and

wherein L96 is a ligand conjugated to the 3'-end of the sense strand as shown in the following schematic



, and wherein X is O.

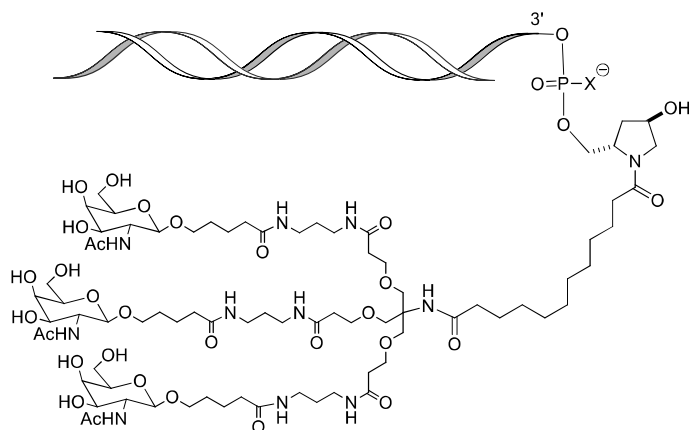
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14. A double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, comprising a sense strand and an antisense strand forming a double stranded region of a dsRNA agent,

wherein the sense strand consists of the nucleotide sequence 5'- asgscugcccUfUfUfggaauaaaguL96-3' (SEQ ID NO:395) and the antisense strand consists of the
15 nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcugsga -3' (SEQ ID NO:521),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage, and

wherein L96 is a ligand conjugated to the 3'-end of the sense strand as shown in the following
20 schematic



, and wherein X is O.

15. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of claim 13 or 14, which is in a sodium salt form.

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16. An isolated cell containing the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 13-15.

17. A pharmaceutical composition comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 13-15, and a pharmaceutically acceptable carrier.

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18. The pharmaceutical composition of claim 17, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is in an unbuffered solution, optionally wherein the unbuffered solution is saline or water.

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19. The pharmaceutical composition of claim 17, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, is in a buffer solution.

20. The pharmaceutical composition of claim 19, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof, optionally wherein the buffer solution is phosphate buffered saline (PBS).

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21. Use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20, in the manufacture of a medicament for inhibiting expression of a Transmembrane protease, serine 6 (TMPRSS6) gene in a cell.

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22. The use of claim 21, wherein the cell is to be obtained from a subject.
23. The use of claim 21, wherein the subject is a human.
- 5 24. The use of claim 22 or 23, wherein the subject has a TMPRSS6-associated disorder, wherein:
- (i) the TMPRSS6-associated disorder is a disorder associated with iron overload or a disorder of ineffective erythropoiesis;
- (ii) the TMPRSS6-associated disorder is selected from the group consisting of hereditary hemochromatosis, β -thalassemia, polycythemia vera, myelodysplastic syndrome, congenital
- 10 dyserythropoietic anemias, pyruvate kinase deficiency, erythropoietic porphyria, Parkinson's Disease, Alzheimer's Disease and Friedreich's Ataxia;
- (iii) the TMPRSS6-associated disorder is β -thalassemia, wherein the β -thalassemia is thalassemia major or thalassemia intermedia;
- (iv) the TMPRSS6-associated disorder is polycythemia vera;
- 15 (v) the TMPRSS6-associated disorder is hereditary hemochromatosis;
- (vi) the TMPRSS6-associated disorder is hemoglobinopathy; or
- (vii) the TMPRSS6-associated disorder is sickle-cell anemia.
25. The use of any one of claims 21-24, wherein:
- 20 (i) contacting the cell with the dsRNA agent, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition results in inhibition of the expression of TMPRSS6 by at least 50%, 60%, 70%, 80%, 90%, or 95%; optionally wherein inhibition of the expression of TMPRSS6 decreases TMPRSS6 protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%; and/or
- (ii) contacting the cell with the dsRNA agent, or a pharmaceutically acceptable salt thereof, or
- 25 the pharmaceutical composition results in an increase of the expression of hepcidin by at least 50%, 60%, 70%, 80%, 90%, or 95%,
- optionally wherein the increase of the expression of hepcidin increases hepcidin protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.
- 30 26. Use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20, in the manufacture of a medicament for treating a subject having a TMPRSS6-associated disorder.

27. Use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20, in the manufacture of a medicament for preventing at least one symptom in a subject having a TMPRSS6-associated disorder.
- 5 28. The use of claim 26 or 27, wherein:
- (i) the TMPRSS6-associated disorder is a disorder associated with iron overload or a disorder of ineffective erythropoiesis;
 - (ii) the TMPRSS6-associated disorder is selected from the group consisting of hereditary hemochromatosis, β -thalassemia, polycythemia vera, myelodysplastic syndrome, congenital
 - 10 dyserythropoietic anemias, pyruvate kinase deficiency, erythropoietic porphyria, Parkinson's Disease, Alzheimer's Disease and Friedreich's Ataxia;
 - (iii) the TMPRSS6-associated disorder is β -thalassemia;
 - (iv) the TMPRSS6-associated disorder is polycythemia vera;
 - (v) the TMPRSS6-associated disorder is hereditary hemochromatosis;
 - 15 (vi) the TMPRSS6-associated disorder is hemoglobinopathy; or
 - (vii) the TMPRSS6-associated disorder is sickle-cell anemia.
29. The use of claim 28, wherein the β -thalassemia is thalassemia major or thalassemia intermedia.
- 20 30. The use of any one of claims 26-29, wherein the subject is a human.
31. The use of any one of claims 26-30, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition is formulated to cause a decrease in iron level, a decrease in ferritin level, a decrease in a transferrin saturation level, or a decrease in TMPRSS6 protein
- 25 accumulation, optionally wherein the TMPRSS6-associated disorder is β -thalassemia and the dsRNA agent, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition is formulated to cause an increase in hemoglobin level and/or an increase in hematocrit level.
32. The use of claim 31, wherein the dsRNA agent, or a pharmaceutically acceptable salt thereof, or
- 30 the pharmaceutical composition is to be administered subcutaneously or intravenously.
33. The use of any one of claims 26-32, further comprising determining the level of TMPRSS6 in a sample(s) from the subject.

34. The use of claim 33, wherein the level of TMPRSS6 in the subject sample(s) is a TMPRSS6 protein level in a blood, serum or liver sample(s).
35. The use of any one of claims 26-34, further comprising determining the level of iron or hepcidin in a sample(s) from the subject.
36. The use of any one of claims 26-35, wherein an additional therapeutic agent for treatment of a TMPRSS6-associated disorder is to be further administered to the subject.
37. The use of claim 36, wherein the additional therapeutic agent is an iron chelator.
38. The use of claim 37, wherein the iron chelator is selected from the group consisting of deferiprone, deferoxamine, and deferasirox.
39. A kit for performing a method of inhibiting expression of TMPRSS6 gene in a cell, comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20.
40. A vial comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20.
41. A syringe comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20.
42. An RNA-induced silencing complex (RISC) comprising an antisense strand of an dsRNA agent, or a pharmaceutically acceptable salt thereof, wherein the nucleotide sequence of the antisense strand differs by no more than 4 bases from the nucleotide sequence 5'- asdCsuudTadTuccadAaGfggcagcusgsa - 3' (SEQ ID NO:521),
 wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Gf and Uf are 2'-deoxy-2'-fluoro (2'-F) G and U, respectively; dC, dA, and dT are 2'-deoxy C, A, and T, respectively; and s is a phosphorothioate linkage.
43. The dsRNA agent, or a pharmaceutically acceptable salt thereof, of any one of claims 1-7 or 13-15, or the pharmaceutical composition of any one of claims 9-12 or 17-20 for use in therapy.