forming the complex C3bB. The C3bB complex, in turn, is cleaved by factor D to yield the active form of the C3 convertase of the AP (C3bBb). Both types of C3 convertases will cleave C3, forming C3b. C3b then either binds to more factor B, enhancing the complement activation through the AP (the so-called alternative or amplification loop), or leads to the formation of the active C5 convertase (C3bBbC3b or C4bC2bC3b), which cleaves C5 and triggers the late events that result in the formation of the membrane attack complex (MAC) (C5b-9).

Inappropriate activation of the complement system is responsible for propagating and/or initiating pathology in many different diseases, including, for example, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), neuromyelitis optica (NMO), multifocal motor neuropathy (MMN), myasthenia gravis (MG), C3 glomerulonephritis, systemic lupus erythmatosis, rheumatoid arthritis, ischemia-reperfusion injuries and neurodegenerative diseases.

There are limited therapies available for the treatment of complement component C3-associated diseases which require time-consuming and invasive administration at a high cost. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having a complement component C3-associated disease.

Summary

The present disclosure provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding complement component C3. The complement component C3 may be within a cell, *e.g.,* a cell within a subject, such as a human subject.

In one aspect, the present disclosure double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by or more than three nucleotides from the antisense strand nucleotide sequence of duplex AD-570714.

In an example, the disclosure provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:5.

In another aspect, the present disclosure provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C3 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 complement component C3, and wherein the region of complementarity comprises at least 15 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, 15, 18, 20-23, 30, and 31.

In one aspect, the present disclosure provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C3 in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of

the nucleotide sequence of nucleotides 475-497, 487-509, 490-512, 491-513, 705-727, 809-831, 813-835, 1147-1169, 1437-1459, 1439-1461, 1447-1469, 2596-2618, 2634-2656, 3012-3034, 3334-3356, 3611-3633, 3614-3636, 3622-3655, 3809-3831, 3846-3868, 3847-3869, 3920-3942, 4047-4069, 4061-4083, 4156-4178, 4157-4177, 4162-4184, 4178-4200, 4226-4248, 4369-4391, 4392-4414, 4521-4543, 4522-4544, 4523-4545, 5012-5034 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

In one example, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequence of nucleotides 705-727, 809-831, or 634-2656 of SEQ ID NO:1. In another example, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of nucleotides 634-2656 of SEQ ID NO:1.

In one example, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-565541.2, AD-564742, AD-567304, AD-568978, AD-569164, AD-569272.2, AD-569765.2, AD-564730.2, AD-567315, AD-564745.2, AD-571715.2, AD-570714, AD-571826, AD-572041.2, AD-572039.2, AD-572387, AD-568586.2, AD-566837.2, AD-566444.2, AD-567700.2, AD-567814.2, AD-568003.2, AD-569164.2, AD-569763.2, AD-565281.2, AD-571539.2, AD-572389.2, AD-567315.2, AD-571752.2, AD-568026.2, AD-571298, AD-572110.2, AD-572062.2, AD-572388.2, AD-572040.2, AD-567713.2, AD-567521.2, AD-567066.2, AD-1181519, AD-569268, or AD-570714.

In one example, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than 0, 1, 2, or 3 nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1181519, AD-569268, or AD-570714. In another example, the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than 0, 1, 2, or 3 nucleotides from the antisense strand nucleotide sequences of a AD-570714.

In one example, the dsRNA agent comprises at least one modified nucleotide.

In one example, substantially all of the nucleotides of the sense strand; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

In one example, all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one example, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide,

2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5’-phosphate, a nucleotide comprising a 5’-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

In one example, the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2’-hydroxyl, and glycol; and combinations thereof.

In one example, at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), *e.g.,* Ggn, Cgn, Tgn, or Agn, and, a vinyl-phosphonate nucleotide; and combinations thereof.

In another example, at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

In one example, the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2’-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA)

The double stranded region may be 19-30 nucleotide pairs in length;19-25 nucleotide pairs in length;19-23 nucleotide pairs in length; 23-27 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

In one example, each strand is independently no more than 30 nucleotides in length.

In one example, the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

The region of complementarity may be at least 17 nucleotides in length; between 19 and 23 nucleotides in length; or 19 nucleotides in length.

In one example, at least one strand comprises a 3’ overhang of at least 1 nucleotide. In another example, at least one strand comprises a 3’ overhang of at least 2 nucleotides.

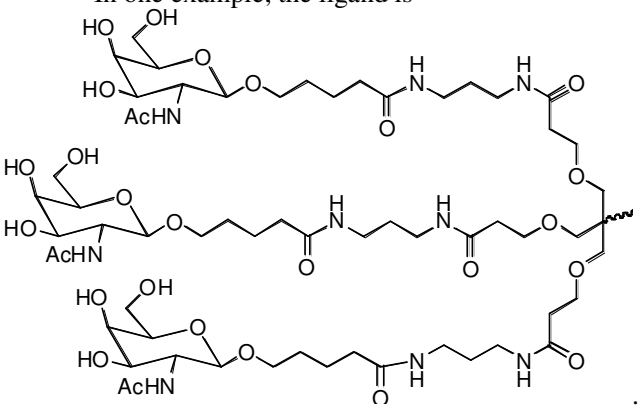
In one example, the dsRNA agent further comprises a ligand.

In one example, the ligand is conjugated to the 3’ end of the sense strand of the dsRNA agent.

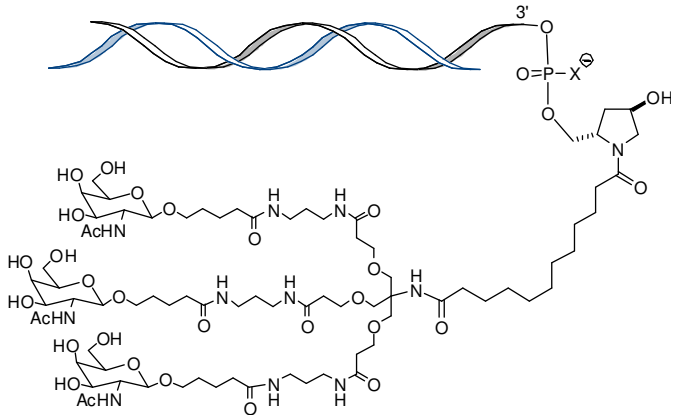
In one example, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

In one example, the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

In one example, the ligand is



In one example, the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

In one example, the X is O.

In one example, the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

In one example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand, *e.g.,* the antisense strand or the sense strand.

In another example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand, *e.g.,* the antisense strand or the sense strand.

In one example, the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand. In one example, the strand is the antisense strand.

In one example, the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

In one aspect, the present disclosure provides for a cell containing the dsRNA agent as disclosed herein. In another aspect, the present disclosure provides for a pharmaceutical composition for inhibiting expression of a gene encoding complement component C3 comprising the dsRNA agent as disclosed herein. The present disclosure also provides cells containing any of the dsRNA agents of the disclosure and pharmaceutical compositions comprising any of the dsRNA agents of the disclosure.

The pharmaceutical composition of the disclosure may include dsRNA agent in an unbuffered solution, *e.g.,* saline or water, or the pharmaceutical composition of the disclosure may include the dsRNA agent is in a buffer solution, *e.g.,* a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

In another aspect, the present disclosure provides an *in vitro* method of inhibiting expression of a complement component C3 gene in a cell, the method comprising contacting the cell with the dsRNA agent as disclosed herein, or the pharmaceutical composition as disclosed herein, thereby inhibiting expression of the complement component C3 gene in the cell. In one example, the present disclosure provides a method of inhibiting expression of a complement component C3 gene in a cell. The method includes contacting the cell with any of the dsRNAs of the disclosure or any of the pharmaceutical compositions of the disclosure, thereby inhibiting expression of the complement component C3 gene in the cell.

In one example, the cell is within a subject, *e.g.,* a human subject, *e.g.,* a subject having a complement component C3-associated disorder, such as a complement component C3-associated disorder selected from the group consisting of cold agglutinin disease (CAD), warm autoimmune hemolytic anemia, and paroxysmal nocturnal hemoglobinuria (PNH), lupis nephritis (LN), bullous pemphigoid, pemphigus, *e.g.*, pemphigus vulgaris (PV) and pemphigus foliaceus (PF), and C3 glomerulopathy.

In one example, contacting the cell with the dsRNA agent inhibits the expression of complement component C3 by at least 50%, 60%, 70%, 80%, 90%, or 95%.

In one example, inhibiting expression of complement component C3 decreases complement component C3 protein level in serum of the subject by at least 50%, 60%, 70%, 80%, 90%, or 95%.

In another aspect, the present disclosure provides for the use of the dsRNA agent as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in complement component C3 expression. In one example, the present disclosure provides a method of treating a subject having a disorder that would benefit from reduction in complement component C3 expression. The method includes administering to the subject a therapeutically effective amount of any of the dsRNAs of the disclosure or any of the pharmaceutical compositions of the disclosure, thereby treating the subject having the disorder that would benefit from reduction in complement component C3 expression.

In another aspect, the present disclosure provides for the use of the dsRNA agent as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in complement component C3 expression. In another example, the present disclosure provides a method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in complement component C3 expression. The method includes administering to the subject a prophylactically effective amount of any of the dsRNAs of the disclosure or any of the pharmaceutical compositions of the disclosure, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in complement component C3 expression.

In one example, the disorder is a complement component C3-associated disorder, *e.g.,* a complement component C3-associated disorder is selected from the group consisting of cold agglutinin disease (CAD), warm autoimmune hemolytic anemia, and paroxysmal nocturnal hemoglobinuria (PNH), lupis nephritis (LN), bullous pemphigoid, pemphigus, e.g., pemphigus vulgaris (PV) and pemphigus foliaceus (PF), and C3 glomerulopathy.

In one example, the complement component C3-associated disorder is cold agglutinin disease (CAD).

In one example, the subject is human.

In one example, the administration of the agent to the subject causes a decrease in hemolysis and/or a decrease in C3 protein accumulation.

In one example, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

In one example, the dsRNA agent is administered to the subject subcutaneously.

In one example, the methods of the disclosure include further determining the level of complement component C3 in a sample(s) from the subject.

In one example, the level of complement component C3 in the subject sample(s) is a complement component C3 protein level in a blood or serum sample(s).

In one example, the methods of the disclosure further include administering to the subject an additional therapeutic agent for treatment of hemolysis.

In another aspect, the present disclosure also provides kits comprising any of the dsRNAs of the disclosure or any of the pharmaceutical compositions of the disclosure, and optionally, instructions for use. In another aspect, the present disclosure provides for a vial comprising the dsRNA agent as disclosed herein or the pharmaceutical composition as disclosed herein. In another aspect, the present disclosure provides for a syringe comprising the dsRNA agent as disclosed herein or the pharmaceutical composition as disclosed herein.

Brief Description of the Drawings

Figure 1 schematically depicts the three complement pathways: alternative, classical and lectin. **Figure 2** is a graph showing C3 mRNA levels in mice (n = 3 per group) subcutaneously administered a single 2 mg/kg dose of the indicated dsRNA duplexes, on day 14 post-dose. C3 mRNA levels are shown relative to control levels detected with PBS treatment.

Figure 3 is a graph showing C3 mRNA levels in mice (n = 3 per group) subcutaneously administered a single 2 mg/kg dose of the indicated dsRNA duplexes, on day 14 post-dose. C3 mRNA levels are shown relative to control levels detected with PBS treatment.

Figure 4 is a graph showing C3 mRNA levels in mice (n = 3 per group) subcutaneously administered a single 2 mg/kg dose of the indicated dsRNA duplexes, on day 14 post-dose. C3 mRNA levels are shown relative to control levels detected with PBS treatment.

Figure 5 is a Table depicting the treatment groups of *Cynomolgus* monkeys subcutaneously administered a single 3 mg/kg or 25 mg/kg dose of the indicated dsRNA duplexes.

Figure 6 is a graph showing the effect of subcutaneous administration of a single 3 mg/kg or 25 mg/kg dose of the indicated dsRNA duplexes on % C3 protein levels remaining normalized to average predose C3 protein level in the serum of *Cynmologous*. The baseline was adjusted to day 1 dosing for all groups.

Figure 7 is a Table depicting the treatment groups of *Cynomolgus* monkeys subcutaneously administered a single 3 mg/kg dose of the indicated dsRNA duplexes.

Figure 8 is a graph showing the effect of subcutaneous administration of a single 3 mg/kg or 25 mg/kg dose of the indicated dsRNA duplexes on % C3 protein levels remaining normalized to average predose C3 protein level in the serum of *Cynmologous*.

Figure 9 is a Table depicting the treatment groups and timing of administration and biopsy of *Cynomolgus* monkeys subcutaneously administered a single 3 mg/kg, 9 mg/kg, or 25 mg/kg dose, or a multi-dose of 3 mg/kg (3 x 3) of the indicated dsRNA duplexes.

Figure 10 is a graph showing the effect of subcutaneous administration of a single 3 mg/kg or 25 mg/kg dose of the indicated dsRNA duplexes on % C3 protein levels remaining normalized to average predose C3 protein level in the serum of *Cynmologous*. For Group 2, Day -6 on the graph corresponds to Day -27 and Day 1 is the day on which the duplex was administered.

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C3 in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by or more than three nucleotides from the antisense strand nucleotide sequence of duplex AD-570714.

2. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C3 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 complement component C3, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7, 15, 18, 20-23, 30, and 31.

3. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C3 in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 475-497, 487-509, 490-512, 491-513, 705-727, 809-831, 813-835, 1147-1169, 1437-1459, 1439-1461, 1447-1469, 2596-2618, 2634-2656, 3012-3034, 3334-3356, 3611-3633, 3614-3636, 3622-3655, 3809-3831, 3846-3868, 3847-3869, 3920-3942, 4047-4069, 4061-4083, 4156-4178, 4157-4177, 4162-4184, 4178-4200, 4226-4248, 4369-4391, 4392-4414, 4521-4543, 4522-4544, 4523-4545, 5012-5034 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

4. The dsRNA agent of claim 3, wherein the the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 705-727, 809-831, or 2634-2656 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

5. The dsRNA agent of claim 4, wherein the the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from the nucleotide sequence of nucleotides 2634-2656 of the nucleotide sequence of SEQ ID NO:1, and the antisense strand comprises at least 19 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:5.

6. The dsRNA agent of any one of claims 1-5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by or more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-565541.2, AD-564742, AD-567304, AD-568978, AD-569164, AD-569272.2, AD-569765.2, AD-564730.2, AD-567315, AD-564745.2, AD-571715.2, AD-570714, AD-571826, AD-572041.2, AD-572039.2, AD-572387, AD-568586.2, AD-566837.2, AD-566444.2, AD-567700.2, AD-567814.2, AD-568003.2, AD-569164.2, AD-569763.2, AD-565281.2, AD-571539.2, AD-572389.2, AD-567315.2, AD-571752.2, AD-568026.2, AD-571298, AD-572110.2, AD-572062.2, AD-572388.2, AD-572040.2, AD-567713.2, AD-567521.2, AD-567066.2, AD-1181519, AD-569268, or AD-570714.

7. The dsRNA agent of claim 6, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by or more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1181519 , AD-569268, or
AD-570714.

8. The dsRNA agent of any one of claims 1-7, wherein the dsRNA agent comprises at least one modified nucleotide.

9. The dsRNA agent of any one of claims 1-8, wherein substantially all of the nucleotides of the sense strand; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.

10. The dsRNA agent of any one of claims 1-9, wherein all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

11. The dsRNA agent of any one of claims 8-10, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2’-amino-modified nucleotide, a 2’-O-allyl-modified nucleotide, 2’-C-alkyl-modified nucleotide, 2’-hydroxly-modified nucleotide, a 2’-methoxyethyl modified nucleotide, a 2’-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide,

a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

12. The dsRNA agent of any one of claims 8-10, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2′-methoxyethyl, 2′-O-alkyl, 2′-O-allyl, 2′-C- allyl, 2′-fluoro, 2′-deoxy, 2'-hydroxyl, and glycol; and combinations thereof.

13. The dsRNA of any one of claims 8-10, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), and, a vinyl-phosphonate nucleotide; and combinations thereof.

14. The dsRNA of any one of claims 8-10 wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.

15. The dsRNA of claim 14, wherein the thermally destabilizing nucleotide modification is selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycerol nucleic acid (GNA)

16. The dsRNA agent of any one of claims 1-15, wherein the double stranded region is 19-30 nucleotide pairs in length.

17. The dsRNA agent of claim 16, wherein the double stranded region is 19-25 nucleotide pairs in length.

18. The dsRNA agent of claim 16, wherein the double stranded region is 19-23 nucleotide pairs in length.

19. The dsRNA agent of claim 16, wherein the double stranded region is 23-27 nucleotide pairs in length.

20. The dsRNA agent of claim 16, wherein the double stranded region is 21-23 nucleotide pairs in length.

21. The dsRNA agent of any one of claims 1-20, wherein each strand is independently no more than 30 nucleotides in length.

22. The dsRNA agent of any one of claims 1-21, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.

23. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is at least 17 nucleotides in length.

24. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is between 19 and 23 nucleotides in length.

25. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is 19 nucleotides in length.

26. The dsRNA agent of any one of claims 1-25, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

27. The dsRNA agent of any one of claims 1-25, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

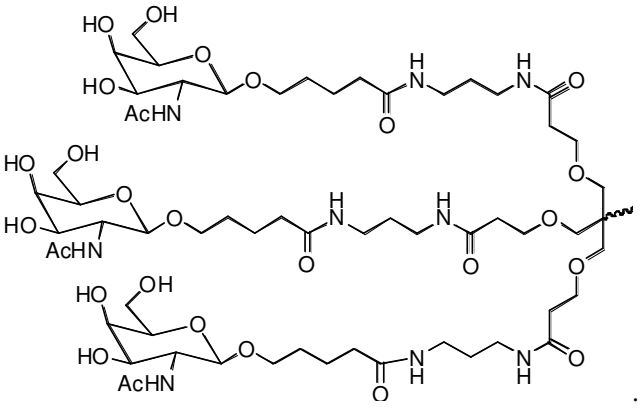
28. The dsRNA agent of any one of claims 1-27, further comprising a ligand.

29. The dsRNA agent of claim 28, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

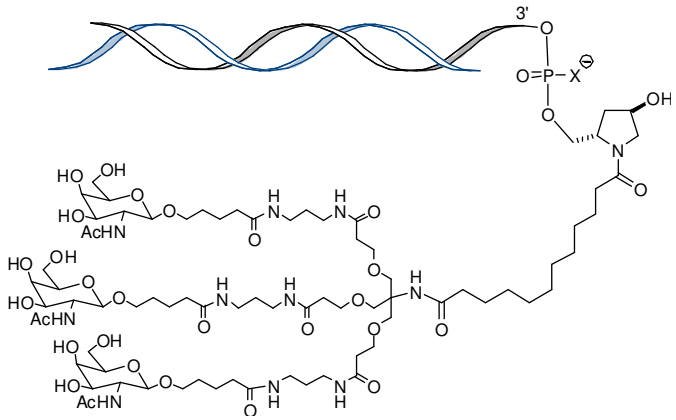
30. The dsRNA agent of claim 28 or 29, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

31. The dsRNA agent of any one of claims 28-30, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

32. The dsRNA agent of claim 30 or 31, wherein the ligand is



33. The dsRNA agent of claim 32, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

34. The dsRNA agent of claim 33, wherein the X is O.

35. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

36. The dsRNA agent of claim 35, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

37. The dsRNA agent of claim 36, wherein the strand is the antisense strand.

38. The dsRNA agent of claim 36, wherein the strand is the sense strand.

39. The dsRNA agent of claim 35, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

40. The dsRNA agent of claim 39, wherein the strand is the antisense strand.

41. The dsRNA agent of claim 39, wherein the strand is the sense strand.

42. The dsRNA agent of claim 35, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

43. The dsRNA agent of claim 42, wherein the strand is the antisense strand.

44. The dsRNA agent of any one of claims 1-43, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

45. A cell containing the dsRNA agent of any one of claims 1-44.

46. A pharmaceutical composition for inhibiting expression of a gene encoding complement component C3 comprising the dsRNA agent of any one of claims 1-44.

47. The pharmaceutical composition of claim 46, wherein dsRNA agent is in an unbuffered solution.

48. The pharmaceutical composition of claim 47, wherein the unbuffered solution is saline or water.

49. The pharmaceutical composition of claim 46, wherein said dsRNA agent is in a buffer solution.

50. The pharmaceutical composition of claim 49, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

51. The pharmaceutical composition of claim 50, wherein the buffer solution is phosphate buffered saline (PBS).

52. An *in vitro* method of inhibiting expression of a complement component C3 gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-44, or the pharmaceutical composition of any one of claims 46-51, thereby inhibiting expression of the complement component C3 gene in the cell.

53. The method of claim 52, wherein contacting the cell with the dsRNA agent inhibits the expression of complement component C3 by at least 50%, 60%, 70%, 80%, 90%, or 95%.

54. Use of the dsRNA agent of any one of claims 1-44, or the pharmaceutical composition of any one of claims 46-51 in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in complement component C3 expression.

55. Use of the dsRNA agent of any one of claims 1-44, or the pharmaceutical composition of any one of claims 46-51 in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in complement component C3 expression.

56. The use of claim 54 or 55, wherein the disorder is a complement component C3-associated disorder.

57. The use of claim 56, wherein the complement component C3-associated disorder is selected from the group consisting of cold agglutinin disease (CAD), warm autoimmune hemolytic anemia, and paroxysmal nocturnal hemoglobinuria (PNH), lupis nephritis (LN), bullous pemphigoid, pemphigus, pemphigus vulgaris (PV) and pemphigus foliaceus (PF), and C3 glomerulopathy.

58. The use of claim 56, wherein the complement component C3-associated disorder is cold agglutinin disease (CAD).

59. The use of claim 56, wherein the subject is human.

60. The use of claim 54 or 55, wherein the agent that is to be administered to the subject causes a decrease in hemolysis and/or a decrease in C3 protein accumulation.

61. The use of any one of claims 54-60, wherein the dsRNA agent is to be administered to the subject at a dose of 0.01 mg/kg to 50 mg/kg.

62. The use of any one of claims 54-61, wherein the dsRNA agent is to be administered to the subject subcutaneously.

63. The use of any one of claims 54-62, further comprising determining the level of complement component C3 in a sample(s) from the subject.

64. The use of claim 63, wherein the level of complement component C3 in the subject sample(s) is a complement component C3 protein level in a blood or serum sample(s).

65. The use of any one of claims 54-64, further comprising that an additional therapeutic agent is to be administered to the subject for treatment of hemolysis.

66. A kit comprising the dsRNA agent of any one of claims 1-44 or the pharmaceutical composition of any one of claims 46-51.

67. A vial comprising the dsRNA agent of any one of claims 1-44 or the pharmaceutical composition of any one of claims 46-51.

68. A syringe comprising the dsRNA agent of any one of claims 1-44 or the pharmaceutical composition of any one of claims 46-51.