the classical pathway can be activated by phosphatidyl serine present in apoptotic bodies in the absence of immune complexes.

The lectin pathway is initiated by the mannose-binding lectins (MBL) that bind to complex carbohydrate residues on the surface of pathogens. The activation of the classical pathway or the lectin pathway leads to activation of the (C4b2b) C3 convertase.

The alternate pathway is activated by the binding of C3b, which is spontaneously generated by the hydrolysis of C3, on targeted surfaces. This surface-bound C3b is then recognized by factor B, 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, atypical hemolytic uremic syndrome, rheumatoid arthritis, ischemia-reperfusion injuries and neurodegenerative diseases.

To date, only one therapeutic that targets the C5-C5a axis is available for the treatment of complement component-associated diseases, the anti-C5 antibody, eculizumab (Soliris®). Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) and is currently being evaluated in clinical trials for additional complement component-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a high cost. Furthermore, approximately 50% of eculizumab-treated PNH subjects have low level of hemolysis and require residual transfusions (Hill A, *et al.* (2010) *Haematologica* 95(4):567-73). Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having a complement component-associated disease.

Summary

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

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

In one aspect, the present disclosure refers to 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, wherein each strand comprises 15-30 nucleotides and said strands form a double-stranded region, and wherein the antisense strand comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the following antisense sequences:

a. GAGAGAAGACCUUGACCACGUAG (SEQ ID NO:282);

b. UAGAGAAGACCUUGACCACGUAG (SEQ ID NO:267);

c. AGAGAGAAGACCUUGACCACGUA (SEQ ID NO:266);

d. AGAGAAGACCUUGACCACGUAGG (SEQ ID NO:299); and wherein at least one nucleotide in said dsRNA comprises a modification.

In another aspect, the present disclosure refers to a cell containing the dsRNA as disclosed herein.

In another aspect, the present disclosure refers to a pharmaceutical composition for inhibiting expression of a complement component C3 gene comprising the dsRNA as disclosed herein.

In another aspect, the present disclosure refers to an *in vitro* method of inhibiting complement component 3 (C3) expression in a cell, the method comprising:

(a) contacting the cell with the dsRNA as disclosed herein or the pharmaceutical composition as disclosed herein; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C3 gene, thereby inhibiting expression of the C3 gene in the cell.

In another aspect, the present disclosure refers to the use of the dsRNA as disclosed herein or the pharmaceutical composition as disclosed hereiin the manufacture of a medicament for treating a complement component-associated disease.

In adition, the present disclosure provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a C9 gene. The C9 gene may be within a cell, *e.g.,* a cell within a subject, such as a human.

The present disclosure also provides methods and combination therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a CFB, C3, and/or C9 gene, *e.g.,* a complement component-associated disease, such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) using iRNA compositions which effect the RNA-induced silencing

complex (RISC)-mediated cleavage of RNA transcripts of a CFB, C3, and/or C9 gene for inhibiting the expression of a CFB, C3, and/or C9 gene.

Accordingly, in one example the present disclosure provides double-stranded ribonucleic acids (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:1-5, 27, and 30, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:12-16, 33, and 36.

In another example the present disclosure provides double-stranded ribonucleic acids (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in Table 3 and 4.

In one example, the sense and antisense strands comprise sequences selected from the group consisting of AD-60304, AD-60331, and AD-60344 and any one of the agents listed in Tables 3 and 4.

In one example the region of complementarity consists of the nucleotide sequence of one of the antisense sequences of any one of Tables 3 and 4.

In one example, the dsRNA comprises a sense strand consisting of the nucleotide sequence of a sense strand sequence selected from the sequence of any one of Tables 3 and 4, and an antisense strand consisting of the nucleotide sequence of an antisense sequence selected from the sequences of any one of Tables 3 and 4.

In another example the present disclosure provides double-stranded ribonucleic acids (dsRNA) for inhibiting expression of complement component C3 in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of

the nucleotide sequence of SEQ ID NOs:6-8, 28, and 31, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:17-19, 34, and 37.

In another example the present disclosure provides double-stranded ribonucleic acids (dsRNA) for inhibiting expression of complement component C3 in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in Table 5 and 6.

In one example, the sense and antisense strands comprise sequences selected from the group consisting of AD-60169 and any one of the agents listed in Tables 5 and 6.

In one example the region of complementarity consists of the nucleotide sequence of one of the antisense sequences of any one of Tables 5 and 6.

In one example, the dsRNA comprises a sense strand consisting of the nucleotide sequence of a sense strand sequence selected from the sequence of any one of Tables 5 and 6, and an antisense strand consisting of the nucleotide sequence of an antisense sequence selected from the sequences of any one of Tables 5 and 6.

In another example the present disclosure provides double-stranded ribonucleic acids (dsRNA)for inhibiting expression of complement component C9 in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:9-11, 29, and 32, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:20-22, 35, and 38.

In another example the present disclosure provides double-stranded ribonucleic acids (dsRNA) for inhibiting expression of complement component C9 in a cell, wherein the dsRNA comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense sequences listed in Table 7 and 8.

In one example, the sense and antisense strands comprise sequences selected from the group consisting of any one of the agents listed in Tables 7 and 8.

In one example the region of complementarity consists of the nucleotide sequence of one of the antisense sequences of any one of Tables 7 and 8.

In one example, the dsRNA comprises a sense strand consisting of the nucleotide sequence of a sense strand sequence selected from the sequence of any one of Tables 7 and 8, and an antisense strand consisting of the nucleotide sequence of an antisense sequence selected from the sequences of any one of Tables 7 and 8.

The dsRNA may include at least one modified nucleotide, *e.g.,*a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, 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 terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group, a 2'-deoxy-2'-fluoro 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, and a nucleotide comprising a 5’-phosphate mimic.

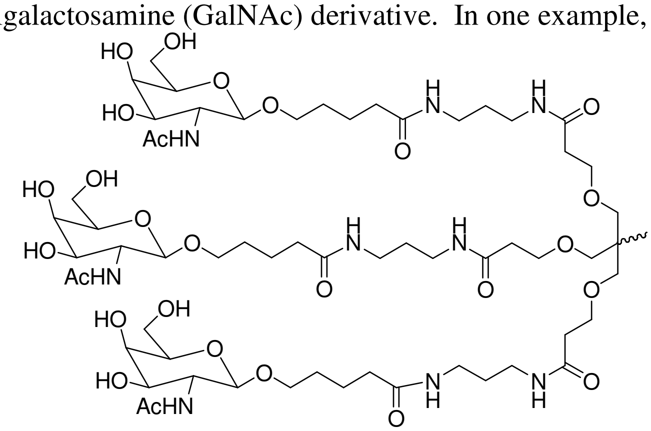
In one example, substantially all the nucleotides of the sense strand and the antisense strand are modified nucleotides. In another example, all the nucleotides of the sense strand and the antisense strand are modified nucleotides.

The the region of complementarity may be at least 17 nucleotides in length, such as 19 nucleotides in length, or no more than 30 nucleotides in length.

The region of complementarity may be between 19 and 21 nucleotides in length.

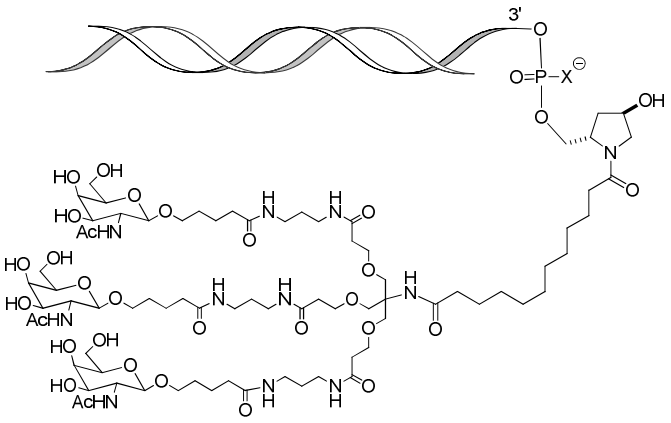
At least one strand of the dsRNA may include a 3’ overhang of at least 1 nucleotide, or at least 2 nucleotides.

The dsRNA omay further include a ligand. In one example, the ligand is conjugated to the 3’ end of the sense strand of the dsRNA. In one example, the ligand is an N-acetylgalactosamine (GalNAc) derivative. In one example, the ligand is



.

In one example, the dsRNA 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 another example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of complement factor B (CFB) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of complement component 3 (C3) in a cell. The agents

include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p′, n_q, and n_q′, each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b′ differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In a further example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of complement component 9 (C9) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In one example, i is 0; j is 0; i is 1; j is 1; both i and j are 0; or both i and j are 1.

In one example, k is 0; l is 0; k is 1; l is 1; both k and l are 0; or both k and l are 1.

In one example, XXX is complementary to X′X′X′, YYY is complementary to Y′Y′Y′, and ZZZ is complementary to Z′Z′Z′.

In one example, the YYY motif occurs at or near the cleavage site of the sense strand.

In one example, the Y′Y′Y′ motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

In one example, the Y′ is 2′-O-methyl.

In one example, formula (III) is represented by formula (IIIa):

sense: 5' n_p -N_a -Y Y Y -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- Y′Y′Y′- $N_{a'}$- $n_{q'}$ 5' (IIIa).

In one example, formula (III) is represented by formula (IIIb):

sense: 5' n_p -N_a -Y Y Y -N_b -Z Z Z -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- Y′Y′Y′-$N_{b'}$-Z′Z′Z′- $N_{a'}$- $n_{q'}$ 5' (IIIb)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In one example, formula (III) is represented by formula (IIIc):

sense: 5' n_p -N_a –X X X -N_b -Y Y Y -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- X′X′X′-$N_{b'}$- Y′Y′Y′- $N_{a'}$- $n_{q'}$ 5' (IIIc)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides.

In one example, formula (III) is represented by formula (IIId):

sense: 5' n_p -N_a –X X X- N_b -Y Y Y -N_b -Z Z Z -N_a - n_q 3'

antisense: 3' $n_{p'}$-$N_{a'}$- X′X′X′- $N_{b'}$-Y′Y′Y′-$N_{b'}$-Z′Z′Z′- $N_{a'}$- $n_{q'}$ 5'

(IIId)

wherein each N_b and N_b' independently represents an oligonucleotide sequence comprising 1-5 modified nucleotides and each N_a and N_a' independently represents an oligonucleotide sequence comprising 2-10 modified nucleotides.

The double-stranded region may 15-30 nucleotide pairs in length, 17-23 nucleotide pairs in length, 17-25 nucleotide pairs in length, 23-27 nucleotide pairs in length, 19-21 nucleotide pairs in length, or 21-23 nucleotide pairs in length.

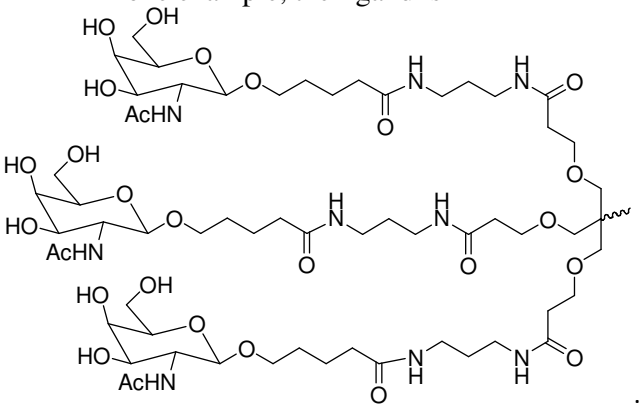
In one example, each strand has 15-30 nucleotides.

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 combinations thereof.

In one example, the modifications on the nucleotides are 2′-O-methyl or 2′-fluoro modifications.

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

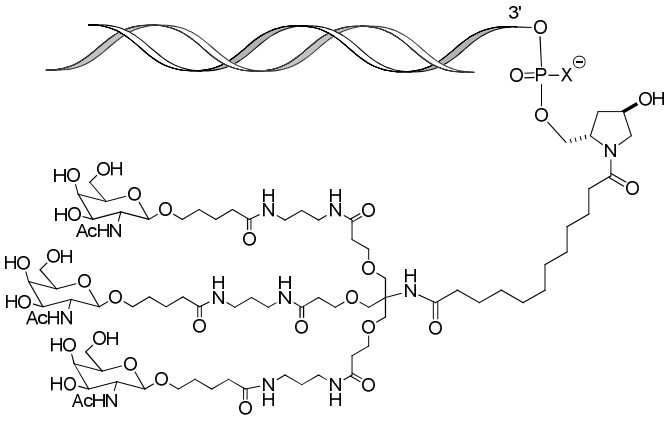
In one example, the ligand is



.

In one example, the ligand is attached to the 3′ end of the sense strand.

In one example, the RNAi 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 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. In one example, the strand is the antisense strand. In another example, the strand is the sense strand.

In another example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand. In one example, the strand is the antisense strand. In another example, the strand is 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 example, the Y nucleotides contain a 2′-fluoro modification.

In one example, the Y′ nucleotides contain a 2′-O-methyl modification.

In one example, p′>0. In another example, p′=2.

In one example, q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA.

In another example, q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

In one example, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

In one example, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage. In another example, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In one example, the RNAi agent is selected from the group of RNAi agents listed in Tables 3 and 4. In one example, the RNAi agent is selected from the group of RNAi agents AD-60304, AD-60331, and AD-60344.

In another example, the RNAi agent is selected from the group of RNAi agents listed in Tables 5 and 6.

In yet another example, the RNAi agent is selected from the group of RNAi agents listed in Tables 7 and 8.

In one example, the present disclosure provides double stranded RNAi agents comprising the RNAi agents listed in any one of Tables 3, 5, and 7.

In one example, the present disclosure provides compositions comprising a modified antisense polynucleotide agent. The agents are capable of inhibiting the expression of Complement Factor B (CFB) in a cell, and include a sequence complementary to a sense sequence selected from the group of the sequences listed in Table 3, wherein the polynucleotide is about 14 to about 30 nucleotides in length.

In another example, the present disclosure provides compositions comprising a modified antisense polynucleotide agent. The agents are capable of inhibiting the expression of Complement Component 3 (C3) in a cell, and include a sequence complementary to a sense sequence selected from the group of the sequences listed in Table 5, wherein the polynucleotide is about 14 to about 30 nucleotides in length.

In yet another example, the present disclosure provides compositions comprising a modified antisense polynucleotide agent. The agents are capable of inhibiting the expression of Complement Component 9 (C9) in a cell, and include a sequence complementary to a sense sequence selected from the group of the sequences listed in Table 7, wherein the polynucleotide is about 14 to about 30 nucleotides in length.

In one example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Factor B (CFB) in a cell. The agent include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p′, n_q, and n_q′, each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b′ differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Factor B (CFB) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to

about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Factor B (CFB) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-

25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In yet a further example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Factor B (CFB) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Factor B (CFB) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding CFB, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -Y Y Y - N_a - n_q 3'

antisense: 3' n_p′-N_a′- Y′Y′Y′- N_a′- n_q′ 5' (IIIa)

wherein:

each n_p, n_q, and n_q′, each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p′ >0 and at least one n_p′ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y′Y′Y′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 3 (C3) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p', n_q, and n_q', each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 3 (C3) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b'

differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 3 (C3) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q′, each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p′ >0 and at least one n_p′ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b′ differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In yet another example, the present invemtion provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 3 (C3) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 3 (C3) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C3, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -Y Y Y - N_a - n_q 3'

antisense: 3' n_p'-N_a'- Y′Y′Y′- N_a'- n_q' 5' (IIIa)

wherein:

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y′Y′Y′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, the present disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 9 (C9) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p′-N_a′-(X′X′X′)$_k$-N_b′-Y′Y′Y′-N_b′-(Z′Z′Z′)$_l$-N_a′- n_q′ 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

p, p', q, and q′ are each independently 0-6;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b′ independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

each n_p, n_p′, n_q, and n_q′, each of which may or may not be present independently represents an overhang nucleotide;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b′ differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In one example, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 9 (C9) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand.

In another example, the imvention provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 9 (C9) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p' >0 and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of Complement Component 9 (C9) in a cell. The agents include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -(X X X) $_i$-N_b -Y Y Y -N_b -(Z Z Z)$_j$ -N_a - n_q 3'

antisense: 3' n_p'-N_a'-(X′X′X′)$_k$-N_b'-Y′Y′Y′-N_b'-(Z′Z′Z′)$_l$-N_a'- n_q' 5' (III)

wherein:

i, j, k, and l are each independently 0 or 1;

each n_p, n_q, and n_q', each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

$n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a' independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 nucleotides which are either modified or unmodified or combinations thereof;

XXX, YYY, ZZZ, X′X′X′, Y′Y′Y′, and Z′Z′Z′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

modifications on N_b differ from the modification on Y and modifications on N_b' differ from the modification on Y′;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In a further example, the present disclosure provises double stranded RNAi agents capable of inhibiting the expression of Complement Component 9 (C9) in a cell. The agent include a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C9, wherein each strand is about 14 to about 30 nucleotides in length, wherein the double stranded RNAi agent is represented by formula (III):

sense: 5' n_p -N_a -Y Y Y - N_a - n_q 3'

antisense: 3' n_p′-N_a′- Y′Y′Y′- N_a′- n_q′ 5' (IIIa)

wherein:

each n_p, n_q, and n_q′, each of which may or may not be present, independently represents an overhang nucleotide;

p, q, and q′ are each independently 0-6;

n_p′ >0 and at least one n_p′ is linked to a neighboring nucleotide via a phosphorothioate linkage;

each N_a and N_a′ independently represents an oligonucleotide sequence comprising 0-25 nucleotides which are either modified or unmodified or combinations thereof, each sequence comprising at least two differently modified nucleotides;

YYY and Y′Y′Y′ each independently represent one motif of three identical modifications on three consecutive nucleotides, and wherein the modifications are 2′-O-methyl or 2′-fluoro modifications;

wherein the sense strand comprises at least one phosphorothioate linkage; and

wherein the sense strand is conjugated to at least one ligand, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, the disclosure provides double stranded RNAi agents for inhibiting expression of complement factor B (CFB) in a cell, wherein the double stranded RNAi 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 3 nucleotides from the nucleotide sequence of any one of SEQ ID NOs:1-5, 27, and 30, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:12-16, 33, and 36, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate

internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In another example, the present disclosure provides double stranded RNAi agents for inhibiting expression of complement component C3 in a cell, wherein the double stranded RNAi 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 3 nucleotides from the nucleotide sequence of any one of SEQ ID NOs:6-8, 28, and 31, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:17-19, 34, and 37, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

In yet another example, the present disclosure provides double stranded RNAi agents for inhibiting expression of complement component C9 in a cell, wherein the double stranded RNAi 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 3 nucleotides from the nucleotide sequence of any one of SEQ ID NOs:9-11, 29, and 32, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the nucleotide sequence of SEQ ID NOs:20-22, 35, and 38, wherein substantially all of the nucleotides of the sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus, wherein substantially all of the nucleotides of the antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification, wherein the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

wherein the sense strand is conjugated to one or more GalNAc derivatives attached through a branched bivalent or trivalent linker at the 3'-terminus.

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

In another example, the present disclosure provides cells containing the agents of the disclosure.

In one example, the disclosure provides vectors encoding at least one strand of the agents of the disclosure.

In another example, the disclosure provides cells comprising the vectors of the disclosure.

In one example, the present disclosure provides pharmaceutical compositions for inhibiting expression of a complement component factor B gene comprising the agents the disclosure.

In another example, the present disclosure provides pharmaceutical compositions for inhibiting expression of a complement component C3 gene comprising the agents of the disclosure.

In yet another example, the present disclosure provides pharmaceutical compositions for inhibiting expression of a complement component C9 gene comprising the agents of the disclosure.

In one example, the RNAi agent is administered in an unbuffered solution.

In one example, the unbuffered solution is saline or water.

In one example, the RNAi agent is administered with a buffer solution.

In one example, the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

In one example, the buffer solution is phosphate buffered saline (PBS).

In one example, the present disclosure provides methods of inhibiting complement factor B (CFB) expression in a cell. The methods include contacting the cell with the agent of athe disclosure or a pharmaceutical composition of the disclosure, and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of a CFB gene, thereby inhibiting expression of the CFB gene in the cell.

In another example, the present disclosure provides methods of inhibiting complement component 3 (C3) expression in a cell. The methods include contacting the cell with the agent of athe disclosure or a pharmaceutical composition of the disclosure, and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of a C3 gene, thereby inhibiting expression of the C3 gene in the cell.

In yet another example, the present disclosure provides methods of inhibiting complement component 9 (C9) expression in a cell. The methods include contacting the cell with the agent of athe disclosure or a pharmaceutical composition of the disclosure, and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of a C9 gene, thereby inhibiting expression of the C9 gene in the cell.

In one example, the cell is within a subject.

In one example, the subject is a human.

In one example, the human subject suffers from a complement component-associated disease.

In one example, the complement component-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), asthma, rheumatoid arthritis, systemic lupus erythmatosis, glomerulonephritis, psoriasis, dermatomyositis bullous pemphigoid, atypical hemolytic uremic syndrome, Shiga toxin *E. coli*-related hemolytic uremic syndrome, myasthenia gravis, neuromyelistis optica, dense deposit disease, C3 neuropathy, age-related macular degeneration, cold agglutinin disease, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, a sensitized recipient of a transplant, and sepsis.

In one example, the complement component-associated disease is paroxysmal nocturnal hemoglobinuria (PNH).

In another example, the complement component-associated disease is atypical hemolytic uremic syndrome (aHUS).

In one example, the CFB expression is inhibited by at least about 30%.

In one example, the C3 expression is inhibited by at least about 30%.

In one example, the C9 expression is inhibited by at least about 30%.

In one example, the agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In another example, the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

In one example, the agent is administered subcutaneously.

In another example, the agent is administered intravenously.

In one example, the present disclosure provides methods of treating a subject having a disorder that would benefit from reduction in complement factor B (CFB) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby treating the subject.

In another example, the present disclosure provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement factor B (CFB) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in CFB expression.

In yet another example, the present disclosure provides methods of treating a subject having a disorder that would benefit from reduction in complement component C3 (C3) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby treating the subject.

In one example, the present disclosure provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C3 (C3) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C3 expression.

In another example, the present disclosure provides methods of treating a subject having a disorder that would benefit from reduction in complement component C9 (C9) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby treating the subject.

In one example, the present disclosure provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C9 (C9) expression. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C9 expression.

In one example, the disorder is a complement component-associated disease.

In one example, the complement component-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), asthma, rheumatoid arthritis, systemic lupus erythmatosis, glomerulonephritis, psoriasis, dermatomyositis bullous pemphigoid, atypical hemolytic uremic syndrome, Shiga toxin *E. coli*-related hemolytic uremic syndrome, myasthenia gravis, neuromyelistis optica, dense deposit disease, C3 neuropathy, age-related macular degeneration, cold agglutinin disease, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, a sensitized recipient of a transplant, and sepsis.

In one example, the complement component -associated disease is paroxysmal nocturnal hemoglobinuria (PNH).

In another example, the complement component-associated disease is atypical hemolytic uremic syndrome (aHUS).

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

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 administration of the agent to the subject causes a decrease in hemolysis and/or a decrease in C9 protein accumulation.

In one example, the methods further include administration of eculizumab to the subject.

In another example, the methods further include administration of compstatin to the subject.

In one example, the agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In another example, the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

In yet another example, the agent is administered at a dose selected from the group consisting of 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg.

In one example, the agent is administered to the subject once a week.

In another example, the agent is administered to the subject twice a month.

In one example, the methods further include measuring LDH levels in the subject.

In one example, the present disclosure provides methods of inhibiting the expression of complement factor B (CFB) in a subject. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby inhibiting the expression of CFB in the subject.

In another example, the present disclosure provides methods of inhibiting the expression of complement component C3 (C3) in a subject. The methods include administering to the subject a therapeutically effective amount of the agent of the disclosure, thereby inhibiting the expression of C3 in the subject.

In yet another example, the present disclosure provides methods of inhibiting the expression of complement component C9 (C9) in a subject. The methods include administering to the subject a therapeutically effective amount of the agent of any one of the disclosure, thereby inhibiting the expression of C9 in the subject.

In one example, the methods further include administering eculizumab to the subject.

In another example, the methods further include administering compstatin to the subject.

In one example, the agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In another example, the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

In yet another example, the agent is administered at a dose selected from the group consisting of 1 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg.

In one example, the agent is administered to the subject once a week.

In another example, the dsRNA agent is administered to the subject twice a month.

We claim:

1. 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, wherein each strand comprises 15-30 nucleotides and said strands form a double-stranded region, and wherein the antisense strand comprising at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the following antisense sequences:

a. GAGAGAAGACCUUGACCACGUAG (SEQ ID NO:282);
b. UAGAGAAGACCUUGACCACGUAG (SEQ ID NO:267);
c. AGAGAGAAGACCUUGACCACGUA (SEQ ID NO:266);
d. AGAGAAGACCUUGACCACGUAGG (SEQ ID NO:299); and wherein at least one nucleotide in said dsRNA comprises a modification.

2. The double stranded RNAi of claim 1, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the following sense sequences:

a. ACGUGGUCAAGGUCUUCUCUC (SEQ ID NO:241);
b. ACGUGGUCAAGGUCUUCUCUA (SEQ ID NO:226);
c. CGUGGUCAAGGUCUUCUCUCU (SEQ ID NO:225); and
d. UACGUGGUCAAGGUCUUCUCU (SEQ ID NO:258).

3. The dsRNA of claim 1 or claim 2, wherein the double-stranded region is 15-23 nucleotide pairs in length.

4. The dsRNA of any one of claims 1-3, wherein the modifications on the nucleotides are selected from the group of modified nucleotides consisting of a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2′-fluoro modified nucleotide, a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group, a 2'-deoxy-2'-fluoro 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, and a nucleotide comprising a 5'-phosphate mimic.

5. The dsRNA of any one of claims 1-4, wherein the modifications on the nucleotides are 2′-O-methyl or 2′-fluoro modifications.

6. The dsRNA of any one of claims 1-5, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

7. The dsRNA of any one of claims 1-6, wherein the ligand is one or more GalNAc derivatives.

8. The dsRNA of any one of claims 1-7, wherein said dsRNA has a phosphorus atom in its internucleoside backbone.

9. The dsRNA of any one of claims 1-8, wherein the backbone includes one or more selected from phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'.

10. A cell containing the dsRNA of any one of claims 1-9.

11. A pharmaceutical composition for inhibiting expression of a complement component C3 gene comprising the dsRNA of any one of claims 1-9.

12. An *in vitro* method of inhibiting complement component 3 (C3) expression in a cell, the method comprising:

(a) contacting the cell with the dsRNA of any one of claims 1-9 or the pharmaceutical composition of claim 11; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C3 gene, thereby inhibiting expression of the C3 gene in the cell.

13. Use of the dsRNA of any one of claims 1-9 or the pharmaceutical composition of claim 11 in the manufacture of a medicament for treating a complement component-associated disease.

14. The use of claim 13, wherein the complement component-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), asthma, rheumatoid arthritis, systemic lupus erythmatosis, glomerulonephritis, psoriasis, dermatomyositis bullous pemphigoid, atypical hemolytic uremic syndrome, Shiga toxin *E. coli*-related hemolytic uremic syndrome, myasthenia gravis, neuromyelistis optica, dense deposit disease, C3 neuropathy, age-related macular degeneration, cold agglutinin disease, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, a sensitized recipient of a transplant, and sepsis.