The present invention 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 adition, the present invention 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 invention 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 aspect the present invention provides~~Disclosed are 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 aspect the present invention provides~~Also disclosed are 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 ~~embodiment~~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 ~~embodiment~~ 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 ~~embodiment~~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~~ one aspect the present invention 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 aspect the present invention 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 embodiment, 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 embodiment 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 embodiment, 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 aspect the present invention provides~~Also disclosed are 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 aspect the present invention provides~~Also disclosed are 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 ~~embodiment~~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 ~~embodiment~~ 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 ~~embodiment~~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'-

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 aspect, the present invention provides~~Also disclosed are 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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~example, the YYY motif occurs at or near the cleavage site of the sense strand.

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

In one ~~embodiment~~example, the Y' is 2'-O-methyl.

In one ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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.

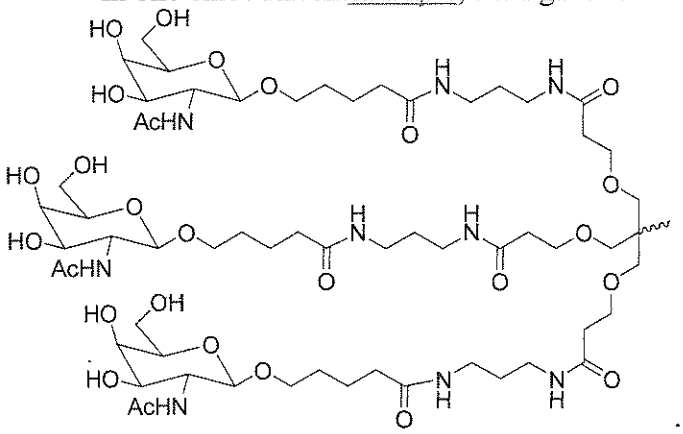
In one ~~embodiment~~example, each strand has 15-30 nucleotides.

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

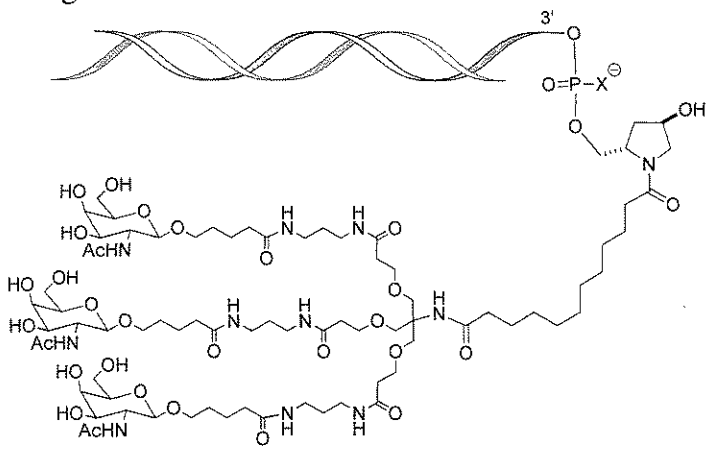
In one ~~embodiment~~example, the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one ~~embodiment~~example, the ligand is



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

In one ~~embodiment~~example, the RNAi agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

In one ~~embodiment~~example, the X is O.

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

In one ~~embodiment~~example, the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand. In one embodiment, the strand is the antisense strand. In another ~~embodiment~~example, the strand is the sense strand.

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

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

In one ~~embodiment~~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 ~~embodiment~~example, the Y nucleotides contain a 2'-fluoro modification.

In one ~~embodiment~~example, the Y' nucleotides contain a 2'-O-methyl modification.

In one ~~embodiment~~example, p'>0. In another embodiment, p'=2.

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

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

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

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

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

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

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

~~In one aspect, the present invention provides~~Also disclosed are double stranded RNAi agents comprising the RNAi agents listed in any one of Tables 3, 5, and 7.

~~In one aspect, the present invention provides~~Also disclosed are 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 aspect, the present invention 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 aspect, the present invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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 aspect, the invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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 aspect, the invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}Y\ Y\ Y\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}Y'Y'Y'\text{-}N_a'\text{-}n_q'\ 5'$ (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 aspect, the present invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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 aspect, the present invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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 aspect, the invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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 aspect, the present invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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 aspect, the invention provides~~Also disclosed are 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: $5'\ n_p\text{-}N_a\text{-}(X\ X\ X)_i\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}(Z\ Z\ Z)_j\text{-}N_a\text{-}n_q\ 3'$

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 aspect, the invention provides~~Also disclosed are 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 aspect, the invention provides~~Also disclosed are 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 aspect, the present invention provises~~Also disclosed are 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 aspect, the invention provides~~Also disclosed are 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 aspect, the present invention 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 aspect, the present invention provides~~Also disclosed are 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 embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In another aspect, the present invention provides cells containing the agents of the invention.

In one aspect, the invention provides vectors encoding at least one strand of the agents of the invention.

In another aspect, the invention provides cells comprising the vectors of the invention.

~~In one aspect, the present invention provides~~ Also disclosed are pharmaceutical compositions for inhibiting expression of a complement component factor B gene comprising the agents the invention.

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

~~In yet another aspect, the present invention provides~~Also disclosed are pharmaceutical compositions for inhibiting expression of a complement component C9 gene comprising the agents of the invention.

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

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

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

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

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

~~In one aspect, the present invention provides~~Also disclosed are methods of inhibiting complement factor B (CFB) expression in a cell. The methods include contacting the cell with the agent of athe invention or a pharmaceutical composition of the invention, 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 aspect, the present invention provides methods of inhibiting complement component 3 (C3) expression in a cell. The methods include contacting the cell with the agent of athe invention or a pharmaceutical composition of the invention, 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 aspect, the present invention provides~~Also disclosed are methods of inhibiting complement component 9 (C9) expression in a cell. The methods include contacting the cell with the agent of athe invention or a pharmaceutical composition of the invention, 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 embodiment, the cell is within a subject.

In one embodiment, the subject is a human.

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

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

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

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

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

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

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

In one embodiment, the agent is administered subcutaneously.

In another embodiment, the agent is administered intravenously.

In one aspect, the present invention 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 invention, thereby treating the subject.

~~In another aspect, the present invention provides~~Also disclosed are 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 invention, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in CFB expression.

~~In yet another aspect, the present invention provides~~Also disclosed are 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 invention, thereby treating the subject.

~~In one aspect, the present invention provides~~Also disclosed are 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 invention, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C3 expression.

~~In another aspect, the present invention provides~~Also disclosed are 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 invention, thereby treating the subject.

~~In one aspect, the present invention provides~~Also disclosed are 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 invention, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C9 expression.

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

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

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

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

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

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

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

We claim:

1. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand, wherein said 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 said 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.

2. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said 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.

3. The dsRNA of claim 2, wherein 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.

4. 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 said 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 said 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.

5. 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, 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.

6. The dsRNA of claim 5, wherein 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.

7. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C9 in a cell, wherein said dsRNA comprises a sense strand and an antisense strand, wherein said 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 said 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.

8. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of complement component C9 in a cell, wherein said 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.

9. The dsRNA of claim 8, wherein the sense and antisense strands comprise sequences selected from the group consisting of any one of the agents listed in Tables 7 and 8.

10. A double stranded RNAi agent capable of inhibiting the expression of complement factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said double stranded RNAi agent is represented by formula (III):

sense: $5'\ n_p\text{-}N_a\text{-}(X\,X\,X)_i\text{-}N_b\text{-}Y\,Y\,Y\text{-}N_b\text{-}(Z\,Z\,Z)_j\text{-}N_a\text{-}n_q\ 3'$

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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.

11. A double stranded RNAi agent capable of inhibiting the expression of complement component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

12. A double stranded RNAi agent capable of inhibiting the expression of complement component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

13. The double stranded RNAi agent of any one of claims 10-12, wherein 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.

14. The double stranded RNAi agent of any one of claims 10-12, wherein 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.

15. The double stranded RNAi agent of any one of claims 10-12, wherein XXX is complementary to X'X'X', YYY is complementary to Y'Y'Y', and ZZZ is complementary to Z'Z'Z'.

16. The double stranded RNAi agent of any one of claims 10-12, wherein the YYY motif occurs at or near the cleavage site of the sense strand.

17. The double stranded RNAi agent of any one of claims 10-12, wherein the Y'Y'Y' motif occurs at the 11, 12 and 13 positions of the antisense strand from the 5'-end.

18. The double stranded RNAi agent of claim 17, wherein the Y' is 2'-O-methyl.

19. The double stranded RNAi agent of any one of claims 10-12, wherein 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).

20. The double stranded RNAi agent of any one of claims 10-12, wherein 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.

21. The double stranded RNAi agent of any one of claims 10-12, wherein 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.

22. The double stranded RNAi agent of any one of claims 10-12, wherein 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.

23. The double stranded RNAi agent of any one of claims 10-12, wherein the double-stranded region is 15-30 nucleotide pairs in length.

24. The double stranded RNAi agent of claim 23, wherein the double-stranded region is 17-23 nucleotide pairs in length.

25. The double stranded RNAi agent of claim 23, wherein the double-stranded region is 17-25 nucleotide pairs in length.

26. The double stranded RNAi agent of claim 23, wherein the double-stranded region is 23-27 nucleotide pairs in length.

27. The double stranded RNAi agent of claim 23, wherein the double-stranded region is 19-21 nucleotide pairs in length.

28. The double stranded RNAi agent of claim 23, wherein the double-stranded region is 21-23 nucleotide pairs in length.

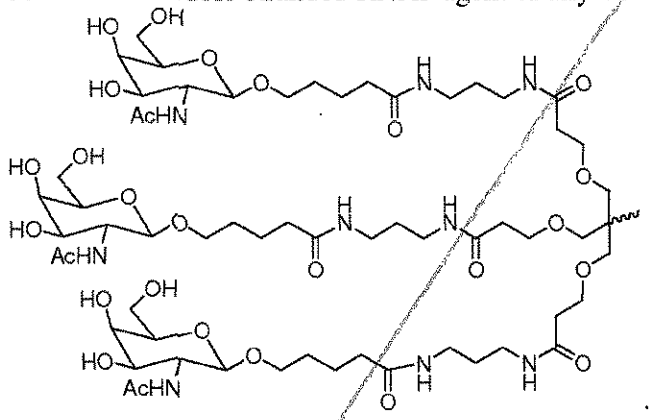
29. The double stranded RNAi agent of any one of claims 10-12, wherein each strand has 15-30 nucleotides.

30. The double stranded RNAi agent of any one of claims 10-12, wherein the modifications on the nucleotides are selected from the group consisting of LNA, CRN, cET, UNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-alkyl, 2'-O-allyl, 2'-C- allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof.

31. The double stranded RNAi agent of claim 30, wherein the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications.

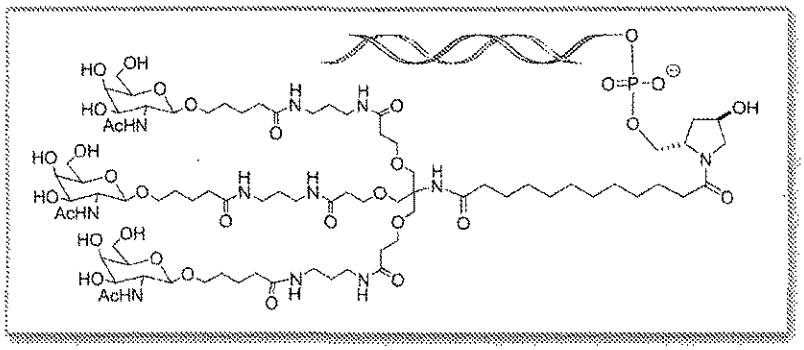
32. The double stranded RNAi agent of any one of claims 10-12, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

33. The double stranded RNAi agent of any one of claims 10-12, wherein the ligand is



34. The double stranded RNAi agent of any one of claims 10-12, wherein the ligand is attached to the 3' end of the sense strand.

35. The double stranded RNAi agent of claim 34, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



36. The double stranded RNAi agent of any one of claims 10-12, wherein said agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

37. The double stranded RNAi agent of claim 36, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

38. The double stranded RNAi agent of claim 37, wherein said strand is the antisense strand.

39. The double stranded RNAi agent of claim 37, wherein said strand is the sense strand.

40. The double stranded RNAi agent of claim 36, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.

41. The double stranded RNAi agent of claim 40, wherein said strand is the antisense strand.

42. The double stranded RNAi agent of claim 40, wherein said strand is the sense strand.

43. The double stranded RNAi agent of claim 36, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.

44. The double stranded RNAi agent of claim 43, wherein said strand is the antisense strand.

45. The double stranded RNAi agent of any one of claims 10-12, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.

46. The double stranded RNAi agent of any one of claims 10-12, wherein the Y nucleotides contain a 2′-fluoro modification.

47. The double stranded RNAi agent of any one of claims 10-12, wherein the Y′ nucleotides contain a 2′-O-methyl modification.

48. The double stranded RNAi agent of any one of claims 10-12, wherein p′>0.

49. The double stranded RNAi agent of any one of claims 10-12, wherein p′=2.

50. The double stranded RNAi agent of claim 49, wherein q'=0, p=0, q=0, and p' overhang nucleotides are complementary to the target mRNA.

51. The double stranded RNAi agent of claim 49, wherein q'=0, p=0, q=0, and p' overhang nucleotides are non-complementary to the target mRNA.

52. The double stranded RNAi agent of claim 49, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

53. The double stranded RNAi agent of any one of claims 48-52, wherein at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage.

54. The double stranded RNAi agent of claim 53, wherein all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

55. The double stranded RNAi agent of claim 10, wherein said RNAi agent is selected from the group of RNAi agents listed in Tables 3 and 4.

56. The double stranded RNAi agent of claim 10, wherein said RNAi agent is selected from the group of RNAi agents AD-60304, AD-60331, and AD-60344.

57. The double stranded RNAi agent of claim 11, wherein said RNAi agent is selected from the group of RNAi agents listed in Tables 5 and 6.

58. The double stranded RNAi agent of claim 12, wherein said RNAi agent is selected from the group of RNAi agents listed in Tables 7 and 8.

59. A double stranded RNAi agent comprising the RNAi agents listed in any one of Tables 3, 5, and 7.

60. A composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of Complement Factor B (CFB) in a cell, and comprises 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.

61. A composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of Complement Component 3 (C3) in a cell, and comprises 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.

62. A composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of Complement Component 9 (C9) in a cell, and comprises 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.

63. A double stranded RNAi agent capable of inhibiting the expression of Complement Factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said double stranded RNAi agent is represented by formula (III):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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.

64. A double stranded RNAi agent capable of inhibiting the expression of Complement Factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

65. A double stranded RNAi agent capable of inhibiting the expression of Complement Factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand

complementary to an antisense strand, wherein said 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 said 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.

66. A double stranded RNAi agent capable of inhibiting the expression of Complement Factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

67. A double stranded RNAi agent capable of inhibiting the expression of Complement Factor B (CFB) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

68. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

69. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

70. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

71. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said double stranded RNAi agent is represented by formula (III):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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.

72. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

73. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

74. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said double stranded RNAi agent is represented by formula (III):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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.

75. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said double stranded RNAi agent is represented by formula (III):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (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.

76. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

77. A double stranded RNAi agent capable of inhibiting the expression of Complement Component 9 (C9) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

78. A double stranded RNAi agent for inhibiting expression of complement factor B (CFB) in a cell,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said 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 said 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 said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

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

79. A double stranded RNAi agent for inhibiting expression of complement component C3 in a cell,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said 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 said 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 said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

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

80. A double stranded RNAi agent for inhibiting expression of complement component C9 in a cell,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said 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 said 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 said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

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

81. The double stranded RNAi agent of any one of claims 78-80, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

82. A cell containing the agent of any one of claims 1, 2, 4, 5, 7, 8, 10-12, and 59-80.

83. A vector encoding at least one strand of the agent of any one of claims 1, 2, 4, 5, 7, 8, 10-12, and 60-80.

84. A cell comprising the vector of claim 83.

85. A pharmaceutical composition for inhibiting expression of a complement component factor B gene comprising the agent of any one of claims 1, 2, 10, 59, 63-67, and 78.

86. A pharmaceutical composition for inhibiting expression of a complement component C3 gene comprising the agent of any one of claims 4, 5, 11, 59, 68-72, and 79.

87. A pharmaceutical composition for inhibiting expression of a complement component C9 gene comprising the agent of any one of claims 7, 8, 12, 59, 73-77, and 80.

88. The pharmaceutical composition of anyone of claims 60-62 and 85-87, wherein agent is administered in an unbuffered solution.

89. The pharmaceutical composition of claim 88, wherein said unbuffered solution is saline or water.

90. The pharmaceutical composition of claim 89, wherein said agent is administered with a buffer solution.

91. The pharmaceutical composition of claim 90, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

92. The pharmaceutical composition of claim 90, wherein said buffer solution is phosphate buffered saline (PBS).

93. A method of inhibiting complement factor B (CFB) expression in a cell, the method comprising:

(a) contacting the cell with the agent of any one of claims 1, 2, 10, 59, 63-67, and 78 or a pharmaceutical composition of any one of claims 60, 85, and 88-92; and

(b) maintaining the cell produced in step (a) 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.

94. A method of inhibiting complement component 3 (C3) expression in a cell, the method comprising:

(a) contacting the cell with the agent of any one of claims 4, 5, 11, 59, 68-72, and 79 or a pharmaceutical composition of any one of claims 61, 86, and 88-92; 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.

95. A method of inhibiting complement component 9 (C9) expression in a cell, the method comprising:

(a) contacting the cell with the agent of any one of claims 7, 8, 12, 59, 73-77, and 80 or a pharmaceutical composition of any one of claims 62 and 87-92; and

(b) maintaining the cell produced in step (a) 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.

96. The method of any one of claims 93-95, wherein said cell is within a subject.

97. The method of claim 96, wherein the subject is a human.

98. The method of claim 97, wherein the human subject suffers from a complement component-associated disease.

99. The method of claim 98, 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.

100. The method of claim 99, wherein the complement component-associated disease is paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), or rheumatoid arthritis.

101. The method of any one of claims 93 and 96-100, wherein the CFB expression is inhibited by at least about 30%.

102. The method of any one of claims 94 and 96-100, wherein the C3 expression is inhibited by at least about 30%.

103. The method of any one of claims 95-100, wherein the C9 expression is inhibited by at least about 30%.

104. The method of claim 100, wherein 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.

105. The method of claim 104, wherein the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

106. The method of claim 100, wherein the agent is administered subcutaneously.

107. The method of claim 100, wherein the agent is administered intravenously.

108. A method of treating a subject having a disorder that would benefit from reduction in complement factor B (CFB) expression, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 1, 2, 10, 59, 63-67, and 78, thereby treating said subject.

109. A method 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, comprising administering to the subject a therapeutically effective amount of the agent of any one of

claims 1, 2, 10, 59, 63-67, and 78 , thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in CFB expression.

110. A method of treating a subject having a disorder that would benefit from reduction in complement component C3 (C3) expression, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 4, 5, 11, 59, 68-72, and 79, thereby treating said subject.

111. A method 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, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 4, 5, 11, 59, 68-72, and 79, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C3 expression.

112. A method of treating a subject having a disorder that would benefit from reduction in complement component C9 (C9) expression, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 7, 8, 12, 59, 73-78, and 80, thereby treating said subject.

113. A method 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, comprising administering to the subject a therapeutically effective amount of the agent of any one of claims 7, 8, 12, 59, 73-78, and 80, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C9 expression.

114. The method of any one of claims 108-113, wherein the disorder is a complement component-associated disease.

115. The method of claim 114, 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.

116. The method of claim 115, wherein the complement component -associated disease is paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic uremic syndrome (aHUS).

117. The method of claim 108 or 109, wherein the administration of the agent to the subject causes a decrease in hemolysis and/or a decrease in CFB protein accumulation.

118. The method of claim 110 or 111, wherein the administration of the agent to the subject causes a decrease in hemolysis and/or a decrease in C3 protein accumulation.

119. The method of claim 112 or 113, wherein the administration of the agent to the subject causes a decrease in hemolysis and/or a decrease in C9 protein accumulation.

120. The method of any one of claims 108-113, further comprising administration of eculizumab to said subject.

121. The method of any one of claims 108-113, further comprising administration of compstatin to said subject.

122. The method of any one of claims 108-113, wherein 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.

123. The method of claim 122, wherein the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

124. The method of claim 122, wherein 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.

125. The method of claim 122, wherein the agent is administered to the subject once a week.

126. The method of claim 122, wherein the agent is administered to the subject twice a month.

127. The method of any one of claims 108-113, further comprising measuring LDH levels in said subject.

128. A method of inhibiting the expression of complement factor B (CFB) in a subject, the method comprising

administering to said subject a therapeutically effective amount of the agent of any one of claims 1, 2, 10, 59, 63-67, and 78, thereby inhibiting the expression of CFB in said subject.

129. A method of inhibiting the expression of complement component C3 (C3) in a subject, the method comprising

administering to said subject a therapeutically effective amount of the agent of any one of claims 4, 5, 11, 59, 68-72, and 79, thereby inhibiting the expression of C3 in said subject.

130. A method of inhibiting the expression of complement component C9 (C9) in a subject, the method comprising

administering to said subject a therapeutically effective amount of the agent of any one of claims 7, 8, 12, 59, 73-77, and 80, thereby inhibiting the expression of C9 in said subject.

131. The method of any one of claims 128-130, further comprising administering eculizumab to said subject.

132. The method of any one of claims 128-130, further comprising administering compstatin to said subject.

133. The method of any one of claims 128-130, wherein 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.

134. The method of claim 133, wherein the agent is administered at a dose of about 10 mg/kg to about 30 mg/kg.

135. The method of claim 133, wherein 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.

136. The method of claim 133, wherein the agent is administered to the subject once a week.

137. The method of claim 133, wherein the 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 said 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 said 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.

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, 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.

3. A double stranded RNAi agent capable of inhibiting the expression of complement component 3 (C3) in a cell, wherein said double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein said 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 said 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.

4. The double stranded RNAi agent of any one of claim 3, wherein the double-stranded region is 15-30 nucleotide pairs in length.

5. The double stranded RNAi agent of claim 4, wherein the double-stranded region is 17-25 nucleotide pairs in length.

6. The double stranded RNAi agent of claim 4, wherein the double-stranded region is 23-27 nucleotide pairs in length.

7. The double stranded RNAi agent of claim 4, wherein the double-stranded region is 19-21 nucleotide pairs in length.

8. The double stranded RNAi agent of claim 4, wherein the double-stranded region is 21-23 nucleotide pairs in length.

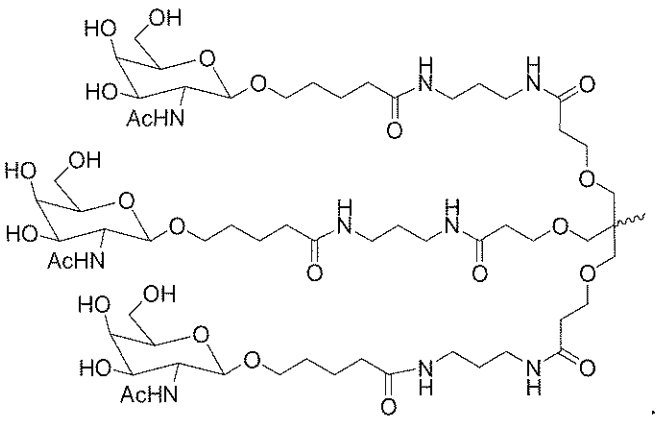
9. The double stranded RNAi agent of claim 3, wherein each strand has 15-30 nucleotides.

10. The double stranded RNAi agent of claim 3, wherein the modifications on the nucleotides are selected from the group consisting of LNA, CRN, cET, UNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-alkyl, 2'-O-allyl, 2'-C- allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and combinations thereof.

11. The double stranded RNAi agent of claim 10, wherein the modifications on the nucleotides are 2'-O-methyl or 2'-fluoro modifications.

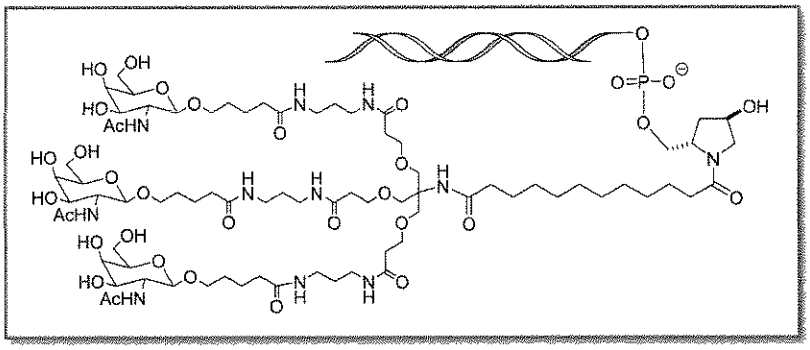
12. The double stranded RNAi agent of claim 3, wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

13. The double stranded RNAi agent of claim 3, wherein the ligand is



14. The double stranded RNAi agent of claim 3, wherein the ligand is attached to the 3′ end of the sense strand.

15. The double stranded RNAi agent of claim 14, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



16. The double stranded RNAi agent of claim 3, wherein the Y nucleotides contain a 2′-fluoro modification.

17. The double stranded RNAi agent of claim 3, wherein the Y′ nucleotides contain a 2′-O-methyl modification.

18. The double stranded RNAi agent of claim 3, wherein said RNAi agent is selected from the group of RNAi agents listed in Tables 5 and 6.

19. A composition comprising a modified antisense polynucleotide agent, wherein said agent is capable of inhibiting the expression of Complement Component 3 (C3) in a cell, and comprises 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.

20. A double stranded RNAi agent for inhibiting expression of complement component C3 in a cell,

wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein said 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 said 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 said sense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus,

wherein substantially all of the nucleotides of said antisense strand comprise a modification selected from the group consisting of a 2'-O-methyl modification and a 2'-fluoro modification,

wherein said antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and

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

21. The double stranded RNAi agent of claim 20, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand comprise a modification.

22. A cell containing the agent of any one of claims 1, 2, 3, and 20.

23. A vector encoding at least one strand of the agent of any one of claims 1, 2, 3, and 20.

24. A cell comprising the vector of claim 23.

25. A pharmaceutical composition for inhibiting expression of a complement component C3 gene comprising the agent of any one of claims 1, 2, 3, and 20.

26. The pharmaceutical composition of anyone of claims 19 and 25, wherein agent is administered in an unbuffered solution.

27. The pharmaceutical composition of claim 26, wherein said unbuffered solution is saline or water.

28. The pharmaceutical composition of claim 27, wherein said agent is administered with a buffer solution.

29. The pharmaceutical composition of claim 28, wherein said buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

30. The pharmaceutical composition of claim 28, wherein said buffer solution is phosphate buffered saline (PBS).

31. A method of inhibiting complement component 3 (C3) expression in a cell, the method comprising:

(a) contacting the cell with the agent of any one of claims 1, 2, 3, and 20 or a pharmaceutical composition of any one of claims 19, 25, and 26-30; 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.