COMPLEMENT COMPONENT C5 iRNA COMPOSITIONS AND METHODS OF USE THEREOF

Related Applications

This application claims the benefit of U.S. Provisional Patent Application No.:61/782,531, filed on March 14, 2013, U.S. Provisional Patent Application No.:61/837,399, filed on June 20, 2013, and U.S. Provisional Patent Application No.:61/904,579, filed on November 15, 2013, U.S. Provisional Patent Application No.:61/912,777, filed on December 6, 2013, and U.S. Provisional Patent Application No.:61/942367, filed February 20, 2014. The entire contents of each of the foregoing provisional patent applications are hereby incorporated herein by reference.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 10, 2014, is named 121301-00520_SL.txt and is 734,486 bytes in size.

Background of the Invention

Complement was first discovered in the 1890s when it was found to aid or "complement" the killing of bacteria by heat-stable antibodies present in normal serum (Walport, M.J. (2001) *N Engl J Med.* 344:1058). The complement system consists of more than 30 proteins that are either present as soluble proteins in the blood or are present as membrane-associated proteins. Activation of complement leads to a sequential cascade of enzymatic reactions, known as complement activation pathways, resulting in the formation of the potent anaphylatoxins C3a and C5a that elicit a plethora of physiological responses that range from chemoattraction to apoptosis. Initially, complement was thought to play a major role in innate immunity where a robust and rapid response is mounted against invading pathogens. However, recently it is becoming increasingly evident that complement also plays an important role in adaptive immunity involving T and B cells that help in elimination of pathogens (Dunkelberger JR and Song WC. (2010) *Cell Res.* 20:34; Molina H, *et al.* (1996) *Proc Natl Acad Sci U S A.* 93:3357), in maintaining immunologic memory preventing pathogenic re-invasion, and is involved in numerous human pathological states (Qu, H, *et al.* (2009) *Mol Immunol.* 47:185; Wagner, E. and Frank MM. (2010) *Nat Rev Drug Discov.* 9:43).

Complement activation is known to occur through three different pathways: alternate, classical, and lectin (Figure 1), involving proteins that mostly exist as inactive zymogens that

are then sequentially cleaved and activated. All pathways of complement activation lead to cleavage of the C5 molecule generating the anaphylatoxin C5a and, C5b that subsequently forms the terminal complement complex (C5b-9). C5a exerts a predominant pro-inflammatory activity through interactions with the classical G-protein coupled receptor C5aR (CD88) as well as with the non-G protein coupled receptor C5L2 (GPR77), expressed on various immune and non-immune cells. C5b-9 causes cytolysis through the formation of the membrane attack complex (MAC), and sub-lytic MAC and soluble C5b-9 also possess a multitude of non-cytolytic immune functions. These two complement effectors, C5a and C5b-9, generated from C5 cleavage, are key components of the complement system responsible for propagating and/or initiating pathology in different diseases, including paroxysmal nocturnal hemoglobinuria, rheumatoid arthritis, ischemia-reperfusion injuries and neurodegenerative diseases.

To date, only one therapeutic that targets the C5-C5a axis is available for the treatment of complement component C5-associated diseases, the anti-C5 antibody, eculizumab (Soliris®). Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) and is currently being evaluated in clinical trials for additional complement component C5-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a yearly cost of about $400,000. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects having a complement component C5-associated disease.

Summary of the Invention

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a C5 gene. The C5 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 C5 gene, *e.g.*, a complement component C5-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 C5 gene for inhibiting the expression of a C5 gene.

Accordingly, in one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, 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 the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5.

In another aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, 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 any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23.

In one embodiment, the sense and antisense strands comprise sequences selected from the group consisting of A-118320, A-118321, A-118316, A-118317, A-118332, A-118333, A-118396, A-118397, A-118386, A-118387, A-118312, A-118313, A-118324, A-118325, A-119324, A-119325, A-119332, A-119333, A-119328, A-119329, A-119322, A-119323, A-119324, A-119325, A-119334, A-119335, A-119330, A-119331, A-119326, A-119327, A-125167, A-125173, A-125647, A-125157, A-125173, and A-125127. In another embodiment, the sense and antisense strands comprise sequences selected from the group consisting of any of the sequences in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23. In one embodiment, the dsRNA agent comprises at least one modified nucleotide.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence AAGCAAGAUAUUUUUAUAAUA (SEQ ID NO:62) and wherein the antisense strand comprises the nucleotide sequence UAUUAUAAAAAUAUCUUGCUUUU (SEQ ID NO:113). In one embodiment, the dsRNA agent comprises at least one modified nucleotide, as described below.

In one aspect, the present invention provides a double stranded RNAi agent for inhibiting expression of complement component C5 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 SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached 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 one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-

fluoro modification and a 3'-terminal deoxy-thymine (dT) nucleotide. In another embodiment, substantially all of the nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal deoxy-thymine (dT) nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, 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, at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

In another embodiment, the modified nucleotides comprise a short sequence of 3'-terminal deoxy-thymine (dT) nucleotides.

In one embodiment, the region of complementarity is at least 17 nucleotides in length. In another embodiment, the region of complementarity is between 19 and 21 nucleotides in length.

In one embodiment, the region of complementarity is 19 nucleotides in length.

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

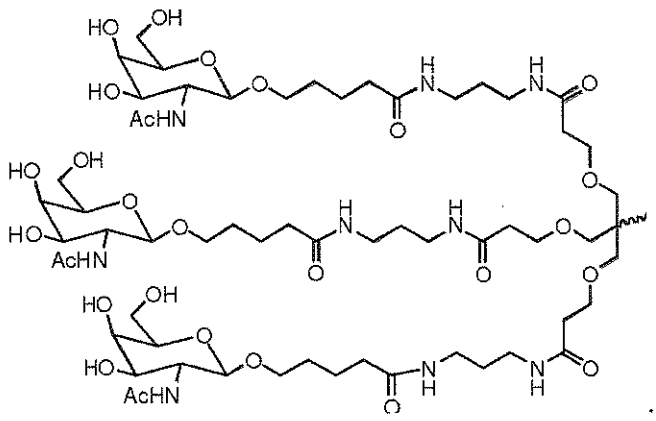
In one embodiment, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment,at least one strand comprises a 3' overhang of at least 2 nucleotides.

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

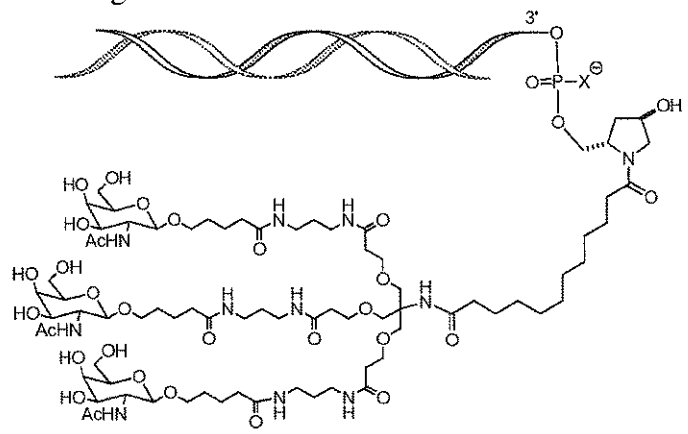
In one embodiment, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

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

In one embodiment, the ligand is



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



and, wherein X is O or S.

In one embodiment, the X is O.

In one embodiment, the region of complementarity consists of one of the antisense sequences of any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23.

In one embodiment, the dsRNA agent is selected from the group consisting of AD-58123, AD-58111, AD-58121, AD-58116, AD-58133, AD-58099, AD-58088, AD-58642, AD-58644, AD-58641, AD-58647, AD-58645, AD-58643, AD-58646, AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651.

In another aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence AAGCAAGAUAUUUUUAUAAUA (SEQ ID NO:62) and wherein the antisense strand comprises the nucleotide sequence UAUUAUAAAAAUAUCUUGCUUUUdTdT (SEQ ID NO:2899).

In another aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein the dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises the nucleotide sequence asasGfcAfaGfaUfAfUfuUfuuAfuAfauaL96 (SEQ ID NO:2876) and

wherein the antisense strand comprises the nucleotide sequence usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT (SEQ ID NO:2889).

In one aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 in a cell, wherein the double stranded RNAi agent comprises a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, 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;

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

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

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

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

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).

In another embodiment, 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 yet another embodiment, 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 another embodiment, 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.

In one embodiment, the double-stranded region is 15-30 nucleotide pairs in length.

In one embodiment, the double-stranded region is 17-23 nucleotide pairs in length. In another embodiment, the double-stranded region is 17-25 nucleotide pairs in length. In another embodiment, the double-stranded region is 23-27 nucleotide pairs in length. In yet another embodiment, the double-stranded region is 19-21 nucleotide pairs in length. In another embodiment, the double-stranded region is 21-23 nucleotide pairs in length.

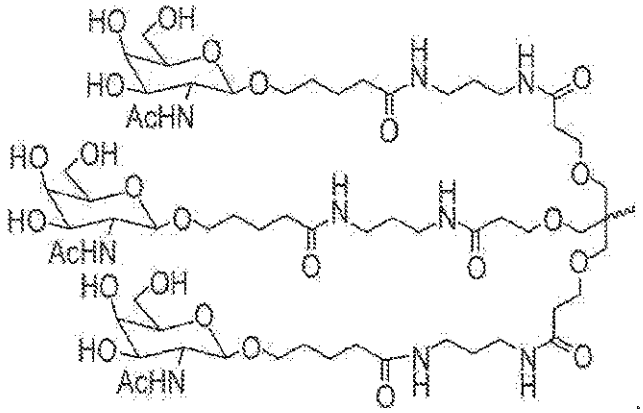
In one embodiment, each strand has 15-30 nucleotides.

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

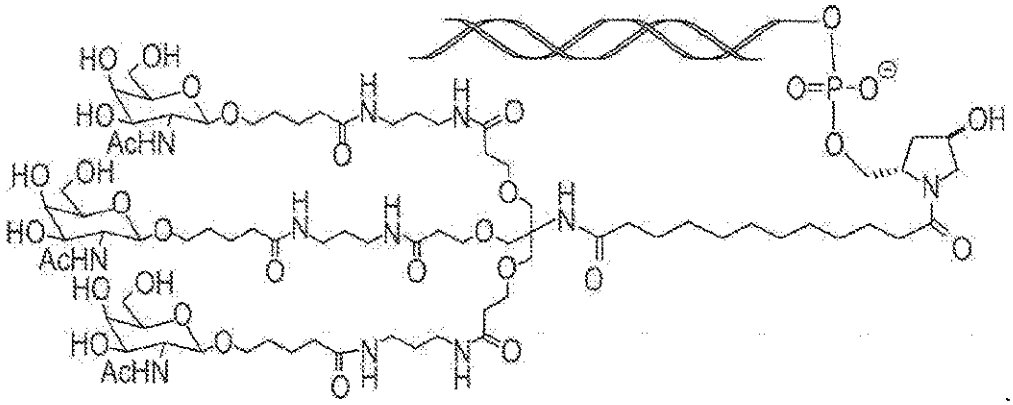
In one embodiment, the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, the ligand is



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

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



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

In one embodiment, 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, the strand is the sense strand.

In one embodiment, 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, the strand is the sense strand.

In one embodiment, 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, 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, the Y nucleotides contain a 2′-fluoro modification.

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

In one embodiment, p'>0.

In one embodiment, p'=2.

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

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

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

In one embodiment, at least one n_p' is linked to a neighboring nucleotide via a phosphorothioate linkage.

In one embodiment, all n_p' are linked to neighboring nucleotides via phosphorothioate linkages.

In one embodiment, the RNAi agent is selected from the group of RNAi agents listed in Table 4, Table 18, Table 19, or Table 23. In another embodiment, the RNAi agent is selected from the group consisting of AD-58123, AD-58111, AD-58121, AD-58116, AD-58133, AD-58099, AD-58088, AD-58642, AD-58644, AD-58641, AD-58647, AD-58645, AD-58643, AD-58646, AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651.

In one aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 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 complement component C5, 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.

In another aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 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 complement component C5, 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.

In another aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 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 complement component C5, 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.

In yet another aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 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 complement component C5, 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.

In another aspect, the present invention provides a double stranded RNAi agent capable of inhibiting the expression of complement component C5 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 complement component C5, 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.

In one aspect, the present invention provides a double stranded RNAi agent for inhibiting expression of complement component C5, 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 SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, 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 are modified nucleotides. In another embodiment, each strand has 19-30 nucleotides.

In one aspect, the present invention provides a cell containing a dsRNA agent of the invention.

In one aspect, the present invention provides a vector encoding at least one strand of a dsRNA agent, wherein the dsRNA agent comprises a region of complementarity to at least a part of an mRNA encoding complement component C5, wherein the dsRNA is 30 base pairs or less in length, and wherein the dsRNA agent targets the mRNA for cleavage.

In one embodiment, the region of complementarity is at least 15 nucleotides in length. In another embodiment, the region of complementarity is 19 to 21 nucleotides in length. In another embodiment, each strand has 19-30 nucleotides.

In one aspect, the present invention provides a cell comprising a vector of the invention.

In one aspect, the present invention provides a pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising a dsRNA agent 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 another embodiment, the buffer solution is phosphate buffered saline (PBS).

In another aspect, the present invention provides a pharmaceutical composition comprising a double stranded RNAi agent of the invention and a lipid formulation.

In one embodiment, the lipid formulation comprises a LNP. In another embodiment,the lipid formulation comprises a MC3.

In one aspect, the present invention provides a composition comprising an antisense polynucleotide agent selected from the group consisting of the sequences listed in any one of Tables 3, 4, 5, 6, 19, 18, 20, 21, and 23.

In another aspect, the present invention provides a composition comprising a sense polynucleotide agent selected from the group consisting of the sequences listed in any one of Tables 3, 4, 5, 6, 19, 18, 20, 21, and 23.

In yet another aspect, the present invention provides a modified antisense polynucleotide agent selected from the group consisting of the antisense sequences listed in any one of Tables 4, 6, 18, 19, 21, and 23.

In a further aspect, the present invention provides a modified sense polynucleotide agent selected from the group consisting of the sense sequences listed in any one of Tables 4, 6, 18, 19, 21, and 23.

In one aspect the present invention provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby treating the subject.

In another aspect, the present invention provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 the nucleotide sequence of SEQ ID NO:1 and the antisense strand

comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression.

In another aspect, the present invention provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, 23, thereby treating the subject.

In yet another aspect, the present invention provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a prophylactically effective amount of a dsRNA agent comprising 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 any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression.

In one aspect, the present invention provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression which include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, 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 SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the

nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, 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 methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression which include administering to the subject a prophylactically effective amount of a double stranded RNAi agent, 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 SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to a ligand at the 3'-terminus.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, 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 aspect, the present invention provides methods of treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, 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;

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, thereby treating the subject, thereby treating a subject having a disease or disorder that would benefit from reduction in complement component C5 expression.

In another aspect, the present invention provides methods of preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression. The methods include administering to the subject a prophylactically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, 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;

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, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression, thereby preventing at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement component C5 expression.

In one embodiment, the administration of the dsRNA to the subject causes a decrease in intravascular hemolysis, a stabilization of hemoglobin levels and/or a decrease in C5 protein accumulation.

In one embodiment, the disorder is a complement component C5-associated disease. In one embodiment, the complement component C5-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin *E. coli*-related hemolytic uremic syndrome, C3 nephropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, an allogenic transplant, sepsis, Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus,

autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, membraneous nephropathy, Guillain-Barre syndrome, and percutaneous transluminal coronary angioplasty (PTCA). In another embodiment, the complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH). In yet another embodiment, the complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

In one embodiment, the subject is human.

In another embodiment, the methods of the invention further include administering an anti-complement component C5 antibody, or antigen-binding fragment thereof, to the subject.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b. In another embodiment, the anti-complement component C5 antibody is eculizumab.

In another embodiment, the methods of the invention further include administering a meningococcal vaccine to the subject.

In one embodiment, eculizumab is administered to the subject weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a

third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In yet another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In another embodiment, the methods of the invention further include plasmapheresis or plasma exchange in the subject. In one such embodiment, eculizumab is administered to the subject at a dose less than about 600 mg or at a dose less than about 300 mg.

In a further embodiment, the methods of the invention further include plasma infusion in the subject. In one such embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, eculizumab is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 15 mg/kg. In another embodiment, eculizumab is administered to the subject at a dose of about 5 mg/kg to about 15 mg/kg.

In one embodiment, eculizumab is administered to the subject at a dose selected from the group consisting of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, 10 mg/kg, and 15 mg/kg.

In one embodiment, eculizumab is administered to the subject via an intravenous infusion.

In another embodiment, eculizumab is administered to the subject subcutaneously.

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

In one embodiment, the dsRNA 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, 5 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject once a week. In another embodiment, the dsRNA agent is administered to the subject twice a week. In another embodiment, the dsRNA agent is administered to the subject twice a month.

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

In one embodiment, the dsRNA agent and the eculizumab are administered to the subject subcutaneously. In another embodiment, the dsRNA agent and the eculizumab are administered to the subject simultaneously.

In one embodiment, the dsRNA agent is administered to the subject first for a period of time sufficient to reduce the levels of complement component C5 in the subject, and eculizumab is administered subsequently at a dose less than about 600 mg.

In one embodiment, the levels of complement component C5 in the subject are reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.

In one embodiment, eculizumab is administered at a dose of about 100-500 mg.

In one embodiment, the methods of the invention further include measuring hemoglobin and/or LDH levels in the subject.

In one embodiment, the dsRNA is conjugated to a ligand.

In one embodiment, the ligand is conjugated to the 3'- end of the sense strand of the dsRNA.

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

In one aspect, the present invention provides methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising 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 the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

In another aspect, the present invention provides methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising 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 any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

In another aspect, the present invention provides methods of inhibiting complement component C5 expression in a cell, which includes contacting the cell with a dsRNA agent comprising a sense strand and an antisense strand comprising a region of complementarity, the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15

contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus; and maintaining the cell produced in the first step for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, 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 methods of inhibiting complement component C5 expression in a cell. The methods include contacting the cell with a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, 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;

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; and maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 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 C5-associated disease.

In one embodiment, the complement component C5-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin *E. coli*-related hemolytic uremic syndrome, C3 nephropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, an allogenic transplant, sepsis, Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement, rotational atherectomy, membraneous nephropathy, Guillain-Barre syndrome, and

percutaneous transluminal coronary angioplasty (PTCA). In another embodiment, the complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH). In another embodiment, the complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

In one embodiment, the methods further include contacting the cell with an anti-complement component C5 antibody, or antigen-binding fragment thereof.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b.

In one embodiment, the anti-complement component C5 antibody, or antigen-binding fragment thereof, is eculizumab.

In one embodiment, the methods further include contacting the cell with a meningococcal vaccine.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In yet another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In another embodiment, the cell is contacted with eculizumab weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the cell is contacted with eculizumab weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the cell is within a subject.

In one embodiment, the methods of the invention further include plasmapheresis or plasma exchange in the subject. In one embodiment, eculizumab is administered to the subject at

a dose less than about 600 mg. In another embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, the methods of the invention further include plasma infusion in the subject. In one embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, the cell is contacted with eculizumab at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 15 mg/kg.

In another embodiment, the cell is contacted with eculizumab at a dose of about 5 mg/kg to about 15 mg/kg.

In one embodiment, the cell is contacted with eculizumab at a dose selected from the group consisting of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5mg/kg, 7 mg/kg, 10 mg/kg, and 15 mg/kg.

In one embodiment, eculizumab is administered to the subject via an intravenous infusion. In another embodiment, eculizumab is administered to the subject subcutaneously.

In one embodiment, the cell is contacted with the dsRNA agent 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 cell is contacted with the dsRNA agent at a dose of about 10 mg/kg to about 30 mg/kg.

In one embodiment, the cell is contacted with the dsRNA agent at a dose selected from the group consisting of 0.5 mg/kg 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, the cell is contacted with the dsRNA agent once a week. In another embodiment, the dsRNA agent is administered to the subject twice a week. In another embodiment, the cell is contacted with the dsRNA agent twice a month.

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

In one embodiment, the dsRNA agent and the eculizumab are administered to the subject subcutaneously. In another embodiment, the dsRNA agent and the eculizumab are administered to the subject simultaneously.

In one embodiment, the cell is contacted with the dsRNA agent and the eculizumab simultaneously.

In one embodiment, the dsRNA agent is administered to the subject first for a period of time sufficient to reduce the levels of complement component C5 in the subject, and eculizumab is administered subsequently at a dose less than about 600 mg.

In one embodiment, the levels of complement component C5 in the subject are reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.

In one embodiment, eculizumab is administered at a dose of about 100-500 mg.

In one embodiment, the cell is contacted with the dsRNA agent first for a period of time sufficient to reduce the levels of complement component C5 in the cell, and the cell is subsequently contacted with eculizumab at a dose less than about 600 mg.

In one embodiment, the levels of complement component C5 in the cell are reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.

In one embodiment, the cell is contacted with eculizumab at a dose of about 100-500 mg.

In one aspect, the present invention provides methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 the nucleotide sequence of SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, thereby inhibiting the expression of C5 in the subject.

In another aspect, the present invention provides methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, thereby inhibiting the expression of C5 in the subject.

In another aspect, the present invention provides methods of inhibiting complement component C5 expression in a subject which include administering to the subject a therapeutically effective amount of a dsRNA agent comprising 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 SEQ ID NO:1 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:5, wherein substantially all of the nucleotides of the antisense strand and substantially all of the nucleotides of the sense strand are modified nucleotides and, wherein the sense strand is conjugated to one or more ligands at the 3'-terminus, thereby inhibiting expression of the C5 gene in the subject.

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, the administration is subcutaneous administration.

In one embodiment, substantially all of the nucleotides of the sense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, substantially all of the

nucleotides of the antisense strand are modified nucleotides selected from the group consisting of a 2'-O-methyl modification, a 2'-fluoro modification and a 3'-terminal dT nucleotide. In another embodiment, the modified nucleotides are a short sequence of deoxy-thymine (dT) nucleotides. In another embodiment, the sense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus. In yet another embodiment, 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 methods of inhibiting the expression of C5 in a subject. The methods include administering to the subject a therapeutically effective amount of a dsRNA agent comprising a sense strand complementary to an antisense strand, wherein the antisense strand comprises a region complementary to part of an mRNA encoding C5, 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;

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, thereby inhibiting the expression of C5 in the subject.

In one embodiment, the methods further include administration of an anti-complement component C5 antibody, or antigen-binding fragment thereof, to the subject.

In one embodiment, the anti-complement component C5 antibody, or antigen-binding fragment thereof, is eculizumab.

In one embodiment, the antibody, or antigen-binding fragment thereof, inhibits cleavage of complement component C5 into fragments C5a and C5b.

In one embodiment, the methods of the invention further include administering a meningococcal vaccine to the subject.

In one embodiment, eculizumab is administered to the subject weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In another embodiment, eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter.

In one embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter.

In another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In yet another embodiment, the subject is less than 18 years of age and eculizumab is administered to the subject weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter.

In one embodiment, the methods further includeplasmapheresis or plasma exchange in the subject. In one embodiment, eculizumab is administered to the subject at a dose less than about 600 mg. In another embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, the methods further include plasma infusion in the subject. In one embodiment, eculizumab is administered to the subject at a dose less than about 300 mg.

In one embodiment, eculizumab is administered to the subject at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 15 mg/kg. In another embodiment, eculizumab is administered to the subject at a dose of about 5 mg/kg to about 15 mg/kg.

In another embodiment, eculizumab is administered to the subject at a dose selected from the group consisting of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, eculizumab is administered to the subject via an intravenous infusion. In another embodiment, eculizumab is administered to the subject subcutaneously.

In one embodiment, the dsRNA 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 15 mg/kg.

In one embodiment, the dsRNA agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In another embodiment,the dsRNA 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, 5 mg/kg, 10 mg/kg, and 30 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject once a week. In another embodiment, the dsRNA agent is administered to the subject twice a week. In another embodiment, the dsRNA agent is administered to the subject twice a month.

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

In one embodiment, the dsRNA agent and the eculizumab are administered to the subject subcutaneously. In another embodiment, the dsRNA agent and the eculizumab are administered to the subject simultaneously.

In one embodiment, the dsRNA agent is administered to the subject first for a period of time sufficient to reduce the levels of complement component C5 in the subject, and eculizumab is administered subsequently at a dose less than about 600 mg.

In one embodiment, the levels of complement component C5 in the subject are reduced by at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%.

In one embodiment, eculizumab is administered at a dose of about 100-500 mg.

In one embodiment, the dsRNA agent is conjugated to a ligand.

In one embodiment, the ligand is conjugated to the 3'- end of the sense strand of the dsRNA agent.

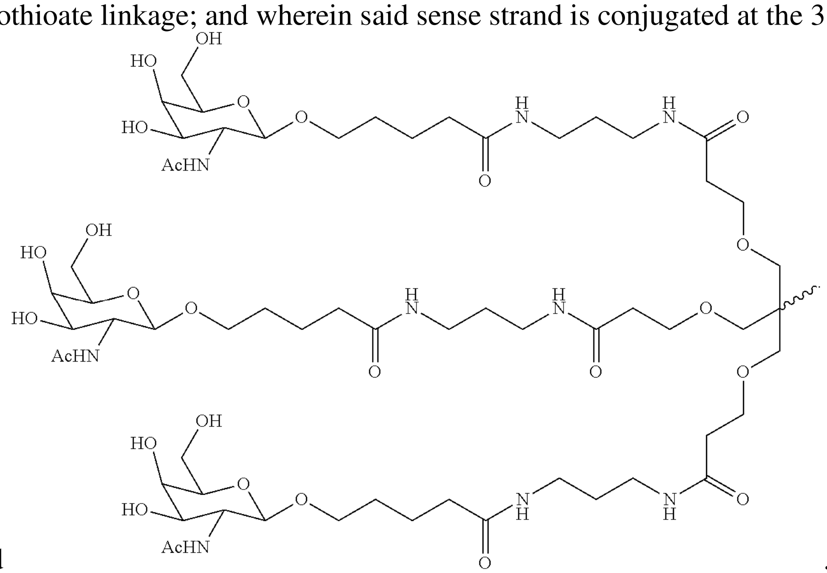
In one embodiment, the ligand is an N-acetylgalactosamine (GalNAc) derivative.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a

region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), and wherein said dsRNA agent comprises at least one modified nucleotide.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, and wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

In one aspect, the present invention provides a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT-3' (SEQ ID NO:2889), wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage; and wherein said sense strand is conjugated at the 3'-terminus to the ligand



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In one aspect, the present invention provides a pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising the dsRNA agent as described herein.

In one aspect, the present invention provides an *in vitro* method of inhibiting complement component C5 expression in a cell, the method comprising: (a) contacting the

cell with the dsRNA agent as described herein; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a complement component C5 gene, thereby inhibiting expression of the complement component C5 gene in the cell.

In one aspect, the present invention provides a use of a therapeutically effective amount of the dsRNA agent as described herein in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

In one aspect, the present invention provides a use of a prophylactically effective amount of the dsRNA agent as described herein in the manufacture of a medicament for preventing at least one symptom in a subject having or prone to having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

In one aspect, there present invention provides a dsRNA agent as described herein for use in therapy.

Brief Description of the Drawings

Figure 1 is a schematic of the three complement pathways: alternattive, classical and lectin.

Figure 2 is a graph showing the percentage of complement component C5 remaining in C57BL/6 mice following a single 10 mg/kg dose of the indicated iRNAs.

Figure 3 is a graph showing the percentage of complement component C5 remaining in C57BL/6 mice following a single 10 mg/kg dose of the indicated iRNAs.

Figure 4 is a graph showing the percentage of complement component C5 remaining in C57BL/6 mice 48 hours after a single 10 mg/kg dose of the indicated iRNAs.

Figure 5A is a graph showing the percentage of hemolysis remaining at days 4 and 7 in rats after a single 2.5 mg/kg, 10 mg/kg, or 25 mg/kg subcutaneous dose of of AD-58642.

Figure 5B is a Western blot showing the amount of complement component C5 remaining at day 7 in rats after a single 2.5 mg/kg, 10 mg/kg, or 25 mg/kg subcutaneous dose of AD-58642.

Figure 6A and 6B are graphs showing the percentage of complement component C5 remaining in C57BL/6 mice 5 days after a single 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg or 25 mg/kg dose of AD-58642.

Figures 7A and 7B are graphs showing the percentage of hemolysis remaining at day 5 in C57BL/6 mice after a single 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg or 25 mg/kg dose of AD-58642.

Figure 8 is a Western blot showing the amount of complement component C5 remaining at day 5 in C57BL/6 mice after a single 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg or 25 mg/kg dose of AD-58642.

Figure 9 is a graph showing the amount of complement component C5 protein remaining at days 5 and 9 in mouse serum after a single 0.625 mg/kg, 1.25 mg/kg, 2.5 mg/kg, 5.0 mg/kg, or 10 mg/kg dose of AD-58641. The lower limit of quantitation (LLOQ) of the assay is shown as a dashed line.

Figure 10 is a is a graph showing the amount of complement component C5 protein remaining at day 8 in mouse serum after a 0.625 mg/kg, 1.25 mg/kg, or 2.5 mg/kg dose of AD-58641 at days 0, 1, 2, and 3. The lower limit of quantitation (LLOQ) of the assay is shown as a dashed line.

Figures 11A and 11B depict the efficacy and cumulative effect of repeat administration of compound AD-58641 in rats. Figure 11A is graph depicting the hemolytic activity remaining in the serum of rats on days 0, 4, 7, 11, 14, 18, 25, and 32 after repeat administration at 2.5 mg/kg/dose or 5.0 mg/kg/dose, q2w x3 (twice a week for 3 weeks). Figure 11B is a Western blot

showing the amount of complement component C5 protein remaining in the serum of the animals.

Figure 12 is a graph showing the amount of complement component C5 protein in cynomolgus macaque serum at various time points before, during and after two rounds of subcutaneous dosing at 2.5 mg/kg or 5 mg/kg of AD-58641 every third day for eight doses. C5 protein levels were normalized to the average of the three pre-dose samples.

Figure 13 is a graph showing the percentage of hemolysis remaining in cynomolgus macaque serum at various time points before, during and after two rounds of subcutaneous dosing at 2.5 mg/kg or 5 mg/kg of AD-58641 every third day for eight doses. Percent hemolysis was calculated relative to maximal hemolysis and to background hemolysis in control samples.

Figure 14 is a graph showing the percentage of complement component C5 protein remaining at day 5 in the serum of C57BL/6 mice following a single 1 mg/kg dose of the indicated iRNAs.

Figure 15 is a graph showing the percentage of complement component C5 protein remaining at day 5 in the serum of C57BL/6 mice following a single 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or 2.0 mg/kg dose of the indicated iRNAs.

Figure 16 is a graph showing the percentage of complement component C5 protein remaining in the serum of C57BL/6 mice at days 6, 13, 20, 27, and 34 following a single 1 mg/kg dose of the indicated iRNAs.

Figure 17 is a graph showing the percentage of hemolysis remaining in rat serum at various time points following administration of a 5 mg/kg dose of the indicated compounds at days 0, 4, and 7.

Figure 18A shows the nucleotide sequence of *Homo sapiens* Complement Component 5 (C5) (SEQ ID NO:1); Figure 18B shows the nucleotide sequence of *Macaca mulatta* Complement Component 5 (C5) (SEQ ID NO:2); Figure 18C shows the nucleotide sequence of *Mus musculus* Complement Component 5 (C5) (SEQ ID NO:3); Figure 18D shows the nucleotide sequence of *Rattus norvegicus* Complement Component 5 (C5) (SEQ ID NO:4); Figure 18E shows the reverse complement of SEQ ID NO:1 (SEQ ID NO:5); Figure 18F shows the reverse complement of SEQ ID NO:2 (SEQ ID NO:6); Figure 18G shows the reverse complement of SEQ ID NO:3 (SEQ ID NO:7); and Figure 18H shows the reverse complement of SEQ ID NO:4 (SEQ ID NO:8).

Detailed Description of the Invention

The present invention provides iRNA agents which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a complement component C5 gene.

The iRNAs of the invention include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a C5 gene. The use of these iRNAs enables the targeted degradation of mRNAs of a C5 gene in mammals. Very low dosages of C5 iRNAs, in particular, can specifically and efficiently mediate RNA interference (RNAi), resulting in significant inhibition of expression of a C5 gene. The present inventors have demonstrated that iRNAs targeting C5 can mediate RNAi *in vitro* and *in vivo*, resulting in significant inhibition of expression of a C5 gene. Thus, methods and compositions including these iRNAs are useful for treating a subject who would benefit by a reduction in the levels and/or activity of a C5 protein, such as a subject having a complement component C5-associated disease, such as paroxysmal nocturnal hemoglobinuria (PNH).

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 C5 gene, *e.g.*, a complement component C5-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 complement component C5 gene.

The present invention also provides methods for preventing at least one symptom, *e.g.*, hemolysis, in a subject having a disorder that would benefit from inhibiting or reducing the expression of a C5 gene, *e.g.*, a complement component C5-associated disease, such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The present invention further provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a complement component C5 gene. The C5 gene may be within a cell, *e.g.*, a cell within a subject, such as a human.

The combination therapies of the present invention include administering to a subject having a complement component C5-associated disease, an RNAi agent of the invention and an additional therapeutic, such as anti-complement component C5 antibody, or antigen-binding fragment thereof, *e.g.*, eculizumab. The combination therapies of the invention reduce C5 levels in the subject (*e.g.*, by about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%,

85%, 90%, 95%, or about 99%) by targeting C5 mRNA with an iRNA agent of the invention and, accordingly, allow the therapeutically (or prophylactically) effective amount of eculizumab required to treat the subject to be reduced, thereby decreasing the costs of treatment and permitting easier and more convenient ways of administering eculizumab, such as subcutaneous administration.

The following detailed description discloses how to make and use compositions containing iRNAs to inhibit the expression of a C5 gene, as well as compositions, uses, and methods for treating subjects having diseases and disorders that would benefit from inhibition and/or reduction of the expression of this gene.

I. Definitions

In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element, *e.g.*, a plurality of elements.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

As used herein, "complement component C5," used interchangeably with the term "C5" refers to the well-known gene and polypeptide, also known in the art as CPAMD4, C3 and PZP-like alpha-2-macroglobulin domain-containing protein, anaphtlatoxin C5a analog, hemolytic complement (Hc), and complement C5. The sequence of a human C5 mRNA transcript can be found at, for example, GenBank Accession No. GI:38016946 (NM_001735.2; SEQ ID NO:1). The sequence of rhesus C5 mRNA can be found at, for example, GenBank Accession No. GI:297270262 (XM_001095750.2; SEQ ID NO:2). The sequence of mouse C5 mRNA can be found at, for example, GenBank Accession No. GI:291575171 (NM_010406.2; SEQ ID NO:3). The sequence of rat C5 mRNA can be found at, for example, GenBank Accession No. GI:392346248 (XM_345342.4; SEQ ID NO:4). Additional examples of C5 mRNA sequences are readily available using publicly available databases, *e.g.*, GenBank.

The term"C5," as used herein, also refers to naturally occurring DNA sequence variations of the C5 gene, such as a single nucleotide polymorphism in the C5 gene. Numerous SNPs within the C5 gene have been identified and may be found at, for example, NCBI dbSNP (see,

e.g., ncbi.nlm.nih.gov/snp). Non-limiting examples of SNPs within the C5 gene may be found at, NCBI dbSNP Accession Nos. rs121909588 and rs121909587.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a C5 gene, including mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, the target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a C5 gene.

The target sequence may be from about 9-36 nucleotides in length, *e.g.*, about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

"G," "C," "A," "T" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base, respectively. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.*, Table 2). The skilled person is well aware that guanine, cytosine, adenine, and uracil can be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can be replaced in the nucleotide sequences of dsRNA featured in the invention by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the invention.

The terms "iRNA", "RNAi agent," "iRNA agent,", "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing

complex (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi). The iRNA modulates, *e.g.*, inhibits, the expression of C5 in a cell, *e.g.*, a cell within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the invention includes a single stranded RNA that interacts with a target RNA sequence, *e.g.*, a C5 target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA (siRNA) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, a C5 gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded siRNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded siRNAs are described in U.S. Patent No. 8,101,348 and in Lima *et al.*, (2012) *Cell* 150: 883-894, the entire contents of each of which are hereby incorporated herein by reference. Any of the antisense nucleotide sequences described herein may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150;:883-894.

In another embodiment, an "iRNA" for use in the compositions, uses, and methods of the invention is a double-stranded RNA and is referred to herein as a "double stranded RNAi agent," "double-stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA", refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.*, a C5 gene. In some embodiments of the invention, a double-stranded RNA (dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, the majority of nucleotides of each strand of a dsRNA molecule are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide and/or a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "RNAi agent" for the purposes of this specification and claims.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 9 to 36 base pairs in length, *e.g.*, about 15-30 base pairs in length, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, and therefore are connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides.

Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker." The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs.

In one embodiment, an RNAi agent of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, *e.g.*, a C5 target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, *et al.*, (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188).

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, *e.g.*, a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or *vice versa*, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end and/or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotide, overhang at the 3'-end and/or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

"Blunt" or "blunt end" means that there are no unpaired nucleotides at that end of the double stranded RNAi agent, *i.e.*, no nucleotide overhang. A "blunt ended" RNAi agent is a dsRNA that is double-stranded over its entire length, *i.e.*, no nucleotide overhang at either end of the molecule. The RNAi agents of the invention include RNAi agents with nucleotide overhangs at one end (*i.e.*, agents with one overhang and one blunt end) or with nucleotide overhangs at both ends.

The term "antisense strand" or "guide strand" refers to the strand of an iRNA, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, a C5 mRNA. As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target

sequence, *e.g.*, a C5 nucleotide sequence, as defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches can be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, *e.g.*, within 5, 4, 3, or 2 nucleotides of the 5'- and/or 3'-terminus of the iRNA.

The term "sense strand," or "passenger strand" as used herein, refers to the strand of an iRNA that includes a region that is substantially complementary to a region of the antisense strand as that term is defined herein.

As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions can include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C for 12-16 hours followed by washing (see, *e.g.*, "Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, *e.g.*, within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they can form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, *e.g.*, inhibition of gene expression via a RISC pathway. However, where two oligonucleotides

are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as "fully complementary" for the purposes described herein.

"Complementary" sequences, as used herein, can also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in so far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs include, but are not limited to, G:U Wobble or Hoogstein base pairing.

The terms "complementary," "fully complementary" and "substantially complementary" herein can be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (*e.g.*, an mRNA encoding C5). For example, a polynucleotide is complementary to at least a part of a C5 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding C5.

In general, the majority of nucleotides of each strand are ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide and/or a modified nucleotide. In addition, an "iRNA" may include ribonucleotides with chemical modifications. Such modifications may include all types of modifications disclosed herein or known in the art. Any such modifications, as used in an iRNA molecule, are encompassed by "iRNA" for the purposes of this specification and claims.

In one aspect of the invention, an agent for use in the methods and compositions of the invention is a single-stranded antisense RNA molecule that inhibits a target mRNA *via* an antisense inhibition mechanism. The single-stranded antisense RNA molecule is complementary to a sequence within the target mRNA. The single-stranded antisense oligonucleotides can inhibit translation in a stoichiometric manner by base pairing to the mRNA and physically obstructing the translation machinery, see Dias, N. *et al.*, (2002) *Mol Cancer Ther* 1:347-355. The single-stranded antisense RNA molecule may be about 15 to about 30 nucleotides in length and have a sequence that is complementary to a target sequence. For example, the single-stranded antisense RNA molecule may comprise a sequence that is at least about 15, 16, 17, 18,

19, 20, or more contiguous nucleotides from any one of the antisense sequences described herein.

The term "lipid nanoparticle" or "LNP" is a vesicle comprising a lipid layer encapsulating a pharmaceutically active molecule, such as a nucleic acid molecule, *e.g.*, an iRNA or a plasmid from which an iRNA is transcribed. LNPs are described in, for example, U.S. Patent Nos. 6,858,225, 6,815,432, 8,158,601, and 8,058,069, the entire contents of which are hereby incorporated herein by reference.

As used herein, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), a non-primate (such as a cow, a pig, a camel, a llama, a horse, a goat, a rabbit, a sheep, a hamster, a guinea pig, a cat, a dog, a rat, a mouse, a horse, and a whale), or a bird (*e.g.*, a duck or a goose). In an embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder or condition that would benefit from reduction in C5 expression; a human at risk for a disease, disorder or condition that would benefit from reduction in C5 expression; a human having a disease, disorder or condition that would benefit from reduction in C5 expression; and/or human being treated for a disease, disorder or condition that would benefit from reduction in C5 expression as described herein.

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alleviation or amelioration of one or more symptoms associated with unwanted complement pathway activation (*e.g.*, hemolysis and/or chronic inflammation); diminishing the extent of unwanted complement pathway activation; stabilization (*i.e.*, not worsening) of the state of chronic inflammation and/or hemolysis; amelioration or palliation of unwanted complement pathway activation (*e.g.*, chronic inflammation and/or hemolysis) whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of the level of a complement component C5 in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or more and is preferably down to a level accepted as within the range of normal for an individual without such disorder.

As used herein, "prevention" or "preventing," when used in reference to a disease, disorder or condition thereof, that would benefit from a reduction in expression of a C5 gene, refers to a reduction in the likelihood that a subject will develop a symptom associated with such a disease, disorder, or condition, *e.g.*, a symptom of unwanted complement activation, such as a

chronic inflammation, hemolysis and/or thrombosis. The likelihood of developing a thrombosis is reduced, for example, when an individual having one or more risk factors for a thrombosis either fails to develop a thrombosis or develops a thrombosis with less severity relative to a population having the same risk factors and not receiving treatment as described herein. The failure to develop a disease, disorder or condition, or the reduction in the development of a symptom associated with such a disease, disorder or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

As used herein, the term "complement component C5-associated disease" is a disease or disorder that is caused by, or associated with complement activation. Such diseases are typically associated with inflammation and/or immune system activation, *e.g.*, membrane attack complex-mediated lysis, anaphylaxis, and/or hemolysis. Non-limiting examples of complement component C5-associated diseases include paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 nephropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (*e.g.*, granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (*e.g.*, tissue damage and ischemia in myocardial infarction), an allogenic transplant, sepsis (*e.g.*, poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis, a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis

following stent placement, rotational atherectomy, membraneous nephropathy, Guillain-Barre syndrome, and percutaneous transluminal coronary angioplasty (PTCA) (see, *e.g.*, Holers (2008) Immunological Reviews 223:300-316; Holers and Thurman (2004) Molecular Immunology 41:147-152; U.S. Patent Publication No. 20070172483).

In one embodiment, a complement component C5-associated disease is paroxysmal nocturnal hemoglobinuria (PNH). The PNH may be classical PNH or PNH in the setting of another bone marrow failure syndrome and/or myelodysplastic syndromes (MDS), *e.g.*, cytopenias. In another embodiment, a complement component C5-associated disease is atypical hemolytic uremic syndrome (aHUS).

II. iRNAs of the Invention

The present invention provides iRNAs which inhibit the expression of a complement component C5 gene. In one embodiment, the iRNA agent includes double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a C5 gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human having a complement component C5-associated disease, *e.g.*, PNH. The dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of a C5 gene. The region of complementarity is about 30 nucleotides or less in length (*e.g.*, about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, or 18 nucleotides or less in length). Upon contact with a cell expressing the C5 gene, the iRNA inhibits the expression of the C5 gene (*e.g.*, a human, a primate, a non-primate, or a bird C5 gene) by at least about 10% as assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, Western Blotting or flowcytometric techniques.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of a C5 gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

Generally, the duplex structure is between 15 and 30 base pairs in length, *e.g.*, between, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-

30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

Similarly, the region of complementarity to the target sequence is between 15 and 30 nucleotides in length, *e.g.*, between 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the invention.

In some embodiments, the dsRNA is between about 15 and about 20 nucleotides in length, or between about 25 and about 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well-known in the art that dsRNAs longer than about 21-23 nucleotides in length may serve as substrates for Dicer. As the ordinarily skilled person will also recognize, the region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a "part" of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 9 to 36 base pairs, *e.g.*, about 10-36, 11-36, 12-36, 13-36, 14-36, 15-36, 9-35, 10-35, 11-35, 12-35, 13-35, 14-35, 15-35, 9-34, 10-34, 11-34, 12-34, 13-34, 14-34, 15-34, 9-33, 10-33, 11-33, 12-33, 13-33, 14-33, 15-33, 9-32, 10-32, 11-32, 12-32, 13-32, 14-32, 15-32, 9-31, 10-31, 11-31, 12-31, 13-32, 14-31, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex, of *e.g.*, 15-30 base pairs, that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an iRNA agent useful to target C5 expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs *e.g.*, 1, 2, 3, or 4 nucleotides. dsRNAs having at least one nucleotide overhang can have unexpectedly superior inhibitory properties relative to their blunt-ended counterparts. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5'-end, 3'-end or both ends of either an antisense or sense strand of a dsRNA.

A dsRNA can be synthesized by standard methods known in the art as further discussed below, *e.g.*, by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc.

iRNA compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double-stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the siRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In one aspect, a dsRNA of the invention includes at least two nucleotide sequences, a sense sequence and an anti-sense sequence. The sense strand is selected from the group of sequences provided in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, and the corresponding antisense strand of the sense strand is selected from the group of sequences of any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated in the expression of a C5 gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23. In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although some of the sequences in Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 are described as modified and/or conjugated sequences, the RNA of the iRNA of the invention *e.g.*, a dsRNA of the invention, may comprise any one of the sequences set forth in Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 that is un-modified, un-conjugated, and/or modified and/or conjugated differently than described therein.

The skilled person is well aware that dsRNAs having a duplex structure of between about 20 and 23 base pairs, *e.g.*, 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, *EMBO* 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes having one of the sequences of any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences of any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, and differing in their ability to inhibit the expression of a C5 gene by not more than about 5, 10, 15, 20, 25, or 30 % inhibition from a dsRNA comprising the full sequence, are contemplated to be within the scope of the present invention.

In addition, the RNAs provided in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 identify a site(s) in a C5 transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within one of these sites. As used herein, an iRNA is said to target within a particular site of an RNA transcript if the iRNA promotes cleavage of the transcript anywhere within that particular site. Such an iRNA will generally include at least about 15 contiguous nucleotides from one of the sequences provided in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a C5 gene.

While a target sequence is generally about 15-30 nucleotides in length, there is wide variation in the suitability of particular sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, *e.g.*, in silico) placed on the target RNA sequence to identify sequences in the size range that can serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays as described herein or as known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best

inhibition of target gene expression. Thus, while the sequences identified, for example, in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23 represent effective target sequences, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified, *e.g.*, in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23, further optimization could be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art and/or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, *e.g.*, the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications as known in the art and/or discussed herein to further optimize the molecule (*e.g.*, increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes) as an expression inhibitor.

An iRNA as described herein can contain one or more mismatches to the target sequence. In one embodiment, an iRNA as described herein contains no more than 3 mismatches. If the antisense strand of the iRNA contains mismatches to a target sequence, it is preferable that the area of mismatch is not located in the center of the region of complementarity. If the antisense strand of the iRNA contains mismatches to the target sequence, it is preferable that the mismatch be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, for a 23 nucleotide iRNA agent the strand which is complementary to a region of a C5 gene, generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of a C5 gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of a C5 gene is important, especially if the particular region of complementarity in a C5 gene is known to have polymorphic sequence variation within the population.

III. Modified iRNAs of the Invention

In one embodiment, the RNA of the iRNA of the invention *e.g.*, a dsRNA, is un-modified, and does not comprise, *e.g.*, chemical modifications and/or conjugations known in the art and described herein. In another embodiment, the RNA of an iRNA of the invention, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the invention, substantially all of the nucleotides of an iRNA of the invention are modified. In other embodiments of the invention, all of the nucleotides of an iRNA of the invention are modified. iRNAs of the invention in which "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotides.

The nucleic acids featured in the invention can be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S.L. *et al.* (Edrs.), John Wiley & Sons, Inc., New York, NY, USA, which is hereby incorporated herein by reference. Modifications include, for example, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); base modifications, *e.g.*, replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; and/or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of iRNA compounds useful in the embodiments described herein include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In some embodiments, a modified iRNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5'-linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6, 239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and US Pat RE39464, the entire contents of each of which are hereby incorporated herein by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, the entire contents of each of which are hereby incorporated herein by reference.

In other embodiments, suitable RNA mimetics are contemplated for use in iRNAs, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use

in the iRNAs of the invention are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

Some embodiments featured in the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2-, --CH_2--$N(CH_3)$--O--CH_2--[known as a methylene (methylimino) or MMI backbone], --CH_2--O--$N(CH_3)$--CH_2--, --CH_2--$N(CH_3)$--$N(CH_3)$--CH_2-- and --$N(CH_3)$--CH_2--CH_2--[wherein the native phosphodiester backbone is represented as --O--P--O--CH_2--] of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Patent No. 5,034,506.

Modified RNAs can also contain one or more substituted sugar moieties. The iRNAs, *e.g.*, dsRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$.

Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878;

5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application,. The entire contents of each of the foregoing are hereby incorporated herein by reference.

An iRNA can also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as deoxy-thymine (dT), 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch *et al.*, Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., dsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Patent Nos. 3,687,808, 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 5,750,692; 6,015,886; 6,147,200; 6,166,197;

6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, the entire contents of each of which are hereby incorporated herein by reference.

The RNA of an iRNA can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. *et al.*, (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. *et al.*, (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. *et al.*, (2003) *Nucleic Acids Research* 31(12):3185-3193).

Representative U.S. Patents that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Patent Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; and 7,399,845, the entire contents of each of which are hereby incorporated herein by reference.

Potentially stabilizing modifications to the ends of RNA molecules can include N-(acetylaminocaproyl)-4-hydroxyprolinol (Hyp-C6-NHAc), N-(caproyl-4-hydroxyprolinol (Hyp-C6), N-(acetyl-4-hydroxyprolinol (Hyp-NHAc), thymidine-2'-0-deoxythymidine (ether), N-(aminocaproyl)-4-hydroxyprolinol (Hyp-C6-amino), 2-docosanoyl-uridine-3"- phosphate, inverted base dT(idT) and others. Disclosure of this modification can be found in PCT Publication No. WO 2011/005861.

A. Modified iRNAs Comprising Motifs of the Invention

In certain aspects of the invention, the double-stranded RNAi agents of the invention include agents with chemical modifications as disclosed, for example, in U.S. Provisional Application No. 61/561,710, filed on November 18, 2011, or in PCT/US2012/065691, filed on November 16, 2012, the entire contents of each of which are incorporated herein by reference.

As shown herein and in Provisional Application No. 61/561,710 or PCT Application No. PCT/US2012/065691, a superior result may be obtained by introducing one or more motifs of three identical modifications on three consecutive nucleotides into a sense strand and/or antisense strand of an RNAi agent, particularly at or near the cleavage site. In some embodiments, the sense strand and antisense strand of the RNAi agent may otherwise be completely modified. The introduction of these motifs interrupts the modification pattern, if present, of the sense and/or antisense strand. The RNAi agent may be optionally conjugated with a GalNAc derivative ligand, for instance on the sense strand. The resulting RNAi agents present superior gene silencing activity.

More specifically, it has been surprisingly discovered that when the sense strand and antisense strand of the double-stranded RNAi agent are completely modified to have one or more motifs of three identical modifications on three consecutive nucleotides at or near the cleavage site of at least one strand of an RNAi agent, the gene silencing acitivity of the RNAi agent was superiorly enhanced.

Accordingly, the invention provides double-stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.*, a complement component C5 (C5) gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may range from 12-30 nucleotides in length. For example, each strand may be between 14-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30 nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 12-30 nucleotide pairs in length. For example, the duplex region can be between 14-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length.

In one embodiment, the RNAi agent may contain one or more overhang regions and/or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified, such as, 2-F, 2'-Omethyl, thymidine (T), 2'-O-methoxyethyl-5-methyluridine (Teo), 2'-O-methoxyethyladenosine (Aeo), 2'-O-methoxyethyl-5-methylcytidine (m5Ceo), and any

combinations thereof. For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In one embodiment, the RNAi agent is a double ended bluntmer of 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, 9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In another embodiment, the RNAi agent is a double ended bluntmer of 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, 10 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In yet another embodiment, the RNAi agent is a double ended bluntmer of 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end.

In one embodiment, the RNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, 11 from the 5'end; the

antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, 13 from the 5'end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang. Preferably, the 2 nucleotide overhang is at the 3'-end of the antisense strand. When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 3'-fluoro, *e.g.*, in an alternating motif. Optionally, the RNAi agent further comprises a ligand (preferably $GalNAc_3$).

In one embodiment, the RNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one

motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region region which is at least 25 nucleotides in length, and the second strand is sufficiently complemenatary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

In one embodiment, the antisense strand of the RNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand

For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, 11 positions; 10, 11, 12 positions; 11, 12, 13 positions; 12, 13, 14 positions; or 13, 14, 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the RNAi from the 5'-end.

The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term

"wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adajacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

Like the sense strand, the antisense strand of the RNAi agent may contain more than one motifs of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end or both ends of the strand.

When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

When the sense strand and the antisense strand of the RNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two or three nucleotides in the duplex region.

In one embodiment, every nucleotide in the sense strand and antisense strand of the RNAi agent, including the nucleotides that are part of the motifs, may be modified. Each nucleotide may be modified with the same or different modification which can include one or more alteration of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens; alteration of a constituent of the ribose sugar, *e.g.*, of the 2′ hydroxyl on the ribose sugar; wholesale replacement of the phosphate moiety with "dephospho" linkers;

modification or replacement of a naturally occurring base; and replacement or modification of the ribose-phosphate backbone.

As nucleic acids are polymers of subunits, many of the modifications occur at a position which is repeated within a nucleic acid, *e.g.*, a modification of a base, or a phosphate moiety, or a non-linking O of a phosphate moiety. In some cases the modification will occur at all of the subject positions in the nucleic acid but in many cases it will not. By way of example, a modification may only occur at a 3' or 5' terminal position, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand. A modification may occur in a double strand region, a single strand region, or in both. A modification may occur only in the double strand region of a RNA or may only occur in a single strand region of a RNA. For example, a phosphorothioate modification at a non-linking O position may only occur at one or both termini, may only occur in a terminal region, *e.g.*, at a position on a terminal nucleotide or in the last 2, 3, 4, 5, or 10 nucleotides of a strand, or may occur in double strand and single strand regions, particularly at termini. The 5' end or ends can be phosphorylated.

It may be possible, *e.g.*, to enhance stability, to include particular bases in overhangs, or to include modified nucleotides or nucleotide surrogates, in single strand overhangs, *e.g.*, in a 5' or 3' overhang, or in both. For example, it can be desirable to include purine nucleotides in overhangs. In some embodiments all or some of the bases in a 3' or 5' overhang may be modified, *e.g.*, with a modification described herein. Modifications can include, *e.g.*, the use of modifications at the 2' position of the ribose sugar with modifications that are known in the art, *e.g.*, the use of deoxyribonucleotides, , 2'-deoxy-2'-fluoro (2'-F) or 2'-O-methyl modified instead of the ribosugar of the nucleobase , and modifications in the phosphate group, *e.g.*, phosphorothioate modifications. Overhangs need not be homologous with the target sequence.

In one embodiment, each residue of the sense strand and antisense strand is independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'- O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-deoxy, 2'-hydroxyl, or 2'-fluoro. The strands can contain more than one modification. In one embodiment, each residue of the sense strand and antisense strand is independently modified with 2'- O-methyl or 2'-fluoro.

At least two different modifications are typically present on the sense strand and antisense strand. Those two modifications may be the 2'- O-methyl or 2'-fluoro modifications, or others.

In one embodiment, the N_a and/or N_b comprise modifications of an alternating pattern. The term "alternating motif" as used herein refers to a motif having one or more modifications, each modification occurring on alternating nucleotides of one strand. The alternating nucleotide may refer to one per every other nucleotide or one per every three nucleotides, or a similar

pattern. For example, if A, B and C each represent one type of modification to the nucleotide, the alternating motif can be "ABABABABABAB...," "AABBAABBAABB...," "AABAABAABAAB...," "AAABAAABAAAB...," "AAABBBAAABBB...," or "ABCABCABCABC...," etc.

The type of modifications contained in the alternating motif may be the same or different. For example, if A, B, C, D each represent one type of modification on the nucleotide, the alternating pattern, *i.e.*, modifications on every other nucleotide, may be the same, but each of the sense strand or antisense strand can be selected from several possibilities of modifications within the alternating motif such as "ABABAB...", "ACACAC..." "BDBDBD..." or "CDCDCD...," etc.

In one embodiment, the RNAi agent of the invention comprises the modification pattern for the alternating motif on the sense strand relative to the modification pattern for the alternating motif on the antisense strand is shifted. The shift may be such that the modified group of nucleotides of the sense strand corresponds to a differently modified group of nucleotides of the antisense strand and *vice versa*. For example, the sense strand when paired with the antisense strand in the dsRNA duplex, the alternating motif in the sense strand may start with "ABABAB" from 5'-3' of the strand and the alternating motif in the antisense strand may start with "BABABA" from 5'-3'of the strand within the duplex region. As another example, the alternating motif in the sense strand may start with "AABBAABB" from 5'-3' of the strand and the alternating motif in the antisenese strand may start with "BBAABBAA" from 5'-3' of the strand within the duplex region, so that there is a complete or partial shift of the modification patterns between the sense strand and the antisense strand.

In one embodiment, the RNAi agent comprises the pattern of the alternating motif of 2'-O-methyl modification and 2'-F modification on the sense strand initially has a shift relative to the pattern of the alternating motif of 2'-O-methyl modification and 2'-F modification on the antisense strand initially, *i.e.*, the 2'-O-methyl modified nucleotide on the sense strand base pairs with a 2'-F modified nucleotide on the antisense strand and vice versa. The 1 position of the sense strand may start with the 2'-F modification, and the 1 position of the antisense strand may start with the 2'- O-methyl modification.

The introduction of one or more motifs of three identical modifications on three consecutive nucleotides to the sense strand and/or antisense strand interrupts the initial modification pattern present in the sense strand and/or antisense strand. This interruption of the modification pattern of the sense and/or antisense strand by introducing one or more motifs of three identical modifications on three consecutive nucleotides to the sense and/or antisense strand surprisingly enhances the gene silencing acitivty to the target gene.

In one embodiment, when the motif of three identical modifications on three consecutive nucleotides is introduced to any of the strands, the modification of the nucleotide next to the motif is a different modification than the modification of the motif. For example, the portion of the sequence containing the motif is "...N_aYYYN_b...," where "Y" represents the modification of the motif of three identical modifications on three consecutive nucleotide, and "N_a" and "N_b" represent a modification to the nucleotide next to the motif "YYY" that is different than the modification of Y, and where N_a and N_b can be the same or different modifications. Altnernatively, N_a and/or N_b may be present or absent when there is a wing modification present.

The RNAi agent may further comprise at least one phosphorothioate or methylphosphonate internucleotide linkage. The phosphorothioate or methylphosphonate internucleotide linkage modification may occur on any nucleotide of the sense strand or antisense strand or both strands in any position of the strand. For instance, the internucleotide linkage modification may occur on every nucleotide on the sense strand and/or antisense strand; each internucleotide linkage modification may occur in an alternating pattern on the sense strand and/or antisense strand; or the sense strand or antisense strand may contain both internucleotide linkage modifications in an alternating pattern. The alternating pattern of the internucleotide linkage modification on the sense strand may be the same or different from the antisense strand, and the alternating pattern of the internucleotide linkage modification on the sense strand may have a shift relative to the alternating pattern of the internucleotide linkage modification on the antisense strand. In one embodiment, a double-standed RNAi agent comprises 6-8phosphorothioate internucleotide linkages. In one embodiment, the antisense strand comprises two phosphorothioate internucleotide linkages at the 5'-terminus and two phosphorothioate internucleotide linkages at the 3'-terminus, and the sense strand comprises at least two phosphorothioate internucleotide linkages at either the 5'-terminus or the 3'-terminus.

In one embodiment, the RNAi comprises a phosphorothioate or methylphosphonate internucleotide linkage modification in the overhang region. For example, the overhang region may contain two nucleotides having a phosphorothioate or methylphosphonate internucleotide linkage between the two nucleotides. Internucleotide linkage modifications also may be made to link the overhang nucleotides with the terminal paired nucleotides within the duplex region. For example, at least 2, 3, 4, or all the overhang nucleotides may be linked through phosphorothioate or methylphosphonate internucleotide linkage, and optionally, there may be additional phosphorothioate or methylphosphonate internucleotide linkages linking the overhang nucleotide with a paired nucleotide that is next to the overhang nucleotide. For instance, there may be at least two phosphorothioate internucleotide linkages between the terminal three nucleotides, in which two of the three nucleotides are overhang nucleotides, and the third is a paired nucleotide next to the overhang nucleotide. These terminal three nucleotides may be at the 3'-end of the

antisense strand, the 3'-end of the sense strand, the 5'-end of the antisense strand, and/or the 5'end of the antisense strand.

In one embodiment, the 2 nucleotide overhang is at the 3'-end of the antisense strand, and there are two phosphorothioate internucleotide linkages between the terminal three nucleotides, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. Optionally, the RNAi agent may additionally have two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand.

In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mistmatch may occur in the overhang region or the duplex region. The base pair may be ranked on the basis of their propensity to promote dissociation or melting (*e.g.*, on the free energy of association or dissociation of a particular pairing, the simplest approach is to examine the pairs on an individual pair basis, though next neighbor or similar analysis can also be used). In terms of promoting dissociation: A:U is preferred over G:C; G:U is preferred over G:C; and I:C is preferred over G:C (I=inosine). Mismatches, *e.g.*, non-canonical or other than canonical pairings (as described elsewhere herein) are preferred over canonical (A:T, A:U, G:C) pairings; and pairings which include a universal base are preferred over canonical pairings.

In one embodiment, the RNAi agent comprises at least one of the first 1, 2, 3, 4, or 5 base pairs within the duplex regions from the 5'- end of the antisense strand independently selected from the group of: A:U, G:U, I:C, and mismatched pairs, *e.g.*, non-canonical or other than canonical pairings or pairings which include a universal base, to promote the dissociation of the antisense strand at the 5'-end of the duplex.

In one embodiment, the nucleotide at the 1 position within the duplex region from the 5'-end in the antisense strand is selected from the group consisting of A, dA, dU, U, and dT. Alternatively, at least one of the first 1, 2 or 3 base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair. For example, the first base pair within the duplex region from the 5'- end of the antisense strand is an AU base pair.

In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxy-thymine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxy-thymine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense and/or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):

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

wherein:

i and j are each independently 0 or 1;

p and q are each independently 0-6;

each N_a independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p and n_q independently represent an overhang nucleotide;

wherein Nb and Y do not have the same modification; and

XXX, YYY and ZZZ each independently represent one motif of three identical modifications on three consecutive nucleotides. Preferably YYY is all 2'-F modified nucleotides.

In one embodiment, the N_a and/or N_b comprise modifications of alternating pattern.

In one embodiment, the YYY motif occurs at or near the cleavage site of the sense strand. For example, when the RNAi agent has a duplex region of 17-23 nucleotides in length, the YYY motif can occur at or the vicinity of the cleavage site (*e.g.*: can occur at positions 6, 7, 8, 7, 8, 9, 8, 9, 10, 9, 10, 11, 10, 11,12 or 11, 12, 13) of - the sense strand, the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end.

In one embodiment, i is 1 and j is 0, or i is 0 and j is 1, or both i and j are 1. The sense strand can therefore be represented by the following formulas:

5' n_p-N_a-YYY-N_b-ZZZ-N_a-n_q 3' (Ib);

5' n_p-N_a-XXX-N_b-YYY-N_a-n_q 3' (Ic); or

5' n_p-N_a-XXX-N_b-YYY-N_b-ZZZ-N_a-n_q 3' (Id).

When the sense strand is represented by formula (Ib), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Ic), N_b represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the sense strand is represented as formula (Id), each N_b independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6 Each N_a can independently represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X, Y and Z may be the same or different from each other.

In other embodiments, i is 0 and j is 0, and the sense strand may be represented by the formula:

5' n_p-N_a-YYY- N_a-n_q 3' (Ia).

When the sense strand is represented by formula (Ia), each N_a independently can represent an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

In one embodiment, the antisense strand sequence of the RNAi may be represented by formula (II):

5' $n_{q'}$-N_a'-(Z`Z'Z')$_k$-N_b'-Y'Y'Y'-N_b'-(X'X'X')$_l$-N'$_a$-n_p' 3' (II)

wherein:

k and l are each independently 0 or 1;

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

each N_a' independently represents an oligonucleotide sequence comprising 0-25 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

each n_p' and n_q' independently represent an overhang nucleotide;

wherein N_b' and Y' do not have the same modification;

and

X'X'X', Y'Y'Y' and Z'Z'Z' each independently represent one motif of three identical modifications on three consecutive nucleotides.

In one embodiment, the N_a' and/or N_b' comprise modifications of alternating pattern.

The Y'Y'Y' motif occurs at or near the cleavage site of the antisense strand. For example, when the RNAi agent has a duplex region of 17-23nucleotidein length, the Y'Y'Y' motif can occur at positions 9, 10, 11;10, 11, 12; 11, 12, 13; 12, 13, 14 ; or 13, 14, 15 of the antisense strand, with the count starting from the 1st nucleotide, from the 5'-end; or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end. Preferably, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In one embodiment, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

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

The antisense strand can therefore be represented by the following formulas:

5' $n_{q'}$-N_a'-Z'Z'Z'-N_b'-Y'Y'Y'-N_a'-n_p' 3' (IIb);

5' $n_{q'}$-N_a'-Y'Y'Y'-N_b'-X'X'X'-n_p' 3' (IIc); or

5' $n_{q'}$-N_a'- Z'Z'Z'-N_b'-Y'Y'Y'-N_b'- X'X'X'-N_a'-n_p' 3' (IId).

When the antisense strand is represented by formula (IIb), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified

nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IIc), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the antisense strand is represented as formula (IId), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0 modified nucleotides. Each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Preferably, N_b is 0, 1, 2, 3, 4, 5 or 6.

In other embodiments, k is 0 and l is 0 and the antisense strand may be represented by the formula:

5' n_p'-N_a'-Y'Y'Y'- N_a'-n_q' 3' (Ia).

When the antisense strand is represented as formula (IIa), each N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

Each of X', Y' and Z' may be the same or different from each other.

Each nucleotide of the sense strand and antisense strand may be independently modified with LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-methyl, 2'-O-allyl, 2'-C- allyl, 2'-hydroxyl, or 2'-fluoro. For example, each nucleotide of the sense strand and antisense strand is independently modified with 2'-O-methyl or 2'-fluoro. Each X, Y, Z, X', Y' and Z', in particular, may represent a 2'-O-methyl modification or a 2'-fluoro modification.

In one embodiment, the sense strand of the RNAi agent may contain YYY motif occurring at 9, 10 and 11 positions of the strand when the duplex region is 21 nt, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y represents 2'-F modification. The sense strand may additionally contain XXX motif or ZZZ motifs as wing modifications at the opposite end of the duplex region; and XXX and ZZZ each independently represents a 2'-OMe modification or 2'-F modification.

In one embodiment the antisense strand may contain Y'Y'Y' motif occurring at positions 11, 12, 13 of the strand, the count starting from the 1st nucleotide from the 5'-end, or optionally, the count starting at the 1st paired nucleotide within the duplex region, from the 5'- end; and Y' represents 2'-O-methyl modification. The antisense strand may additionally contain X'X'X' motif or Z'Z'Z' motifs as wing modifications at the opposite end of the duplex region; and X'X'X' and Z'Z'Z' each independently represents a 2'-OMe modification or 2'-F modification.

The sense strand represented by any one of the above formulas (Ia), (Ib), (Ic), and (Id) forms a duplex with a antisense strand being represented by any one of formulas (IIa), (IIb), (IIc), and (IId), respectively.

Accordingly, the RNAi agents for use in the methods of the invention may comprise a sense strand and an antisense strand, each strand having 14 to 30 nucleotides, the RNAi duplex 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 modified nucleotides, each sequence comprising at least two differently modified nucleotides;

each N_b and N_b' independently represents an oligonucleotide sequence comprising 0-10 modified nucleotides;

wherein

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

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.

In one embodiment, i is 0 and j is 0; or i is 1 and j is 0; or i is 0 and j is 1; or both i and j are 0; or both i and j are 1. In another embodiment, k is 0 and l is 0; or k is 1 and l is 0; k is 0 and l is 1; or both k and l are 0; or both k and l are 1.

Exemplary combinations of the sense strand and antisense strand forming a RNAi duplex include the formulas below:

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

3' n_p'-N_a'-Y'Y'Y' -$N_a'$$n_q'$ 5'

(IIIa)

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

3' n_p'-N_a'-Y'Y'Y'-N_b'-Z'Z'Z'-$N_a'$$n_q'$ 5'

(IIIb)

5' n_p-N_a- X X X -N_b-Y Y Y - N_a-n_q 3'

3' n_p'-N_a'-X'X'X'-N_b'-Y'Y'Y'-N_a'-n_q' 5'

(IIIc)

$5'\ n_p\text{-}N_a\text{-}X\ X\ X\text{-}N_b\text{-}Y\ Y\ Y\text{-}N_b\text{-}Z\ Z\ Z\text{-}N_a\text{-}n_q\ 3'$

$3'\ n_p'\text{-}N_a'\text{-}X'X'X'\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}Z'Z'Z'\text{-}N_a\text{-}n_q'\ 5'$

(IIId)

When the RNAi agent is represented by formula (IIIa), each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented by formula (IIIb), each N_b independently represents an oligonucleotide sequence comprising 1-10, 1-7, 1-5 or 1-4 modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIIc), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each N_a independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides.

When the RNAi agent is represented as formula (IIId), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified nucleotides. Each N_a, N_a' independently represents an oligonucleotide sequence comprising 2-20, 2-15, or 2-10 modified nucleotides. Each of N_a, N_a', N_b and N_b' independently comprises modifications of alternating pattern.

Each of X, Y and Z in formulas (III), (IIIa), (IIIb), (IIIc), and (IIId) may be the same or different from each other.

When the RNAi agent is represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), at least one of the Y nucleotides may form a base pair with one of the Y′ nucleotides. Alternatively, at least two of the Y nucleotides form base pairs with the corresponding Y′ nucleotides; or all three of the Y nucleotides all form base pairs with the corresponding Y′ nucleotides.

When the RNAi agent is represented by formula (IIIb) or (IIId), at least one of the Z nucleotides may form a base pair with one of the Z′ nucleotides. Alternatively, at least two of the Z nucleotides form base pairs with the corresponding Z′ nucleotides; or all three of the Z nucleotides all form base pairs with the corresponding Z′ nucleotides.

When the RNAi agent is represented as formula (IIIc) or (IIId), at least one of the X nucleotides may form a base pair with one of the X′ nucleotides. Alternatively, at least two of the X nucleotides form base pairs with the corresponding X′ nucleotides; or all three of the X nucleotides all form base pairs with the corresponding X′ nucleotides.

In one embodiment, the modification on the Y nucleotide is different than the modification on the Y' nucleotide, the modification on the Z nucleotide is different than the

modification on the Z' nucleotide, and/or the modification on the X nucleotide is different than the modification on the X' nucleotide.

In one embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications and $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide a via phosphorothioate linkage. In yet another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications , $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIId), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications , $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, when the RNAi agent is represented by formula (IIIa), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications , $n_p' > 0$ and at least one n_p' is linked to a neighboring nucleotide via phosphorothioate linkage, the sense strand comprises at least one phosphorothioate linkage, and the sense strand is conjugated to one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, two RNAi agents represented by formula (III), (IIIa), (IIIb), (IIIc), and (IIId) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can target same gene at two different target sites.

Various publications describe multimeric RNAi agents that can be used in the methods of the invention. Such publications include WO2007/091269, US Patent No. 7858769,

WO2010/141511, WO2007/117686, WO2009/014887 and WO2011/031520 the entire contents of each of which are hereby incorporated herein by reference.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to a RNAi agent can optimize one or more properties of the RNAi agent. In many cases, the carbohydrate moiety will be attached to a modified subunit of the RNAi agent. For example, the ribose sugar of one or more ribonucleotide subunits of a dsRNA agent can be replaced with another moiety, *e.g.*, a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS). A cyclic carrier may be a carbocyclic ring system, *i.e.*, all ring atoms are carbon atoms, or a heterocyclic ring system, *i.e.*, one or more ring atoms may be a heteroatom, *e.g.*, nitrogen, oxygen, sulfur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, *e.g.* fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds.

The ligand may be attached to the polynucleotide via a carrier. The carriers include (i) at least one "backbone attachment point," preferably two "backbone attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, *e.g.* a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier into the backbone, *e.g.*, the phosphate, or modified phosphate, *e.g.*, sulfur containing, backbone, of a ribonucleic acid. A "tethering attachment point" (TAP) in some embodiments refers to a constituent ring atom of the cyclic carrier, *e.g.*, a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The moiety can be, *e.g.*, a carbohydrate, *e.g.* monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the cyclic carrier. Thus, the cyclic carrier will often include a functional group, *e.g.*, an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, *e.g.*, a ligand to the constituent ring.

The RNAi agents may be conjugated to a ligand *via* a carrier, wherein the carrier can be cyclic group or acyclic group; preferably, the cyclic group is selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalin; preferably, the acyclic group is selected from serinol backbone or diethanolamine backbone.

In certain specific embodiments, the RNAi agent for use in the methods of the invention is an agent selected from the group of agents listed in any one of Tables 3, 4, 5, 6, 18, 19, 20, 21, and 23. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the invention involves chemically linking to the RNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger *et al.*, *Proc. Natl. Acid. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1994, 4:1053-1060), a thioether, *e.g.*, beryl-S-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan *et al.*, *Biorg. Med. Chem. Let.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J*, 1991, 10:1111-1118; Kabanov *et al.*, *FEBS Lett.*, 1990, 259:327-330; Svinarchuk *et al.*, *Biochimie*, 1993, 75:49-54), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea *et al.*, *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke *et al.*, J. *Pharmacol. Exp. Ther.*, 1996, 277:923-937).

In one embodiment, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In preferred embodiments a ligand provides an enhanced affinity for a selected target, *e.g.*, molecule, cell or cell type, compartment, *e.g.*, a cellular or organ compartment, tissue, organ or region of the body, as, *e.g.*, compared to a species absent such a ligand. Preferred ligands will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (*e.g.*, human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (*e.g.*, a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylgalactosamine, or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, *e.g.*, a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or

polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

Ligands can also include targeting groups, *e.g.*, a cell or tissue targeting agent, *e.g.*, a lectin, glycoprotein, lipid or protein, *e.g.*, an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucoseamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, vitamin A, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), lipophilic molecules, *e.g.*, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine)and peptide conjugates (*e.g.*, antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases (*e.g.*, imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, *e.g.*, glycoproteins, or peptides, *e.g.*, molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as a hepatic cell. Ligands can also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF-κB.

The ligand can be a substance, *e.g.*, a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, *e.g.*, by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for

example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In some embodiments, a ligand attached to an iRNA as described herein acts as a pharmacokinetic modulator (PK modulator). PK modulators include lipophiles, bile acids, steroids, phospholipid analogues, peptides, protein binding agents, PEG, vitamins *etc*. Exemplary PK modulators include, but are not limited to, cholesterol, fatty acids, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, phospholipids, sphingolipids, naproxen, ibuprofen, vitamin E, biotin *etc*. Oligonucleotides that comprise a number of phosphorothioate linkages are also known to bind to serum protein, thus short oligonucleotides, *e.g.*, oligonucleotides of about 5 bases, 10 bases, 15 bases or 20 bases, comprising multiple of phosphorothioate linkages in the backbone are also amenable to the present invention as ligands (*e.g.* as PK modulating ligands). In addition, aptamers that bind serum components (*e.g.* serum proteins) are also suitable for use as PK modulating ligands in the embodiments described herein.

Ligand-conjugated oligonucleotides of the invention may be synthesized by the use of an oligonucleotide that bears a pendant reactive functionality, such as that derived from the attachment of a linking molecule onto the oligonucleotide (described below). This reactive oligonucleotide may be reacted directly with commercially-available ligands, ligands that are synthesized bearing any of a variety of protecting groups, or ligands that have a linking moiety attached thereto.

The oligonucleotides used in the conjugates of the present invention may be conveniently and routinely made through the well-known technique of solid-phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is also known to use similar techniques to prepare other oligonucleotides, such as the phosphorothioates and alkylated derivatives.

In the ligand-conjugated oligonucleotides and ligand-molecule bearing sequence-specific linked nucleosides of the present invention, the oligonucleotides and oligonucleosides may be assembled on a suitable DNA synthesizer utilizing standard nucleotide or nucleoside precursors, or nucleotide or nucleoside conjugate precursors that already bear the linking moiety, ligand-nucleotide or nucleoside-conjugate precursors that already bear the ligand molecule, or non-nucleoside ligand-bearing building blocks.

When using nucleotide-conjugate precursors that already bear a linking moiety, the synthesis of the sequence-specific linked nucleosides is typically completed, and the ligand molecule is then reacted with the linking moiety to form the ligand-conjugated oligonucleotide. In some embodiments, the oligonucleotides or linked nucleosides of the present invention are synthesized by an automated synthesizer using phosphoramidites derived from ligand-nucleoside

conjugates in addition to the standard phosphoramidites and non-standard phosphoramidites that are commercially available and routinely used in oligonucleotide synthesis.

A. Lipid Conjugates

In one embodiment, the ligand or conjugate is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule preferably binds a serum protein, *e.g.*, human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, naproxen or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, *e.g.*, HSA.

A lipid based ligand can be used to inhibit, *e.g.*, control the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In a preferred embodiment, the lipid based ligand binds HSA. Preferably, it binds HSA with a sufficient affinity such that the conjugate will be preferably distributed to a non-kidney tissue. However, it is preferred that the affinity not be so strong that the HSA-ligand binding cannot be reversed.

In another preferred embodiment, the lipid based ligand binds HSA weakly or not at all, such that the conjugate will be preferably distributed to the kidney. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

In another aspect, the ligand is a moiety, *e.g.*, a vitamin, which is taken up by a target cell, *e.g.*, a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, *e.g.*, of the malignant or non-malignant type, *e.g.*, cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, *e.g.*, folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by target cells such as liver cells. Also included are HSA and low density lipoprotein (LDL).

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, *e.g.*, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (*e.g.*, consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 9). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 10) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO: 11) and the Drosophila Antennapedia protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 12) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam *et al.*, Nature, 354:82-84, 1991). Examples of a peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit for cell targeting purposes is an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide for use in the compositions and methods of the invention may be linear or cyclic, and may be modified, *e.g.*, glycosylated or methylated, to facilitate targeting to a specific tissue(s). RGD-containing peptides and peptidiomimemtics may include D-amino acids, as well as synthetic RGD mimics. In addition to RGD, one can use other moieties that target the integrin ligand. Preferred conjugates of this ligand target PECAM-1 or VEGF.

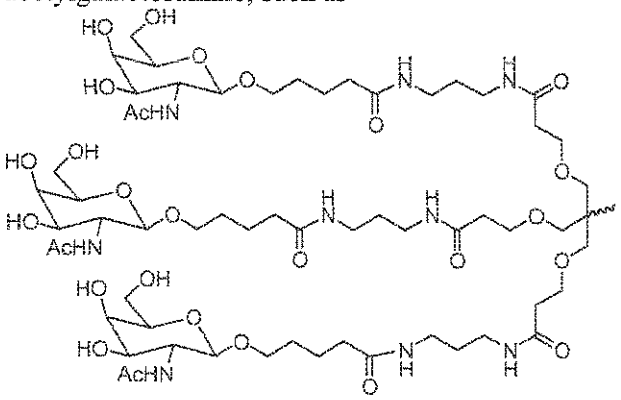
A "cell permeation peptide" is capable of permeating a cell, *e.g.*, a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, a α-helical linear peptide (*e.g.*, LL-37 or Ceropin P1), a disulfide bond-containing peptide (*e.g.*, α -defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (*e.g.*, PR-39 or indolicidin). A cell

permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni *et al.*, Nucl. Acids Res. 31:2717-2724, 2003).

C. Carbohydrate Conjugates

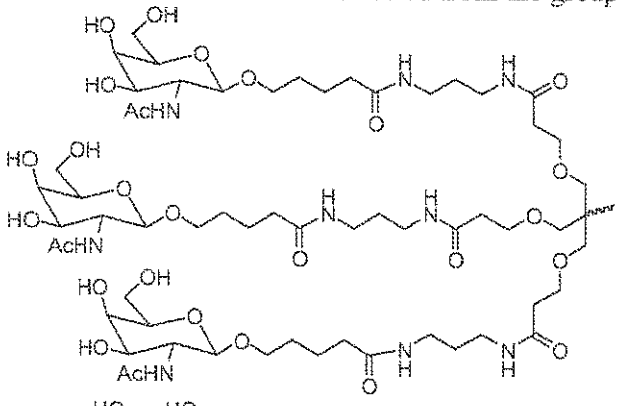
In some embodiments of the compositions and methods of the invention, an iRNA oligonucleotide further comprises a carbohydrate. The carbohydrate conjugated iRNA are advantageous for the *in vivo* delivery of nucleic acids, as well as compositions suitable for *in vivo* therapeutic use, as described herein. As used herein, "carbohydrate" refers to a compound which is either a carbohydrate *per se* made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which can be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (*e.g.*, C5, C6, C7, or C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In one embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In one embodiment, the monosaccharide is an N-acetylgalactosamine, such as

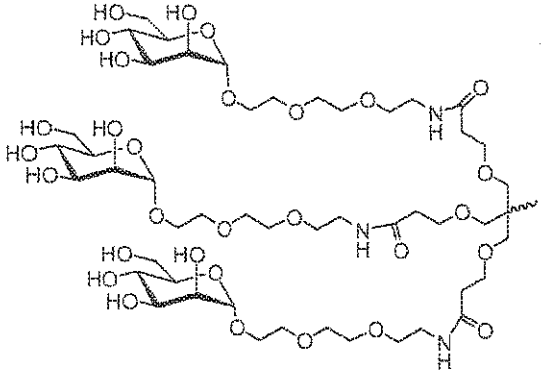


Formula II.

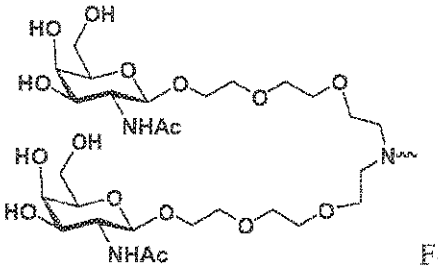
In another embodiment, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



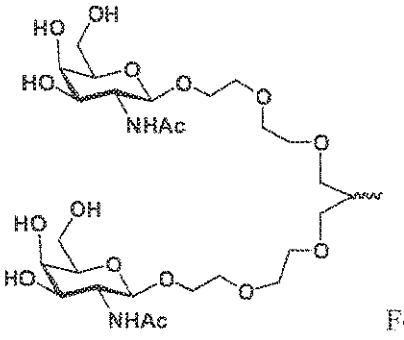
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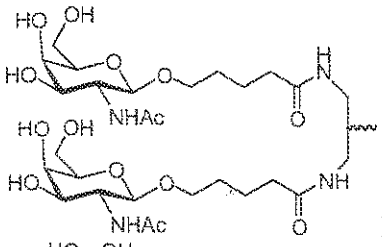
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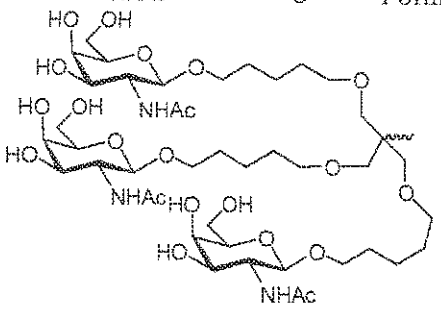
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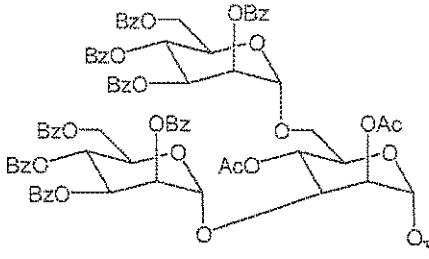
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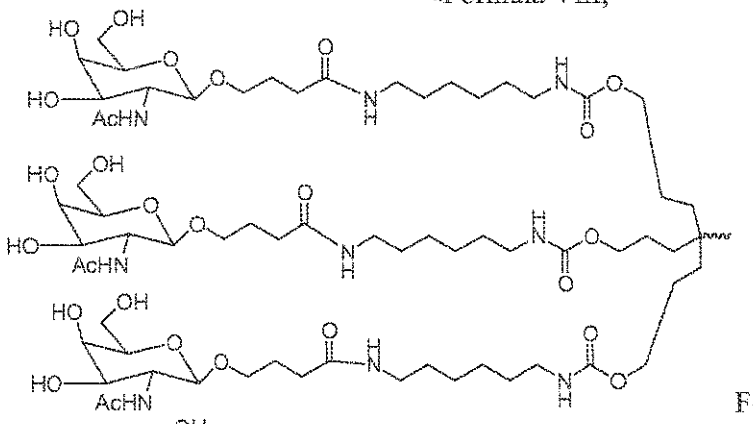
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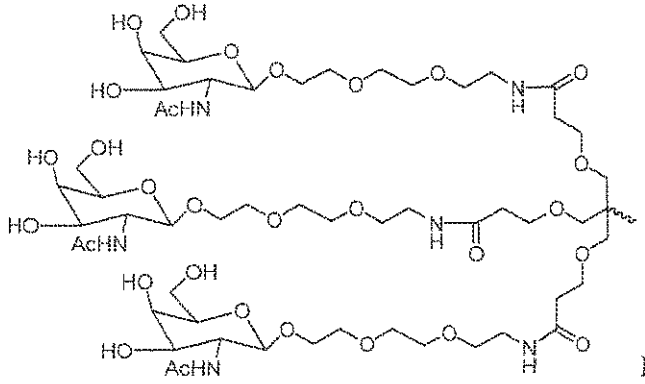
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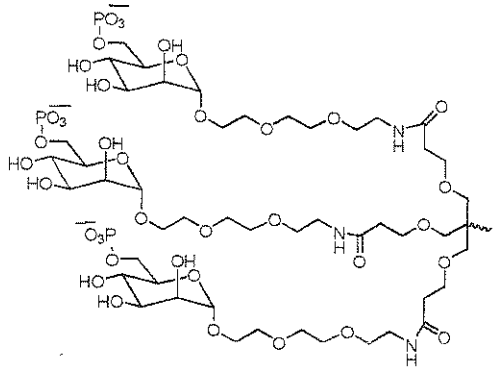
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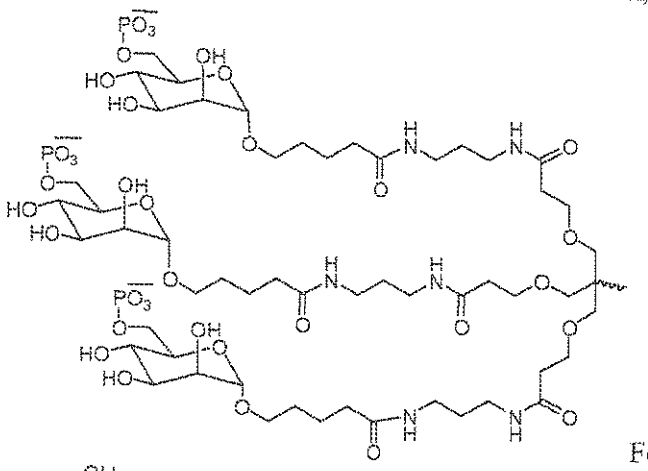
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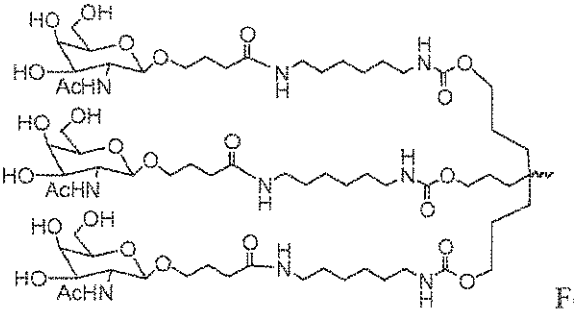
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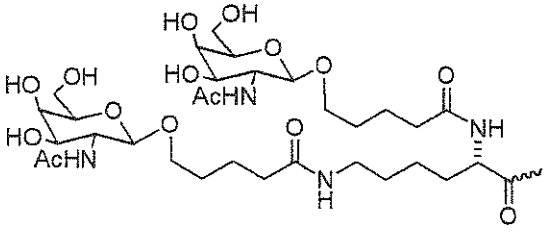
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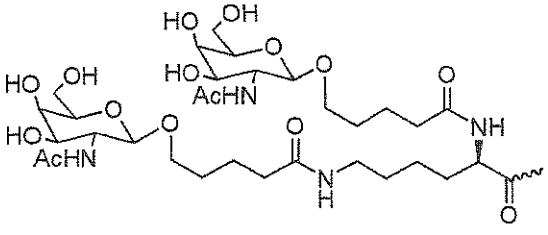
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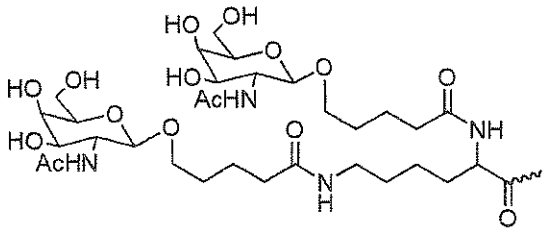
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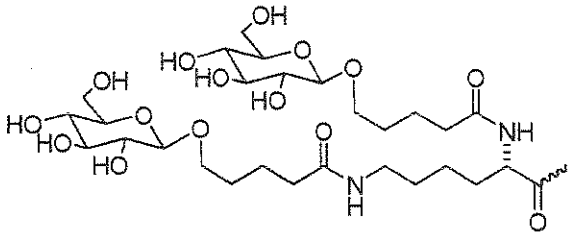
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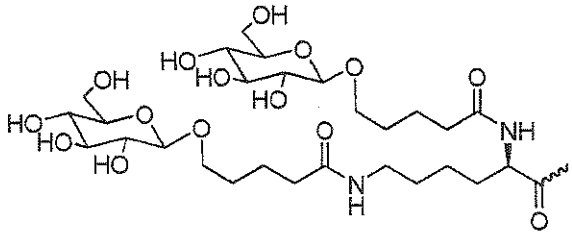
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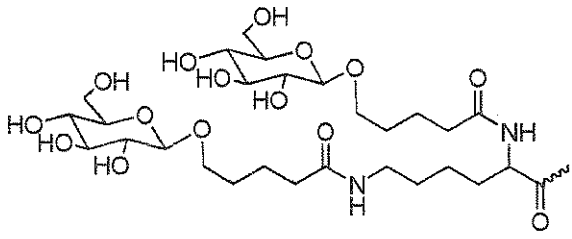
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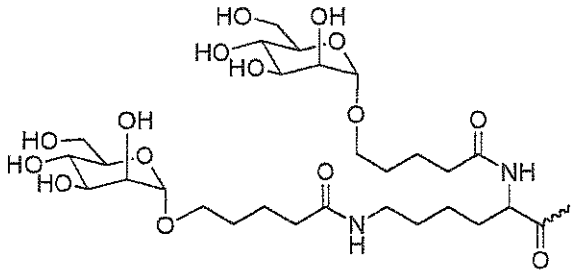
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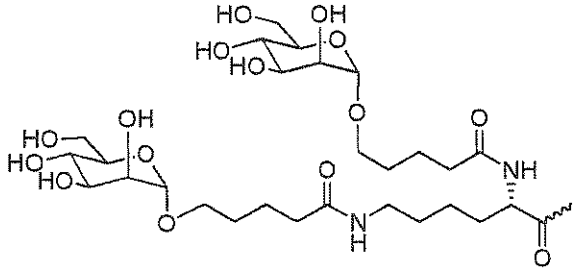
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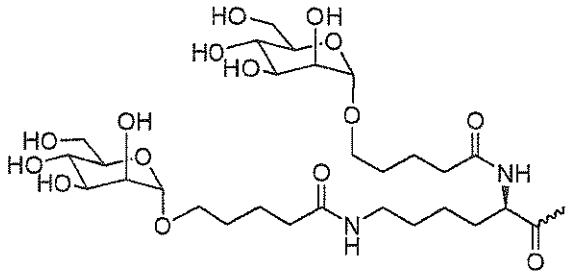
Formula XIX,



Formula XX,

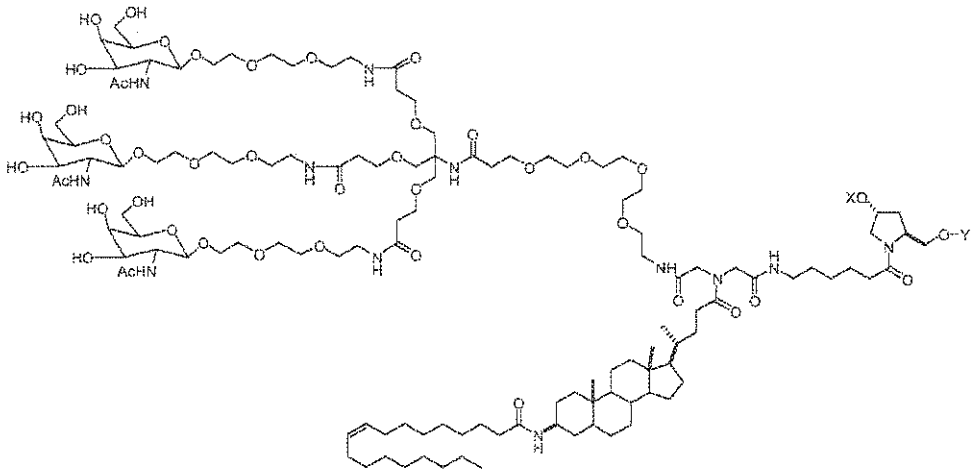


Formula XXI,



Formula XXII.

Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to



(Formula XXIII),

when one of X or Y is an oligonucleotide, the other is a hydrogen.

In some embodiments, the carbohydrate conjugate further comprises one or more additional ligands as described above, such as, but not limited to, a PK modulator and/or a cell permeation peptide.

D. Linkers

In some embodiments, the conjugate or ligand described herein can be attached to an iRNA oligonucleotide with various linkers that can be cleavable or non-cleavable.

The term "linker" or "linking group" means an organic moiety that connects two parts of a compound, *e.g.*, covalently attaches two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR8, C(O), C(O)NH, SO, SO_2, SO_2NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl,

alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO_2, N(R8), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R8 is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker is between about 1-24 atoms, 2-24, 3-24, 4-24, 5-24, 6-24, 6-18, 7-18, 8-18 atoms, 7-17, 8-17, 6-16, 7-16, or 8-16 atoms.

A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least about 10 times, 20, times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times or more, or at least about 100 times faster in a target cell or under a first reference condition (which can, *e.g.*, be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, *e.g.*, be selected to mimic or represent conditions found in the blood or serum).

Cleavable linking groups are susceptible to cleavage agents, *e.g.*, pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, *e.g.*, oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, *e.g.*, those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at

a preferred pH, thereby releasing a cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, *e.g.*, blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It can be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In preferred embodiments, useful candidate compounds are cleaved at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

i. Redox cleavable linking groups

In one embodiment, a cleavable linking group is a redox cleavable linking group that is cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (-S-S-). To determine if a candidate cleavable linking group is a suitable "reductively cleavable linking group," or for example is suitable for use with a particular iRNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents know in the art, which mimic the rate of cleavage which would be observed in a cell, *e.g.*, a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In one, candidate compounds are cleaved by at most about 10% in the blood. In other embodiments, useful candidate compounds are degraded at least about 2, 4, 10, 20, 30, 40, 50, 60, 70, 80, 90, or about 100 times faster in the cell (or

under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

ii. Phosphate-based cleavable linking groups

In another embodiment, a cleavable linker comprises a phosphate-based cleavable linking group. A phosphate-based cleavable linking group is cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups are -O-P(O)(ORk)-O-, -O-P(S)(ORk)-O-, -O-P(S)(SRk)-O-, -S-P(O)(ORk)-O-, -O-P(O)(ORk)-S-, -S-P(O)(ORk)-S-, -O-P(S)(ORk)-S-, -S-P(S)(ORk)-O-, -O-P(O)(Rk)-O-, -O-P(S)(Rk)-O-, -S-P(O)(Rk)-O-, -S-P(S)(Rk)-O-, -S-P(O)(Rk)-S-, -O-P(S)(Rk)-S-. Preferred embodiments are -O-P(O)(OH)-O-, -O-P(S)(OH)-O-, -O-P(S)(SH)-O-, -S-P(O)(OH)-O-, -O-P(O)(OH)-S-, -S-P(O)(OH)-S-, -O-P(S)(OH)-S-, -S-P(S)(OH)-O-, -O-P(O)(H)-O-, -O-P(S)(H)-O-, -S-P(O)(H)-O, -S-P(S)(H)-O-, -S-P(O)(H)-S-, -O-P(S)(H)-S-. A preferred embodiment is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

In another embodiment, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (*e.g.*, about 6.0, 5.75, 5.5, 5.25, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula -C=NN-, C(O)O, or -OC(O). A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

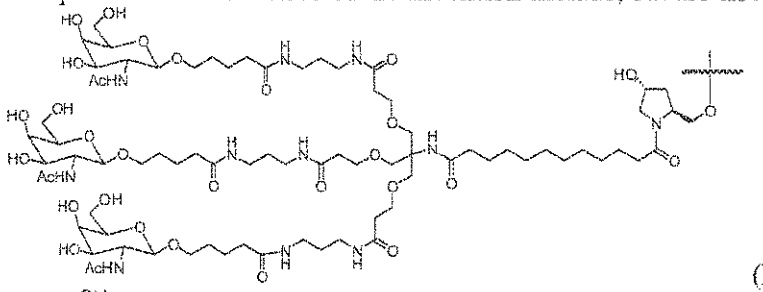
iv. Ester-based linking groups

In another embodiment, a cleavable linker comprises an ester-based cleavable linking group. An ester-based cleavable linking group is cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula -C(O)O-, or -OC(O)-. These candidates can be evaluated using methods analogous to those described above.

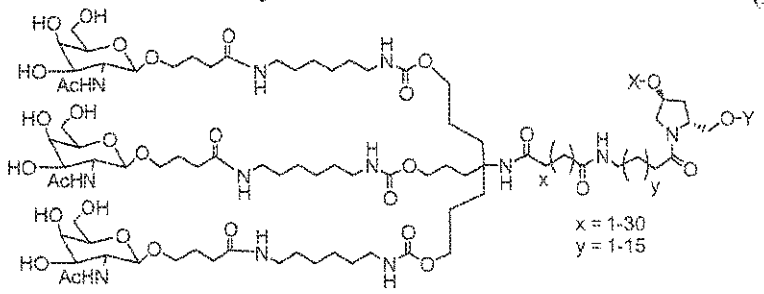
v. Peptide-based cleaving groups

In yet another embodiment, a cleavable linker comprises a peptide-based cleavable linking group. A peptide-based cleavable linking group is cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (*e.g.*, dipeptides, tripeptides *etc.*) and polypeptides. Peptide-based cleavable groups do not include the amide group (-C(O)NH-). The amide group can be formed between any alkylene, alkenylene or alkynelene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (*i.e.*, the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula – NHCHRAC(O)NHCHRBC(O)-, where RA and RB are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

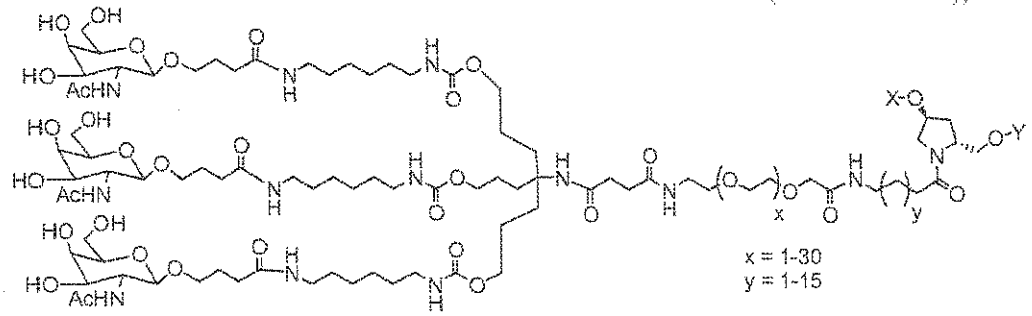
In one embodiment, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



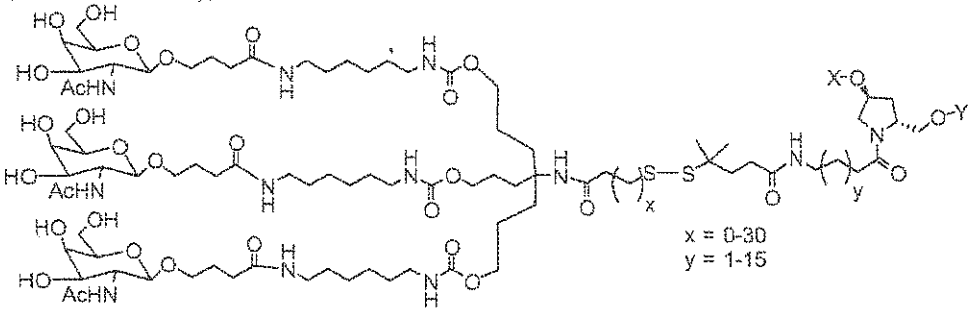
(Formula XXIV),



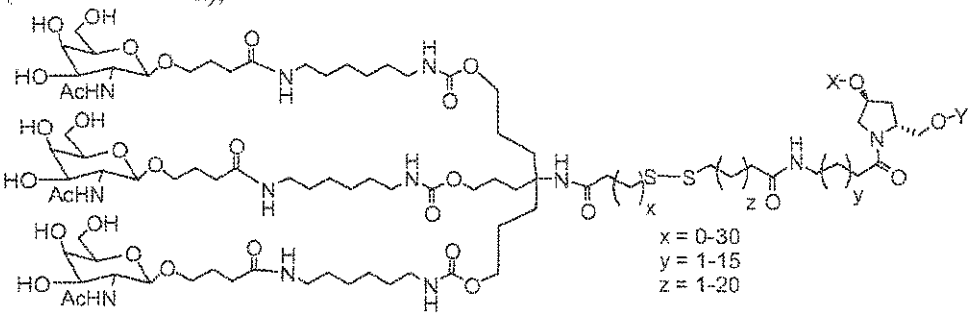
(Formula XXV),



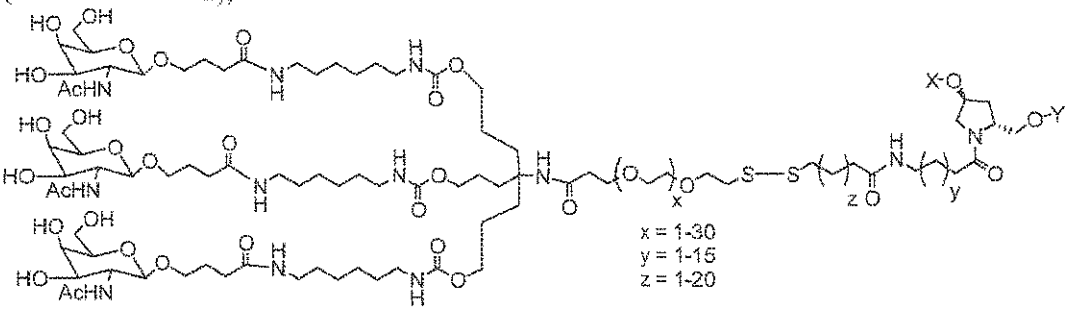
(Formula XXVI),



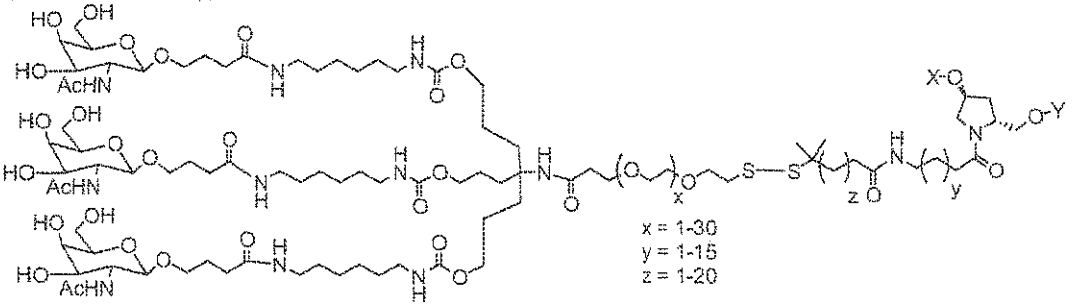
(Formula XXVII),



(Formula XXVIII),



(Formula XXIX), and

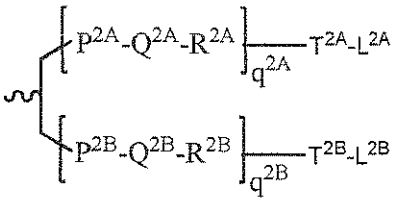


(Formula XXX), when one of X or Y is an oligonucleotide, the other is a hydrogen.

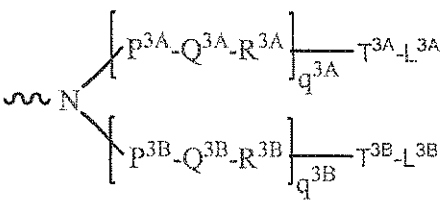
In certain embodiments of the compositions and methods of the invention, a ligand is one or more "GalNAc" (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XXXI) – (XXXIV):

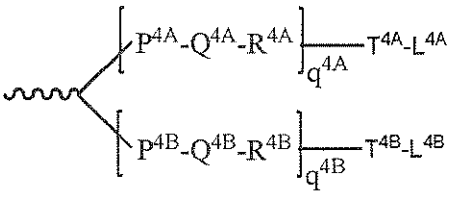
Formula XXXI



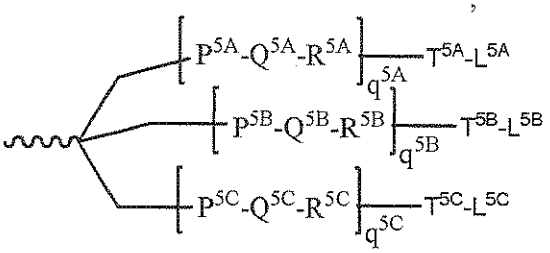
Formula XXXII



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, or ;

Formula XXXIII

Formula XXXIV

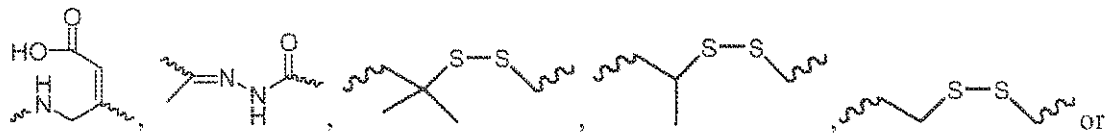
wherein:

q2A, q2B, q3A, q3B, q4A, q4B, q5A, q5B and q5C represent independently for each occurrence 0-20 and wherein the repeating unit can be the same or different;

P^{2A}, P^{2B}, P^{3A}, P^{3B}, P^{4A}, P^{4B}, P^{5A}, P^{5B}, P^{5C}, T^{2A}, T^{2B}, T^{3A}, T^{3B}, T^{4A}, T^{4B}, T^{4A}, T^{5B}, T^{5C} are each independently for each occurrence absent, CO, NH, O, S, OC(O), NHC(O), CH_2, CH_2NH or CH_2O;

Q^{2A}, Q^{2B}, Q^{3A}, Q^{3B}, Q^{4A}, Q^{4B}, Q^{5A}, Q^{5B}, Q^{5C} are independently for each occurrence absent, alkylene, substituted alkylene wherin one or more methylenes can be interrupted or terminated by one or more of O, S, S(O), SO_2, $N(R^N)$, C(R')=C(R''), C≡C or C(O);

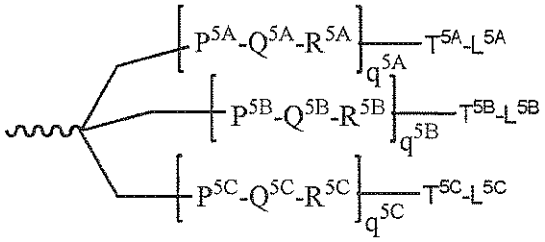
R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{5C} are each independently for each occurrence absent, NH, O, S, CH_2, C(O)O, C(O)NH, $NHCH(R^a)C(O)$, -C(O)-$CH(R^a)$-NH-, CO, CH=N-O,



heterocyclyl;

L^{2A}, L^{2B}, L^{3A}, L^{3B}, L^{4A}, L^{4B}, L^{5A}, L^{5B} and L^{5C} represent the ligand; *i.e.* each independently for each occurrence a monosaccharide (such as GalNAc), disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, or polysaccharide; andR^a is H or amino acid side chain.Trivalent conjugating GalNAc derivatives are particularly useful for use with RNAi agents for inhibiting the expression of a target gene, such as those of formula (XXXV):

Formula XXXV



,

wherein L^{5A}, L^{5B} and L^{5C} represent a monosaccharide, such as GalNAc derivative.

Examples of suitable bivalent and trivalent branched linker groups conjugating GalNAc derivatives include, but are not limited to, the structures recited above as formulas II, VII, XI, X, and XIII.

Representative U.S. patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; 8,106,022, the entire contents of each of which are hereby incorporated herein by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single

compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are chimeric compounds.

"Chimeric" iRNA compounds or "chimeras," in the context of this invention, are iRNA compounds, preferably dsRNAs, which contain two or more chemically distinct regions, each made up of at least one monomer unit, *i.e.*, a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the iRNA can serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. *et al., Biochem. Biophys. Res. Comm.*, 2007, 365(1):54-61; Letsinger *et al., Proc. Natl. Acad. Sci. USA*, 1989, 86:6553), cholic acid (Manoharan *et al., Bioorg. Med. Chem. Lett.*, 1994, 4:1053), a thioether, *e.g.*, hexyl-S-tritylthiol (Manoharan *et al., Ann. N.Y. Acad. Sci.*, 1992, 660:306; Manoharan *et al., Bioorg. Med. Chem. Let.*, 1993, 3:2765), a thiocholesterol (Oberhauser *et al., Nucl. Acids Res.*, 1992, 20:533), an aliphatic chain, *e.g.*, dodecandiol or undecyl residues (Saison-Behmoaras *et al., EMBO J.*, 1991, 10:111; Kabanov *et al., FEBS Lett.*, 1990, 259:327; Svinarchuk *et al., Biochimie*, 1993, 75:49), a phospholipid, *e.g.*, di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan *et al., Tetrahedron Lett.*, 1995, 36:3651; Shea *et al., Nucl. Acids Res.*, 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan *et al., Nucleosides & Nucleotides*, 1995, 14:969), or adamantane acetic acid (Manoharan *et al., Tetrahedron Lett.*, 1995, 36:3651), a palmityl moiety (Mishra *et al., Biochim. Biophys. Acta*, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al., J. Pharmacol. Exp. Ther.*, 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of an RNAs bearing an aminolinker at one or more positions of the

sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction can be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

IV. Delivery of an iRNA of the Invention

The delivery of an iRNA of the invention to a cell *e.g.*, a cell within a subject, such as a human subject (*e.g.*, a subject in need thereof, such as a subject having a complement component C5-associated disease) can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an iRNA of the invention either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an iRNA, *e.g.*, a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an iRNA of the invention (see *e.g.*, Akhtar S. and Julian RL. (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). For *in vivo* delivery, factors to consider in order to deliver an iRNA molecule include, for example, biological stability of the delivered molecule, prevention of non-specific effects, and accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA can be minimized by local administration, for example, by direct injection or implantation into a tissue or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, MJ., *et al* (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, SJ., *et al* (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J., *et al* (2005) *Mol. Ther.*11:267-274) and can prolong survival of tumor-bearing mice (Kim, WJ., *et al* (2006) *Mol. Ther.* 14:343-350; Li, S., *et al* (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G., *et al.* (2004) *Nucleic Acids* 32:e49; Tan, PH., *et al* (2005) *Gene Ther.* 12:59-66; Makimura, H., *et al* (2002) *BMC Neurosci.* 3:18; Shishkina, GT., *et al* (2004) *Neuroscience* 129:521-528; Thakker, ER., *et al* (2004) *Proc. Natl.*

Acad. Sci. U.S.A. 101:17270-17275; Akaneya,Y., *et al* (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, KA., *et al* (2006) *Mol. Ther.* 14:476-484; Zhang, X., *et al* (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V., *et al* (2005) *Nat. Med.* 11:50-55). For administering an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases *in vivo*. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J., *et al* (2004) *Nature* 432:173-178). Conjugation of an iRNA to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, JO., *et al* (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the iRNA can be delivered using drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see *e.g.*, Kim SH., *et al* (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic- iRNA complexes are well within the abilities of one skilled in the art (see *e.g.*, Sorensen, DR., *et al* (2003) *J. Mol. Biol* 327:761-766; Verma, UN., *et al* (2003) Clin. *Cancer Res.* 9:1291-1300; Arnold, AS *et al* (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, DR., *et al* (2003), supra; Verma, UN., *et al* (2003), *supra*), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, TS., *et al* (2006) *Nature* 441:111-114), cardiolipin (Chien, PY., *et al* (2005) *Cancer Gene Ther.* 12:321-328; Pal, A., *et al* (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet ME., *et al* (2008) *Pharm. Res.* Aug 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, DA., *et al* (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., *et al* (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and

pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Patent No. 7,427,605, which is herein incorporated by reference in its entirety.

A. Vector encoded iRNAs of the Invention

iRNA targeting the C5 gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; Skillern, A., *et al.*, International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054,299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, *et al.*, *Proc. Natl. Acad. Sci. USA* (1995) 92:1292).

The individual strand or strands of an iRNA can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (*e.g.*, by transfection or infection) into a target cell. Alternatively each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

iRNA expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA as described herein. Eukaryotic cell expression vectors are well known in the art and are available from a number of commercial sources. Typically, such vectors are provided containing convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of iRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

iRNA expression plasmids can be transfected into target cells as a complex with cationic lipid carriers (*e.g.*, Oligofectamine) or non-cationic lipid-based carriers (*e.g.*, Transit-TKO™). Multiple lipid transfections for iRNA-mediated knockdowns targeting different regions of a target RNA over a period of a week or more are also contemplated by the invention. Successful introduction of vectors into host cells can be monitored using various known methods. For example, transient transfection can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of cells *ex vivo* can be ensured

using markers that provide the transfected cell with resistance to specific environmental factors (*e.g.*, antibiotics and drugs), such as hygromycin B resistance.

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, *etc.*; (c) adeno- associated virus vectors; (d) herpes simplex virus vectors; (e) SV 40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, *e.g.*, vaccinia virus vectors or avipox, *e.g.* canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are further described below.

Vectors useful for the delivery of an iRNA will include regulatory elements (promoter, enhancer, *etc.*) sufficient for expression of the iRNA in the desired target cell or tissue. The regulatory elements can be chosen to provide either constitutive or regulated/inducible expression.

Expression of the iRNA can be precisely regulated, for example, by using an inducible regulatory sequence that is sensitive to certain physiological regulators, *e.g.*, circulating glucose levels, or hormones (Docherty *et al.*, 1994, *FASEB J.* 8:20-24). Such inducible expression systems, suitable for the control of dsRNA expression in cells or in mammals include, for example, regulation by ecdysone, by estrogen, progesterone, tetracycline, chemical inducers of dimerization, and isopropyl-beta-D1 -thiogalactopyranoside (IPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the iRNA transgene.

Viral vectors that contain nucleic acid sequences encoding an iRNA can be used. For example, a retroviral vector can be used (see Miller *et al.*, *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding an iRNA are cloned into one or more vectors, which facilitate delivery of the nucleic acid into a patient. More detail about retroviral vectors can be found, for example, in Boesen *et al.*, *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, *J. Clin.*

Invest. 93:644-651 (1994); Kiem *et al.*, *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993). Lentiviral vectors contemplated for use include, for example, the HIV based vectors described in U.S. Patent Nos. 6,143,520; 5,665,557; and 5,981,276, which are herein incorporated by reference.

Adenoviruses are also contemplated for use in delivery of iRNAs of the invention. Adenoviruses are especially attractive vehicles, *e.g.*, for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, *Science* 252:431-434 (1991); Rosenfeld *et al.*, *Cell* 68:143-155 (1992); Mastrangeli *et al.*, *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, *et al.*, *Gene Therapy* 2:775-783 (1995). A suitable AV vector for expressing an iRNA featured in the invention, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia H *et al.* (2002), *Nat. Biotech.* 20: 1006-1010.

Adeno-associated virus (AAV) vectors may also be used to delivery an iRNA of the invention (Walsh *et al.*, Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Pat. No. 5,436,146). In one embodiment, the iRNA can be expressed as two separate, complementary single-stranded RNA molecules from a recombinant AAV vector having, for example, either the U6 or H1 RNA promoters, or the cytomegalovirus (CMV) promoter. Suitable AAV vectors for expressing the dsRNA featured in the invention, methods for constructing the recombinant AV vector, and methods for delivering the vectors into target cells are described in Samulski R *et al.* (1987), *J. Virol.* 61: 3096-3101; Fisher K J *et al.* (1996), *J. Virol*, 70: 520-532; Samulski R *et al.* (1989), *J. Virol.* 63: 3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are herein incorporated by reference.

Another viral vector suitable for delivery of an iRNA of the inevtion is a pox virus such as a vaccinia virus, for example an attenuated vaccinia such as Modified Virus Ankara (MVA) or NYVAC, an avipox such as fowl pox or canary pox.

The tropism of viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate. For example, lentiviral vectors can be pseudotyped with surface proteins

from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors can be made to target different cells by engineering the vectors to express different capsid protein serotypes; see, *e.g.*, Rabinowitz J E *et al.* (2002), *J Virol* 76:791-801, the entire disclosure of which is herein incorporated by reference.

The pharmaceutical preparation of a vector can include the vector in an acceptable diluent, or can include a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

V. Pharmaceutical Compositions of the Invention

The present invention also includes pharmaceutical compositions and formulations which include the iRNAs of the invention. In one embodiment, provided herein are pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium state, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-

free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

The pharmaceutical compositions containing the iRNA are useful for treating a disease or disorder associated with the expression or activity of a C5 gene, *e.g.* a complement component C5-associated disease. Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by subcutaneous (SC) or intravenous (IV) delivery. Another example is compositions that are formulated for direct delivery into the brain parenchyma, *e.g.*, by infusion into the brain, such as by continuous pump infusion. The pharmaceutical compositions of the invention may be administered in dosages sufficient to inhibit expression of a C5 gene. In general, a suitable dose of an iRNA of the invention will be in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day. For example, the dsRNA can be administered at about 0.01 mg/kg, about 0.05 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 3 mg/kg, about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose.

For example, the dsRNA may be administered at a dose of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

In another embodiment, the dsRNA is administered at a dose of about 0.1 to about 50 mg/kg, about 0.25 to about 50 mg/kg, about 0.5 to about 50 mg/kg, about 0.75 to about 50 mg/kg, about 1 to about 50 mg/mg, about 1.5 to about 50 mg/kb, about 2 to about 50 mg/kg, about 2.5 to about 50 mg/kg, about 3 to about 50 mg/kg, about 3.5 to about 50 mg/kg, about 4 to about 50 mg/kg, about 4.5 to about 50 mg/kg, about 5 to about 50 mg/kg, about 7.5 to about 50 mg/kg, about 10 to about 50 mg/kg, about 15 to about 50 mg/kg, about 20 to about 50 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 50 mg/kg, about 30 to about 50 mg/kg, about 35 to about 50 mg/kg, about 40 to about 50 mg/kg, about 45 to about 50 mg/kg, about 0.1 to about 45 mg/kg, about 0.25 to about 45 mg/kg, about 0.5 to about 45 mg/kg, about 0.75 to about 45 mg/kg, about 1 to about 45 mg/mg, about 1.5 to about 45 mg/kb, about 2 to about 45 mg/kg, about 2.5 to about 45 mg/kg, about 3 to about 45 mg/kg, about 3.5 to

about 45 mg/kg, about 4 to about 45 mg/kg, about 4.5 to about 45 mg/kg, about 5 to about 45 mg/kg, about 7.5 to about 45 mg/kg, about 10 to about 45 mg/kg, about 15 to about 45 mg/kg, about 20 to about 45 mg/kg, about 20 to about 45 mg/kg, about 25 to about 45 mg/kg, about 25 to about 45 mg/kg, about 30 to about 45 mg/kg, about 35 to about 45 mg/kg, about 40 to about 45 mg/kg, about 0.1 to about 40 mg/kg, about 0.25 to about 40 mg/kg, about 0.5 to about 40 mg/kg, about 0.75 to about 40 mg/kg, about 1 to about 40 mg/mg, about 1.5 to about 40 mg/kb, about 2 to about 40 mg/kg, about 2.5 to about 40 mg/kg, about 3 to about 40 mg/kg, about 3.5 to about 40 mg/kg, about 4 to about 40 mg/kg, about 4.5 to about 40 mg/kg, about 5 to about 40 mg/kg, about 7.5 to about 40 mg/kg, about 10 to about 40 mg/kg, about 15 to about 40 mg/kg, about 20 to about 40 mg/kg, about 20 to about 40 mg/kg, about 25 to about 40 mg/kg, about 25 to about 40 mg/kg, about 30 to about 40 mg/kg, about 35 to about 40 mg/kg, about 0.1 to about 30 mg/kg, about 0.25 to about 30 mg/kg, about 0.5 to about 30 mg/kg, about 0.75 to about 30 mg/kg, about 1 to about 30 mg/mg, about 1.5 to about 30 mg/kb, about 2 to about 30 mg/kg, about 2.5 to about 30 mg/kg, about 3 to about 30 mg/kg, about 3.5 to about 30 mg/kg, about 4 to about 30 mg/kg, about 4.5 to about 30 mg/kg, about 5 to about 30 mg/kg, about 7.5 to about 30 mg/kg, about 10 to about 30 mg/kg, about 15 to about 30 mg/kg, about 20 to about 30 mg/kg, about 20 to about 30 mg/kg, about 25 to about 30 mg/kg, about 0.1 to about 20 mg/kg, about 0.25 to about 20 mg/kg, about 0.5 to about 20 mg/kg, about 0.75 to about 20 mg/kg, about 1 to about 20 mg/mg, about 1.5 to about 20 mg/kb, about 2 to about 20 mg/kg, about 2.5 to about 20 mg/kg, about 3 to about 20 mg/kg, about 3.5 to about 20 mg/kg, about 4 to about 20 mg/kg, about 4.5 to about 20 mg/kg, about 5 to about 20 mg/kg, about 7.5 to about 20 mg/kg, about 10 to about 20 mg/kg, or about 15 to about 20 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

For example, the dsRNA may be administered at a dose of about 0..01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

In another embodiment, the dsRNA is administered at a dose of about 0.5 to about 50 mg/kg, about 0.75 to about 50 mg/kg, about 1 to about 50 mg/mg, about 1.5 to about 50 mg/kb, about 2 to about 50 mg/kg, about 2.5 to about 50 mg/kg, about 3 to about 50 mg/kg, about 3.5 to about 50 mg/kg, about 4 to about 50 mg/kg, about 4.5 to about 50 mg/kg, about 5 to about 50 mg/kg, about 7.5 to about 50 mg/kg, about 10 to about 50 mg/kg, about 15 to about 50 mg/kg, about 20 to about 50 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25

to about 50 mg/kg, about 30 to about 50 mg/kg, about 35 to about 50 mg/kg, about 40 to about 50 mg/kg, about 45 to about 50 mg/kg, about 0.5 to about 45 mg/kg, about 0.75 to about 45 mg/kg, about 1 to about 45 mg/mg, about 1.5 to about 45 mg/kb, about 2 to about 45 mg/kg, about 2.5 to about 45 mg/kg, about 3 to about 45 mg/kg, about 3.5 to about 45 mg/kg, about 4 to about 45 mg/kg, about 4.5 to about 45 mg/kg, about 5 to about 45 mg/kg, about 7.5 to about 45 mg/kg, about 10 to about 45 mg/kg, about 15 to about 45 mg/kg, about 20 to about 45 mg/kg, about 20 to about 45 mg/kg, about 25 to about 45 mg/kg, about 25 to about 45 mg/kg, about 30 to about 45 mg/kg, about 35 to about 45 mg/kg, about 40 to about 45 mg/kg, about 0.5 to about 40 mg/kg, about 0.75 to about 40 mg/kg, about 1 to about 40 mg/mg, about 1.5 to about 40 mg/kb, about 2 to about 40 mg/kg, about 2.5 to about 40 mg/kg, about 3 to about 40 mg/kg, about 3.5 to about 40 mg/kg, about 4 to about 40 mg/kg, about 4.5 to about 40 mg/kg, about 5 to about 40 mg/kg, about 7.5 to about 40 mg/kg, about 10 to about 40 mg/kg, about 15 to about 40 mg/kg, about 20 to about 40 mg/kg, about 20 to about 40 mg/kg, about 25 to about 40 mg/kg, about 25 to about 40 mg/kg, about 30 to about 40 mg/kg, about 35 to about 40 mg/kg, about 0.5 to about 30 mg/kg, about 0.75 to about 30 mg/kg, about 1 to about 30 mg/mg, about 1.5 to about 30 mg/kb, about 2 to about 30 mg/kg, about 2.5 to about 30 mg/kg, about 3 to about 30 mg/kg, about 3.5 to about 30 mg/kg, about 4 to about 30 mg/kg, about 4.5 to about 30 mg/kg, about 5 to about 30 mg/kg, about 7.5 to about 30 mg/kg, about 10 to about 30 mg/kg, about 15 to about 30 mg/kg, about 20 to about 30 mg/kg, about 20 to about 30 mg/kg, about 25 to about 30 mg/kg, about 0.5 to about 20 mg/kg, about 0.75 to about 20 mg/kg, about 1 to about 20 mg/mg, about 1.5 to about 20 mg/kb, about 2 to about 20 mg/kg, about 2.5 to about 20 mg/kg, about 3 to about 20 mg/kg, about 3.5 to about 20 mg/kg, about 4 to about 20 mg/kg, about 4.5 to about 20 mg/kg, about 5 to about 20 mg/kg, about 7.5 to about 20 mg/kg, about 10 to about 20 mg/kg, or about 15 to about 20 mg/kg. In one embodiment, the dsRNA is administered at a dose of about 10mg/kg to about 30 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

For example, subjects can be administered, *e.g.*, subcutaneously or intravenously, a single therapeutic amount of iRNA, such as about 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.275, 0.3, 0.325, 0.35, 0.375, 0.4, 0.425, 0.45, 0.475, 0.5, 0.525, 0.55, 0.575, 0.6, 0.625, 0.65, 0.675, 0.7, 0.725, 0.75, 0.775, 0.8, 0.825, 0.85, 0.875, 0.9, 0.925, 0.95, 0.975, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 31, 32, 33, 34, 34, 35, 36, 37, 38, 39, 40,

41, 42, 43, 44, 45, 46, 47, 48, 49, or about 50 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

In some embodiments, subjects are administered, *e.g.*, subcutaneously or intravenously, multiple doses of a therapeutic amount of iRNA, such as a dose about 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.275, 0.3, 0.325, 0.35, 0.375, 0.4, 0.425, 0.45, 0.475, 0.5, 0.525, 0.55, 0.575, 0.6, 0.625, 0.65, 0.675, 0.7, 0.725, 0.75, 0.775, 0.8, 0.825, 0.85, 0.875, 0.9, 0.925, 0.95, 0.975, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 31, 32, 33, 34, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or about 50 mg/kg. A multi-dose regimine may include administration of a therapeutic amount of iRNA daily, such as for two days, three days, four days, five days, six days, seven days, or longer.

In other embodiments, subjects are administered, *e.g.*, subcutaneously or intravenously, a repeat dose of a therapeutic amount of iRNA, such as a dose about 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.275, 0.3, 0.325, 0.35, 0.375, 0.4, 0.425, 0.45, 0.475, 0.5, 0.525, 0.55, 0.575, 0.6, 0.625, 0.65, 0.675, 0.7, 0.725, 0.75, 0.775, 0.8, 0.825, 0.85, 0.875, 0.9, 0.925, 0.95, 0.975, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 31, 32, 33, 34, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or about 50 mg/kg. A repeat-dose regimine may include administration of a therapeutic amount of iRNA on a regular basis, such as every other day, every third day, every fourth day, twice a week, once a week, every other week, or once a month.

The pharmaceutical composition can be administered by intravenous infusion over a period of time, such as over a 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21, 22, 23, 24, or about a 25 minute period. The administration may be repeated, for example, on a regular basis, such as weekly, biweekly (*i.e.*, every two weeks) for one month, two months, three months, four months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration weekly or biweekly for three months, administration can be repeated once per month, for six months or a year or longer.

The pharmaceutical composition can be administered once daily, or the iRNA can be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the iRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, *e.g.*, using a conventional sustained release formulation which provides sustained release of the iRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5 day intervals, or at not more than 1, 2, 3, or 4 week intervals. In some embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered once per week. In other embodiments of the invention, a single dose of the pharmaceutical compositions of the invention is administered bi-monthly.

The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and *in vivo* half-lives for the individual iRNAs encompassed by the invention can be made using conventional methodologies or on the basis of *in vivo* testing using an appropriate animal model, as described elsewhere herein.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as a disorder that would benefit from reduction in the expression of C5. Such models can be used for *in vivo* testing of iRNA, as well as for determining a therapeutically effective dose. Suitable mouse models are known in the art and include, for example, collagen-induced arthritis mouse model (Courtenay, J.S., *et al.* (1980) *Nature* 283, 666–668), myocardial ischemia (Homeister JW and Lucchesi BR (1994) *Annu Rev Pharmacol Toxicol* 34:17–40), ovalbumin induced asthma mouse models (*e.g.*, Tomkinson A., *et al.* (2001). *J. Immunol.* 166, 5792–5800), (NZB×NZW)F1, MRL/Fas^{lpr} (MRL/lpr) and BXSB mouse models (Theofilopoulos, A. N. and Kono, D. H. 1999. Murine lupus models: gene-specific and genome-wide studies. In Lahita R. G., ed., *Systemic Lupus Erythematosus*, 3rd edn, p. 145. Academic Press, San Diego, CA), mouse aHUS model (Goicoechea de Jorge *et al.* (2011) *The development*

of atypical hemolytic uremic syndrome depeds on complement C5, J Am Soc Nephrol 22:137-145.

The pharmaceutical compositions of the present invention can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, *e.g.*, via an implanted device; or intracranial, *e.g.*, by intraparenchymal, intrathecal or intraventricular, administration.

The iRNA can be delivered in a manner to target a particular tissue, such as the liver (*e.g.*, the hepatocytes of the liver).

Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the iRNAs featured in the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (*e.g.*, dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (*e.g.*, dimyristoylphosphatidyl glycerol DMPG) and cationic (*e.g.*, dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the invention can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs can be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-20} alkyl ester (*e.g.*, isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof). Topical formulations are described in detail in U.S. Patent No. 6,747,014, which is incorporated herein by reference.

A. iRNA Formulations Comprising Membranous Molecular Assemblies

An iRNA for use in the compositions and methods of the invention can be formulated for delivery in a membranous molecular assembly, *e.g.*, a liposome or a micelle. As used herein, the term "liposome" refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and

multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the iRNA composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the iRNA composition, although in some examples, it may. Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the iRNA are delivered into the cell where the iRNA can specifically bind to a target RNA and can mediate RNAi. In some cases the liposomes are also specifically targeted, *e.g.*, to direct the iRNA to particular cell types.

A liposome containing a RNAi agent can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The RNAi agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the RNAi agent and condense around the RNAi agent to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of RNAi agent.

If necessary a carrier compound that assists in condensation can be added during the condensation reaction, *e.g.*, by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (*e.g.*, spermine or spermidine). pH can also adjusted to favor condensation.

Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, e.g., WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al., Proc. Natl. Acad. Sci., USA* 8:7413-7417, 1987; U.S. Pat. No. 4,897,355; U.S. Pat. No. 5,171,678; Bangham, *et al. M. Mol. Biol.* 23:238, 1965; Olson, *et al. Biochim. Biophys. Acta* 557:9, 1979; Szoka, *et al. Proc. Natl. Acad. Sci.* 75: 4194, 1978; Mayhew, *et al. Biochim. Biophys. Acta* 775:169, 1984; Kim, *et al. Biochim. Biophys. Acta* 728:339, 1983; and Fukunaga, *et al. Endocrinol.* 115:757, 1984. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer, *et al. Biochim. Biophys. Acta* 858:161, 1986). Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform

aggregates are desired (Mayhew, *et al. Biochim. Biophys. Acta* 775:169, 1984). These methods are readily adapted to packaging RNAi agent preparations into liposomes.

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang *et al.*, *Biochem. Biophys. Res. Commun.*, 1987, 147, 980-985).

Liposomes which are pH-sensitive or negatively-charged, entrap nucleic acids rather than complex with it. Since both the nucleic acid and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some nucleic acid is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver nucleic acids encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou *et al.*, *Journal of Controlled Release*, 1992, 19, 269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include U.S. Pat. No. 5,283,185; U.S. Pat. No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, *J. Biol. Chem.* 269:2550, 1994; Nabel, *Proc. Natl. Acad. Sci.* 90:11307, 1993; Nabel, *Human Gene Ther.* 3:649, 1992; Gershon, *Biochem.* 32:7143, 1993; and Strauss *EMBO J.* 11:417, 1992.

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporine A into different layers of the skin (Hu *et al.* *S.T.P.Pharma. Sci.*, 1994, 4(6) 466).

Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen *et al.*, *FEBS Letters*, 1987, 223, 42; Wu *et al.*, *Cancer Research*, 1993, 53, 3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos *et al.* (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon *et al.* (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen *et al.*, disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside G_{M1} or a galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb *et al.*) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim *et al*).

In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages in vivo and can be used to deliver RNAi agents to macrophages.

Further advantages of liposomes include: liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated RNAi agents in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting

in delivery of RNAi agent (see, e.g., Felgner, P. L. et al., Proc. Natl. Acad. Sci., USA 8:7413-7417, 1987 and U.S. Pat. No. 4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoleoylamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, e.g., U.S. Pat. No. 5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., *Biochim. Biophys. Res. Commun.* 179:280, 1991). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. et al., *Biochim. Biophys. Acta* 1065:8, 1991). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells

and also to enhance the penetration of RNAi agent into dermal tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al., Journal of Drug Targeting*, 1992, vol. 2,405-410 and du Plessis *et al., Antiviral Research*, 18, 1992, 259-265; Mannino, R. J. and Fould-Fogerite, S., *Biotechniques* 6:682-690, 1988; Itani, T. *et al. Gene* 56:267-276. 1987; Nicolau, C. *et al. Meth. Enz.* 149:157-176, 1987; Straubinger, R. M. and Papahadjopoulos, D. *Meth. Enz.* 101:512-527, 1983; Wang, C. Y. and Huang, L., *Proc. Natl. Acad. Sci. USA* 84:7851-7855, 1987).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome II (glyceryl distearate/ cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver a drug into the dermis of mouse skin. Such formulations with RNAi agent are useful for treating a dermatological disorder.

Liposomes that include iRNA can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are a type of deformable liposomes. Transferosomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent to keratinocytes in the skin. In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. In addition, due to the lipid properties, these transferosomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

Other formulations amenable to the present invention are described in United States provisional application serial Nos. 61/018,616, filed January 2, 2008; 61/018,611, filed January 2, 2008; 61/039,748, filed March 26, 2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May 8, 2008. PCT application no PCT/US2007/080331, filed October 3, 2007 also describes formulations that are amenable to the present invention.

Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, *e.g.*, they are self-optimizing (adaptive to the shape of pores

in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in "Pharmaceutical Dosage Forms", Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in "Pharmaceutical Dosage Forms", Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

The iRNA for use in the methods of the invention can also be provided as micellar formulations. "Micelles" are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, an alkali metal C_8 to C_{22} alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

In one method a first micellar composition is prepared which contains the siRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the siRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

Phenol and/or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol and/or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.*, there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.*, through a

metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2 tetrafluoroethane) may be used.

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, *e.g.*, at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

B. *Lipid particles*

iRNAs, *e.g.*, dsRNAs of in the invention may be fully encapsulated in a lipid formulation, *e.g.*, a LNP, or other nucleic acid-lipid particle.

As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (*e.g.*, sites physically separated from the administration site). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present invention typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid- lipid particles of the present invention are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, *e.g.*, U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; U.S. Publication No. 2010/0324120 and PCT Publication No. WO 96/40964.

In one embodiment, the lipid to drug ratio (mass/mass ratio) (*e.g.*, lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1. Ranges intermediate to the above recited ranges are also contemplated to be part of the invention.

The cationic lipid can be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(I -(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(I -(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane

(DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (Tech G1), or a mixture thereof. The cationic lipid can comprise from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

In another embodiment, the compound 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane can be used to prepare lipid-siRNA nanoparticles. Synthesis of 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane is described in United States provisional patent application number 61/107,998 filed on October 23, 2008, which is herein incorporated by reference.

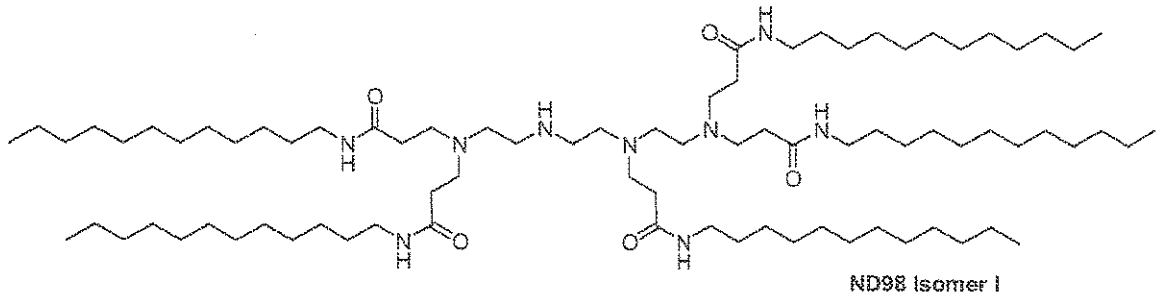
In one embodiment, the lipid-siRNA particle includes 40% 2, 2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane: 10% DSPC: 40% Cholesterol: 10% PEG-C-DOMG (mole percent) with a particle size of 63.0 ± 20 nm and a 0.027 siRNA/Lipid Ratio.

The ionizable/non-cationic lipid can be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl- phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1- carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), 16-O-monomethyl PE, 16-O-dimethyl PE, 18-1 -trans PE, 1 -stearoyl-2-oleoyl- phosphatidyethanolamine (SOPE), cholesterol, or a mixture thereof. The non-cationic lipid can be from about 5 mol % to about 90 mol %, about 10 mol %, or about 58 mol % if cholesterol is included, of the total lipid present in the particle.

The conjugated lipid that inhibits aggregation of particles can be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate can be, for example, a PEG-dilauryloxypropyl (C_{12}), a PEG-dimyristyloxypropyl (C_{14}), a PEG-dipalmityloxypropyl (C_{16}), or a PEG- distearyloxypropyl (C_{18}). The conjugated lipid that prevents aggregation of particles can be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

In some embodiments, the nucleic acid-lipid particle further includes cholesterol at, *e.g.*, about 10 mol % to about 60 mol % or about 48 mol % of the total lipid present in the particle.

In one embodiment, the lipidoid ND98·4HCl (MW 1487) (see U.S. Patent Application No. 12/056,230, filed 3/26/2008, which is incorporated herein by reference), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) can be used to prepare lipid-dsRNA nanoparticles (*i.e.*, LNP01 particles). Stock solutions of each in ethanol can be prepared as follows: ND98, 133 mg/ml; Cholesterol, 25 mg/ml, PEG-Ceramide C16, 100 mg/ml. The ND98, Cholesterol, and PEG-Ceramide C16 stock solutions can then be combined in a, *e.g.*, 42:48:10 molar ratio. The combined lipid solution can be mixed with aqueous dsRNA (*e.g.*, in sodium acetate pH 5) such that the final ethanol concentration is about 35-45% and the final sodium acetate concentration is about 100-300 mM. Lipid-dsRNA nanoparticles typically form spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture can be extruded through a polycarbonate membrane (*e.g.*, 100 nm cut-off) using, for example, a thermobarrel extruder, such as Lipex Extruder (Northern Lipids, Inc). In some cases, the extrusion step can be omitted. Ethanol removal and simultaneous buffer exchange can be accomplished by, for example, dialysis or tangential flow filtration. Buffer can be exchanged with, for example, phosphate buffered saline (PBS) at about pH 7, *e.g.*, about pH 6.9, about pH 7.0, about pH 7.1, about pH 7.2, about pH 7.3, or about pH 7.4.



Formula 1

LNP01 formulations are described, *e.g.*, in International Application Publication No. WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are described in Table 1.

Table 1

	Ionizable/Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP-1	l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
2-XTC	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA ~ 7:1
LNP05	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 6:1
LNP06	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA ~ 11:1
LNP07	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 6:1
LNP08	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA ~ 11:1
LNP09	2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10	(3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11	(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12	1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (Tech G1)	Tech G1/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13	XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1

LNP14	MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15	MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP17	MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19	MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20	MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21	C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22	XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPC: dipalmitoylphosphatidylcholine

PEG-DMG: PEG-didimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

SNALP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed April 15, 2009, which is hereby incorporated by reference.

XTC comprising formulations are described, *e.g.*, in U.S. Provisional Serial No. 61/148,366, filed January 29, 2009; U.S. Provisional Serial No. 61/156,851, filed March 2, 2009; U.S. Provisional Serial No. filed June 10, 2009; U.S. Provisional Serial No. 61/228,373, filed July 24, 2009; U.S. Provisional Serial No. 61/239,686, filed September 3, 2009, and International Application No. PCT/US2010/022614, filed January 29, 2010, which are hereby incorporated by reference.

MC3 comprising formulations are described, *e.g.*, in U.S. Publication No. 2010/0324120, filed June 10, 2010, the entire contents of which are hereby incorporated by reference.

ALNY-100 comprising formulations are described, *e.g.*, International patent application number PCT/US09/63933, filed on November 10, 2009, which is hereby incorporated by reference.

C12-200 comprising formulations are described in U.S. Provisional Serial No. 61/175,770, filed May 5, 2009 and International Application No. PCT/US10/33777, filed May 5, 2010, which are hereby incorporated by reference.

Synthesis of ionizable/cationic lipids

Any of the compounds, *e.g.*, cationic lipids and the like, used in the nucleic acid-lipid particles of the invention can be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. All substituents are as defined below unless indicated otherwise.

"Alkyl" means a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like.

"Alkenyl" means an alkyl, as defined above, containing at least one double bond between adjacent carbon atoms. Alkenyls include both cis and trans isomers. Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like.

"Alkynyl" means any alkyl or alkenyl, as defined above, which additionally contains at least one triple bond between adjacent carbons. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Acyl" means any alkyl, alkenyl, or alkynyl wherein the carbon at the point of attachment is substituted with an oxo group, as defined below. For example, -C(=O)alkyl, -C(=O)alkenyl, and -C(=O)alkynyl are acyl groups.

"Heterocycle" means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be

optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle can be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined below. Heterocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizynyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

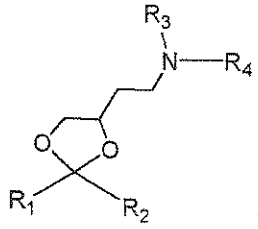
The terms "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted acyl", and "optionally substituted heterocycle" means that, when substituted, at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent (=O) two hydrogen atoms are replaced. In this regard, substituents include oxo, halogen, heterocycle, -CN, -ORx, -NRxRy, -NRxC(=O)Ry, -NRxSO2Ry, -C(=O)Rx, -C(=O)ORx, -C(=O)NRxRy, –SOnRx and -SOnNRxRy, wherein n is 0, 1 or 2, Rx and Ry are the same or different and independently hydrogen, alkyl or heterocycle, and each of said alkyl and heterocycle substituents can be further substituted with one or more of oxo, halogen, -OH, -CN, alkyl, -ORx, heterocycle, -NRxRy, -NRxC(=O)Ry, -NRxSO2Ry, -C(=O)Rx, -C(=O)ORx, -C(=O)NRxRy, -SOnRx and -SOnNRxRy.

"Halogen" means fluoro, chloro, bromo and iodo.

In some embodiments, the methods of the invention can require the use of protecting groups. Protecting group methodology is well known to those skilled in the art (see, for example, Protective Groups in Organic Synthesis, Green, T.W. *et al.*, Wiley-Interscience, New York City, 1999). Briefly, protecting groups within the context of this invention are any group that reduces or eliminates unwanted reactivity of a functional group. A protecting group can be added to a functional group to mask its reactivity during certain reactions and then removed to reveal the original functional group. In some embodiments an "alcohol protecting group" is used. An "alcohol protecting group" is any group which decreases or eliminates unwanted reactivity of an alcohol functional group. Protecting groups can be added and removed using techniques well known in the art.

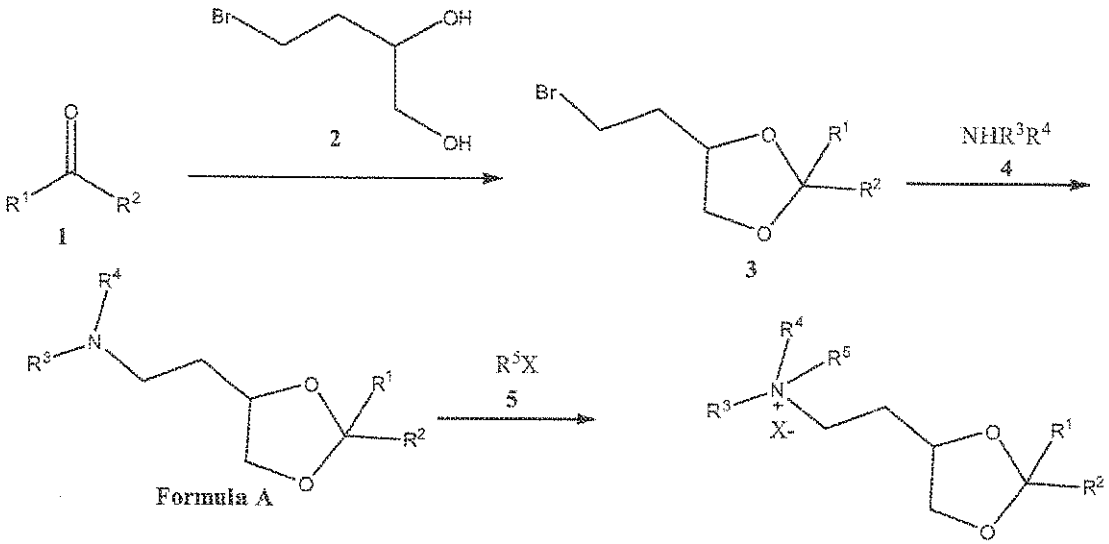
Synthesis of Formula A

In some embodiments, nucleic acid-lipid particles of the invention are formulated using a cationic lipid of formula A:



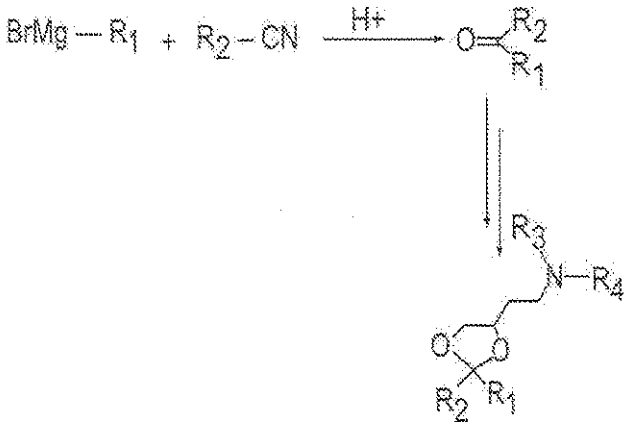
where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring. In some embodiments, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane). In general, the lipid of formula A above can be made by the following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

Scheme 1



Lipid A, where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring, can be prepared according to Scheme 1. Ketone 1 and bromide 2 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 1 and 2 yields ketal 3. Treatment of ketal 3 with amine 4 yields lipids of formula A. The lipids of formula A can be converted to the corresponding ammonium salt with an organic salt of formula 5, where X is anion counter ion selected from halogen, hydroxide, phosphate, sulfate, or the like.

Scheme 2

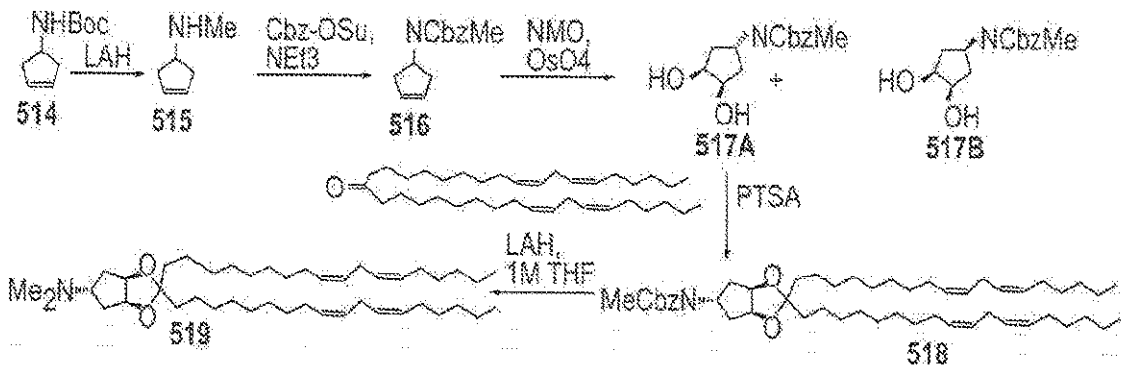


Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids of formula A is as described in Scheme 1.

Synthesis of MC3

Preparation of DLin-M-C3-DMA (*i.e.*, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate) was as follows. A solution of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (0.53 g), 4-N,N-dimethylaminobutyric acid hydrochloride (0.51 g), 4-N,N-dimethylaminopyridine (0.61g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) in dichloromethane (5 mL) was stirred at room temperature overnight. The solution was washed with dilute hydrochloric acid followed by dilute aqueous sodium bicarbonate. The organic fractions were dried over anhydrous magnesium sulphate, filtered and the solvent removed on a rotovap. The residue was passed down a silica gel column (20 g) using a 1-5% methanol/dichloromethane elution gradient. Fractions containing the purified product were combined and the solvent removed, yielding a colorless oil (0.54 g). *Synthesis of ALNY-100*

Synthesis of ketal 519 [ALNY-100] was performed using the following scheme 3:



Synthesis of 515

To a stirred suspension of LiAlH4 (3.74 g, 0.09852 mol) in 200 ml anhydrous THF in a two neck RBF (1L), was added a solution of 514 (10g, 0.04926mol) in 70 mL of THF slowly at 0 0C under nitrogen atmosphere. After complete addition, reaction mixture was warmed to room temperature and then heated to reflux for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction (by TLC) the mixture was cooled to 0 0C and quenched with careful addition of saturated Na2SO4 solution. Reaction mixture was stirred for 4 h at room temperature and filtered off. Residue was washed well with THF. The filtrate and washings were mixed and diluted with 400 mL dioxane and 26 mL conc. HCl and stirred for 20 minutes at room temperature. The volatilities were stripped off under vacuum to furnish the hydrochloride salt of 515 as a white solid. Yield: 7.12 g 1H-NMR (DMSO, 400MHz): δ= 9.34 (broad, 2H), 5.68 (s, 2H), 3.74 (m, 1H), 2.66-2.60 (m, 2H), 2.50-2.45 (m, 5H).

Synthesis of 516

To a stirred solution of compound 515 in 100 mL dry DCM in a 250 mL two neck RBF, was added NEt3 (37.2 mL, 0.2669 mol) and cooled to 0 0C under nitrogen atmosphere. After a slow addition of N-(benzyloxy-carbonyloxy)-succinimide (20 g, 0.08007 mol) in 50 mL dry DCM, reaction mixture was allowed to warm to room temperature. After completion of the reaction (2-3 h by TLC) mixture was washed successively with 1N HCl solution (1 x 100 mL) and saturated NaHCO3 solution (1 x 50 mL). The organic layer was then dried over anhyd. Na2SO4 and the solvent was evaporated to give crude material which was purified by silica gel column chromatography to get 516 as sticky mass. Yield: 11g (89%). 1H-NMR (CDCl3, 400MHz): δ = 7.36-7.27(m, 5H), 5.69 (s, 2H), 5.12 (s, 2H), 4.96 (br., 1H) 2.74 (s, 3H), 2.60(m, 2H), 2.30-2.25(m, 2H). LC-MS [M+H] -232.3 (96.94%).

Synthesis of 517A and 517B

The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of OsO4 (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~ 3 h), the mixture was quenched with addition of solid Na2SO3 and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2 x 100 mL) followed by saturated NaHCO3 (1 x 50 mL) solution, water (1 x 30 mL) and finally with brine (1x 50 mL). Organic phase was dried over an.Na2SO4 and solvent was removed in vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC. Yield: - 6 g crude

517A - Peak-1 (white solid), 5.13 g (96%). 1H-NMR (DMSO, 400MHz): δ= 7.39-7.31(m, 5H), 5.04(s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47(d, 2H), 3.94-3.93(m, 2H), 2.71(s, 3H), 1.72- 1.67(m, 4H). LC-MS - [M+H]-266.3, [M+NH4 +]-283.5 present, HPLC-97.86%. Stereochemistry confirmed by X-ray.

Synthesis of 518

Using a procedure analogous to that described for the synthesis of compound 505, compound 518 (1.2 g, 41%) was obtained as a colorless oil. 1H-NMR (CDCl3, 400MHz): δ= 7.35-7.33(m, 4H), 7.30-7.27(m, 1H), 5.37-5.27(m, 8H), 5.12(s, 2H), 4.75(m,1H), 4.58-4.57(m,2H), 2.78-2.74(m,7H), 2.06-2.00(m,8H), 1.96-1.91(m, 2H), 1.62(m, 4H), 1.48(m, 2H), 1.37-1.25(br m, 36H), 0.87(m, 6H). HPLC-98.65%.

General Procedure for the Synthesis of Compound 519

A solution of compound 518 (1 eq) in hexane (15 mL) was added in a drop-wise fashion to an ice-cold solution of LAH in THF (1 M, 2 eq). After complete addition, the mixture was heated at 40oC over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous Na2SO4 then filtered through celite and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil. 13C NMR δ = 130.2, 130.1 (x2), 127.9 (x3), 112.3, 79.3, 64.4, 44.7, 38.3, 35.4, 31.5, 29.9 (x2), 29.7, 29.6 (x2), 29.5 (x3), 29.3 (x2), 27.2 (x3), 25.6, 24.5, 23.3, 226, 14.1; Electrospray MS (+ve): Molecular weight for C44H80NO2 (M + H)+ Calc. 654.6, Found 654.6.

Formulations prepared by either the standard or extrusion-free method can be characterized in similar manners. For example, formulations are typically characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles can be measured by light scattering using, for example, a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be about 20-300 nm, such as 40-100 nm in size. The particle size distribution should be unimodal. The total dsRNA concentration in the formulation, as well as the entrapped fraction,

is estimated using a dye exclusion assay. A sample of the formulated dsRNA can be incubated with an RNA-binding dye, such as Ribogreen (Molecular Probes) in the presence or absence of a formulation disrupting surfactant, *e.g.*, 0.5% Triton-X100. The total dsRNA in the formulation can be determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the "free" dsRNA content (as measured by the signal in the absence of surfactant) from the total dsRNA content. Percent entrapped dsRNA is typically >85%. For SNALP formulation, the particle size is at least 30 nm, at least 40 nm, at least 50 nm, at least 60 nm, at least 70 nm, at least 80 nm, at least 90 nm, at least 100 nm, at least 110 nm, and at least 120 nm. The suitable range is typically about at least 50 nm to about at least 110 nm, about at least 60 nm to about at least 100 nm, or about at least 80 nm to about at least 90 nm.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders can be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the invention are administered in conjunction with one or more penetration enhancer surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (*e.g.*, sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the invention can be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines,

protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (*e.g.*, p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Patent 6,887,906, US Publn. No. 20030027780, and U.S. Patent No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration can include sterile aqueous solutions which can also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the liver when treating hepatic disorders such as hepatic carcinoma.

The pharmaceutical formulations of the present invention, which can conveniently be presented in unit dosage form, can be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions of the present invention can be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

C. Additional Formulations

i. Emulsions

The compositions of the present invention can be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1μm in diameter (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott

Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi *et al.*, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions can be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions can contain additional components in addition to the dispersed phases, and the active drug which can be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion can be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that can be incorporated into either phase of the emulsion. Emulsifiers can broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and

Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199).

Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants can be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic and amphoteric (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that can readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used can be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

ii. Microemulsions

In one embodiment of the present invention, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion can be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial

films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (see *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, LV., Popovich NG., and Ansel HC., 2004, Lippincott Williams & Wilkins (8th ed.), New York, NY; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase can include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been

proposed to enhance the oral bioavailability of drugs, including peptides (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, *Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see *e.g.*, U.S. Patent Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides *et al.*, *Pharmaceutical Research*, 1994, 11, 1385; Ho *et al.*, *J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or iRNAs. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of iRNAs and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of iRNAs and nucleic acids.

Microemulsions of the present invention can also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the iRNAs and nucleic acids of the present invention. Penetration enhancers used in the microemulsions of the present invention can be classified as belonging to one of five broad categories--surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

iii. Microparticles

an RNAi agent of the invention may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. Penetration Enhancers

In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs can cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers can be classified as belonging to one of five broad categories, *i.e.*, surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

Surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of iRNAs through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi *et al.*, *J. Pharm. Pharmacol.*, 1988, 40, 252).

Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-20} alkyl esters thereof (*e.g.*, methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (*i.e.*, oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, *etc.*) (see *e.g.*, Touitou, E., *et al.* Enhancement in Drug Delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, p.92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; El Hariri *et al.*, *J. Pharm. Pharmacol.*, 1992, 44, 651-654).

The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Brunton, Chapter 38 in: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman *et al.* Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid

(UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see *e.g.*, Malmsten, M. Surfactants and polymers in drug delivery, Informa Health Care, New York, NY, 2002; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Swinyard, Chapter 39 In: Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Yamamoto *et al.*, *J. Pharm. Exp. Ther.*, 1992, 263, 25; Yamashita *et al.*, *J. Pharm. Sci.*, 1990, 79, 579-583).

Chelating agents, as used in connection with the present invention, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of iRNAs through the mucosa is enhanced. With regards to their use as penetration enhancers in the present invention, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (*e.g.*, sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9 and N-amino acyl derivatives of beta-diketones (enamines)(see *e.g.*, Katdare, A. *et al.*, Excipient development for pharmaceutical, biotechnology, and drug delivery, CRC Press, Danvers, MA, 2006; Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33; Buur *et al.*, *J. Control Rel.*, 1990, 14, 43-51).

As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of iRNAs through the alimentary mucosa (see *e.g.*, Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee *et al.*, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita *et al.*, *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of iRNAs at the cellular level can also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi *et al*, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo *et al.*, PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, CA), Lipofectamine 2000™ (Invitrogen; Carlsbad, CA), 293fectin™ (Invitrogen; Carlsbad, CA),

Cellfectin™ (Invitrogen; Carlsbad, CA), DMRIE-C™ (Invitrogen; Carlsbad, CA), FreeStyle™ MAX (Invitrogen; Carlsbad, CA), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, CA), Lipofectamine™ (Invitrogen; Carlsbad, CA), RNAiMAX (Invitrogen; Carlsbad, CA), Oligofectamine™ (Invitrogen; Carlsbad, CA), Optifect™ (Invitrogen; Carlsbad, CA), X-tremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Fugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, WI), TransFast™ Transfection Reagent (Promega; Madison, WI), Tfx™-20 Reagent (Promega; Madison, WI), Tfx™-50 Reagent (Promega; Madison, WI), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass[a] D1 Transfection Reagent (New England Biolabs; Ipswich, MA, USA), LyoVec™/LipoGen™ (Invitrogen; San Diego, CA, USA), PerFectin Transfection Reagent (Genlantis; San Diego, CA, USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), GenePORTER Transfection reagent (Genlantis; San Diego, CA, USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego, CA, USA), Cytofectin Transfection Reagent (Genlantis; San Diego, CA, USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, CA, USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, CA, USA), RiboFect (Bioline; Taunton, MA, USA), PlasFect (Bioline; Taunton, MA, USA), UniFECTOR (B-Bridge International; Mountain View, CA, USA), SureFECTOR (B-Bridge International; Mountain View, CA, USA), or HiFect™ (B-Bridge International, Mountain View, CA, USA), among others.

Other agents can be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

v. Carriers

Certain compositions of the present invention also incorporate carrier compounds in the formulation. As used herein, "carrier compound" or "carrier" can refer to a nucleic acid, or analog thereof, which is inert (*i.e.*, does not possess biological activity *per se*) but is recognized as a nucleic acid by *in vivo* processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate dsRNA in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or

4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid (Miyao *et al.*, DsRNA Res. Dev., 1995, 5, 115-121; Takakura *et al.*, DsRNA & Nucl. Acid Drug Dev., 1996, 6, 177-183.

vi. Excipients

In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, *etc.*, when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, *etc.*); fillers (*e.g.*, lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, *etc.*); lubricants (*e.g.*, magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, *etc.*); disintegrants (*e.g.*, starch, sodium starch glycolate, *etc.*); and wetting agents (*e.g.*, sodium lauryl sulphate, *etc*).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids can include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions can also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

vii. Other Components

The compositions of the present invention can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local

anesthetics or anti-inflammatory agents, or can contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA compounds and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating a hemolytic disorder. Examples of such agents include, but are not limited to an anti-inflammatory agent, anti-steatosis agent, anti-viral, and/or anti-fibrosis agent. In addition, other substances commonly used to protect the liver, such as silymarin, can also be used in conjunction with the *iRNAs described herein*. Other agents useful for treating liver diseases include telbivudine, entecavir, and protease inhibitors such as telaprevir and other disclosed, for example, in Tung *et al.*, U.S. Application Publication Nos. 2005/0148548, 2004/0167116, and 2003/0144217; and in Hale *et al.*, U.S. Application Publication No. 2004/0127488.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured herein in the invention lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods featured in the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target

sequence (*e.g.*, achieving a decreased concentration of the polypeptide) that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the invention can be administered in combination with other known agents effective in treatment of pathological processes mediated by C5 expression. In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VI. Methods For Inhibiting C5 Expression

The present invention provides methods of inhibiting expression of C5 in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, in an amount effective to inhibit expression of the C5 in the cell, thereby inhibiting expression of the C5 in the cell.

Contacting of a cell with a double stranded RNAi agent may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. Contacting may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished via a targeting ligand, including any ligand described herein or known in the art. In preferred embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a $GalNAc_3$ ligand, or any other ligand that directs the RNAi agent to a site of interest, *e.g.*, the liver of a subject.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating" and other similar terms, and includes any level of inhibition.

The phrase "inhibiting expression of a C5" is intended to refer to inhibition of expression of any C5 gene (such as, *e.g.*, a mouse C5 gene, a rat C5 gene, a monkey C5 gene, or a human C5 gene) as well as variants or mutants of a C5 gene. Thus, the C5 gene may be a wild-type C5 gene, a mutant C5 gene, or a transgenic C5 gene in the context of a genetically manipulated cell, group of cells, or organism.

"Inhibiting expression of a C5 gene" includes any level of inhibition of a C5 gene, *e.g.*, at least partial suppression of the expression of a C5 gene. The expression of the C5 gene may be assessed based on the level, or the change in the level, of any variable associated with C5 gene expression, *e.g.*, C5 mRNA level, C5 protein level, or for example, CH_{50} activity as a measure of total hemolytic complement, AH_{50} to measure the hemolytic activity of the alternate pathway of

complement, and/or lactate dehydrogenase (LDH) levels as a measure of intravascular hemolysis, and/or hemoglobin levels. Levels of C5a, C5b, and soluble C5b-9 complex may also be measured to assess C5 expression. This level may be assessed in an individual cell or in a group of cells, including, for example, a sample derived from a subject.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more variables that are associated with C5 expression compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

In some embodiments of the methods of the invention, expression of a C5 gene is inhibited by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99%.

Inhibition of the expression of a C5 gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a C5 gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the invention, or by administering an RNAi agent of the invention to a subject in which the cells are or were present) such that the expression of a C5 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s)). In preferred embodiments, the inhibition is assessed by expressing the level of mRNA in treated cells as a percentage of the level of mRNA in control cells, using the following formula:

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} * 100\%$$

Alternatively, inhibition of the expression of a C5 gene may be assessed in terms of a reduction of a parameter that is functionally linked to C5 gene expression, *e.g.*, C5 protein expression, hepcidin gene or protein expression, or iron levels in tissues or serum. C5 gene silencing may be determined in any cell expressing C5, either constitutively or by genomic engineering, and by any assay known in the art. The liver is the major site of C5 expression. Other significant sites of expression include the kidneys and the uterus.

Inhibition of the expression of a C5 protein may be manifested by a reduction in the level of the C5 protein that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed

in a sample derived from a subject). As explained above for the assessment of mRNA suppression, the inhibiton of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells.

A control cell or group of cells that may be used to assess the inhibition of the expression of a C5 gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the invention. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

The level of C5 mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of C5 in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the C5 gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy RNA preparation kits (Qiagen) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays (Melton *et al.*, *Nuc. Acids Res.* 12:7035), Northern blotting, *in situ* hybridization, and microarray analysis.

In one embodiment, the level of expression of C5 is determined using a nucleic acid probe. The term "probe", as used herein, refers to any molecule that is capable of selectively binding to a specific C5. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to C5 mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of C5 mRNA.

An alternative method for determining the level of expression of C5 in a sample involves the process of nucleic acid amplification and/or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in

Mullis, 1987, U.S. Pat. No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi et al., U.S. Pat. No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, the level of expression of C5 is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System).

The expression levels of C5 mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as Northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Pat. Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of C5 expression level may also comprise using nucleic acid probes in solution.

In preferred embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of these methods is described and exemplified in the Examples presented herein.

The level of C5 protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, Western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like.

The term "sample" as used herein refers to a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, lymph, urine, cerebrospinal fluid, saliva, ocular fluids, and the like. Tissue samples may include samples from tissues, organs or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the liver (*e.g.*, whole liver or certain segments of liver or certain types of cells in the liver, such as, *e.g.*, hepatocytes). In preferred embodiments, a "sample derived from a

subject" refers to blood or plasma drawn from the subject. In further embodiments, a "sample derived from a subject" refers to liver tissue derived from the subject.

In some embodiments of the methods of the invention, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of C5 may be assessed using measurements of the level or change in the level of C5 mRNA or C5 protein in a sample derived from fluid or tissue from the specific site within the subject. In preferred embodiments, the site is sthe liver. The site may also be a subsection or subgroup of cells from any one of the aforementioned sites. The site may also include cells that express a particular type of receptor.

The phrase "contacting a cell with an RNAi agent," such as a dsRNA, as used herein, includes contacting a cell by any possible means. Contacting a cell with an RNAi agent includes contacting a cell *in vitro* with the iRNA or contacting a cell *in vivo* with the iRNA. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that will permit or cause it to subsequently come into contact with the cell.

Contacting a cell *in vitro* may be done, for example, by incubating the cell with the RNAi agent. Contacting a cell *in vivo* may be done, for example, by injecting the RNAi agent into or near the tissue where the cell is located, or by injecting the RNAi agent into another area, *e.g.*, the bloodstream or the subcutaneous space, such that the agent will subsequently reach the tissue where the cell to be contacted is located. For example, the RNAi agent may contain and/or be coupled to a ligand, *e.g.*, GalNAc3, that directs the RNAi agent to a site of interest, *e.g.*, the liver. Combinations of *in vitro* and *in vivo* methods of contacting are also possible. For example, a cell may also be contacted *in vitro* with an RNAi agent and subsequently transplanted into a subject.

In one embodiment, contacting a cell with an iRNA includes "introducing" or "delivering the iRNA into the cell" by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an iRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an iRNA into a cell may be *in vitro* and/or *in vivo*. For example, for *in vivo* introduction, iRNA can be injected into a tissue site or administered systemically. *In vivo* delivery can also be done by a beta-glucan delivery system, such as those described in U.S. Patent Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, the entire contents of which are hereby incorporated herein by reference. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below and/or are known in the art.

VII. Methods for Treating or Preventing a Complement Component C5-Associated Disorder

The present invention also provides therapeutic and prophylactic methods which include administering to a subject having a complement component C5-associated disease, *e.g.*, PNH or aHUS, an iRNA agent, pharmaceutical compositions comprising an iRNA agent, or vector comprising an iRNA of the invention. In some aspects of the invention, the methods further include administering to the subject an additional therapeutic agent, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab).

In one aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS. The treatment methods (and uses) of the invention include administering to the subject, *e.g.*, a human, a therapeutically effective amount of an iRNA agent targeting a C5 gene or a pharmaceutical composition comprising an iRNA agent targeting a C5 gene, thereby treating the subject having a disorder that would benefit from reduction in C5 expression.

In another aspect, the present invention provides methods of treating a subject having a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS, which include administering to the subject, *e.g.*, a human, a therapeutically effective amount of an iRNA agent targeting a C5 gene or a pharmaceutical composition comprising an iRNA agent targeting a C5 gene, and an additional therapeutic agent, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), thereby treating the subject having a disorder that would benefit from reduction in C5 expression.

In one aspect, the invention provides methods of preventing at least one symptom in a subject having a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS. The methods include administering to the subject a prohpylactically effective amount of the iRNA agent, *e.g.*, dsRNA, or vector of the invention, thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression. For example, the invention provides methods for preventing hemolysis in a subject suffering from a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In another aspect, the invention provides methods of preventing at least one symptom in a subject having a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS. The methods include administering to the subject a prohpylactically effective amount of the iRNA agent, *e.g.*, dsRNA, or vector of the invention, and an additional therapeutic agent, such as an anti-complement component C5

antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), thereby preventing at least one symptom in the subject having a disorder that would benefit from reduction in C5 expression.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent or anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), that, when administered to a subject having a complement component C5-associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the RNAi agent or antibody, or antigen-binding fragment thereof, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

"Prophylactically effective amount," as used herein, is intended to include the amount of an iRNA agent or anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), that, when administered to a subject having a complement component C5-associate disease but not yet (or currently) experiencing or displaying symptoms of the disease, and/or a subject at risk of developing a complement component C5-associated disease, *e.g.*, a subject having a graft and/or transplant, *e.g.*, a sensitized or allogenic recipient, a subject having sepsis, and/or a subject having a myocardial infarction, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the iRNA agent or anti-complement component C5 antibody, or antigen-binding fragment thereof, how the agent or anti-complement component C5 antibody, or antigen-binding fragment thereof, is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A "therapeutically effective amount" or "prophylactically effective amount" also includes an amount of an RNAi agent or anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. iRNA agents employed in the methods of the present invention may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

In another aspect, the present invention provides uses of a therapeutically effective amount of an iRNA agent of the invention for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of C5 expression.

In another aspect, the present invention provides uses of a therapeutically effective amount of an iRNA agent of the invention and an additional therapeutic agent, such as an anti-

complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of C5 expression.

In yet another aspect, the present invention provides use of an iRNA agent, *e.g.*, a dsRNA, of the invention targeting a C5 gene or a pharmaceutical composition comprising an iRNA agent targeting a C5 gene in the manufacture of a medicament for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of C5 expression, such as a subject having a disorder that would benefit from reduction in C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In another aspect, the present invention provides uses of an iRNA agent, *e.g.*, a dsRNA, of the invention targeting a C5 gene or a pharmaceutical composition comprising an iRNA agent targeting a C5 gene in the manufacture of a medicament for use in combination with an additional therapeutic agent, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), for treating a subject, *e.g.*, a subject that would benefit from a reduction and/or inhibition of C5 expression, *e.g.*, a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In another aspect, the invention provides uses of an iRNA, *e.g.*, a dsRNA, of the invention for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of C5 expression, such as a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In yet another aspect, the invention provides uses of an iRNA agent, *e.g.*, a dsRNA, of the invention, and an additional therapeutic agent, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of C5 expression, such as a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In a further aspect, the present invention provides uses of an iRNA agent of the invention in the manufacture of a medicament for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of C5 expression, such as a a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In a further aspect, the present invention provides uses of an iRNA agent of the invention in the manufacture of a medicament for use in combination with an additional therapeutic agent, such as an anti-complement component C5 antibody, or antigen-binding fragment thereof (*e.g.*, eculizumab), for preventing at least one symptom in a subject suffering from a disorder that would benefit from a reduction and/or inhibition of C5 expression, such as a a complement component C5-associated disease, *e.g.*, PNH or aHUS.

In one embodiment, an iRNA agent targeting C5 is administered to a subject having a complement component C5-associated disease such that C5 levels, *e.g.*, in a cell, tissue, blood, urine or other tissue or fluid of the subject are reduced by at least about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 62%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% or more and, subsequently, an additional therapeutic (as described below) is administered to the subject.

The additional therapeutic may be an anti-complement component C5 antibody, or antigen-binding fragment or derivative thereof. In one embodiment, the anti-complement component C5 antibody is eculizumab (SOLIRIS®), or antigen-binding fragment or derivative thereof. Eculizumab is a humanized monoclonal IgG2/4, kappa light chain antibody that specifically binds complement component C5 with high affinity and inhibits cleavage of C5 to C5a and C5b, thereby inhibiting the generation of the terminal complement complex C5b-9. Eculizumab is described in U.S. Patent No. 6,355,245, the entire contents of which are incorporated herein by reference.

The methods of the invention comprising administration of an iRNA agent of the invention and eculizumab to a subject may further comprise administration of a meningococcal vaccine to the subject.

The additional therapeutic, *e.g.*, eculizumab and/or a meningococcal vaccine, may be administered to the subject at the same time as the iRNA agent targeting C5 or at a different time.

Moreover, the additional therapeutic, *e.g.*, eculizumab, may be administered to the subject in the same formulation as the iRNA agent targeting C5 or in a different formulation as the iRNA agent targeting C5.

Eculizumab dosage regimens are described in, for example, the product insert for eculizumab (SOLIRIS®) and in U.S. Patent Application No. 2012/0225056, the entire contents of each of which are incorporated herein by reference. In exemplary methods of the invention for treating a complement component C5-associated disease, *e.g.*, PNH or aHUS, an iRNA agent targeting C5 is administered (*e.g.*, subcutaneously) to the subject first, such that the C5 levels in the subject are reduced (*e.g.*, by at least about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 62%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%,

76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% or more) and subsequently eculizumab is administered at doses lower than the ones described in the product insert for SOLIRIS®. For example, eculizumab may be adminsitered to the subject weekly at a dose less than about 600 mg for 4 weeks followed by a fifth dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter. Eculizumab may also be administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter. If the subject is less than 18 years of age, eculizumab may be administered to the subject weekly at a dose less than about 900 mg for 4 weeks followed by a fifth dose at about one week later of less than about 1200 mg, followed by a dose less than about 1200 mg about every two weeks thereafter; or if the subject is less than 18 years of age, eculizumab may be administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 900 mg, followed by a dose less than about 900 mg about every two weeks thereafter; or if the subject is less than 18 years of age, eculizumab may be administered to the subject weekly at a dose less than about 600 mg for 2 weeks followed by a third dose at about one week later of less than about 600 mg, followed by a dose less than about 600 mg about every two weeks thereafter; or if the subject is less than 18 years of age, eculizumab may be administered to the subject weekly at a dose less than about 600 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter; or if the subject is less than 18 years of age, eculizumab may be administered to the subject weekly at a dose less than about 300 mg for 1 week followed by a second dose at about one week later of less than about 300 mg, followed by a dose less than about 300 mg about every two weeks thereafter. If the subject is receiving plamapheresis or plasma exchange, eculizumab may be administered to the subject at a dose less than about 300 mg (*e.g.*, if the most recent does of eculizumab was about 300 mg) or less than about 600 mg (*e.g.*, if the most recent does of eculizumab was about 600 mg or more). If the subject is receiving plasma infusion, eculizumab may be administered to the subject at a dose less than about 300 mg (*e.g.*, if the most recent does of eculizumab was about 300 mg or more). The lower doses of eculizumab allow for either subcutaneous or intravenous administration of eculizumab.

In the combination therapies of the present invention comprising eculizumab, eculizumab may be adminisitered to the subject, *e.g.*, subcutaneously, at a dose of about 0.01 mg/kg to about 10 mg/kg, or about 5 mg/kg to about 10 mg/kg, or about 0.5 mg/kg to about 15 mg/kg. For example, eculizumab may be administered to the subject, *e.g.*, subcutaneously, at a dose of 0.5

mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, 5 mg/kg, 5.5 mg/kg, 6 mg/kg, 6.5 mg/kg, 7 mg/kg, 7.5 mg/kg, 8 mg/kg, 8.5 mg/kg, 9 mg/kg, 9.5 mg/kg, 10 mg/kg, 10.5 mg/kg, 11 mg/kg, 11.5 mg/kg, 12 mg/kg, 12.5 mg/kg, 13 mg/kg, 13.5 mg/kg, 14 mg/kg, 14.5 mg/kg, or15 mg/kg.

The methods and uses of the invention include administering a composition described herein such that expression of the target C5 gene is decreased, such as for about 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 18, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, or about 80 hours. In one embodiment, expression of the target C5 gene is decreased for an extended duration, *e.g.*, at least about two, three, four, five, six, seven days or more, *e.g.*, about one week, two weeks, three weeks, or about four weeks or longer.

Administration of the dsRNA according to the methods and uses of the invention may result in a reduction of the severity, signs, symptoms, and/or markers of such diseases or disorders in a patient with a complement component C5-associated disease. By "reduction" in this context is meant a statistically significant decrease in such level. The reduction can be, for example, at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or about 100%.

Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of a hemolytic disorder may be assessed, for example, by periodic monitoring of LDH and CH_{50} levels. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an iRNA targeting C5 or pharmaceutical composition thereof, "effective against" a complement component C5-associated disease indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating a complement component C5-associated disease and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop

symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given iRNA drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

Alternatively, the efficacy can be measured by a reduction in the severity of disease as determined by one skilled in the art of diagnosis based on a clinically accepted disease severity grading scale, as but one example the Rheumatoid Arthritis Severity Scale (RASS). Any positive change resulting in *e.g.*, lessening of severity of disease measured using the appropriate scale, represents adequate treatment using an iRNA or iRNA formulation as described herein.

Subjects can be administered a therapeutic amount of iRNA, such as about 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.35 mg/kg, 0.4 mg/kg, 0.45 mg/kg, 0.5 mg/kg, 0.55 mg/kg, 0.6 mg/kg, 0.65 mg/kg, 0.7 mg/kg, 0.75 mg/kg, 0.8 mg/kg, 0.85 mg/kg, 0.9 mg/kg, 0.95 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1mg/kg, 2.2mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg dsRNA, 2.6 mg/kg dsRNA, 2.7 mg/kg dsRNA, 2.8 mg/kg dsRNA, 2.9 mg/kg dsRNA, 3.0 mg/kg dsRNA, 3.1 mg/kg dsRNA, 3.2 mg/kg dsRNA, 3.3 mg/kg dsRNA, 3.4 mg/kg dsRNA, 3.5 mg/kg dsRNA, 3.6 mg/kg dsRNA, 3.7 mg/kg dsRNA, 3.8 mg/kg dsRNA, 3.9 mg/kg dsRNA, 4.0 mg/kg dsRNA, 4.1 mg/kg dsRNA, 4.2 mg/kg dsRNA, 4.3 mg/kg dsRNA, 4.4 mg/kg dsRNA, 4.5 mg/kg dsRNA, 4.6 mg/kg dsRNA, 4.7 mg/kg dsRNA, 4.8 mg/kg dsRNA, 4.9 mg/kg dsRNA, 5.0 mg/kg dsRNA, 5.1 mg/kg dsRNA, 5.2 mg/kg dsRNA, 5.3 mg/kg dsRNA, 5.4 mg/kg dsRNA, 5.5 mg/kg dsRNA, 5.6 mg/kg dsRNA, 5.7 mg/kg dsRNA, 5.8 mg/kg dsRNA, 5.9 mg/kg dsRNA, 6.0 mg/kg dsRNA, 6.1 mg/kg dsRNA, 6.2 mg/kg dsRNA, 6.3 mg/kg dsRNA, 6.4 mg/kg dsRNA, 6.5 mg/kg dsRNA, 6.6 mg/kg dsRNA, 6.7 mg/kg dsRNA, 6.8 mg/kg dsRNA, 6.9 mg/kg dsRNA, 7.0 mg/kg dsRNA, 7.1 mg/kg dsRNA, 7.2 mg/kg dsRNA, 7.3 mg/kg dsRNA, 7.4 mg/kg dsRNA, 7.5 mg/kg dsRNA, 7.6 mg/kg dsRNA, 7.7 mg/kg dsRNA, 7.8 mg/kg dsRNA, 7.9 mg/kg dsRNA, 8.0 mg/kg dsRNA, 8.1 mg/kg dsRNA, 8.2 mg/kg dsRNA, 8.3 mg/kg dsRNA, 8.4 mg/kg dsRNA, 8.5 mg/kg dsRNA, 8.6 mg/kg dsRNA, 8.7 mg/kg dsRNA, 8.8 mg/kg dsRNA, 8.9 mg/kg dsRNA, 9.0 mg/kg dsRNA, 9.1 mg/kg dsRNA, 9.2 mg/kg dsRNA, 9.3 mg/kg dsRNA, 9.4 mg/kg dsRNA, 9.5 mg/kg dsRNA, 9.6 mg/kg dsRNA, 9.7 mg/kg dsRNA, 9.8 mg/kg dsRNA, 9.9 mg/kg dsRNA, 9.0 mg/kg dsRNA, 10 mg/kg dsRNA, 15 mg/kg dsRNA, 20 mg/kg dsRNA, 25 mg/kg dsRNA, 30 mg/kg dsRNA, 35 mg/kg dsRNA, 40 mg/kg dsRNA, 45 mg/kg dsRNA, or about 50 mg/kg dsRNA. Values and ranges intermediate to the recited values are also intended to be part of this invention.

In certain embodiments, for example, when a composition of the invention comprises a dsRNA as described herein and a lipid, subjects can be administered a therapeutic amount of iRNA, such as about 0.01 mg/kg to about 5 mg/kg, about 0.01 mg/kg to about 10 mg/kg, about 0.05 mg/kg to about 5 mg/kg, about 0.05 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.2 mg/kg to about 5 mg/kg, about 0.2 mg/kg to about 10 mg/kg, about 0.3 mg/kg to about 5 mg/kg, about 0.3 mg/kg to about 10 mg/kg, about 0.4 mg/kg to about 5 mg/kg, about 0.4 mg/kg to about 10 mg/kg, about 0.5 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 10 mg/kg, about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 10 mg/kg, about 1.5 mg/kg to about 5 mg/kg, about 1.5 mg/kg to about 10 mg/kg, about 2 mg/kg to about about 2.5 mg/kg, about 2 mg/kg to about 10 mg/kg, about 3 mg/kg to about 5 mg/kg, about 3 mg/kg to about 10 mg/kg, about 3.5 mg/kg to about 5 mg/kg, about 4 mg/kg to about 5 mg/kg, about 4.5 mg/kg to about 5 mg/kg, about 4 mg/kg to about 10 mg/kg, about 4.5 mg/kg to about 10 mg/kg, about 5 mg/kg to about 10 mg/kg, about 5.5 mg/kg to about 10 mg/kg, about 6 mg/kg to about 10 mg/kg, about 6.5 mg/kg to about 10 mg/kg, about 7 mg/kg to about 10 mg/kg, about 7.5 mg/kg to about 10 mg/kg, about 8 mg/kg to about 10 mg/kg, about 8.5 mg/kg to about 10 mg/kg, about 9 mg/kg to about 10 mg/kg, or about 9.5 mg/kg to about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

For example, the dsRNA may be administered at a dose of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or about 10 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

In other embodiments, for example, when a composition of the invention comprises a dsRNA as described herein and an N-acetylgalactosamine, subjects can be administered a therapeutic amount of iRNA, such as a dose of about 0.1 to about 50 mg/kg, about 0.25 to about 50 mg/kg, about 0.5 to about 50 mg/kg, about 0.75 to about 50 mg/kg, about 1 to about 50 mg/mg, about 1.5 to about 50 mg/kb, about 2 to about 50 mg/kg, about 2.5 to about 50 mg/kg, about 3 to about 50 mg/kg, about 3.5 to about 50 mg/kg, about 4 to about 50 mg/kg, about 4.5 to about 50 mg/kg, about 5 to about 50 mg/kg, about 7.5 to about 50 mg/kg, about 10 to about 50 mg/kg, about 15 to about 50 mg/kg, about 20 to about 50 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 50 mg/kg, about 30 to about 50 mg/kg, about 35 to about 50 mg/kg, about 40 to about 50 mg/kg, about 45 to about 50 mg/kg, about 0.1 to about 45 mg/kg, about 0.25 to about 45 mg/kg, about 0.5 to about 45 mg/kg, about 0.75 to about 45 mg/kg, about 1 to about 45 mg/mg, about 1.5 to about 45 mg/kb, about 2 to about 45 mg/kg,

about 2.5 to about 45 mg/kg, about 3 to about 45 mg/kg, about 3.5 to about 45 mg/kg, about 4 to about 45 mg/kg, about 4.5 to about 45 mg/kg, about 5 to about 45 mg/kg, about 7.5 to about 45 mg/kg, about 10 to about 45 mg/kg, about 15 to about 45 mg/kg, about 20 to about 45 mg/kg, about 20 to about 45 mg/kg, about 25 to about 45 mg/kg, about 25 to about 45 mg/kg, about 30 to about 45 mg/kg, about 35 to about 45 mg/kg, about 40 to about 45 mg/kg, about 0.1 to about 40 mg/kg, about 0.25 to about 40 mg/kg, about 0.5 to about 40 mg/kg, about 0.75 to about 40 mg/kg, about 1 to about 40 mg/mg, about 1.5 to about 40 mg/kb, about 2 to about 40 mg/kg, about 2.5 to about 40 mg/kg, about 3 to about 40 mg/kg, about 3.5 to about 40 mg/kg, about 4 to about 40 mg/kg, about 4.5 to about 40 mg/kg, about 5 to about 40 mg/kg, about 7.5 to about 40 mg/kg, about 10 to about 40 mg/kg, about 15 to about 40 mg/kg, about 20 to about 40 mg/kg, about 20 to about 40 mg/kg, about 25 to about 40 mg/kg, about 25 to about 40 mg/kg, about 30 to about 40 mg/kg, about 35 to about 40 mg/kg, about 0.1 to about 30 mg/kg, about 0.25 to about 30 mg/kg, about 0.5 to about 30 mg/kg, about 0.75 to about 30 mg/kg, about 1 to about 30 mg/mg, about 1.5 to about 30 mg/kb, about 2 to about 30 mg/kg, about 2.5 to about 30 mg/kg, about 3 to about 30 mg/kg, about 3.5 to about 30 mg/kg, about 4 to about 30 mg/kg, about 4.5 to about 30 mg/kg, about 5 to about 30 mg/kg, about 7.5 to about 30 mg/kg, about 10 to about 30 mg/kg, about 15 to about 30 mg/kg, about 20 to about 30 mg/kg, about 20 to about 30 mg/kg, about 25 to about 30 mg/kg, about 0.1 to about 20 mg/kg, about 0.25 to about 20 mg/kg, about 0.5 to about 20 mg/kg, about 0.75 to about 20 mg/kg, about 1 to about 20 mg/mg, about 1.5 to about 20 mg/kb, about 2 to about 20 mg/kg, about 2.5 to about 20 mg/kg, about 3 to about 20 mg/kg, about 3.5 to about 20 mg/kg, about 4 to about 20 mg/kg, about 4.5 to about 20 mg/kg, about 5 to about 20 mg/kg, about 7.5 to about 20 mg/kg, about 10 to about 20 mg/kg, or about 15 to about 20 mg/kg. In one embodiment, when a composition of the invention comprises a dsRNA as described herein and an N-acetylgalactosamine, subjects can be administered a therapeutic amount of about 10 to about 30 mg/kg of dsRNA. Values and ranges intermediate to the recited values are also intended to be part of this invention.

For example, subjects can be administered a therapeutic amount of iRNA, such as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 31, 32, 33, 34, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or about 50 mg/kg. Values and ranges intermediate to the recited values are also intended to be part of this invention.

The iRNA can be administered by intravenous infusion over a period of time, such as over a 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or about a 25 minute period. The administration may be repeated, for example, on a regular basis, such as weekly, biweekly (*i.e.*, every two weeks) for one month, two months, three months, four months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration weekly or biweekly for three months, administration can be repeated once per month, for six months or a year or longer.

Administration of the iRNA can reduce C5 levels, *e.g.*, in a cell, tissue, blood, urine or other compartment of the patient by at least about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% or more.

Before administration of a full dose of the iRNA, patients can be administered a smaller dose, such as a 5% infusion, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Owing to the inhibitory effects on C5 expression, a composition according to the invention or a pharmaceutical composition prepared therefrom can enhance the quality of life.

An iRNA of the invention may be administered in "naked" form, or as a "free iRNA." A naked iRNA is administered in the absence of a pharmaceutical composition. The naked iRNA may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the iRNA can be adjusted such that it is suitable for administering to a subject.

Alternatively, an iRNA of the invention may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from a reduction and/or inhibition of C5gene expression are those having a complement component C5-associated disease or disorder as described herein. In one embodiment, a subject having a complement component C5-associated disease has paroxysmal nocturnal hemoglobinuria (PNH). In another embodiment, a subject having a complement component C5-associated disease has asthma. In another embodiment, a subject having a complement component C5-associated disease has rheumatoid arthritis. In yet another embodiment, a subject having a complement component C5-associated disease has systemic

lupus erythmatosis. In one embodiment, a subject having a complement component C5-associated disease has glomerulonephritis. In another embodiment, a subject having a complement component C5-associated disease has psoriasis. In yet another embodiment, a subject having a complement component C5-associated disease has dermatomyositis bullous pemphigoid. In one embodiment, a subject having a complement component C5-associated disease has atypical hemolytic uremic syndrome. In another embodiment, a subject having a complement component C5-associated disease has Shiga toxin *E. coli*-related hemolytic uremic syndrome. In anothre embodiment, a subject having a complement component C5-associated disease has myasthenia gravis. In yet another embodiment, a subject having a complement component C5-associated disease has neuromyelistis optica. In one embodiment, a subject having a complement component C5-associated disease has dense deposit disease. In one embodiment, a subject having a complement component C5-associated disease has C3 neuropathy. In another embodiment, a subject having a complement component C5-associated disease has age-related macular degeneration. In another embodiment, a subject having a complement component C5-associated disease has cold agglutinin disease. In one embodiment, a subject having a complement component C5-associated disease has anti-neutrophil cytoplasmic antibody-associated vasculitis. In another embodiment, a subject having a complement component C5-associated disease has humoral and vascular transplant rejection. In one embodiment, a subject having a complement component C5-associated disease has graft dysfunction. In one embodiment, a subject having a complement component C5-associated disease has had a myocardial infarction. In another embodiment, a subject having a complement component C5-associated disease is a sensitized recipient of a transplant. In yet another embodiment, a subject having a complement component C5-associated disease has sepsis.

Treatment of a subject that would benefit from a reduction and/or inhibition of C5 gene expression includes therapeutic and prophylactic (*e.g.*, the subject is to undergo sensitized (or allogenic) transplant surgery) treatment.

The invention further provides methods and uses of an iRNA agent or a pharmaceutical composition thereof (including methods and uses of an iRNA agent or a pharmaceutical composition comprising an iRNA agent and an anti-complement component C5 antibody, or antigen-bidning fragment thereof) for treating a subject that would benefit from reduction and/or inhibition of C5 expression, *e.g.*, a subject having a complement component C5-associated disease, in combination with other pharmaceuticals and/or other therapeutic methods, *e.g.*, with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an iRNA targeting C5 is administered in combination with, *e.g.*, an agent useful in treating a complement component C5-associated disease as described elsewhere herein.

For example, additional therapeutics and therapeutic methods suitable for treating a subject that would benefit from reducton in C5 expression, *e.g.*, a subject having a complement component C5-associated disease, include plasmaphoresis, thrombolytic therapy (*e.g.*, streptokinase), antiplatelet agents, folic acid, corticosteroids; immunosuppressive agents; estrogens, methotrexate, 6-MP, azathioprine sulphasalazine, mesalazine, olsalazine, chloroquinine/hydroxychloroquine, pencillamine, aurothiomalate (intramuscular and oral), azathioprine, cochicine, corticosteroids (oral, inhaled and local injection), beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral), xanthines (theophylline, aminophylline), cromoglycate, nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines, such as TNF-α or IL-1 (*e.g.*, IRAK, NIK, IKK, p38 or MAP kinase inhibitors), IL-1β converting enzyme inhibitors, TNFαconverting enzyme (TACE) inhibitors, T-cell signalling inhibitors, such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (*e.g.*, soluble p55 or p75 TNF receptors and the derivatives p75TNFRIgG (Enbrel™ and p55TNFRIgG (Lenercept)), sIL-1RI, sIL-1RII, and sIL-6R), antiinflammatory cytokines (*e.g.*, IL-4, IL-10, IL-11, IL-13 and TGFβ), celecoxib, folic acid, hydroxychloroquine sulfate, rofecoxib, etanercept, infliximonoclonal antibody, naproxen, valdecoxib, sulfasalazine, methylprednisolone, meloxicam, methylprednisolone acetate, gold sodium thiomalate, aspirin, triamcinolone acetonide, propoxyphene napsylate/apap, folate, nabumetone, diclofenac, piroxicam, etodolac, diclofenac sodium, oxaprozin, oxycodone hcl, hydrocodone bitartrate/apap, diclofenac sodium/misoprostol, fentanyl, anakinra, human recombinant, tramadol hcl, salsalate, sulindac, cyanocobalamin/fa/pyridoxine, acetaminophen, alendronate sodium, prednisolone, morphine sulfate, lidocaine hydrochloride, indomethacin, glucosamine sulf/chondroitin, amitriptyline hcl, sulfadiazine, oxycodone hcl/acetaminophen, olopatadine hcl, misoprostol, naproxen sodium, omeprazole, cyclophosphamide, rituximonoclonal antibody, IL-1 TRAP, MRA, CTLA4-IG, IL-18 BP, anti-IL-18, Anti-IL15, BIRB-796, SCIO-469, VX-702, AMG-548, VX-740, Roflumilast, IC-485, CDC-801, Mesopram, cyclosporine, cytokine suppressive anti-inflammatory drug(s) (CSAIDs); CDP-571/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2/infliximonoclonal antibody (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG/etanercept (75 kD TNF receptor-IgG fusion protein; Immunex; see *e.g.*, (1994) Arthr. Rheum. 37: S295; (1996) J. Invest. Med. 44: 235A); 55 kdTNF-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IDEC-CE9.1/SB 210396 (non-depleting primatized anti-CD4 antibody; IDEC/SmithKline; see *e.g.*,

(1995) Arthr. Rheum. 38: S185); DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins; Seragen; see *e.g.*, (1993) Arthrit. Rheum. 36: 1223); Anti-Tac (humanized anti-IL-2Rα; Protein Design Labs/Roche); IL-4 (anti-inflammatory cytokine; DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10, anti-inflammatory cytokine; DNAX/Schering); IL-4; IL-10 and/or IL-4 agonists (*e.g.*, agonist antibodies); IL-1RA (IL-1 receptor antagonist; Synergen/Amgen); anakinra (Kineret®/Amgen); TNF-bp/s-TNF (soluble TNF binding protein; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement)): S284; (1995) Amer. J. Physiol. - Heart and Circ. Physiol. 268: 37-42); R973401 (phosphodiesterase Type IV inhibitor; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S282); MK-966 (COX-2 Inhibitor; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S81); Iloprost (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S82); methotrexate; thalidomide (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S282) and thalidomide-related drugs (*e.g.*, Celgen); leflunomide (anti-inflammatory and cytokine inhibitor; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S131; (1996) Inflamm. Res. 45: 103-107); tranexamic acid (inhibitor of plasminogen activation; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S284); T-614 (cytokine inhibitor; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S282); prostaglandin E1 (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S282); Tenidap (non-steroidal anti-inflammatory drug; see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S280); Naproxen (non-steroidal anti-inflammatory drug; see *e.g.*, (1996) Neuro. Report 7: 1209-1213); Meloxicam (non-steroidal anti-inflammatory drug); Ibuprofen (non-steroidal anti-inflammatory drug); Piroxicam (non-steroidal anti-inflammatory drug); Diclofenac (non-steroidal anti-inflammatory drug); Indomethacin (non-steroidal anti-inflammatory drug); Sulfasalazine (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S281); Azathioprine (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S281); ICE inhibitor (inhibitor of the enzyme interleukin-1β converting enzyme); zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck); VEGF inhibitor and/or VEGF-R inhibitor (inhibitors of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor; inhibitors of angiogenesis); corticosteroid anti-inflammatory drugs (*e.g.*, SB203580); TNF-convertase inhibitors; anti-IL-12 antibodies; anti-IL-18 antibodies; interleukin-11 (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S296); interleukin-13 (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S308); interleukin -17 inhibitors (see *e.g.*, (1996) Arthr. Rheum. 39(9 (supplement): S120); gold; penicillamine; chloroquine; chlorambucil; hydroxychloroquine; cyclosporine; cyclophosphamide; total lymphoid irradiation; anti-thymocyte globulin; anti-CD4 antibodies; CD5-toxins; orally-administered peptides and collagen; lobenzarit disodium; Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligo-deoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); prednisone; orgotein;

glycosaminoglycan polysulphate; minocycline; anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids; see *e.g.*, DeLuca *et al.* (1995) Rheum. Dis. Clin. North Am. 21: 759-777); auranofin; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; azaribine; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-chlorodeoxyadenosine); methotrexate; bcl-2 inhibitors (see Bruncko, M. *et al.* (2007) J. Med. Chem. 50(4): 641-662); antivirals and immune-modulating agents, small molecule inhibitor of KDR, small molecule inhibitor of Tie-2; methotrexate; prednisone; celecoxib; folic acid; hydroxychloroquine sulfate; rofecoxib; etanercept; infliximonoclonal antibody; leflunomide; naproxen; valdecoxib; sulfasalazine; methylprednisolone; ibuprofen; meloxicam; methylprednisolone acetate; gold sodium thiomalate; aspirin; azathioprine; triamcinolone acetonide; propxyphene napsylate/apap; folate; nabumetone; diclofenac; piroxicam; etodolac; diclofenac sodium; oxaprozin; oxycodone hcl; hydrocodone bitartrate/apap; diclofenac sodium/misoprostol; fentanyl; anakinra, human recombinant; tramadol hcl; salsalate; sulindac; cyanocobalamin/fa/pyridoxine; acetaminophen; alendronate sodium; prednisolone; morphine sulfate; lidocaine hydrochloride; indomethacin; glucosamine sulfate/chondroitin; cyclosporine; amitriptyline hcl; sulfadiazine; oxycodone hcl/acetaminophen; olopatadine hcl; misoprostol; naproxen sodium; omeprazole; mycophenolate mofetil; cyclophosphamide; rituximonoclonal antibody; IL-1 TRAP; MRA; CTLA4-IG; IL-18 BP; IL-12/23; anti-IL 18; anti-IL 15; BIRB-796; SCIO-469; VX-702; AMG-548; VX-740; Roflumilast; IC-485; CDC-801; mesopram, albuterol, salmeterol/fluticasone, montelukast sodium, fluticasone propionate, budesonide, prednisone, salmeterol xinafoate, levalbuterol hcl, albuterol sulfate/ipratropium, prednisolone sodium phosphate, triamcinolone acetonide, beclomethasone dipropionate, ipratropium bromide, azithromycin, pirbuterol acetate, prednisolone, theophylline anhydrous, methylprednisolone sodium succinate, clarithromycin, zafirlukast, formoterol fumarate, influenza virus vaccine, methylprednisolone, amoxicillin trihydrate, flunisolide, allergy injection, cromolyn sodium, fexofenadine hydrochloride, flunisolide/menthol, amoxicillin/clavulanate, levofloxacin, inhaler assist device, guaifenesin, dexamethasone sodium phosphate, moxifloxacin hcl, doxycycline hyclate, guaifenesin/d-methorphan, p-ephedrine/cod/chlorphenir, gatifloxacin, cetirizine hydrochloride, mometasone furoate, salmeterol xinafoate, benzonatate, cephalexin, pe/hydrocodone/chlorphenir, cetirizine hcl/pseudoephed, phenylephrine/cod/promethazine, codeine/promethazine, cefprozil, dexamethasone, guaifenesin/pseudoephedrine, chlorpheniramine/hydrocodone, nedocromil sodium, terbutaline sulfate, epinephrine, methylprednisolone, metaproterenol sulfate, aspirin, nitroglycerin, metoprolol tartrate, enoxaparin sodium, heparin sodium, clopidogrel bisulfate, carvedilol, atenolol, morphine sulfate, metoprolol succinate, warfarin sodium, lisinopril, isosorbide mononitrate, digoxin, furosemide, simvastatin, ramipril, tenecteplase, enalapril

maleate, torsemide, retavase, losartan potassium, quinapril hcl/mag carb, bumetanide, alteplase, enalaprilat, amiodarone hydrochloride, tirofiban hcl m-hydrate, diltiazem hydrochloride, captopril, irbesartan, valsartan, propranolol hydrochloride, fosinopril sodium, lidocaine hydrochloride, eptifibatide, cefazolin sodium, atropine sulfate, aminocaproic acid, spironolactone, interferon, sotalol hydrochloride, potassium chloride, docusate sodium, dobutamine hcl, alprazolam, pravastatin sodium, atorvastatin calcium, midazolam hydrochloride, meperidine hydrochloride, isosorbide dinitrate, epinephrine, dopamine hydrochloride, bivalirudin, rosuvastatin, ezetimibe/simvastatin, avasimibe, and cariporide.

The iRNA agent (and/or an anti-complement component C5 antibody) and an additional therapeutic agent and/or treatment may be administered at the same time and/or in the same combination, *e.g.*, parenterally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times and/or by another method known in the art or described herein.

The present invention also provides methods of using an iRNA agent of the invention and/or a composition containing an iRNA agent of the invention to reduce and/or inhibit complement component C5 expression in a cell. In other aspects, the present invention provides an iRNA of the invention and/or a composition comprising an iRNA of the invention for use in reducing and/or inhibiting C5 expression in a cell. In yet other aspects, use of an iRNA of the invention and/or a composition comprising an iRNA of the invention for the manufactuire of a medicament for reducing and/or inhibiting C5 expression in a cell are provided.

The methods and uses include contacting the cell with an iRNA, *e.g.*, a dsRNA, of the invention and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a C5 gene, thereby inhibiting expression of the C5 gene in the cell.

Reduction in gene expression can be assessed by any methods known in the art. For example, a reduction in the expression of C5 may be determined by determining the mRNA expression level of C5 using methods routine to one of ordinary skill in the art, *e.g.*, Northern blotting, qRT-PCR, by determining the protein level of C5 using methods routine to one of ordinary skill in the art, such as Western blotting, immunological techniques, flow cytometry methods, ELISA, and/or by determining a biological activity of C5, such as CH_{50} or AH_{50} hemolysis assay, and/or by determining the biological activity of one or more molecules associated with the complement system, *e.g.*, C5 products, such as C5a and C5b (or, in an *in vivo* setting, *e.g.*, hemolysis).

In the methods and uses of the invention the cell may be contacted *in vitro* or *in vivo*, *i.e.*, the cell may be within a subject. In embodiments of the invention in which the cell is within a subject, the methods may include further contacting the cell with an anti-complement component C5 antibody, *e.g.*, eculizumab.

A cell suitable for treatment using the methods of the invention may be any cell that expresses a C5 gene. A cell suitable for use in the methods and uses of the invention may be a mammalian cell, *e.g.*, a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a cow cell, a pig cell, a camel cell, a llama cell, a horse cell, a goat cell, a rabbit cell, a sheep cell, a hamster, a guinea pig cell, a cat cell, a dog cell, a rat cell, a mouse cell, a lion cell, a tiger cell, a bear cell, or a buffalo cell), a bird cell (*e.g.*, a duck cell or a goose cell), or a whale cell. In one embodiment, the cell is a human cell, *e.g.*, a human liver cell.

C5 expression may be inhibited in the cell by at least about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or about 100%.

The *in vivo* methods and uses of the invention may include administering to a subject a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the C5 gene of the mammal to be treated. When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to subcutaneous, intravenous, oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal and intrathecal), intramuscular, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by subcutaneous or intravenous infusion or injection.

In some embodiments, the administration is *via* a depot injection. A depot injection may release the iRNA in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of C5, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intravenous, subcutaneous, arterial, or epidural infusions. In preferred

embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the iRNA to the liver.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present invention also provides methods for inhibiting the expression of a C5 gene in a mammal, *e.g.*, a human. The present invention also provides a composition comprising an iRNA, *e.g.*, a dsRNA, that targets a C5 gene in a cell of a mammal for use in inhibiting expression of the C5 gene in the mammal. In another aspect, the present invention provides use of an iRNA, *e.g.*, a dsRNA, that targets a C5 gene in a cell of a mammal in the manufacture of a medicament for inhibiting expression of the C5 gene in the mammal.

The methods and uses include administering to the mammal, *e.g.*, a human, a composition comprising an iRNA, *e.g.*, a dsRNA, that targets a C5 gene in a cell of the mammal and maintaining the mammal for a time sufficient to obtain degradation of the mRNA transcript of the C5 gene, thereby inhibiting expression of the C5 gene in the mammal. In some embodiment, the methods further comprise administering an anti-complement component C5 antibody, *e.g.*, eculizumab, to the subject.

Reduction in gene expression can be assessed by any methods known it the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known it the art and by methods, *e.g.*, ELISA or Western blotting, described herein. In one embodiment, a puncture liver biopsy sample serves as the tissue material for monitoring the reduction in C5 gene and/or protein expression. In another embodiment, a blood sample serves as the tissue material for monitoring the reduction in C5 gene and/or protein expression. In other embodiments, inhibition of the expression of a C5 gene is monitored indirectly by, for example, determining the expression and/or activity of a gene in a C5 pathway, including, for example, C5a, C5b, and soluble C5b-9 (see, *e.g.*, Figure 1). For example, the activity of CD59 may be monitored to determine the inhibition of expression of a C5 gene. CH_{50}, AH_{50}, clot formation and/or serum lactate dehydrogenase (LDH), in a sample, *e.g.*, a blood or liver sample, may also be measured. Suitable assays are further described in the Examples section below.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the iRNAs and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and

other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

EXAMPLES

Example 1. iRNA Synthesis

Source of reagents

Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

Transcripts

siRNA design was carried out to identify siRNAs targeting human, rhesus (*Macaca mulatta*), mouse, and rat C5 transcripts annotated in the NCBI Gene database (http://www.ncbi.nlm.nih.gov/gene/). Design used the following transcripts from the NCBI RefSeq collection: Human - NM_001735.2; Rhesus - XM_001095750.2; Mouse - NM_010406.2; Rat - XM_345342.4. SiRNA duplexes were designed in several separate batches, including but not limited to batches containing duplexes matching human and rhesus transcripts only; human, rhesus, and mouse transcripts only; human, rhesus, mouse, and rat transcripts only; and mouse and rat transcripts only. All siRNA duplexes were designed that shared 100% identity with the listed human transcript and other species transcripts considered in each design batch (above).

siRNA Design, Specificity, and Efficacy Prediction

The predicted specificity of all possible 19mers was predicted from each sequence. Candidate 19mers were then selected that lacked repeats longer than 7 nucleotides. These 2971 candidate human/rhesus, 142 human/rhesus/mouse, 54 human/rhesus/mouse/rat, and 807 mouse/rat siRNAs were used in comprehensive searches against the appropriate transcriptomes (defined as the set of NM_ and XM_ records within the human, rhesus, dog, mouse, or rat NCBI Refseq sets) using an exhaustive "brute-force" algorithm implemented in the python script 'BruteForce.py'. The script next parsed the transcript-oligo alignments to generate a score based on the position and number of mismatches between the siRNA and any potential 'off-target' transcript. The off-target score is weighted to emphasize differences in the 'seed' region of siRNAs, in positions 2-9 from the 5'-end of the molecule.

Each oligo-transcript pair from the brute-force search was given a mismatch score by summing the individual mismatch scores; mismatches in the position 2-9 were counted as 2.8, mismatches in the cleavage site positions 10-11 were counted as 1.2, and mismatches in region 12-19 counted as 1.0. An additional off-target prediction was carried out by comparing the

frequency of heptamers and octomers derived from 3 distinct, seed-derived hexamers of each oligo. The hexamers from positions 2-7 relative to the 5' start were used to create 2 heptamers and one octamer. 'Heptamer1' was created by adding a 3'-A to the hexamer; heptamer2 was created by adding a 5'-A to the hexamer; the octomer was created by adding an A to both 5'- and 3'-ends of the hexamer. The frequency of octamers and heptamers in the human, rhesus, mouse, or rat 3'-UTRome (defined as the subsequence of the transcriptome from NCBI's Refseq database where the end of the coding region, the 'CDS', is clearly defined) was pre-calculated. The octamer frequency was normalized to the heptamer frequency using the median value from the range of octamer frequencies. A 'mirSeedScore' was then calculated by calculating the sum of ((3 X normalized octamer count) + (2 X heptamer2 count) + (1 X heptamer1 count)).

Both siRNAs strands were assigned to a category of specificity according to the calculated scores: a score above 3 qualifies as highly specific, equal to 3 as specific and between 2.2 and 2.8 as moderately specific. The duplexes were sorted by the specificity of the antisense strand and those duplexes whose antisense oligos lacked GC at the first position, lacked G at both positions 13 and 14, and had 3 or more Us or As in the seed region were selected.

For GalNaC-conjugated duplexes, sense 21mer and antisense 23mer oligos were designed by extending antisense 19mers (described above) to 23 nucleotides of target-complementary sequence. All species transcripts included in the design batch were checked for complementarity. Only 23mers that preserved 100% sequence complementarity in at least 2 species were used. For each duplex, the sense 21mer was specified as the reverse complement of the first 21 nucleotides of the antisense strand.

siRNA sequence selection

A total of 23 sense and 23 antisense derived human/rhesus, 6 sense and 6 antisense human/rhesus/mouse, 6 sense and 6 antisense derived human/rhesus/mouse/mouse/rat, and 13 sense and 13 antisense derived mouse/rat siRNA 19mer oligos were synthesized and formed into duplexes.

The above 19mer sets were extended to 21/23mer duplexes for GalNac conjugate design and re-classified according to their new species matches. Twenty-seven sense and 27 antisense derived human/rhesus, 1 sense and 1 sense derived human/rhesus/mouse, 3 sense and 3 antisense derived human/rhesus/rat, 4 sense and 4 antisense derived human/rhesus/mouse/rat, and 13 sense and 13 antisense derived mouse/rat 21mer (sense) and 23mer (antisense) oligos were synthesized and formed into duplexes.

A detailed list of C5 sense and antisense strand sequences is shown in Tables 3-6.

siRNA Synthesis

General Small and Medium Scale RNA Synthesis Procedure

RNA oligonucleotides were synthesized at scales between 0.2–500 µmol using commercially available 5'-*O*-(4,4'-dimethoxytrityl)-2'-*O*-t-butyldimethylsilyl-3'-*O*-(2-cyanoethyl-*N,N*-diisopropyl)phosphoramidite monomers of uridine, 4-*N*-acetylcytidine, 6-*N*-benzoyladenosine and 2-*N*-isobutyrylguanosine and the corresponding 2'-*O*-methyl and 2'-fluoro phosphoramidites according to standard solid phase oligonucleotide synthesis protocols. The amidite solutions were prepared at 0.1-0.15 M concentration and 5-ethylthio-1H-tetrazole (0.25-0.6 M in acetonitrile) was used as the activator. Phosphorothioate backbone modifications were introduced during synthesis using 0.2 M phenylacetyl disulfide (PADS) in lutidine:acetonitrile (1:1) (v;v) or 0.1 M 3-(dimethylaminomethylene) amino-3H-1,2,4-dithiazole-5-thione (DDTT) in pyridine for the oxidation step. After completion of synthesis, the sequences were cleaved from the solid support and deprotected using methylamine followed by triethylamine.3HF to remove any 2'-*O*-t-butyldimethylsilyl protecting groups present.

For synthesis scales between 5–500 µmol and fully 2' modified sequences (2'-fluoro and/or 2'-*O*-methyl or combinations thereof) the oligonucleotides where deprotected using 3:1 (v/v) ethanol and concentrated (28-32%) aqueous ammonia either at 35°C 16 h or 55°C for 5.5 h. Prior to ammonia deprotection the oligonucleotides where treated with 0.5 M piperidine in acetonitrile for 20 min on the solid support. The crude oligonucleotides were analyzed by LC–MS and anion-exchange HPLC (IEX-HPLC). Purification of the oligonucleotides was carried out by IEX HPLC using: 20 mM phosphate, 10%-15% ACN, pH = 8.5 (buffer A) and 20 mM phosphate, 10%-15% ACN, 1 M NaBr, pH = 8.5 (buffer B). Fractions were analyzed for purity by analytical HPLC. The product-containing fractions with suitable purity were pooled and concentrated on a rotary evaporator prior to desalting. The samples were desalted by size exclusion chromatography and lyophilized to dryness. Equal molar amounts of sense and antisense strands were annealed in 1x PBS buffer to prepare the corresponding siRNA duplexes.

For small scales (0.2–1 µmol), synthesis was performed on a MerMade 192 synthesizer in a 96 well format. In case of fully 2'-modified sequences (2'-fluoro and/or 2'-*O*-methyl or combinations thereof) the oligonucleotides where deprotected using methylamine at room temperature for 30-60 min followed by incubation at 60°C for 30 min or using 3:1 (v/v) ethanol and concentrated (28-32%) aqueous ammonia at room temperature for 30-60 min followed by incubation at 40°C for 1.5 hours. The crude oligonucleotides were then precipitated in a solution of acetonitrile:acetone (9:1) and isolated by centrifugation and decanting the supernatant. The crude oligonucleotide pellet was re-suspended in 20 mM NaOAc buffer and analyzed by LC-MS and anion exchange HPLC. The crude oligonucleotide sequences were desalted in 96 deep well plates on a 5 mL HiTrap Sephadex G25 column (GE Healthcare). In each well about 1.5 mL

samples corresponding to an individual sequence was collected. These purified desalted oligonucleotides were analyzed by LC-MS and anion exchange chromatography. Duplexes were prepared by annealing equimolar amounts of sense and antisense sequences on a Tecan robot. Concentration of duplexes was adjusted to 10 µM in 1x PBS buffer.

Synthesis of GalNAc-Conjugated Oligonucleotides for *In Vivo* Analysis

Oligonucleotides conjugated with GalNAc ligand at their 3'-terminus were synthesized at scales between 0.2–500 µmol using a solid support pre-loaded with a Y-shaped linker bearing a 4,4'-dimethoxytrityl (DMT)-protected primary hydroxy group for oligonucleotide synthesis and a GalNAc ligand attached through a tether.

For synthesis of GalNAc conjugates in the scales between 5–500 µmol, the above synthesis protocol for RNA was followed with the following adaptions: For polystyrene-based synthesis supports 5% dichloroacetic acid in toluene was used for DMT-cleavage during synthesis. Cleavage from the support and deprotection was performed as described above. Phosphorothioate-rich sequences (usually > 5 phorphorothioates) were synthesized without removing the final 5'-DMT group ("DMT-on") and, after cleavage and deprotection as described above, purified by reverse phase HPLC using 50 mM ammonium acetate in water (buffer A) and 50 mM ammoniumacetate in 80% acetonitirile (buffer B). Fractions were analyzed for purity by analytical HPLC and/or LC-MS. The product-containing fractions with suitable purity were pooled and concentrated on a rotary evaporator. The DMT-group was removed using 20%-25% acetic acid in water until completion. The samples were desalted by size exclusion chromatography and lyophilized to dryness. Equal molar amounts of sense and antisense strands were annealed in 1x PBS buffer to prepare the corresponding siRNA duplexes.

For small scale synthesis of GalNAc conjugates (0.2–1 µmol), including sequences with multiple phosphorothioate linkages, the protocols described above for synthesis of RNA or fully 2'-F/2'-OMe-containing sequences on MerMade platform were applied. Synthesis was performed on pre-packed columns containing GalNAc-functionalized controlled pore glass support.

Example 2. *In vitro* screening

Cell culture and transfections

Hep3B cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO2 in Eagle's Minimum Essential Medium (ATCC) supplemented with 10% FBS, streptomycin, and glutamine (ATCC) before being released from the plate by trypsinization. Cells were washed and re-suspended at $0.25x10^6$ cells/ml. During transfections, cells were plated onto a 96-well plate with about 20,000 cells per well.

Primary mouse hepatocytes (PMH) were freshly isolated from a C57BL/6 female mouse (Charles River Labortories International, Inc. Willmington, MA) less than 1 hour prior to transfections and grown in primary hepatocyte media. Cells were resuspended at $0.11x10^6$ cells/ml in InVitroGRO CP Rat (plating) medium (Celsis In Vitro Technologies, catalog number S01494). During transfections, cells were plated onto a BD BioCoat 96 well collagen plate (BD, 356407) at 10,000 cells per well and incubated at 37°C in an atmosphere of 5% CO_2.

Cryopreserved Primary *Cynomolgus* Hepatocytes (Celsis In Vitro Technologies, M003055-P) were thawed at 37°C water bath immediately prior to usage and re-suspended at $0.26x10^6$ cells/ml in InVitroGRO CP (plating) medium (Celsis In Vitro Technologies, catalog number Z99029). During transfections, cells were plated onto a BD BioCoat 96 well collagen plate (BD, 356407) at 25,000 cells per well and incubated at 37°C in an atmosphere of 5% CO_2.

For Hep3B, PMH, and primary *Cynomolgus* hepatocytes, transfection was carried out by adding 14.8 µl of Opti-MEM plus 0.2 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. catalog number13778-150) to 5 µl of each siRNA duplex to an individual well in a 96-well plate. The mixture was then incubated at room temperature for 20 minutes. Eighty µl of complete growth media without antibiotic containing the appropriate cell number were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification.

Single dose experiments were performed at 10nM and 0.1nM final duplex concentration for GalNAc modified sequences or at 1nM and 0.01nM final duplex concentration for all other sequences. Dose response experiments were done at 3, 1, 0.3, 0.1, 0.037, 0.0123, 0.00412, and 0.00137 nM final duplex concentration for primary mouse hepatocytes and at 3, 1, 0.3, 0.1, 0.037, 0.0123, 0.00412, 0.00137, 0.00046, 0.00015, 0.00005, and 0.000017 nM final duplex concentration for Hep3B cells.

Free uptake transfection

Free uptake experiments were performed by adding 10µl of siRNA duplexes in PBS per well into a 96 well plate. Ninety µl of complete growth media containing appropriate cell number for the cell type was then added to the siRNA. Cells were incubated for 24 hours prior to RNA purification. Single dose experiments were performed at 500nM and 5nM final duplex concentration and dose response experiments were done at 1000, 333, 111, 37, 12.3, 4.12, 1.37, 0.46 nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen, part #: 610-12)

Cells were harvested and lysed in 150 µl of Lysis/Binding Buffer then mixed for 5 minutes at 850 rpm using an Eppendorf Thermomixer (the mixing speed was the same throughout the process). Ten microliters of magnetic beads and 80 µl Lysis/Binding Buffer

mixture were added to a round bottom plate and mixed for 1 minute. Magnetic beads were captured using a magnetic stand and the supernatant was removed without disturbing the beads. After removing the supernatant, the lysed cells were added to the remaining beads and mixed for 5 minutes. After removing the supernatant, magnetic beads were washed 2 times with 150 µl Wash Buffer A and mixed for 1 minute. The beads were capturedagain and the supernatant was removed. The beads were then washed with 150 µl Wash Buffer B, captured and the supernatant was removed. The beads were next washed with 150 µl Elution Buffer, captured and the supernatant removed. Finally, the beads were allowed to dry for 2 minutes. After drying, 50 µl of Elution Buffer was added and mixed for 5 minutes at 70°C. The beads were captured on magnet for 5 minutes. Forty-five µl of supernatant was removed and added to another 96 well plate.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

A master mix of 2 µl 10X Buffer, 0.8 µl 25X dNTPs, 2 µl Random primers, 1 µl Reverse Transcriptase, 1 µl RNase inhibitor and 3.2 µl of H2O per reaction as prepared. Equal volumes master mix and RNA were mixed for a final volume of 12µl for *in vitro* screened or 20µl for *in vivo* screened samples. cDNA was generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, CA) through the following steps: 25°C for 10 minutes, 37°C for 120 minutes, 85°C for 5 seconds, and 4°C hold.

Real time PCR

Two µl of cDNA were added to a master mix containing 2µl of H_2O, 0.5µl GAPDH TaqMan Probe (Life Technologies catalog number 4326317E for Hep3B cells, catalog number 352339E for primary mouse hepatocytes or custom probe for cynomolgus primary hepatocytes), 0.5µl C5 TaqMan probe (Life Technologies c catalog number Hs00156197_m1 for Hep3B cells or mm00439275_m1 for Primary Mouse Hepatoctyes or custom probe for cynomolgus primary hepatocytes) and 5µl Lightcycler 480 probe master mix (Roche catalog number 04887301001) per well in a 384 well plates (Roche catalog number 04887301001). Real time PCR was performed in an Roche LC480 Real Time PCR system (Roche) using the ΔΔCt(RQ) assay. For *in vitro* screening, each duplex was tested with two biological replicates unless otherwise noted and each Real Time PCR was performed in duplicate technical replicates. For *in vivo* screening, each duplex was tested in one or more experiments (3 mice per group) and each Real Time PCR was run in duplicate technical replicates.

To calculate relative fold change in C5 mRNA levels, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10 nM AD-

1955, or mock transfected cells. IC_{50}s were calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 over the same dose range, or to its own lowest dose.

The sense and antisense sequences of AD-1955 are:

SENSE: cuuAcGcuGAGuAcuucGAdTsdT (SEQ ID NO: 13);

ANTISENSE: UCGAAGuACUcAGCGuAAGdTsdT (SEQ ID NO: 14).

Table 7 shows the results of a single dose screen in Hep3B cells transfected with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 8 shows the results of a single dose transfection screen in primary mouse hepatocytes transfected with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 9 shows the results of a single dose free uptake screen in primary *Cynomolgus* hepatocytes with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 10 shows the results of a single dose free uptake screen in primary mouse hepatocytes with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 11 shows the dose response of a free uptake screen in primary *Cynomolgus* hepatocytes with the indicated GalNAC conjugated modified iRNAs. The indicated IC_{50} values represent the IC_{50} values relative to untreated cells.

Table 12 shows the dose response of a free uptake screen in primary mouse hepatocytes with the indicated GalNAC conjugated modified iRNAs. The indicated IC_{50} values represent the IC_{50} values relative to untreated cells.

Table 13 shows the results of a single dose screen in Hep3B cells transfected with the indicated modified and unmodified iRNAs. Data are expressed as percent of message remaining relative to untreated cells. The 0.01nM dose was a single biological transfection and the 1nM dose was a duplicate biological transfection.

Table 14 shows the results of a single dose screen in primary mouse hepatocytes transfected with the indicated modified and unmodified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 15 shows the dose response in Hep3B cells transfected with the indicated modified and unmodified iRNAs. The indicated IC_{50} values represent the IC_{50} values relative to untreated cells.

Table 16 shows the dose response in primary mouse hepatocytes transfected with the indicated modified and unmodified iRNAs. The indicated IC_{50} values represent the IC_{50} values relative to untreated cells.

Table 2: Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds.

Abbreviation	**Nucleotide(s)**
A	Adenosine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Afs	2'-fluoroadenosine-3'-phosphorothioate
As	adenosine-3'-phosphorothioate
C	cytidine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Cfs	2'-fluorocytidine-3'-phosphorothioate
Cs	cytidine-3'-phosphorothioate
G	guanosine-3'-phosphate
Gf	2'-fluoroguanosine-3'-phosphate
Gfs	2'-fluoroguanosine-3'-phosphorothioate
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide (G, A, C, T or U)
a	2'-O-methyladenosine-3'-phosphate
as	2'-O-methyladenosine-3'- phosphorothioate
c	2'-O-methylcytidine-3'-phosphate
cs	2'-O-methylcytidine-3'- phosphorothioate
g	2'-O-methylguanosine-3'-phosphate
gs	2'-O-methylguanosine-3'- phosphorothioate

Abbreviation	Nucleotide(s)
t	2'-O-methyl-5-methyluridine-3'-phosphate
ts	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u	2'-O-methyluridine-3'-phosphate
us	2'-O-methyluridine-3'-phosphorothioate
s	phosphorothioate linkage
L96	N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol Hyp-(GalNAc-alkyl)3
(dt)	deoxy-thymine

Table 3. Unmodified Sense and Antisense Strand Sequences of C5 dsRNAs

Duplex ID	Sense strand	Sense Unmodified Sequence	SEQ ID NO:	Antisense	Antisense Unmodified Sequence	SEQ ID NO:	Species _ Oligo name[1]
AD-58093.1[2] UM[3]	A-118310.1	AAUAACUCACUAUAAUUACUU	15	A-118311.1	AAGUAAUUAUAGUGAGUUAUUUU	66	NM_001735.2_1517-1539_as
AD-58099.1 UM	A-118312.1	UGACAAAAUAACUCACUAUAA	16	A-118313.1	UUAUAGUGAGUUAUUUUGUCAAU	67	NM_001735.2_1511-1533_as
AD-58105.1 UM	A-118314.1	CUUCCUCUGGAAAUUGGCCUU	17	A-118315.1	AAGGCCAAUUUCCAGAGGAAGCA	68	NM_001735.2_2733-2755_as
AD-58111.1 UM	A-118316.1	GACAAAAUAACUCACUAUAAU	18	A-118317.1	AUUAUAGUGAGUUAUUUUGUCAA	69	NM_001735.2_1512-1534_as
AD-58117.1 UM	A-118318.1	UCCUCUGGAAAUUGGCCUUCA	19	A-118319.1	UGAAGGCCAAUUUCCAGAGGAAG	70	NM_001735.2_2735-2757_as
AD-58123.1 UM	A-118320.1	AAGCAAGAUAUUUUUAUAAUA	20	A-118321.1	UAUUAUAAAAAUAUCUUGCUUUU	71	NM_001735.2_784-806_as
AD-58129.1 UM	A-118322.1	AAAAUGUUUUUGUCAAGUACA	21	A-118323.1	UGUACUUGACAAAAACAUUUUCU	72	NM_001735.2_4744-4766_as
AD-58088.1 UM	A-118324.1	AUUUAAACAACAAGUACCUUU	22	A-118325.1	AAAGGUACUUGUUGUUUAAAUCU	73	NM_001735.2_982-1004_as
AD-58094.1 UM	A-118326.1	AUUCAGAAAGUCUGUGAAGGA	23	A-118327.1	UCCUUCACAGACUUUCUGAAUUU	74	NM_001735.2_4578-4600_as
AD-58100.1 UM	A-118328.1	ACACUGAAGCAUUUGAUGCAA	24	A-118329.1	UUGCAUCAAAUGCUUCAGUGUAU	75	NM_001735.2_169-191_as
AD-58106.1 UM	A-118330.1	GCAGUUCUGUGUUAAAAUGUC	25	A-118331.1	GACAUUUUAACACAGAACUGCAU	76	NM_001735.2_2591-2613_as
AD-58112.1 UM	A-118332.1	AGGAUUUUGAGUGUAAAAGGA	26	A-118333.1	UCCUUUUACACUCAAAAUCCUUU	77	NM_001735.2_2955-2977_as
AD-58118.1 UM	A-118334.1	AAUGAUGAACCUUGUAAAGAA	27	A-118335.1	UUCUUUACAAGGUUCAUCAUUUU	78	NM_001735.2_2025-2047_as
AD-58124.1 UM	A-118336.1	AUCAUUGGAACAUUUUUCAUU	28	A-118337.1	AAUGAAAAAUGUUCCAAUGAUUU	79	NM_001735.2_3118-3140_as
AD-58130.1 UM	A-118338.1	AGCCAGAAAUUCGGAGUUAUU	29	A-118339.1	AAUAACUCCGAAUUUCUGGCUUG	80	NM_001735.2_2317-2339_as
AD-58089.1 UM	A-118340.1	UCCCUGGGAGAUAAAACUCAC	30	A-118341.1	GUGAGUUUUAUCUCCCAGGGAAA	81	NM_001735.2_3618-3640_as
AD-58095.1 UM	A-118342.1	GAAAAUGAUGAACCUUGUAAA	31	A-118343.1	UUUACAAGGUUCAUCAUUUUCUU	82	NM_001735.2_2022-2044_as
AD-58101.1 UM	A-118344.1	AUUGCUCAAGUCACAUUUGAU	32	A-118345.1	AUCAAAUGUGACUUGAGCAAUUC	83	NM_001735.2_918-940_as
AD-58107.1 UM	A-118346.1	GAGAUUGCAUAUGCUUAUAAA	33	A-118347.1	UUUAUAAGCAUAUGCAAUCUCUG	84	NM_001735.2_4698-4720_as

[1] The Species Oligo name reflects the GenBank record (*e.g.*, NM_001735.2) and the position in the nucleotide sequence of the GenBank record (*e.g.*, 1517-1539) that the antisense strand targets.
[2] The number following the decimal point refers to the lot number.
[3] UM = unmodified

AD-58113.1 UM	A-118348.1	GUUAUCCUGAUAAAAAAUUUA	34	A-118349.1	UAAAUUUUUUAUCAGGAUAACUU	85	NM_001735.2_205-227_as
AD-58119.1 UM	A-118350.1	AGGAAGUUUGCAGCUUUUAUU	35	A-118351.1	AAUAAAAGCUGCAAACUUCCUCA	86	NM_001735.2_4147-4169_as
AD-58125.1 UM	A-118352.1	GAAGAAAUUGAUCAUAUUGGA	36	A-118353.1	UCCAAUAUGAUCAAUUUCUUCUA	87	NM_001735.2_555-577_as
AD-58131.1 UM	A-118354.1	AUCCUGAUAAAAAAUUUAGUU	37	A-118355.1	AACUAAAAUUUUUUAUCAGGAUAA	88	NM_001735.2_208-230_as
AD-58090.1 UM	A-118356.1	UGGAAAAGAAAUCUUAGUAAA	38	A-118357.1	UUUACUAAGAUUUCUUUUCCAAA	89	NM_001735.2_2786-2808_as
AD-58096.1 UM	A-118358.1	UCUUAUCAAAGUAUAAACAUU	39	A-118359.1	AAUGUUUAUACUUUGAUAAGAUG	90	NM_001735.2_1596-1618_as
AD-58102.1 UM	A-118360.1	UCCCUACAAACUGAAUUUGGU	40	A-118361.1	ACCAAAUUCAGUUUGUAGGGAGA	91	NM_001735.2_1082-1104_as
AD-58108.1 UM	A-118362.1	CAGGAGCAAACAUAUGUCAUU	41	A-118363.1	AAUGACAUAUGUUUGCUCCUGUC	92	NM_001735.2_87-109_as
AD-58114.1 UM	A-118364.1	ACAUGUAACAACUGUAGUUCA	42	A-118365.1	UGAACUACAGUUGUUACAUGUAC	93	NM_001735.2_4109-4131_as
AD-58120.1 UM	A-118366.1	CAGGAAAUCAUUGGAACAUUU	43	A-118367.1	AAAUGUUCCAAUGAUUUCCUGUU	94	NM_001735.2_3112-3134_as
AD-58126.1 UM	A-118368.1	UUUAAGAAUUUUGAAAUUACU	44	A-118369.1	AGUAAUUUCAAAAUUCUUAAAGU	95	NM_001735.2_759-781_as
AD-58132.1 UM	A-118370.1	UAUUCUGCAACUGAAUUCGAU	45	A-118371.1	AUCGAAUUCAGUUGCAGAAUAAC	96	NM_001735.2_4412-4434_as
AD-58091.1 UM	A-118372.1	GCCCUUGGAAAGAGUAUUUCA	46	A-118373.1	UGAAAUACUCUUUCCAAGGGCUU	97	NM_001735.2_1886-1908_as
AD-58097.1 UM	A-118374.1	CCUGAUAAAAAAUUUAGUUAC	47	A-118375.1	GUAACUAAAUUUUUUAUCAGGAU	98	NM_001735.2_210-232_as
AD-58103.1 UM	A-118376.1	CCCUUGGAAAGAGUAUUUCAA	48	A-118377.1	UUGAAAUACUCUUUCCAAGGGCU	99	NM_001735.2_1887-1909_as
AD-58121.1 UM	A-118382.1	UGCAGAUCAAACACAAUUUCA	49	A-118383.1	UGAAAUUGUGUUUGAUCUGCAGA	100	NM_010406.2_4943-4965_as
AD-58133.1 UM	A-118386.1	CAGAUCAAACACAAUUUCAGU	50	A-118387.1	ACUGAAAUUGUGUUUGAUCUGCA	101	NM_010406.2_4945-4967_as
AD-58116.1 UM	A-118396.1	GUUCCGGAUAUUUGAACUUUU	51	A-118397.1	AAAAGUUCAAAUAUCCGGAACCG	102	NM_010406.2_4500-4522_as
AD-58644.1 UM	A-119328.1	AUUUAAACAACAAGUACCUUU	52	A-119329.1	AAAGGUACUUGUUGUUUAAAUCU	103	NM_001735.2_982-1004_as
AD-58651.1 UM	A-119328.2	AUUUAAACAACAAGUACCUUU	53	A-119339.1	AAAGGUACUUGUUGUUUAAAUCU	104	NM_001735.2_982-1004_as
AD-58641.1 UM	A-119322.1	UGACAAAAUAACUCACUAUAA	54	A-119323.1	UUAUAGUGAGUUAUUUUGUCAAU	105	NM_001735.2_1511-1533_as
AD-58648.1 UM	A-119322.2	UGACAAAAUAACUCACUAUAA	55	A-119336.1	UUAUAGUGAGUUAUUUUGUCAAU	106	NM_001735.2_1511-1533_as
AD-58642.1 UM	A-119324.1	GACAAAAUAACUCACUAUAAU	56	A-119325.1	AUUAUAGUGAGUUAUUUUGUCAA	107	NM_001735.2_1512-1534_as
AD-58649.1 UM	A-119324.2	GACAAAAUAACUCACUAUAAU	57	A-119337.1	AUUAUAGUGAGUUAUUUUGUCAA	108	NM_001735.2_1512-1534_as
AD-58647.1 UM	A-119334.1	GUUCCGGAUAUUUGAACUUUU	58	A-119335.1	AAAAGUUCAAAUAUCCGGAACCG	109	NM_010406.2_4500-4522_as
AD-58654.1 UM	A-119334.2	GUUCCGGAUAUUUGAACUUUU	59	A-119342.1	AAAAGUUCAAAUAUCCGGAACCG	110	NM_010406.2_4500-4522_as
AD-58645.1 UM	A-119330.1	UGCAGAUCAAACACAAUUUCA	60	A-119331.1	UGAAAUUGUGUUUGAUCUGCAGA	111	NM_010406.2_4943-4965_as

AD-58652.1 UM	A-119330.2	UGCAGAUCAAACACAAUUUCA	61	A-119340.1	UGAAAUUGUGUUUGAUCUGCAGA	112	NM_010406.2_4943-4965_as
AD-58649.1 UM	A-119326.1	AAGCAAGAUAUUUUUAUAAUA	62	A-119327.1	UAUUAUAAAAAUAUCUUGCUUUU	113	NM_001735.2_784-806_as
AD-58650.1 UM	A-119326.2	AAGCAAGAUAUUUUUAUAAUA	63	A-119338.1	UAUUAUAAAAAUAUCUUGCUUUU	114	NM_001735.2_784-806_as
AD-58646.1 UM	A-119332.1	CAGAUCAAACACAAUUUCAGU	64	A-119333.1	ACUGAAAUUGUGUUUGAUCUGCA	115	NM_010406.2_4945-4967_as
AD-58653.1 UM	A-119332.2	CAGAUCAAACACAAUUUCAGU	65	A-119341.1	ACUGAAAUUGUGUUUGAUCUGCA	116	NM_010406.2_4945-4967_as

Table 4. GalNAC Conujugated Modified Sense and Antisense Strand Sequences of C5 dsRNAs

Duplex ID	Sense strand	Sense sequence	SEQ ID NO:	Antisense	Antisense sequence	SEQ ID NO:	Species _ Oligo name[4]
AD-58093.1	A-118310.1	AfaUfaAfcUfcAfCfUfaUfaAfuUfaCfuUfL96	117	A-118311.1	aAfgUfaAfuUfaUfaguGfaGfuUfaUfusUfsu	168	
AD-58099.1	A-118312.1	UfgAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	118	A-118313.1	uUfaUfaGfuGfaGfuuaUfuUfuGfuCfasAfsu	169	
AD-58105.1	A-118314.1	CfuUfcCfuCfuGfGfAfaAfuUfgGfcCfuUfL96	119	A-118315.1	aAfgGfcCfaAfuUfuccAfgAfgGfaAfgsCfsa	170	
AD-58111.1	A-118316.1	GfaCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	120	A-118317.1	aUfuAfuAfgUfgAfguuAfuUfuUfgUfcsAfsa	171	
AD-58117.1	A-118318.1	UfcCfuCfuGfgAfAfAfuUfgGfcCfuUfcAfL96	121	A-118319.1	uGfaAfgGfcCfaAfuuuCfcAfgAfgGfasAfsg	172	
AD-58123.1	A-118320.1	AfaGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	122	A-118321.1	uAfuUfaUfaAfaAfauaUfcUfuGfcUfusUfsu	173	
AD-58129.1	A-118322.1	AfaAfaUfgUfuUfUfUfgUfcAfaGfuAfcAfL96	123	A-118323.1	uGfuAfcUfuGfaCfaaaAfaCfaUfuUfusCfsu	174	
AD-58088.1	A-118324.1	AfuUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	124	A-118325.1	aAfaGfgUfaCfuUfguuGfuUfuAfaAfusCfsu	175	
AD-58094.1	A-118326.1	AfuUfcAfgAfaAfGfUfcUfgUfgAfaGfgAfL96	125	A-118327.1	uCfcUfuCfaCfaGfacuUfuCfuGfaAfusUfsu	176	
AD-58100.1	A-118328.1	AfcAfcUfgAfaGfCfAfuUfuGfaUfgCfaAfL96	126	A-118329.1	uUfgCfaUfcAfaAfugcUfuCfaGfuGfusAfsu	177	
AD-58106.1	A-118330.1	GfcAfgUfuCfuGfUfGfuUfaAfaAfuGfuCfL96	127	A-118331.1	gAfcAfuUfuUfaAfcacAfgAfaCfuGfcsAfsu	178	
AD-58112.1	A-118332.1	AfgGfaUfuUfuGfAfGfuGfuAfaAfaGfgAfL96	128	A-118333.1	uCfcUfuUfuAfcAfcucAfaAfaUfcCfusUfsu	179	
AD-58118.1	A-118334.1	AfaUfgAfuGfaAfCfCfuUfgUfaAfaGfaAfL96	129	A-118335.1	uUfcUfuUfaCfaAfgguUfcAfuCfaUfusUfsu	180	
AD-58124.1	A-118336.1	AfuCfaUfuGfgAfAfCfaUfuUfuUfcAfuUfL96	130	A-118337.1	aAfuGfaAfaAfaUfguuCfcAfaUfgAfusUfsu	181	
AD-58130.1	A-118338.1	AfgCfcAfgAfaAfUfUfcGfgAfgUfuAfuUfL96	131	A-118339.1	aAfuAfaCfuCfcGfaauUfuCfuGfgCfusUfsg	182	
AD-58089.1	A-118340.1	UfcCfcUfgGfgAfGfAfuAfaAfaCfuCfaCfL96	132	A-118341.1	gUfgAfgUfuUfuAfucuCfcCfaGfgGfasAfsa	183	
AD-58095.1	A-118342.1	GfaAfaAfuGfaUfGfAfaCfcUfuGfuAfaAfL96	133	A-118343.1	uUfuAfcAfaGfgUfucaUfcAfuUfuUfcsUfsu	184	

AD-58101.1	A-118344.1	AfuUfgCfuCfaAfGfUfcAfcAfuUfuGfaUfL96	134	A-118345.1	aUfcAfaAfuGfuGfacuUfgAfgCfaAfusUfsc	185	
AD-58107.1	A-118346.1	GfaGfaUfuGfcAfUfAfuGfcUfuAfuAfaAfL96	135	A-118347.1	uUfuAfuAfaGfcAfuauGfcAfaUfcUfcsUfsg	186	
AD-58113.1	A-118348.1	GfuUfaUfcCfuGfAfUfaAfaAfaAfuUfuAfL96	136	A-118349.1	uAfaAfuUfuUfuUfaucAfgGfaUfaAfcsUfsu	187	
AD-58119.1	A-118350.1	AfgGfaAfgUfuUfGfCfaGfcUfuUfuAfuUfL96	137	A-118351.1	aAfuAfaAfaGfcUfgcaAfaCfuUfcCfusCfsa	188	
AD-58125.1	A-118352.1	GfaAfgAfaAfuUfGfAfuCfaUfaUfuGfgAfL96	138	A-118353.1	uCfcAfaUfaUfgAfucaAfuUfuCfuUfcsUfsa	189	
AD-58131.1	A-118354.1	AfuCfcUfgAfuAfAfAfaAfaUfuUfaGfuUfL96	139	A-118355.1	aAfcUfaAfaUfuUfuuuAfuCfaGfgAfusAfsa	190	
AD-58090.1	A-118356.1	UfgGfaAfaAfgAfAfAfuCfuUfaGfuAfaAfL96	140	A-118357.1	uUfuAfcUfaAfgAfuuuCfuUfuUfcCfasAfsa	191	
AD-58096.1	A-118358.1	UfcUfuAfuCfaAfAfGfuAfuAfaAfcAfuUfL96	141	A-118359.1	aAfuGfuUfuAfuAfcuuUfgAfuAfaGfasUfsg	192	
AD-58102.1	A-118360.1	UfcCfcUfaCfaAfAfCfuGfaAfuUfuGfgUfL96	142	A-118361.1	aCfcAfaAfuUfcAfguuUfgUfaGfgGfasGfsa	193	
AD-58108.1	A-118362.1	CfaGfgAfgCfaAfAfCfaUfaUfgUfcAfuUfL96	143	A-118363.1	aAfuGfaCfaUfaUfguuUfgCfuCfcUfgsUfsc	194	
AD-58114.1	A-118364.1	AfcAfuGfuAfaCfAfAfcUfgUfaGfuUfcAfL96	144	A-118365.1	uGfaAfcUfaCfaGfuugUfuAfcAfuGfusAfsc	195	
AD-58120.1	A-118366.1	CfaGfgAfaAfuCfAfUfuGfgAfaCfaUfuUfL96	145	A-118367.1	aAfaUfgUfuCfcAfaugAfuUfuCfcUfgsUfsu	196	
AD-58126.1	A-118368.1	UfuUfaAfgAfaUfUfUfuGfaAfaUfuAfcUfL96	146	A-118369.1	aGfuAfaUfuUfcAfaaaUfuCfuUfaAfasGfsu	197	
AD-58132.1	A-118370.1	UfaUfuCfuGfcAfAfCfuGfaAfuUfcGfaUfL96	147	A-118371.1	aUfcGfaAfuUfcAfguuGfcAfgAfaUfasAfsc	198	
AD-58091.1	A-118372.1	GfcCfcUfuGfgAfAfAfgAfgUfaUfuUfcAfL96	148	A-118373.1	uGfaAfaUfaCfuCfuuuCfcAfaGfgGfcsUfsu	199	
AD-58097.1	A-118374.1	CfcUfgAfuAfaAfAfAfaUfuUfaGfuUfaCfL96	149	A-118375.1	gUfaAfcUfaAfaUfuuuUfuAfuCfaGfgsAfsu	200	
AD-58103.1	A-118376.1	CfcCfuUfgGfaAfAfGfaGfuAfuUfuCfaAfL96	150	A-118377.1	uUfgAfaAfuAfcUfcuuUfcCfaAfgGfgsCfsu	201	
AD-58121.1	A-118382.1	UfgCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	151	A-118383.1	uGfaAfaUfuGfuGfuuuGfaUfcUfgCfasGfsa	202	
AD-58133.1	A-118386.1	CfaGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	152	A-118387.1	aCfuGfaAfaUfuGfuguUfuGfaUfcUfgsCfsa	203	
AD-58116.1	A-118396.1	GfuUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	153	A-118397.1	aAfaAfgUfuCfaAfauaUfcCfgGfaAfcsCfsg	204	
AD-58644.1	A-119328.1	AfsusUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	154	A-119329.1	asAfsaGfgUfaCfuUfguuGfuUfuAfaAfuscsu	205	
AD-58651.1	A-119328.2	AfsusUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	155	A-119339.1	asAfsaGfsgUfsaCfsuUfsguuGfsuUfsuAfsaAfsuscsu	206	
AD-58641.1	A-119322.1	UfsgsAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	156	A-119323.1	usUfsaUfaGfuGfaGfuuaUfuUfuGfuCfasasu	207	
AD-58648.1	A-119322.2	UfsgsAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	157	A-119336.1	usUfsaUfsaGfsuGfsaGfsuuaUfsuUfsuGfsuCfsasasu	208	
AD-58642.1	A-119324.1	GfsasCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	158	A-119325.1	asUfsuAfuAfgUfgAfguuAfuUfuUfgUfcsasa	209	
AD-58649.1	A-119324.2	GfsasCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	159	A-119337.1	asUfsuAfsuAfsgUfsgAfsguuAfsuUfsuUfsgUfscsasa	210	
AD-58647.1	A-119334.1	GfsusUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	160	A-119335.1	asAfsaAfgUfuCfaAfauaUfcCfgGfaAfcscsg	211	

AD-58654.1	A-119334.2	GfsusUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	161	A-119342.1	asAfsaAfsgUfsuCfsaAfsauaUfscCfsgGfsaAfscscsg	212	
AD-58645.1	A-119330.1	UfsgsCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	162	A-119331.1	usGfsaAfaUfuGfuGfuuuGfaUfcUfgCfasgsa	213	
AD-58652.1	A-119330.2	UfsgsCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	163	A-119340.1	usGfsaAfsaUfsuGfsuGfsuuuGfsaUfscUfsgCfsasgsa	214	
AD-58643.1	A-119326.1	AfsasGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	164	A-119327.1	usAfsuUfaUfaAfaAfauaUfcUfuGfcUfususu	215	
AD-58650.1	A-119326.2	AfsasGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	165	A-119338.1	usAfsuUfsaUfsaAfsaAfsauaUfscUfsuGfscUfsususu	216	
AD-58646.1	A-119332.1	CfsasGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	166	A-119333.1	asCfsuGfaAfaUfuGfuguUfuGfaUfcUfgscsa	217	
AD-58653.1	A-119332.2	CfsasGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	167	A-119341.1	asCfsuGfsaAfsaUfsuGfsuguUfsuGfsaUfscUfsgscsa	218	

[4] The Species Oligo name and the position in the nucleotide sequence of the GenBank record that the antisense strand targets correspond to those shown in Table 3.

Table 5. Unmodified Sense and Antisense Strand Sequences of C5 dsRNAs

Duplex ID	Sense strand	Sense Unmodified Sequence	SEQ ID NO:	Antisense	Antisense Unmodified Sequence	SEQ ID NO:	Species _ Oligo name
AD-58143.1 UM	A-118423.1	CACUAUAAUUACUUGAUUU	219	A-118424.1	AAAUCAAGUAAUUAUAGUG	302	NM_001735.2_1522-1540_as
AD-58149.1 UM	A-118425.1	UAACUCACUAUAAUUACUU	220	A-118426.1	AAGUAAUUAUAGUGAGUUA	303	NM_001735.2_1517-1535_as
AD-58155.1 UM	A-118427.1	ACAAAAUAACUCACUAUAA	221	A-118428.1	UUAUAGUGAGUUAUUUUGU	304	NM_001735.2_1511-1529_as
AD-58161.1 UM	A-118429.1	UCCUCUGGAAAUUGGCCUU	222	A-118430.1	AAGGCCAAUUUCCAGAGGA	305	NM_001735.2_2733-2751_as
AD-58167.1 UM	A-118431.1	CAAAAUAACUCACUAUAAU	223	A-118432.1	AUUAUAGUGAGUUAUUUUG	306	NM_001735.2_1512-1530_as
AD-58173.1 UM	A-118433.1	CUCUGGAAAUUGGCCUUCA	224	A-118434.1	UGAAGGCCAAUUUCCAGAG	307	NM_001735.2_2735-2753_as
AD-58179.1 UM	A-118435.1	GCAAGAUAUUUUUAUAAUA	225	A-118436.1	UAUUAUAAAAAUAUCUUGC	308	NM_001735.2_784-802_as
AD-58185.1 UM	A-118437.1	AAUGUUUUUGUCAAGUACA	226	A-118438.1	UGUACUUGACAAAAACAUU	309	NM_001735.2_4744-4762_as
AD-58144.1 UM	A-118439.1	UUAAACAACAAGUACCUUU	227	A-118440.1	AAAGGUACUUGUUGUUUAA	310	NM_001735.2_982-1000_as
AD-58150.1 UM	A-118441.1	UCAGAAAGUCUGUGAAGGA	228	A-118442.1	UCCUUCACAGACUUUCUGA	311	NM_001735.2_4578-4596_as
AD-58156.1 UM	A-118443.1	ACUGAAGCAUUUGAUGCAA	229	A-118444.1	UUGCAUCAAAUGCUUCAGU	312	NM_001735.2_169-187_as
AD-58162.1 UM	A-118445.1	AGUUCUGUGUUAAAAUGUC	230	A-118446.1	GACAUUUUAACACAGAACU	313	NM_001735.2_2591-2609_as
AD-58168.1 UM	A-118447.1	GAUUUUGAGUGUAAAAGGA	231	A-118448.1	UCCUUUUACACUCAAAAUC	314	NM_001735.2_2955-2973_as
AD-58174.1 UM	A-118449.1	UGAUGAACCUUGUAAAGAA	232	A-118450.1	UUCUUUACAAGGUUCAUCA	315	NM_001735.2_2025-2043_as
AD-58180.1 UM	A-118451.1	CAUUGGAACAUUUUUCAUU	233	A-118452.1	AAUGAAAAAUGUUCCAAUG	316	NM_001735.2_3118-3136_as

AD-58186.1 UM	A-118453.1	CCAGAAAUUCGGAGUUAUU	234	A-118454.1	AAUAACUCCGAAUUUCUGG	317	NM_001735.2_2317-2335_as
AD-58145.1 UM	A-118455.1	CCUGGGAGAUAAAACUCAC	235	A-118456.1	GUGAGUUUUAUCUCCCAGG	318	NM_001735.2_3618-3636_as
AD-58151.1 UM	A-118457.1	AAAUGAUGAACCUUGUAAA	236	A-118458.1	UUUACAAGGUUCAUCAUUU	319	NM_001735.2_2022-2040_as
AD-58157.1 UM	A-118459.1	UGCUCAAGUCACAUUUGAU	237	A-118460.1	AUCAAAUGUGACUUGAGCA	320	NM_001735.2_918-936_as
AD-58163.1 UM	A-118461.1	GAUUGCAUAUGCUUAUAAA	238	A-118462.1	UUUAUAAGCAUAUGCAAUC	321	NM_001735.2_4698-4716_as
AD-58169.1 UM	A-118463.1	UAUCCUGAUAAAAAAUUUA	239	A-118464.1	UAAAUUUUUUAUCAGGAUA	322	NM_001735.2_205-223_as
AD-58175.1 UM	A-118465.1	GAAGUUUGCAGCUUUUAUU	240	A-118466.1	AAUAAAAGCUGCAAACUUC	323	NM_001735.2_4147-4165_as
AD-58181.1 UM	A-118467.1	AGAAAUUGAUCAUAUUGGA	241	A-118468.1	UCCAAUAUGAUCAAUUUCU	324	NM_001735.2_555-573_as
AD-58187.1 UM	A-118469.1	CCUGAUAAAAAAUUUAGUU	242	A-118470.1	AACUAAAUUUUUUAUCAGG	325	NM_001735.2_208-226_as
AD-58146.1 UM	A-118471.1	GAAAAGAAAUCUUAGUAAA	243	A-118472.1	UUUACUAAGAUUUCUUUUC	326	NM_001735.2_2786-2804_as
AD-58152.1 UM	A-118473.1	UUAUCAAAGUAUAAACAUU	244	A-118474.1	AAUGUUUAUACUUUGAUAA	327	NM_001735.2_1596-1614_as
AD-58158.1 UM	A-118475.1	CCUACAAACUGAAUUUGGU	245	A-118476.1	ACCAAAUUCAGUUUGUAGG	328	NM_001735.2_1082-1100_as
AD-58164.1 UM	A-118477.1	GGAGCAAACAUAUGUCAUU	246	A-118478.1	AAUGACAUAUGUUUGCUCC	329	NM_001735.2_87-105_as
AD-58170.1 UM	A-118479.1	AUGUAACAACUGUAGUUCA	247	A-118480.1	UGAACUACAGUUGUUACAU	330	NM_001735.2_4109-4127_as
AD-58176.1 UM	A-118481.1	GGAAAUCAUUGGAACAUUU	248	A-118482.1	AAAUGUUCCAAUGAUUUCC	331	NM_001735.2_3112-3130_as
AD-58182.1 UM	A-118483.1	UAAGAAUUUUGAAAUUACU	249	A-118484.1	AGUAAUUUCAAAAUUCUUA	332	NM_001735.2_759-777_as
AD-58188.1 UM	A-118485.1	UUCUGCAACUGAAUUCGAU	250	A-118486.1	AUCGAAUUCAGUUGCAGAA	333	NM_001735.2_4412-4430_as
AD-58147.1 UM	A-118487.1	CCUUGGAAAGAGUAUUUCA	251	A-118488.1	UGAAAUACUCUUUCCAAGG	334	NM_001735.2_1886-1904_as
AD-58153.1 UM	A-118489.1	UGAUAAAAAAUUUAGUUAC	252	A-118490.1	GUAACUAAAUUUUUUAUCA	335	NM_001735.2_210-228_as
AD-58159.1 UM	A-118491.1	CUUGGAAAGAGUAUUUCAA	253	A-118492.1	UUGAAAUACUCUUUCCAAG	336	NM_001735.2_1887-1905_as
AD-58190.1 UM	A-118519.1	CACUAUAAUUACUUGAUUU	254	A-118520.1	AAAUCAAGUAAUUAUAGUG	337	NM_001735.2_1522-1540_as
AD-58196.1 UM	A-118521.1	UAACUCACUAUAAUUACUU	255	A-118522.1	AAGUAAUUAUAGUGAGUUA	338	NM_001735.2_1517-1535_as
AD-58202.1 UM	A-118523.1	ACAAAAUAACUCACUAUAA	256	A-118524.1	UUAUAGUGAGUUAUUUUGU	339	NM_001735.2_1511-1529_as
AD-58208.1 UM	A-118525.1	UCCUCUGGAAAUUGGCCUU	257	A-118526.1	AAGGCCAAUUUCCAGAGGA	340	NM_001735.2_2733-2751_as
AD-58214.1 UM	A-118527.1	CAAAAUAACUCACUAUAAU	258	A-118528.1	AUUAUAGUGAGUUAUUUUG	341	NM_001735.2_1512-1530_as
AD-58220.1 UM	A-118529.1	CUCUGGAAAUUGGCCUUCA	259	A-118530.1	UGAAGGCCAAUUUCCAGAG	342	NM_001735.2_2735-2753_as
AD-58226.1 UM	A-118531.1	GCAAGAUAUUUUUAUAAUA	260	A-118532.1	UAUUAUAAAAAUAUCUUGC	343	NM_001735.2_784-802_as

AD-58231.1 UM	A-118533.1	AAUGUUUUUGUCAAGUACA	261	A-118534.1	UGUACUUGACAAAAACAUU	344	NM_001735.2_4744-4762_as
AD-58191.1 UM	A-118535.1	UUAAACAACAAGUACCUUU	262	A-118536.1	AAAGGUACUUGUUGUUUAA	345	NM_001735.2_982-1000_as
AD-58197.1 UM	A-118537.1	UCAGAAAGUCUGUGAAGGA	263	A-118538.1	UCCUUCACAGACUUUCUGA	346	NM_001735.2_4578-4596_as
AD-58203.1 UM	A-118539.1	ACUGAAGCAUUUGAUGCAA	264	A-118540.1	UUGCAUCAAAUGCUUCAGU	347	NM_001735.2_169-187_as
AD-58209.1 UM	A-118541.1	AGUUCUGUGUUAAAAUGUC	265	A-118542.1	GACAUUUUAACACAGAACU	348	NM_001735.2_2591-2609_as
AD-58233.1 UM	A-118565.1	CACUAUAAUUACUUGAUUU	266	A-118566.1	AAAUCAAGUAAUUAUAGUG	349	NM_001735.2_1522-1540_as
AD-58193.1 UM	A-118567.1	UAACUCACUAUAAUUACUU	267	A-118568.1	AAGUAAUUAUAGUGAGUUA	350	NM_001735.2_1517-1535_as
AD-58199.1 UM	A-118569.1	ACAAAAUAACUCACUAUAA	268	A-118570.1	UUAUAGUGAGUUAUUUUGU	351	NM_001735.2_1511-1529_as
AD-58205.1 UM	A-118571.1	UCCUCUGGAAAUUGGCCUU	269	A-118572.1	AAGGCCAAUUUCCAGAGGA	352	NM_001735.2_2733-2751_as
AD-58211.1 UM	A-118573.1	CAAAAUAACUCACUAUAAU	270	A-118574.1	AUUAUAGUGAGUUAUUUUG	353	NM_001735.2_1512-1530_as
AD-58217.1 UM	A-118575.1	CUCUGGAAAUUGGCCUUCA	271	A-118576.1	UGAAGGCCAAUUUCCAGAG	354	NM_001735.2_2735-2753_as
AD-58223.1 UM	A-118577.1	GCAAGAUAUUUUUAUAAUA	272	A-118578.1	UAUUAUAAAAAUAUCUUGC	355	NM_001735.2_784-802_as
AD-58229.1 UM	A-118579.1	AAUGUUUUUGUCAAGUACA	273	A-118580.1	UGUACUUGACAAAAACAUU	356	NM_001735.2_4744-4762_as
AD-58234.1 UM	A-118581.1	UUAAACAACAAGUACCUUU	274	A-118582.1	AAAGGUACUUGUUGUUUAA	357	NM_001735.2_982-1000_as
AD-58194.1 UM	A-118583.1	UCAGAAAGUCUGUGAAGGA	275	A-118584.1	UCCUUCACAGACUUUCUGA	358	NM_001735.2_4578-4596_as
AD-58200.1 UM	A-118585.1	ACUGAAGCAUUUGAUGCAA	276	A-118586.1	UUGCAUCAAAUGCUUCAGU	359	NM_001735.2_169-187_as
AD-58206.1 UM	A-118587.1	AGUUCUGUGUUAAAAUGUC	277	A-118588.1	GACAUUUUAACACAGAACU	360	NM_001735.2_2591-2609_as
AD-58236.1 UM	A-118423.2	CACUAUAAUUACUUGAUUU	278	A-118644.1	AAAUCAAGUAAUUAUAGUG	361	NM_001735.2_1522-1540_as
AD-58242.1 UM	A-118425.2	UAACUCACUAUAAUUACUU	279	A-118645.1	AAGUAAUUAUAGUGAGUUA	362	NM_001735.2_1517-1535_as
AD-58248.1 UM	A-118427.2	ACAAAAUAACUCACUAUAA	280	A-118646.1	UUAUAGUGAGUUAUUUUGU	363	NM_001735.2_1511-1529_as
AD-58254.1 UM	A-118429.2	UCCUCUGGAAAUUGGCCUU	281	A-118647.1	AAGGCCAAUUUCCAGAGGA	364	NM_001735.2_2733-2751_as
AD-58260.1 UM	A-118431.2	CAAAAUAACUCACUAUAAU	282	A-118648.1	AUUAUAGUGAGUUAUUUUG	365	NM_001735.2_1512-1530_as
AD-58266.1 UM	A-118433.2	CUCUGGAAAUUGGCCUUCA	283	A-118649.1	UGAAGGCCAAUUUCCAGAG	366	NM_001735.2_2735-2753_as
AD-58272.1 UM	A-118435.2	GCAAGAUAUUUUUAUAAUA	284	A-118650.1	UAUUAUAAAAAUAUCUUGC	367	NM_001735.2_784-802_as
AD-58277.1 UM	A-118437.2	AAUGUUUUUGUCAAGUACA	285	A-118651.1	UGUACUUGACAAAAACAUU	368	NM_001735.2_4744-4762_as
AD-58237.1 UM	A-118439.2	UUAAACAACAAGUACCUUU	286	A-118652.1	AAAGGUACUUGUUGUUUAA	369	NM_001735.2_982-1000_as
AD-58243.1 UM	A-118441.2	UCAGAAAGUCUGUGAAGGA	287	A-118653.1	UCCUUCACAGACUUUCUGA	370	NM_001735.2_4578-4596_as

AD-58249.1 UM	A-118443.2	ACUGAAGCAUUUGAUGCAA	288	A-118654.1	UUGCAUCAAAUGCUUCAGU	371	NM_001735.2_169-187_as
AD-58255.1 UM	A-118445.2	AGUUCUGUGUUAAAAUGUC	289	A-118655.1	GACAUUUUAACACAGAACU	372	NM_001735.2_2591-2609_as
AD-58279.1 UM	A-118423.3	CACUAUAAUUACUUGAUUU	290	A-118667.1	AAAUCAAGUAAUUAUAGUG	373	NM_001735.2_1522-1540_as
AD-58239.1 UM	A-118425.3	UAACUCACUAUAAUUACUU	291	A-118668.1	AAGUAAUUAUAGUGAGUUA	374	NM_001735.2_1517-1535_as
AD-58245.1 UM	A-118427.3	ACAAAAUAACUCACUAUAA	292	A-118669.1	UUAUAGUGAGUUAUUUUGU	375	NM_001735.2_1511-1529_as
AD-58251.1 UM	A-118429.3	UCCUCUGGAAAUUGGCCUU	293	A-118670.1	AAGGCCAAUUUCCAGAGGA	376	NM_001735.2_2733-2751_as
AD-58257.1 UM	A-118431.3	CAAAAUAACUCACUAUAAU	294	A-118671.1	AUUAUAGUGAGUUAUUUUG	377	NM_001735.2_1512-1530_as
AD-58263.1 UM	A-118433.3	CUCUGGAAAUUGGCCUUCA	295	A-118672.1	UGAAGGCCAAUUUCCAGAG	378	NM_001735.2_2735-2753_as
AD-58269.1 UM	A-118435.3	GCAAGAUAUUUUUAUAAUA	296	A-118673.1	UAUUAUAAAAAUAUCUUGC	379	NM_001735.2_784-802_as
AD-58275.1 UM	A-118437.3	AAUGUUUUUGUCAAGUACA	297	A-118674.1	UGUACUUGACAAAAACAUU	380	NM_001735.2_4744-4762_as
AD-58280.1 UM	A-118439.3	UUAAACAACAAGUACCUUU	298	A-118675.1	AAAGGUACUUGUUGUUUAA	381	NM_001735.2_982-1000_as
AD-58240.1 UM	A-118441.3	UCAGAAAGUCUGUGAAGGA	299	A-118676.1	UCCUUCACAGACUUUCUGA	382	NM_001735.2_4578-4596_as
AD-58246.1 UM	A-118443.3	ACUGAAGCAUUUGAUGCAA	300	A-118677.1	UUGCAUCAAAUGCUUCAGU	383	NM_001735.2_169-187_as
AD-58252.1 UM	A-118445.3	AGUUCUGUGUUAAAAUGUC	301	A-118678.1	GACAUUUUAACACAGAACU	384	NM_001735.2_2591-2609_as

Table 6. Modified Sense and Antisense Strand Sequences of C5 dsRNAs

Duplex ID	Sense strand	Sense sequence	SEQ ID NO:	Antisense	Antisense sequence	SEQ ID NO:	Species_Oligo name[5]
AD-58143.1	A-118423.1	cAcuAuAAuuAcuuGAuuudTsdT	385	A-118424.1	AAAUcAAGuAAUuAuAGUGdTsdT	468	
AD-58149.1	A-118425.1	uAAcucAcuAuAAuuAcuudTsdT	386	A-118426.1	AAGuAAUuAuAGUGAGUuAdTsdT	469	
AD-58155.1	A-118427.1	AcAAAAuAAcucAcuAuAAdTsdT	387	A-118428.1	UuAuAGUGAGUuAUUUUGUdTsdT	470	
AD-58161.1	A-118429.1	uccucuGGAAAuuGGccuudTsdT	388	A-118430.1	AAGGCcAAUUUCcAGAGGAdTsdT	471	
AD-58167.1	A-118431.1	cAAAAuAAcucAcuAuAAudTsdT	389	A-118432.1	AUuAuAGUGAGUuAUUUUGdTsdT	472	
AD-58173.1	A-118433.1	cucuGGAAAuuGGccuucAdTsdT	390	A-118434.1	UGAAGGCcAAUUUCcAGAGdTsdT	473	
AD-58179.1	A-118435.1	GcAAGAuAuuuuuAuAAuAdTsdT	391	A-118436.1	uAUuAuAAAAAuAUCUUGCdTsdT	474	
AD-58185.1	A-118437.1	AAuGuuuuuGucAAGuAcAdTsdT	392	A-118438.1	UGuACUUGAcAAAAAcAUUdTsdT	475	

AD-58144.1	A-118439.1	uuAAAcAAcAAGuAccuuudTsdT	393	A-118440.1	AAAGGuACUUGUUGUUuAAdTsdT	476	
AD-58150.1	A-118441.1	ucAGAAAGucuGuGAAGGAdTsdT	394	A-118442.1	UCCUUcAcAGACUUUCUGAdTsdT	477	
AD-58156.1	A-118443.1	AcuGAAGcAuuuGAuGcAAdTsdT	395	A-118444.1	UUGcAUcAAAUGCUUcAGUdTsdT	478	
AD-58162.1	A-118445.1	AGuucuGuGuuAAAAuGucdTsdT	396	A-118446.1	GAcAUUUuAAcAcAGAACUdTsdT	479	
AD-58168.1	A-118447.1	GAuuuuGAGuGuAAAAGGAdTsdT	397	A-118448.1	UCCUUUuAcACUcAAAAUCdTsdT	480	
AD-58174.1	A-118449.1	uGAuGAAccuuGuAAAGAAdTsdT	398	A-118450.1	UUCUUuAcAAGGUUcAUcAdTsdT	481	
AD-58180.1	A-118451.1	cAuuGGAAcAuuuuucAuudTsdT	399	A-118452.1	AAUGAAAAAUGUUCcAAUGdTsdT	482	
AD-58186.1	A-118453.1	ccAGAAAuucGGAGuuAuudTsdT	400	A-118454.1	AAuAACUCCGAAUUUCUGGdTsdT	483	
AD-58145.1	A-118455.1	ccuGGGAGAuAAAAcucAcdTsdT	401	A-118456.1	GUGAGUUUuAUCUCCcAGGdTsdT	484	
AD-58151.1	A-118457.1	AAAuGAuGAAccuuGuAAAdTsdT	402	A-118458.1	UUUAcAAGGUUcAUcAUUUdTsdT	485	
AD-58157.1	A-118459.1	uGcucAAGucAcAuuuGAudTsdT	403	A-118460.1	AUcAAAUGUGACUUGAGcAdTsdT	486	
AD-58163.1	A-118461.1	GAuuGcAuAuGcuuAuAAAdTsdT	404	A-118462.1	UUuuAuAAGcAuAUGcAAUCdTsdT	487	
AD-58169.1	A-118463.1	uAuccuGAuAAAAAAuuuAdTsdT	405	A-118464.1	uAAAUUUUUuAUcAGGAuAdTsdT	488	
AD-58175.1	A-118465.1	GAAGuuuGcAGcuuuuAuudTsdT	406	A-118466.1	AAuAAAAGCUGcAAACUUCdTsdT	489	
AD-58181.1	A-118467.1	AGAAAuuGAucAuAuuGGAdTsdT	407	A-118468.1	UCcAAuAUGAUcAAUUUCUdTsdT	490	
AD-58187.1	A-118469.1	ccuGAuAAAAAAuuuAGuudTsdT	408	A-118470.1	AACuAAAUUUUUuAUcAGGdTsdT	491	
AD-58146.1	A-118471.1	GAAAAGAAAucuuAGuAAAdTsdT	409	A-118472.1	UUuACuAAGAUUUCUUUUCdTsdT	492	
AD-58152.1	A-118473.1	uuAucAAAGuAuAAAcAuudTsdT	410	A-118474.1	AAUGUUuAuACUUUGAuAAdTsdT	493	
AD-58158.1	A-118475.1	ccuAcAAAcuGAAuuuGGudTsdT	411	A-118476.1	ACcAAAUUcAGUUUGuAGGdTsdT	494	
AD-58164.1	A-118477.1	GGAGcAAAcAuAuGucAuudTsdT	412	A-118478.1	AAUGAcAuAUGUUUGCUCCdTsdT	495	
AD-58170.1	A-118479.1	AuGuAAcAAcuGuAGuucAdTsdT	413	A-118480.1	UGAACuAcAGUUGUuAcAUdTsdT	496	
AD-58176.1	A-118481.1	GGAAAucAuuGGAAcAuuudTsdT	414	A-118482.1	AAAUGUUCcAAUGAUUUCCdTsdT	497	
AD-58182.1	A-118483.1	uAAGAAuuuuGAAAuuAcudTsdT	415	A-118484.1	AGuAAUUUcAAAAUUCUuAdTsdT	498	
AD-58188.1	A-118485.1	uucuGcAAcuGAAuucGAudTsdT	416	A-118486.1	AUCGAAUUcAGUUGcAGAAdTsdT	499	
AD-58147.1	A-118487.1	ccuuGGAAAGAGuAuuucAdTsdT	417	A-118488.1	UGAAAuACUCUUUCcAAGGdTsdT	500	
AD-58153.1	A-118489.1	uGAuAAAAAAuuuAGuuAcdTsdT	418	A-118490.1	GuAACuAAAUUUUUuAUcAdTsdT	501	
AD-58159.1	A-118491.1	cuuGGAAAGAGuAuuucAAdTsdT	419	A-118492.1	UUGAAAuACUCUUUCcAAGdTsdT	502	

AD-58190.1	A-118519.1	CACUAUAAUUACUUGAUUUdTdT	420	A-118520.1	AAAUCAAGUAAUUAUAGUGdTdT	503	
AD-58196.1	A-118521.1	UAACUCACUAUAAUUACUUdTdT	421	A-118522.1	AAGUAAUUAUAGUGAGUUAdTdT	504	
AD-58202.1	A-118523.1	ACAAAAUAACUCACUAUAAdTdT	422	A-118524.1	UUAUAGUGAGUUAUUUUGUdTdT	505	
AD-58208.1	A-118525.1	UCCUCUGGAAAUUGGCCUUdTdT	423	A-118526.1	AAGGCCAAUUUCCAGAGGAdTdT	506	
AD-58214.1	A-118527.1	CAAAAUAACUCACUAUAAUdTdT	424	A-118528.1	AUUAUAGUGAGUUAUUUUGdTdT	507	
AD-58220.1	A-118529.1	CUCUGGAAAUUGGCCUUCAdTdT	425	A-118530.1	UGAAGGCCAAUUUCCAGAGdTdT	508	
AD-58226.1	A-118531.1	GCAAGAUAUUUUUAUAAUAdTdT	426	A-118532.1	UAUUAUAAAAAUAUCUUGCdTdT	509	
AD-58231.1	A-118533.1	AAUGUUUUUGUCAAGUACAdTdT	427	A-118534.1	UGUACUUGACAAAAACAUUdTdT	510	
AD-58191.1	A-118535.1	UUAAACAACAAGUACCUUUdTdT	428	A-118536.1	AAAGGUACUUGUUGUUUAAdTdT	511	
AD-58197.1	A-118537.1	UCAGAAAGUCUGUGAAGGAdTdT	429	A-118538.1	UCCUUCACAGACUUUCUGAdTdT	512	
AD-58203.1	A-118539.1	ACUGAAGCAUUUGAUGCAAdTdT	430	A-118540.1	UUGCAUCAAAUGCUUCAGUdTdT	513	
AD-58209.1	A-118541.1	AGUUCUGUGUUAAAAUGUCdTdT	431	A-118542.1	GACAUUUUAACACAGAACUdTdT	514	
AD-58233.1	A-118565.1	CfACfUfAUfAAUfUfACfUfUfGAUfUfUfdTsdT	432	A-118566.1	AAAUCfAAGUfAAUUfAUfAGUGdTsdT	515	
AD-58193.1	A-118567.1	UfAACfUfCfACfUfAUfAAUfUfACfUfUfdTsdT	433	A-118568.1	AAGUfAAUUfAUfAGUGAGUUfAdTsdT	516	
AD-58199.1	A-118569.1	ACfAAAAUfAACfUfCfACfUfAUfAAdTsdT	434	A-118570.1	UUfAUfAGUGAGUUfAUUUUGUdTsdT	517	
AD-58205.1	A-118571.1	UfCfCfUfCfUfGGAAAUfUfGGCfCfUfUfdTsdT	435	A-118572.1	AAGGCCfAAUUUCCfAGAGGAdTsdT	518	
AD-58211.1	A-118573.1	CfAAAAUfAACfUfCfACfUfAUfAAUfdTsdT	436	A-118574.1	AUUfAUfAGUGAGUUfAUUUUGdTsdT	519	
AD-58217.1	A-118575.1	CfUfCfUfGGAAAUfUfGGCfCfUfUfCfAdTsdT	437	A-118576.1	UGAAGGCCfAAUUUCCfAGAGdTsdT	520	
AD-58223.1	A-118577.1	GCfAAGAUfAUfUfUfUfUfAUfAAUfAdTsdT	438	A-118578.1	UfAUUfAUfAAAAAUfAUCUUGCdTsdT	521	
AD-58229.1	A-118579.1	AAUfGUfUfUfUfUfGUfCfAAGUfACfAdTsdT	439	A-118580.1	UGUfACUUGACfAAAAACfAUUdTsdT	522	
AD-58234.1	A-118581.1	UfUfAAACfAACfAAGUfACfCfUfUfUfdTsdT	440	A-118582.1	AAAGGUfACUUGUUGUUUfAAdTsdT	523	
AD-58194.1	A-118583.1	UfCfAGAAAGUfCfUfGUfGAAGGAdTsdT	441	A-118584.1	UCCUUCfACfAGACUUUCUGAdTsdT	524	
AD-58200.1	A-118585.1	ACfUfGAAGCfAUfUfUfGAUfGCfAAdTsdT	442	A-118586.1	UUGCfAUCfAAAUGCUUCfAGUdTsdT	525	
AD-58206.1	A-118587.1	AGUfUfCfUfGUfGUfUfAAAAUfGUfCfdTsdT	443	A-118588.1	GACfAUUUUfAACfACfAGAACUdTsdT	526	
AD-58236.1	A-118423.2	cAcuAuAAuuAcuuGAuuudTsdT	444	A-118644.1	AAAUcAAGuAAUuAuAGuGdTsdT	527	
AD-58242.1	A-118425.2	uAAcucAcuAuAAuuAcuudTsdT	445	A-118645.1	AAGuAAUuAuAGuGAGUuAdTsdT	528	
AD-58248.1	A-118427.2	AcAAAAuAAcucAcuAuAAdTsdT	446	A-118646.1	UuAuAGuGAGUuAuUuuGUdTsdT	529	

AD-58254.1	A-118429.2	uccucuGGAAAuuGGccuudTsdT	447	A-118647.1	AAGGCcAAuUUCcAGAGGAdTsdT	530	
AD-58260.1	A-118431.2	cAAAAuAAcucAcuAuAAudTsdT	448	A-118648.1	AUuAuAGuGAGUuAuUuuGdTsdT	531	
AD-58266.1	A-118433.2	cucuGGAAAuuGGccuucAdTsdT	449	A-118649.1	uGAAGGCcAAuUUCcAGAGdTsdT	532	
AD-58272.1	A-118435.2	GcAAGAuAuuuuuAuAAuAdTsdT	450	A-118650.1	uAUuAuAAAAAuAUCuuGCdTsdT	533	
AD-58277.1	A-118437.2	AAuGuuuuuGucAAGuAcAdTsdT	451	A-118651.1	uGuACuuGAcAAAAAcAuUdTsdT	534	
AD-58237.1	A-118439.2	uuAAAcAAcAAGuAccuuudTsdT	452	A-118652.1	AAAGGuACuuGuuGuUuAAdTsdT	535	
AD-58243.1	A-118441.2	ucAGAAAGucuGuGAAGGAdTsdT	453	A-118653.1	UCCuUcAcAGACuUUCuGAdTsdT	536	
AD-58249.1	A-118443.2	AcuGAAGcAuuuGAuGcAAdTsdT	454	A-118654.1	uuGcAUcAAAuGCuUcAGUdTsdT	537	
AD-58255.1	A-118445.2	AGuucuGuGuuAAAAuGucdTsdT	455	A-118655.1	GAcAuUUuAAcAcAGAACUdTsdT	538	
AD-58279.1	A-118423.3	cAcuAuAAuuAcuuGAuuudTsdT	456	A-118667.1	AAAUCAAGuAAuuAuAgugdTsdT	539	
AD-58239.1	A-118425.3	uAAcucAcuAuAAuuAcuudTsdT	457	A-118668.1	AAGuAAuUAuAGuGAGuuadTsdT	540	
AD-58245.1	A-118427.3	AcAAAAuAAcucAcuAuAAdTsdT	458	A-118669.1	UuAuAGuGAGuuAuuuugudTsdT	541	
AD-58251.1	A-118429.3	uccucuGGAAAuuGGccuudTsdT	459	A-118670.1	AAGGCCAAuUuCCAGAggadTsdT	542	
AD-58257.1	A-118431.3	cAAAAuAAcucAcuAuAAudTsdT	460	A-118671.1	AuUAuAGuGAGuuAuuuugdTsdT	543	
AD-58263.1	A-118433.3	cucuGGAAAuuGGccuucAdTsdT	461	A-118672.1	UGAAGGCCAAuuuCCAgagdTsdT	544	
AD-58269.1	A-118435.3	GcAAGAuAuuuuuAuAAuAdTsdT	462	A-118673.1	UAuUAuAAAAAuAuCuugcdTsdT	545	
AD-58275.1	A-118437.3	AAuGuuuuuGucAAGuAcAdTsdT	463	A-118674.1	UGuACuUGACAAAAACauudTsdT	546	
AD-58280.1	A-118439.3	uuAAAcAAcAAGuAccuuudTsdT	464	A-118675.1	AAAGGuACuUGuuGuuuaadTsdT	547	
AD-58240.1	A-118441.3	ucAGAAAGucuGuGAAGGAdTsdT	465	A-118676.1	UCCuUCACAGACuuuCugadTsdT	548	
AD-58246.1	A-118443.3	AcuGAAGcAuuuGAuGcAAdTsdT	466	A-118677.1	UuGCAUCAAAuGCuuCagudTsdT	549	
AD-58252.1	A-118445.3	AGuucuGuGuuAAAAuGucdTsdT	467	A-118678.1	GACAuUuUAACACAGAacudTsdT	550	

[5] The Species Oligo name and the position in the nucleotide sequence of the GenBank record that the antisense strand targets correspond to those shown in Table 5.

Table 7 – C5 single dose screen in Hep3B cells with GalNAC conjugated iRNAs

Duplex ID	10nM AVG	0.1nM AVG	10nM STDEV	0.1nM STDEV
AD-58093.1	15.62	21.60	7.48	6.52
AD-58099.1	9.07	14.70	1.18	4.65
AD-58105.1	36.71	60.23	5.07	19.83
AD-58111.1	11.83	22.78	3.51	12.75
AD-58117.1	12.43	33.46	2.00	23.56
AD-58123.1	8.05	15.18	2.89	7.94
AD-58129.1	10.77	40.06	1.30	19.66
AD-58088.1	6.55	16.40	1.24	4.58
AD-58094.1	19.59	40.68	7.64	12.30
AD-58100.1	10.92	20.12	0.74	8.38
AD-58106.1	10.97	37.23	2.49	19.95
AD-58112.1	13.24	29.32	2.90	14.08
AD-58118.1	6.63	15.23	0.54	5.72
AD-58124.1	7.17	13.00	1.44	6.48
AD-58130.1	10.38	17.92	3.36	6.92
AD-58089.1	8.81	30.67	2.91	10.53
AD-58095.1	8.72	14.66	1.04	3.37
AD-58101.1	8.17	19.36	1.30	5.69
AD-58107.1	4.84	18.10	1.66	7.21
AD-58113.1	8.78	14.62	1.77	7.89
AD-58119.1	8.90	15.01	0.91	7.35
AD-58125.1	11.13	17.04	2.61	9.03
AD-58131.1	13.50	40.14	1.08	12.07
AD-58090.1	7.90	21.57	2.95	6.61
AD-58096.1	8.02	16.56	1.54	6.68
AD-58102.1	12.40	27.93	1.83	11.78
AD-58108.1	12.02	15.07	2.88	5.74
AD-58114.1	11.86	25.05	1.48	9.46
AD-58120.1	7.65	10.57	0.58	3.56
AD-58126.1	8.45	15.39	2.08	7.42

AD-58132.1	8.50	19.36	2.52	9.38
AD-58091.1	8.68	18.05	2.95	6.62
AD-58097.1	9.31	23.02	0.67	10.10
AD-58103.1	8.53	17.23	2.90	7.27
AD-1955	57.41	81.16	10.76	5.29
Mock	78.61	75.97	5.70	2.76
Untreated	100	100	6.13	5.98

Table 8 – C5 single dose transfection screen in primary mouse hepatocytes with GalNAC conjugated iRNAs

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Duplex ID	10nM AVG	0.1nM AVG	10nM STDEV	0.1nM STDEV
AD-58093.1	1.53	1.65	0.17	0.25
AD-58099.1	1.65	1.50	0.61	0.22
AD-58105.1	11.20	46.95	0.08	3.89
AD-58111.1	2.49	2.13	0.26	0.20
AD-58117.1	3.57	31.91	0.93	0.62
AD-58123.1	4.29	2.97	0.11	2.22
AD-58129.1	1.19	8.53	0.23	0.72
AD-58088.1	0.84	1.34	0.68	0.07
AD-58094.1	11.34	66.82	0.17	3.01
AD-58100.1	2.78	1.51	0.43	0.33
AD-58106.1	6.79	52.91	4.42	6.78
AD-58121.1	1.94	2.15	0.04	0.91
AD-58133.1	1.74	3.25	0.19	1.64
AD-58116.1	1.76	2.21	1.27	0.78
AD-1955	87.39	91.71	5.77	4.68
Mock	79.67	89.02	1.51	3.91
Untreated	100	100	6.39	13.11

Table 9 – C5 single dose screen in primary *Cynomolgus* hepatocytes with GalNAC conjugated iRNAs

Duplex ID	500nM AVG	5nM AVG	500nM STDEV	5nM STDEV
AD-58093.1	63.94	83.09	2.14	12.65
AD-58099.1	61.34	85.85	12.32	21.95
AD-58105.1	91.98	97.57	6.09	11.48
AD-58111.1	71.27	92.28	1.93	12.72
AD-58117.1	73.42	88.82	3.24	11.08
AD-58123.1	75.14	73.06	7.72	9.71
AD-58129.1	81.66	90.62	2.13	4.77
AD-58088.1	53.63	87.03	5.93	19.86
AD-58094.1	89.62	93.65	0.87	14.76
AD-58100.1	79.56	96.70	4.31	1.10
AD-58106.1	116.24	125.99	14.28	40.65
AD-58112.1	97.19	107.81	N/A	3.13
AD-58118.1	67.40	97.38	5.28	22.64
AD-58124.1	58.04	96.14	8.72	10.64
AD-58130.1	84.19	88.65	10.50	4.34
AD-58089.1	83.83	83.44	1.91	12.26
AD-58095.1	58.53	78.02	15.07	12.45
AD-58101.1	76.68	76.73	3.95	6.35
AD-58107.1	57.37	86.78	14.71	2.99
AD-58113.1	37.79	71.10	8.27	7.76
AD-58119.1	36.77	83.16	3.42	9.66
AD-58125.1	72.40	96.53	4.46	4.96
AD-58131.1	95.58	101.69	10.17	2.21
AD-58090.1	56.37	75.00	3.21	4.97
AD-58096.1	44.33	57.99	11.46	25.17
AD-58102.1	95.46	89.35	0.83	1.76
AD-58108.1	41.54	56.41	8.41	0.14
AD-58114.1	88.32	101.88	20.02	30.29
AD-58120.1	37.34	56.41	0.73	2.14
AD-58126.1	84.97	105.90	2.39	7.96

AD-58132.1	81.55	85.12	12.93	8.94
AD-58091.1	78.88	84.60	44.66	17.40
AD-58097.1	106.06	98.16	13.74	3.14
AD-58103.1	57.21	89.46	6.40	5.93
Untreated	100	100	8.77	10.33

Table 10 – C5 single dose free uptake screen in primary mouse hepatocytes with GalNAC conjugated iRNAs

Duplex ID	500nM AVG	5nM AVG	500nM STDEV	5nM STDEV
AD-58093.1	31.62	64.91	7.13	8.39
AD-58099.1	9.46	29.63	1.29	5.66
AD-58105.1	84.77	96.41	5.22	1.89
AD-58111.1	17.35	50.95	1.21	3.16
AD-58117.1	94.95	139.52	15.43	43.39
AD-58123.1	13.07	44.58	2.11	3.49
AD-58129.1	68.87	85.04	2.62	4.42
AD-58088.1	17.61	48.22	2.22	3.40
AD-58094.1	95.92	104.23	4.16	6.53
AD-58100.1	34.92	61.71	1.30	2.15
AD-58106.1	85.26	107.53	2.30	3.38
AD-58121.1	12.88	43.76	1.41	1.28
AD-58133.1	20.97	42.76	0.24	0.11
AD-58116.1	8.35	38.04	1.35	1.40
Untreated	100.00	100.00	3.85	4.38

Table 11 –IC_{50} data in primary *Cynomolgus* hepatocytes with GalNAC conjugated iRNAs

Duplex ID	IC_{50} (nM)	STDEV
AD-58099.1	3.131	1.141
AD-58111.1	12.750	5.280
AD-58123.1	0.679	7.587

AD-58088.1	0.218	3.487
AD-58113.1	7.296	3.540
AD-58119.1	33.240	14.740
AD-58096.1	10.380	4.199
AD-58108.1	0.953	10.080
AD-58120.1	36.170	88.070

Table 12 –IC_{50} data in primary mouse hepatocytes with GalNAC conjugated iRNAs

Duplex ID	IC_{50} (nM)	STDEV
AD-58099	3.777	0.122
AD-58111	0.622	2.421
AD-58123	0.549	1.626
AD-58088	9.513	2.588
AD-58121	2.169	1.176
AD-58133	3.802	1.006
AD-58116	2.227	0.604
AD-58644.1	4.596	0.3506
AD-58651.1	59.76	51.99
AD-58641.1	0.82	0.2618
AD-58648.1	7.031	1.256
AD-58642.1	0.5414	0.7334
AD-58649.1	3.32	4.922
AD-58647.1	1.356	0.5215
AD-58654.1	2.09	0.8338
AD-58645.1	2.944	0.3315
AD-58652.1	5.316	2.477
AD-58643.1	2.179	1.112
AD-58650.1	8.223	3.76
AD-58646.1	2.581	0.8186
AD-58653.1	2.451	1.249

Table 13 – C5 single dose screen in Hep3B cells with modified and unmodified iRNAs

Duplex	1nM AVG	0.01nM AVG	1nM STDEV	0.01nM STDEV
AD-58143.1	12.13	100.58	3.47	3.94
AD-58149.1	10.46	64.97	0.98	0.00
AD-58155.1	44.88	76.24	1.56	3.74
AD-58161.1	8.51	102.30	1.06	0.50
AD-58167.1	6.54	76.24	1.15	3.74
AD-58173.1	6.85	107.44	0.85	4.74
AD-58179.1	10.19	78.07	0.59	1.15
AD-58185.1	29.46	79.99	3.64	0.78
AD-58144.1	16.82	81.95	1.09	0.40
AD-58150.1	11.05	76.20	2.55	0.00
AD-58156.1	25.92	76.73	2.72	1.50
AD-58162.1	13.25	71.89	0.43	3.87
AD-58168.1	9.74	45.16	0.52	1.11
AD-58174.1	4.84	70.14	0.25	2.75
AD-58180.1	9.41	56.77	1.91	1.95
AD-58186.1	9.97	68.91	1.03	0.34
AD-58145.1	14.29	103.38	1.94	2.03
AD-58151.1	10.16	81.17	1.71	4.77
AD-58157.1	4.72	63.19	1.05	0.00
AD-58163.1	4.95	40.13	1.65	0.59
AD-58169.1	17.02	83.10	1.88	2.04
AD-58175.1	8.30	62.54	0.28	0.31
AD-58181.1	21.89	55.26	4.22	3.52
AD-58187.1	61.96	71.12	2.61	2.79
AD-58146.1	14.25	95.23	2.64	6.53
AD-58152.1	11.22	70.09	0.80	7.88
AD-58158.1	7.96	98.86	0.76	4.36
AD-58164.1	11.60	43.83	2.06	3.43
AD-58170.1	12.28	39.59	0.96	1.36
AD-58176.1	6.89	38.77	1.04	1.33
AD-58182.1	18.65	55.78	0.96	0.55

AD-58188.1	5.40	69.39	1.07	0.34
AD-58147.1	8.22	106.66	0.77	2.61
AD-58153.1	68.10	104.17	4.44	18.29
AD-58159.1	8.76	81.41	1.54	2.79
AD-58190.1	21.94	77.26	2.23	0.76
AD-58196.1	15.97	72.43	1.07	5.32
AD-58202.1	11.99	93.83	5.34	2.76
AD-58208.1	18.63	52.07	12.88	2.55
AD-58214.1	6.85	94.15	0.51	2.31
AD-58220.1	11.50	78.34	3.85	0.77
AD-58226.1	5.77	57.75	1.71	1.13
AD-58231.1	7.23	75.67	1.07	0.74
AD-58191.1	35.40	66.17	5.50	4.21
AD-58197.1	12.05	67.49	1.70	0.33
AD-58203.1	15.16	66.80	1.46	1.31
AD-58209.1	7.58	71.23	3.58	6.28
AD-58233.1	27.01	86.02	0.86	0.42
AD-58193.1	15.37	99.85	1.44	0.00
AD-58199.1	21.52	78.39	6.02	16.40
AD-58205.1	24.13	78.88	5.46	0.77
AD-58211.1	16.38	32.37	2.61	0.48
AD-58217.1	12.23	70.16	0.29	3.44
AD-58223.1	8.51	72.85	3.01	1.79
AD-58229.1	5.50	75.93	1.96	0.37
AD-58234.1	46.86	101.94	15.59	0.00
AD-58194.1	14.49	107.05	2.47	4.20
AD-58200.1	16.21	61.04	0.96	1.20
AD-58206.1	13.25	37.73	2.82	2.03
AD-58236.1	8.29	119.17	1.16	2.92
AD-58242.1	12.05	102.69	0.44	4.03
AD-58248.1	62.78	83.41	15.22	3.27
AD-58254.1	11.18	100.54	1.59	0.00
AD-58260.1	8.42	71.84	1.10	0.35
AD-58266.1	14.05	92.21	1.91	2.26
AD-58272.1	22.63	81.11	1.62	1.59

AD-58277.1	70.51	75.67	4.80	0.74
AD-58237.1	28.10	98.56	1.96	5.79
AD-58243.1	14.16	86.05	1.11	2.95
AD-58249.1	77.08	96.45	15.14	0.95
AD-58255.1	12.27	47.89	2.58	0.00
AD-58279.1	25.78	94.13	5.52	0.46
AD-58239.1	22.98	83.45	0.28	4.91
AD-58245.1	89.60	90.93	15.24	0.45
AD-58251.1	28.39	86.32	7.29	0.00
AD-58257.1	48.97	64.53	9.10	1.90
AD-58263.1	9.14	83.39	1.27	1.63
AD-58269.1	83.84	75.94	15.90	1.12
AD-58275.1	10.29	86.32	0.73	0.85
AD-58280.1	72.77	110.04	7.44	3.24
AD-58240.1	65.42	75.69	3.82	2.23
AD-58246.1	59.19	65.88	28.95	0.65
AD-58252.1	15.35	97.26	1.14	7.62
Mock	76.53	66.57	14.26	4.72
AD-1955	72.30	82.72	19.54	49.99
Untreated	100.00	100.00	21.68	26.78

Table 14 – C5 single dose screen in primary mouse hepatocytes with modified and unmodified iRNAs

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Duplex ID	1nM AVG	0.1nM AVG	1nM STDEV	0.1nM STDEV
AD-58143.1	4.51	81.77	3.13	8.75
AD-58149.1	4.65	73.16	3.14	20.17
AD-58155.1	65.56	79.74	4.66	9.36
AD-58161.1	16.82	81.11	6.22	7.43
AD-58167.1	4.72	77.12	1.17	14.25
AD-58173.1	5.57	76.00	3.14	13.52
AD-58179.1	14.55	77.88	1.44	18.40
AD-58185.1	15.69	72.59	8.67	7.81
AD-58144.1	8.70	91.49	0.90	7.08

AD-58150.1	12.51	84.01	1.64	8.20
AD-58156.1	18.23	97.32	1.47	19.50
AD-58162.1	7.72	78.89	5.19	13.80
AD-58190.1	11.86	92.80	2.82	4.41
AD-58196.1	7.27	82.71	1.39	31.81
AD-58202.1	10.67	87.11	1.04	35.79
AD-58208.1	32.21	74.39	8.60	27.45
AD-58214.1	4.24	67.63	0.45	17.85
AD-58220.1	13.64	96.14	4.56	14.36
AD-58226.1	3.83	63.44	1.30	11.94
AD-58231.1	5.95	82.24	2.80	17.36
AD-58191.1	14.50	99.50	5.48	5.53
AD-58197.1	16.12	93.09	0.81	3.21
AD-58203.1	12.52	104.63	5.98	6.02
AD-58209.1	8.79	59.35	3.05	13.07
AD-58233.1	9.50	64.26	5.69	8.70
AD-58193.1	8.88	89.60	3.36	3.08
AD-58199.1	13.56	87.14	2.18	6.44
AD-58205.1	46.84	89.13	4.48	17.16
AD-58211.1	13.10	111.62	1.10	21.54
AD-58217.1	29.79	117.49	11.85	20.41
AD-58223.1	20.53	105.44	1.94	2.98
AD-58229.1	13.76	98.15	1.05	9.03
AD-58234.1	12.33	71.34	0.72	4.17
AD-58194.1	14.02	90.60	1.39	15.64
AD-58200.1	5.25	90.95	1.37	31.70
AD-58206.1	8.19	109.47	3.99	21.75
AD-58236.1	2.07	70.19	0.80	20.59
AD-58242.1	4.76	53.26	1.59	11.56
AD-58248.1	62.42	78.23	5.47	25.85
AD-58254.1	16.47	70.22	2.92	21.74
AD-58260.1	2.84	75.65	0.38	11.59
AD-58266.1	40.70	89.88	16.05	11.57
AD-58272.1	21.42	59.44	13.29	10.98
AD-58277.1	71.72	121.44	16.35	21.16

AD-58237.1	11.85	112.68	9.22	12.88
AD-58243.1	10.46	90.64	3.42	4.33
AD-58249.1	71.47	113.30	4.30	3.84
AD-58255.1	6.86	78.55	2.22	28.37
AD-58279.1	7.15	74.96	2.84	4.72
AD-58239.1	13.64	106.45	1.87	8.25
AD-58245.1	68.67	112.08	21.89	7.73
AD-58251.1	47.01	133.20	4.69	7.14
AD-58257.1	30.68	87.51	2.87	32.84
AD-58263.1	7.22	83.23	2.55	37.50
AD-58269.1	78.90	106.06	5.07	3.04
AD-58275.1	8.92	95.77	1.91	7.14
AD-58280.1	16.67	78.47	4.15	6.06
AD-58240.1	71.03	138.54	5.32	10.87
AD-58246.1	71.87	89.02	4.95	8.63
AD-58252.1	4.04	56.10	1.23	12.02
Mock	66.84	82.81	2.75	17.19
AD-1955	87.44	102.07	3.64	4.08
Untreated	100.00	100.00	15.25	18.37

Table 15 –IC_{50} data in Hep3B cells with modified and unmodified iRNAs

Duplex ID	IC_{50} (pM)	STDEV
AD-58143.1	36.35	12.26
AD-58149.1	5.735	6.196
AD-58161.1	78.12	26.64
AD-58167.1	31.03	18.14
AD-58173.1	29.12	16.53
AD-58236.1	52.73	32.02
AD-58242.1	8.859	4.321
AD-58260.1	7.706	5.094
AD-58263.1	96.64	47.61

Table 16 –IC_{50} data in primary mouse hepatocytes with modified and unmodified iRNAs

Duplex ID	IC_{50} (pM)	STDEV
AD-58260.1	1.015	0.9676
AD-58149.1	1.309	1.749
AD-58167.1	1.991	2.477
AD-58242.1	0.5866	1.8
AD-58236.1	0.4517	0.06392
AD-58143.1	0.8876	0.1613
AD-58279.1	3.116	0.7368
AD-58252.1	7.153	1.021
AD-58173.1	7.144	19.88
AD-58263.1	3.224	5.478

Example 3. *In vivo* screening

A subset of seven GalNAC conjugated iRNAs was selected for further *in vivo* evaluation.

C57BL/6 mice (N=3 per group) were injected subcutaneously with 10mg/kg of GalNAc conjugated duplexes or an equal volume of 1x Dulbecco's Phosphate-Buffered Saline (DPBS) (Life Technologies, Cat# 14040133). Forty-eight hours later, mice were euthanized and the livers were dissected and flash frozen in liquid nitrogen. Livers were ground in a 2000 Geno/Grinder (SPEX SamplePrep, Metuchen, NJ). Approximately 10mg of liver powder per sample was used for RNA isolation. Samples were first homogenized in a TissueLyserII (Qiagen Inc, Valencia, CA) and then RNA was extracted using a RNeasy 96 Universal Tissue Kit (Qiagen Inc, , Cat#74881) following manufacturer's protocol using vacuum/spin technology. RNA concentration was measured by a NanoDrop 8000 (Thermo Scientific, Wilmington, DE) and was adjusted to 100ng/µl. cDNA and RT-PCR were performed as described above.

The results of the single dose screen are depicted in Figure 2. Table 17 shows the results of an *in vivo* single dose screen with the indicated GalNAC conjugated modified iRNAs. Data are expressed as percent of mRNA remaining relative to DPBS treated mice. The "Experiments" column lists the number of experiments from which the average was calculated. The standard deviation is calculated from all mice in a group across all experiments analyzed.

Table 17 – *In vivo* C5 single dose screen

Duplex ID	Experiments	AVG	STDEV
AD-58088.2	2	82.66	13.54
AD-58644.1	1	37.79	9.63
AD-58651.1	1	75.33	5.21
AD-58099.2	2	71.94	15.45
AD-58641.1	1	20.09	4.09
AD-58648.1	1	48.43	9.07
AD-58111.2	3	67.17	13.60
AD-58642.1	2	21.78	5.32
AD-58649.1	1	45.30	14.02
AD-58116.2	2	70.16	10.32
AD-58647.1	1	26.77	4.14
AD-58654.1	1	50.06	27.85
AD-58121.2	2	52.56	13.00
AD-58645.1	1	34.60	1.39
AD-58652.1	1	52.67	3.87
AD-58123.2	2	65.70	9.60
AD-58643.1	1	23.21	2.41
AD-58650.1	1	46.75	14.10
AD-58133.2	3	51.98	13.45
AD-58646.1	2	28.67	5.34
AD-58653.1	1	43.02	10.61
PBS	3	100.00	9.03

Two of the most efficacious GalNAC conjugated iRNAs were further modified to include additional phosphorothioate linkages (Table 18) and the efficacy of these duplexes was determined *in vivo* as described above. The results of the single dose screen are depicted in Figure 3 and demonstrate that the iRNA agents with additional phosphorothiate linkages are more efficacious than those iRNA agents without or with fewer phosphorothioate linkages.

Table 18 – Phosphorothioate Modifed GalNAC Conjugated C5 iRNAs

Duplex ID	Sense strand	Sense sequence	SEQ ID NO:	Antisense	Antisense sequence	SEQ ID NO:	Cross Reactivity
AD-58642.1	A-119324.1	GfsasCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	551	A-119325.1	asUfsuAfuAfgUfgAfguuAfuUfuUfgUfcsasa	555	HumRheMusRat
AD-58111.2	A-118316.1	GfaCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	552	A-118317.1	aUfuAfuAfgUfgAfguuAfuUfuUfgUfcsAfsa	556	HumRheMusRat
AD-58646.1	A-119332.1	CfsasGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	553	A-119333.1	asCfsuGfaAfaUfuGfuguUfuGfaUfcUfgscsa	557	MusRat
AD-58133.2	A-118386.1	CfaGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	554	A-118387.1	aCfuGfaAfaUfuGfuguUfuGfaUfcUfgsCfsa	558	MusRat

Given the impact of the additional phosphorothioate linkages on the silencing ability of the iRNA agents described above, the efficacy of additional GalNAC conjugated iRNA duplexes including phosphoriothioate linkages (Table 19) was determined *in vivo* as described above. The results of this single dose screen are depicted in Figure 4.

The duration of silencing of AD-58642 *in vivo* was determined by administering a single 2.5 mg/kg, 10 mg/kg, or 25 mg/kg dose to rats and determining the amount of C5 protein (Figure 5B) present on day 7 and the activity of C5 protein (Figure 5A) present on days 4 and 7. As demonstrated in Figure 5, there is a 50% reduction in the activity of C5 protein by Day 4 at a 25 mg/kg dose and at Day 7, a greater than 70% reduction in the activity of C5 protein.

The amount of C5 protein was determined by Western blot analysis of whole serum. The activity of C5 protein was determined by a hemolysis assay. Briefly, a fixed dilution of human C5 depleted human serum was mixed with mouse serum and incubated with antibody-coated sheep red blood cells for 1 hour. The hemoglobin absorbance was measured and the % hemolysis as compared to a reference curve (prepared using a dilution series of mouse serum) was calculated.

The efficacy of AD-58642 *in vivo* was also assayed in mice following a single subcutaneous injection of 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, 10 mg/kg, and 25 mg/kg of AD-58642. At day 5 C5 mRNA was assayed in liver samples using qPCR, C5 activity was assayed for hemolysis, and the amount of C5 protein was determined by Western blot analysis of whole serum.

As depicted in Figures 6A and 6B, although there is only a minor improvement (*i.e.*, about 5%) in efficacy of AD-58642 to inhibit C5 mRNA at a dose of 25 mg/kg as compared to a 10 mg/kg dose, there is an average of 85% silencing with a 25 mg/kg dose. In addition, there is a dose response effect with an IC_{50} of about 2.5 mg/kg.

Figures 7A and 7B and 8 demonstrate that AD-58642 is efficacious for decreasing the amount of C5 protein (Figure 8) and C5 protein activity (Figures 7A and 7B).

The duration of silencing of AD-58641 *in vivo* was also determined by subcutaneously administering a single 0.625 mg/kg, 1.25 mg/kg, 2.5 mg/kg, 5.0 mg/kg, or 10 mg/kg dose of AD-58641 to C57Bl/6 (n=3) mice and determining the amount of C5 protein present in these animals on days 5 and 9 by ELISA. Briefly, serum was collected on day 0, pre-bleed, day 5, and day 9 and the levels of C5 proteins were quantified by ELISA. C5 protein levels were normalized to the day 0 pre-bleed level. As depicted in Figure 9, the results demonstrate that there is a dose dependent potent and durable knock-down of C5 serum protein. (The single dose ED_{50} was 0.6 mg/kg).

Compound AD-58641 was also tested for efficacy in C57Bl/6 mice using a multi-dosing administration protocol. Mice were subcutaneously administered compound AD-58641 at a

0.625 mg/kg, 1.25 mg/kg, or 2.5 mg/kg dose at days 0, 1, 2, and 3. Serum was collected at days 0 and 8 as illustrated in Figure 10 and analyzed for C5 protein levels by ELISA. C5 levels were normalized to the day 0 pre-bleed level. Figure 10 shows that multi-dosing of AD-58641 achieves silencing of C5 protein at all of the does tested, with a greater than 90% silencing of C5 protein at a dose of 2.5 mg/kg.

Compound AD-58641 was further tested for efficacy and to evaluate the cumulative effect of the compound in rats using a repeat administration protocol. Wild-type Sprague Dawley rats were subcutaneously injected with compound AD-58641 at a 2.5 mg/kg/dose or 5.0 mg/kg/dose twice a week for 3 weeks (q2w x3). Serum was collected on days 0, 4, 7, 11, 14, 18, 25, and 32. Serum hemolytic activity was quantified using a hemolysis assay in which a 1:150 dilution of rat serum was incubated with sensitized sheep rat blood cells in GVB++ buffer for 1 hour and hemoglobin release was quantified by measuring absorbance at 415 nm (see Figure 11A). The amount of C5 protein present in the samples was also determined by ELISA (Figure 11B). The results demonstrate a dose dependent potent and durable decrease in hemolytic activity, achieving about 90% hemolytic activity inhibition.

Table 19 – Additional Phosphorothioate Modifed GalNAC Conjugated C5 iRNAs

Duplex ID	Sense strand	Sense sequence	SEQ ID NO:	Antisense	Antisense sequence	SEQ ID NO:	Start position	Cross Reactivity	PS#
AD-58088.2	A-118324.1	AfuUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	559	A-118325.1	aAfaGfgUfaCfuUfguuGfuUfuAfaAfusCfsu	580	984	HumRheMus	2
AD-58644.1	A-119328.1	AfsusUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	560	A-119329.1	asAfsaGfgUfaCfuUfguuGfuUfuAfaAfuscsu	581	984	HumRheMus	6
AD-58651.1	A-119328.2	AfsusUfuAfaAfcAfAfCfaAfgUfaCfcUfuUfL96	561	A-119339.1	asAfsaGfsgUfsaCfsuUfsguuGfsuUfsuAfsaAfsuscsu	582	984	HumRheMus	14
AD-58099.2	A-118312.1	UfgAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	562	A-118313.1	uUfaUfaGfuGfaGfuuaUfuUfuGfuCfasAfsu	583	1513	HumRheMusRat	2
AD-58641.1	A-119322.1	UfsgsAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	563	A-119323.1	usUfsaUfaGfuGfaGfuuaUfuUfuGfuCfasasu	584	1513	HumRheMusRat	6
AD-58648.1	A-119322.2	UfsgsAfcAfaAfaUfAfAfcUfcAfcUfaUfaAfL96	564	A-119336.1	usUfsaUfsaGfsuGfsaGfsuuaUfsuUfsuGfsuCfsasasu	585	1513	HumRheMusRat	14
AD-58111.2	A-118316.1	GfaCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	565	A-118317.1	aUfuAfuAfgUfgAfguuAfuUfuUfgUfcsAfsa	586	1514	HumRheMusRat	2
AD-58642.1	A-119324.1	GfsasCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	566	A-119325.1	asUfsuAfuAfgUfgAfguuAfuUfuUfgUfcsasa	587	1514	HumRheMusRat	6
AD-58649.1	A-119324.2	GfsasCfaAfaAfuAfAfCfuCfaCfuAfuAfaUfL96	567	A-119337.1	asUfsuAfsuAfsgUfsgAfsguuAfsuUfsuUfsgUfscsasa	588	1514	HumRheMusRat	14
AD-58116.2	A-118396.1	GfuUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	568	A-118397.1	aAfaAfgUfuCfaAfauaUfcCfgGfaAfcsCfag	589	4502	MusRat	2
AD-58647.1	A-119334.1	GfsusUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	569	A-119335.1	asAfsaAfgUfuCfaAfauaUfcCfgGfaAfcscsg	590	4502	MusRat	6
AD-58654.1	A-119334.2	GfsusUfcCfgGfaUfAfUfuUfgAfaCfuUfuUfL96	570	A-119342.1	asAfsaAfsgUfsuCfsaAfsauaUfscCfsgGfsaAfscscsg	591	4502	MusRat	14
AD-58121.2	A-118382.1	UfgCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	571	A-118383.1	uGfaAfaUfuGfuGfuuuGfaUfcUfgCfasGfsa	592	4945	MusRat	2
AD-58645.1	A-119330.1	UfsgsCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	572	A-119331.1	usGfsaAfaUfuGfuGfuuuGfaUfcUfgCfasgsa	593	4945	MusRat	6
AD-58652.1	A-119330.2	UfsgsCfaGfaUfcAfAfAfcAfcAfaUfuUfcAfL96	573	A-119340.1	usGfsaAfsaUfsuGfsuGfsuuuGfsaUfscUfsgCfsasgsa	594	4945	MusRat	14

AD-58123.2	A-118320.1	AfaGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	574	A-118321.1	uAfuUfaUfaAfaAfauaUfcUfuGfcUfusUfsu	595	786	HumRheMus	2
AD-58643.1	A-119326.1	AfsasGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	575	A-119327.1	usAfsuUfaUfaAfaAfauaUfcUfuGfcUfususu	596	786	HumRheMus	6
AD-58650.1	A-119326.2	AfsasGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	576	A-119338.1	usAfsuUfsaUfsaAfsaAfsauaUfscUfsuGfscUfsususu	597	786	HumRheMus	14
AD-58133.2	A-118386.1	CfaGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	577	A-118387.1	aCfuGfaAfaUfuGfuguUfuGfaUfcUfgsCfsa	598	4947	MusRat	2
AD-58646.1	A-119332.1	CfsasGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	578	A-119333.1	asCfsuGfaAfaUfuGfuguUfuGfaUfcUfgscsa	599	4947	MusRat	6
AD-58653.1	A-119332.2	CfsasGfaUfcAfaAfCfAfcAfaUfuUfcAfgUfL96	579	A-119341.1	asCfsuGfsaAfsaUfsuGfsuguUfsuGfsaUfscUfsgscsa	600	4947	MusRat	14

Example 4: Design, Synthesis, and *in Vitro* Screening of Additional siRNAs

siRNA design

C5 duplexes, 19 nucleotides long for both the sense and antisense strand, were designed using the human C5 mRNA sequence set forth in GenBank Accession No. NM_001735.2. Five-hundred and sixty-nine duplexes were initially identified that did not contain repeats longer than 7 nucleotides, spanning substantially the entire 5480 nucleotide transcript. All 569 duplexes are then scored for predicted efficacy according to a linear model that evaluates the nucleotide pair at each duplex position, and the dose and cell line to be used for screening. The duplexes are also matched against all transcripts in the human RefSeq collection using a custom brute force algorithm, and scored for lowest numbers of mismatches (per strand) to transcripts other than C5. Duplexes to be synthesized and screened are then selected from the 569, according to the following scheme: Beginning at the 5' end of the transcript, a duplex is selected within a "window" of every 10 ± 2 nucleotides that

1) had the highest predicted efficacy,
2) had at least one mismatch in both strands to all transcripts other than SERPINC1,
3) had not already been synthesized and screened as part of other duplex sets.

If no duplex is identified within a given window that satisfied all criteria, that window was skipped.

A detailed list of the 569 C5 sense and antisense strand sequences is shown in Table 20.

The *in vitro* efficacy of duplexes comprising the sense and antisense sequences listed in Table 20 is determined using the following methods.

Cell culture and transfections

HepG2 cells (ATCC, Manassas, VA) are grown to near confluence at 37°C in an atmosphere of 5% CO2 in Eagle's Minimum Essential Medium (ATCC) supplemented with 10% FBS, streptomycin, and glutamine (ATCC) before being released from the plate by trypsinization. Transfection is carried out by adding 14.8µl of Opti-MEM plus 0.2µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of each of the 164 siRNA duplexes to an individual well in a 96-well plate. The mixture is then incubated at room temperature for 15 minutes. 80µl of complete growth media without antibiotic containing ~2.5 x10^4 HepG2 cells is then added to the siRNA mixture. Cells are incubated for 24 hours

prior to RNA purification. Experiments are performed at 20nM and included naïve cells and cells transfected with AD-1955, a luciferase targeting siRNA as negative controls.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen, part #: 610-12)

Cells are harvested and lysed in 150µl of Lysis/Binding Buffer then mixed for 5 minute at 700 rpm on a platform shaker (the mixing speed was the same throughout the process). Ten microliters of magnetic beads and 80µl Lysis/Binding Buffer mixture are added to a round bottom plate and mixed for 1 minute. Magnetic beads are captured using magnetic stand and the supernatant is removed without disturbing the beads. After removing supernatant, the lysed cells are added to the remaining beads and mixed for 5 minutes. After removing supernatant, magnetic beads are washed 2 times with 150µl Wash Buffer A and mixed for 1 minute. Beads are captured again and supernatant removed. Beads are then washed with 150µl Wash Buffer B, captured and supernatant is removed. Beads are next washed with 150µl Elution Buffer, captured and supernatant removed. Beads are allowed to dry for 2 minutes. After drying, 50µl of Elution Buffer is added and mixed for 5 minutes at 70°C. Beads are captured on magnet for 5 minutes. Forty µl of supernatant, containg the isolated RNA is removed and added to another 96 well plate.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

A master mix of 2µl 10X Buffer, 0.8µl 25X dNTPs, 2µl Random primers, 1µl Reverse Transcriptase, 1µl RNase inhibitor and 3.2µl of H2O per reaction is added into 10µl total RNA. cDNA is generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, CA) through the following steps: 25°C 10 min, 37°C 120 min, 85°C 5 sec, 4°C hold.

Real time PCR

Two µl of cDNA is added to a master mix containing 0.5µl human GAPDH TaqMan Probe (Applied Biosystems Cat #4326317E), 0.5µl human SERPINC1 TaqMan probe (Applied Biosystems cat # Hs00892758_m1) and 5µl Lightcycler 480 probe master mix (Roche Cat #04887301001) per well in a 384-well plate (Roche cat # 04887301001). Real time PCR is performed in an LC480 Real Time PCR machine (Roche).

To calculate relative fold change, real time data is analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 20nM AD-1955.

Table 20: Additional C5 unmodified sense and antisense strand sequences

Oligo Name	Position in NM_001735.2	Sense Sequence	SEQ ID NO:	Antisense Sequence	SEQ ID NO:
NM_001735.2_3-21_s	3-21	UAUCCGUGGUUUCCUGCUA	601	UAGCAGGAAACCACGGAUA	1170
NM_001735.2_10-28_s	10-28	GGUUUCCUGCUACCUCCAA	602	UUGGAGGUAGCAGGAAACC	1171
NM_001735.2_22-40_s	22-40	CCUCCAACCAUGGGCCUUU	603	AAAGGCCCAUGGUUGGAGG	1172
NM_001735.2_33-51_s	33-51	GGGCCUUUUGGGAAUACUU	604	AAGUAUUCCCAAAAGGCCC	1173
NM_001735.2_43-61_s	43-61	GGAAUACUUUGUUUUUUAA	605	UUAAAAAAACAAAGUAUUCC	1174
NM_001735.2_49-67_s	49-67	CUUUGUUUUUUAAUCUUCC	606	GGAAGAUUAAAAAAACAAAG	1175
NM_001735.2_63-81_s	63-81	CUUCCUGGGGAAAACCUGG	607	CCAGGUUUUCCCCAGGAAG	1176
NM_001735.2_71-89_s	71-89	GGAAAACCUGGGGACAGGA	608	UCCUGUCCCCAGGUUUUCC	1177
NM_001735.2_81-99_s	81-99	GGGACAGGAGCAAACAUAU	609	AUAUGUUUGCUCCUGUCCC	1178
NM_001735.2_91-109_s	91-109	CAAACAUAUGUCAUUUCAG	610	CUGAAAUGACAUAUGUUUG	1179
NM_001735.2_102-120_s	102-120	CAUUUCAGCACCAAAAAUA	611	UAUUUUUGGUGCUGAAAUG	1180
NM_001735.2_109-127_s	109-127	GCACCAAAAAUAUUCCGUG	612	CACGGAAUAUUUUUGGUGC	1181
NM_001735.2_123-141_s	123-141	CCGUGUUGGAGCAUCUGAA	613	UUCAGAUGCUCCAACACGG	1182
NM_001735.2_130-148_s	130-148	GGAGCAUCUGAAAAUAUUG	614	CAAUAUUUUCAGAUGCUCC	1183
NM_001735.2_139-157_s	139157	GAAAAUAUUGUGAUUCAAG	615	CUUGAAUCACAAUAUUUUC	1184
NM_001735.2_150-168_s	150-168	GAUUCAAGUUUAUGGAUAC	616	GUAUCCAUAAACUUGAAUC	1185
NM_001735.2_163-181_s	163-181	GGAUACACUGAAGCAUUUG	617	CAAAUGCUUCAGUGUAUCC	1186

NM_001735.2_172-190_s	172-190	GAAGCAUUUGAUGCAACAA	618	UUGUUGCAUCAAAUGCUUC	1187
NM_001735.2_183-201_s	183-201	UGCAACAAUCUCUAUUAAA	619	UUUAAUAGAGAUUGUUGCA	1188
NM_001735.2_189-207_s	189-207	AAUCUCUAUUAAAAGUUAU	620	AUAACUUUUAAUAGAGAUU	1189
NM_001735.2_201-219_s	201-219	AAGUUAUCCUGAUAAAAAA	621	UUUUUUAUCAGGAUAACUU	1190
NM_001735.2_209-227_s	209-227	CUGAUAAAAAAUUUAGUUA	622	UAACUAAAUUUUUUUAUCAG	1191
NM_001735.2_221-239_s	221-239	UUAGUUACUCCUCAGGCCA	623	UGGCCUGAGGAGUAACUAA	1192
NM_001735.2_230-248_s	230-248	CCUCAGGCCAUGUUCAUUU	624	AAAUGAACAUGGCCUGAGG	1193
NM_001735.2_242-260_s	242-260	UUCAUUUAUCCUCAGAGAA	625	UUCUCUGAGGAUAAAUGAA	1194
NM_001735.2_252-270_s	252-270	CUCAGAGAAUAAAUUCCAA	626	UUGGAAUUUAUUCUCUGAG	1195
NM_001735.2_259-277_s	259-277	AAUAAAUUCCAAAACUCUG	627	CAGAGUUUUGGAAUUUAUU	1196
NM_001735.2_273-291_s	273-291	CUCUGCAAUCUUAACAAUA	628	UAUUGUUAAGAUUGCAGAG	1197
NM_001735.2_282-300_s	282-300	CUUAACAAUACAACCAAAA	629	UUUUGGUUGUAUUGUUAAG	1198
NM_001735.2_292-310_s	292-310	CAACCAAAACAAUUGCCUG	630	CAGGCAAUUGUUUUGGUUG	1199
NM_001735.2_301-319_s	301-319	CAAUUGCCUGGAGGACAAA	631	UUUGUCCUCCAGGCAAUUG	1200
NM_001735.2_313-331_s	313-331	GGACAAAACCCAGUUUCUU	632	AAGAAACUGGGUUUUGUCC	1201
NM_001735.2_322-340_s	322-340	CCAGUUUCUUAUGUGUAUU	633	AAUACACAUAAGAAACUGG	1202
NM_001735.2_332-350_s	332-350	AUGUGUAUUUGGAAGUUGU	634	ACAACUUCCAAAUACACAU	1203
NM_001735.2_342-360_s	342-360	GGAAGUUGUAUCAAAGCAU	635	AUGCUUUGAUACAACUUCC	1204
NM_001735.2_349-367_s	349-367	GUAUCAAAGCAUUUUUCAA	636	UUGAAAAAUGCUUUGAUAC	1205
NM_001735.2_361-379_s	361-379	UUUUCAAAAUCAAAAAGAA	637	UUCUUUUUUGAUUUUGAAAA	1206
NM_001735.2_371-389_s	371-389	CAAAAAGAAUGCCAAUAAC	638	GUUAUUGGCAUUCUUUUUG	1207

NM_001735.2_381-399_s	381-399	GCCAAUAACCUAUGACAAU	639	AUUGUCAUAGGUUAUUGGC	1208
NM_001735.2_389-407_s	389-407	CCUAUGACAAUGGAUUUCU	640	AGAAAUCCAUUGUCAUAGG	1209
NM_001735.2_399-417_s	399-417	UGGAUUUCUCUUCAUUCAU	641	AUGAAUGAAGAGAAAUCCA	1210
NM_001735.2_411-429_s	411-429	CAUUCAUACAGACAAACCU	642	AGGUUUGUCUGUAUGAAUG	1211
NM_001735.2_419-437_s	419-437	CAGACAAACCUGUUUAUAC	643	GUAUAAACAGGUUUGUCUG	1212
NM_001735.2_430-448_s	430-448	GUUUAUACUCCAGACCAGU	644	ACUGGUCUGGAGUAUAAAC	1213
NM_001735.2_441-459_s	441-459	AGACCAGUCAGUAAAAGUU	645	AACUUUUACUGACUGGUCU	1214
NM_001735.2_450-468_s	450-468	AGUAAAAGUUAGAGUUUAU	646	AUAAACUCUAACUUUUACU	1215
NM_001735.2_460-478_s	460-478	AGAGUUUAUUCGUUGAAUG	647	CAUUCAACGAAUAAACUCU	1216
NM_001735.2_470-488_s	470-488	CGUUGAAUGACGACUUGAA	648	UUCAAGUCGUCAUUCAACG	1217
NM_001735.2_483-501_s	483-501	CUUGAAGCCAGCCAAAAGA	649	UCUUUUGGCUGGCUUCAAG	1218
NM_001735.2_490-508_s	490-508	CCAGCCAAAAGAGAAACUG	650	CAGUUUCUCUUUUGGCUGG	1219
NM_001735.2_503-521_s	503-521	AAACUGUCUUAACUUUCAU	651	AUGAAAGUUAAGACAGUUU	1220
NM_001735.2_513-531_s	513-531	AACUUUCAUAGAUCCUGAA	652	UUCAGGAUCUAUGAAAGUU	1221
NM_001735.2_519-537_s	519-537	CAUAGAUCCUGAAGGAUCA	653	UGAUCCUUCAGGAUCUAUG	1222
NM_001735.2_529-547_s	529-547	GAAGGAUCAGAAGUUGACA	654	UGUCAACUUCUGAUCCUUC	1223
NM_001735.2_543-561_s	543-561	UGACAUGGUAGAAGAAAUU	655	AAUUUCUUCUACCAUGUCA	1224
NM_001735.2_553-571_s	553-571	GAAGAAAUUGAUCAUAUUG	656	CAAUAUGAUCAAUUUCUUC	1225
NM_001735.2_562-580_s	562-580	GAUCAUAUUGGAAUUAUCU	657	AGAUAAUUCCAAUAUGAUC	1226
NM_001735.2_571-589_s	571-589	GGAAUUAUCUCUUUUCCUG	658	CAGGAAAAGAGAUAAUUCC	1227
NM_001735.2_579-597_s	579-597	CUCUUUUCCUGACUUCAAG	659	CUUGAAGUCAGGAAAAGAG	1228

NM_001735.2_590-608_s	590-608	ACUUCAAGAUUCCGUCUAA	660	UUAGACGGAAUCUUGAAGU	1229
NM_001735.2_601-619_s	601-619	CCGUCUAAUCCUAGAUAUG	661	CAUAUCUAGGAUUAGACGG	1230
NM_001735.2_610-628_s	610-628	CCUAGAUAUGGUAUGUGGA	662	UCCACAUACCAUAUCUAGG	1231
NM_001735.2_623-641_s	623-641	UGUGGACGAUCAAGGCUAA	663	UUAGCCUUGAUCGUCCACA	1232
NM_001735.2_629-647_s	629-647	CGAUCAAGGCUAAAUAUAA	664	UUAUAUUUAGCCUUGAUCG	1233
NM_001735.2_642-660_s	642-660	AUAUAAAGAGGACUUUUCA	665	UGAAAAGUCCUCUUUAUAU	1234
NM_001735.2_649-667_s	649-667	GAGGACUUUUCAACAACUG	666	CAGUUGUUGAAAAGUCCUC	1235
NM_001735.2_662-680_s	662-680	CAACUGGAACCGCAUAUUU	667	AAAUAUGCGGUUCCAGUUG	1236
NM_001735.2_672-690_s	672-690	CGCAUAUUUUGAAGUUAAA	668	UUUAACUUCAAAAUAUGCG	1237
NM_001735.2_683-701_s	683-701	AAGUUAAAGAAUAUGUCUU	669	AAGACAUAUUCUUUAACUU	1238
NM_001735.2_691-709_s	691-709	GAAUAUGUCUUGCCACAUU	670	AAUGUGGCAAGACAUAUUC	1239
NM_001735.2_703-721_s	703-721	CCACAUUUUUCUGUCUCAA	671	UUGAGACAGAAAAAUGUGG	1240
NM_001735.2_713-731_s	713-731	CUGUCUCAAUCGAGCCAGA	672	UCUGGCUCGAUUGAGACAG	1241
NM_001735.2_719-737_s	719-737	CAAUCGAGCCAGAAUAUAA	673	UUAUAUUCUGGCUCGAUUG	1242
NM_001735.2_730-748_s	730-748	GAAUAUAAUUUCAUUGGUU	674	AACCAAUGAAAUUAUAUUC	1243
NM_001735.2_742-760_s	742-760	AUUGGUUACAAGAACUUUA	675	UAAAGUUCUUGUAACCAAU	1244
NM_001735.2_752-770_s	752-770	AGAACUUUAAGAAUUUUGA	676	UCAAAAUUCUUAAAGUUCU	1245
NM_001735.2_762-780_s	762-780	GAAUUUUGAAAUUACUAUA	677	UAUAGUAAUUUCAAAAUUC	1246
NM_001735.2_769-787_s	769-787	GAAAUUACUAUAAAAGCAA	678	UUGCUUUUAUAGUAAUUUC	1247
NM_001735.2_781-799_s	781-799	AAAGCAAGAUAUUUUUAUA	679	UAUAAAAAUAUCUUGCUUU	1248
NM_001735.2_789-807_s	789-807	AUAUUUUUAUAAUAAAGUA	680	UACUUUAUUAUAAAAAUAU	1249

NM_001735.2_803-821_s	803-821	AAGUAGUCACUGAGGCUGA	681	UCAGCCUCAGUGACUACUU	1250
NM_001735.2_810-828_s	810-828	CACUGAGGCUGACGUUUAU	682	AUAAACGUCAGCCUCAGUG	1251
NM_001735.2_822-840_s	822-840	CGUUUAUAUCACAUUUGGA	683	UCCAAAUGUGAUAUAAACG	1252
NM_001735.2_831-849_s	831-849	CACAUUUGGAAUAAGAGAA	684	UUCUCUUAUUCCAAAUGUG	1253
NM_001735.2_840-858_s	840-858	AAUAAGAGAAGACUUAAAA	685	UUUUAAGUCUUCUCUUAUU	1254
NM_001735.2_852-870_s	852-870	CUUAAAAGAUGAUCAAAAA	686	UUUUUGAUCAUCUUUUAAG	1255
NM_001735.2_859-877_s	859-877	GAUGAUCAAAAAGAAAUGA	687	UCAUUUCUUUUUGAUCAUC	1256
NM_001735.2_872-890_s	872-890	AAAUGAUGCAAACAGCAAU	688	AUUGCUGUUUGCAUCAUUU	1257
NM_001735.2_883-901_s	883-901	ACAGCAAUGCAAAACACAA	689	UUGUGUUUUGCAUUGCUGU	1258
NM_001735.2_893-911_s	893-911	AAAACACAAUGUUGAUAAA	690	UUUAUCAACAUUGUGUUUU	1259
NM_001735.2_899-917_s	899-917	CAAUGUUGAUAAAUGGAAU	691	AUUCCAUUUAUCAACAUUG	1260
NM_001735.2_913-931_s	913-931	GGAAUUGCUCAAGUCACAU	692	AUGUGACUUGAGCAAUUCC	1261
NM_001735.2_919-937_s	919-937	GCUCAAGUCACAUUUGAUU	693	AAUCAAAUGUGACUUGAGC	1262
NM_001735.2_930-948_s	930-948	AUUUGAUUCUGAAACAGCA	694	UGCUGUUUCAGAAUCAAAU	1263
NM_001735.2_939-957_s	939-957	UGAAACAGCAGUCAAAGAA	695	UUCUUUGACUGCUGUUUCA	1264
NM_001735.2_951-969_s	951-969	CAAAGAACUGUCAUACUAC	696	GUAGUAUGACAGUUCUUUG	1265
NM_001735.2_962-980_s	962-980	CAUACUACAGUUUAGAAGA	697	UCUUCUAAACUGUAGUAUG	1266
NM_001735.2_969-987_s	969-987	CAGUUUAGAAGAUUUAAAC	698	GUUUAAAUCUUCUAAACUG	1267
NM_001735.2_983-1001_s	983-1001	UAAACAACAAGUACCUUUA	699	UAAAGGUACUUGUUGUUUA	1268
NM_001735.2_990-1008_s	990-1008	CAAGUACCUUUAUAUUGCU	700	AGCAAUAUAAAGGUACUUG	1269
NM_001735.2_1002-1020_s	1002-1020	UAUUGCUGUAACAGUCAUA	701	UAUGACUGUUACAGCAAUA	1270

NM_001735.2_1011-1029_s	1011-1029	AACAGUCAUAGAGUCUACA	702	UGUAGACUCUAUGACUGUU	1271
NM_001735.2_1020-1038_s	1020-1038	AGAGUCUACAGGUGGAUUU	703	AAAUCCACCUGUAGACUCU	1272
NM_001735.2_1033-1051_s	1033-1051	GGAUUUUCUGAAGAGGCAG	704	CUGCCUCUUCAGAAAAUCC	1273
NM_001735.2_1042-1060_s	1042-1060	GAAGAGGCAGAAAUACCUG	705	CAGGUAUUUCUGCCUCUUC	1274
NM_001735.2_1050-1068_s	1050-1068	AGAAAUACCUGGCAUCAAA	706	UUUGAUGCCAGGUAUUUCU	1275
NM_001735.2_1061-1079_s	1061-1079	GCAUCAAAUAUGUCCUCUC	707	GAGAGGACAUAUUUGAUGC	1276
NM_001735.2_1071-1089_s	1071-1089	UGUCCUCUCUCCCUACAAA	708	UUUGUAGGGAGAGAGGACA	1277
NM_001735.2_1092-1110_s	1092-1110	GAAUUUGGUUGCUACUCCU	709	AGGAGUAGCAACCAAAUUC	1278
NM_001735.2_1102-1120_s	1102-1120	GCUACUCCUCUUUUCCUGA	710	UCAGGAAAAGAGGAGUAGC	1279
NM_001735.2_1109-1127_s	1109-1127	CUCUUUUCCUGAAGCCUGG	711	CCAGGCUUCAGGAAAAGAG	1280
NM_001735.2_1123-1141_s	1123-1141	CCUGGGAUUCCAUAUCCCA	712	UGGGAUAUGGAAUCCCAGG	1281
NM_001735.2_1133-1151_s	1133-1151	CAUAUCCCAUCAAGGUGCA	713	UGCACCUUGAUGGGAUAUG	1282
NM_001735.2_1139-1157_s	1139-1157	CCAUCAAGGUGCAGGUUAA	714	UUAACCUGCACCUUGAUGG	1283
NM_001735.2_1150-1168_s	1150-1168	CAGGUUAAAGAUUCGCUUG	715	CAAGCGAAUCUUUAACCUG	1284
NM_001735.2_1161-1179_s	1161-1179	UUCGCUUGACCAGUUGGUA	716	UACCAACUGGUCAAGCGAA	1285
NM_001735.2_1170-1188_s	1170-1188	CCAGUUGGUAGGAGGAGUC	717	GACUCCUCCUACCAACUGG	1286
NM_001735.2_1180-1198_s	1180-1198	GGAGGAGUCCCAGUAACAC	718	GUGUUACUGGGACUCCUCC	1287
NM_001735.2_1190-1208_s	1190-1208	CAGUAACACUGAAUGCACA	719	UGUGCAUUCAGUGUUACUG	1288
NM_001735.2_1200-1218_s	1200-1218	GAAUGCACAAACAAUUGAU	720	AUCAAUUGUUUGUGCAUUC	1289
NM_001735.2_1209-1227_s	1209-1227	AACAAUUGAUGUAAACCAA	721	UUGGUUUACAUCAAUUGUU	1290
NM_001735.2_1220-1238_s	1220-1238	UAAACCAAGAGACAUCUGA	722	UCAGAUGUCUCUUGGUUUA	1291

NM_001735.2_1232-1250_s	1232-1250	CAUCUGACUUGGAUCCAAG	723	CUUGGAUCCAAGUCAGAUG	1292
NM_001735.2_1243-1261_s	1243-1261	GAUCCAAGCAAAAGUGUAA	724	UUACACUUUUGCUUGGAUC	1293
NM_001735.2_1251-1269_s	1251-1269	CAAAAGUGUAACACGUGUU	725	AACACGUGUUACACUUUUG	1294
NM_001735.2_1260-1278_s	1260-1278	AACACGUGUUGAUGAUGGA	726	UCCAUCAUCAACACGUGUU	1295
NM_001735.2_1272-1290_s	1272-1290	UGAUGGAGUAGCUUCCUUU	727	AAAGGAAGCUACUCCAUCA	1296
NM_001735.2_1279-1297_s	1279-1297	GUAGCUUCCUUUGUGCUUA	728	UAAGCACAAAGGAAGCUAC	1297
NM_001735.2_1293-1311_s	1293-1311	GCUUAAUCUCCCAUCUGGA	729	UCCAGAUGGGAGAUUAAGC	1298
NM_001735.2_1303-1321_s	1303-1321	CCAUCUGGAGUGACGGUGC	730	GCACCGUCACUCCAGAUGG	1299
NM_001735.2_1313-1331_s	1313-1331	UGACGGUGCUGGAGUUUAA	731	UUAAACUCCAGCACCGUCA	1300
NM_001735.2_1320-1338_s	1320-1338	GCUGGAGUUUAAUGUCAAA	732	UUUGACAUUAAACUCCAGC	1301
NM_001735.2_1332-1350_s	1332-1350	UGUCAAAACUGAUGCUCCA	733	UGGAGCAUCAGUUUUGACA	1302
NM_001735.2_1342-1360_s	1342-1360	GAUGCUCCAGAUCUUCCAG	734	CUGGAAGAUCUGGAGCAUC	1303
NM_001735.2_1349-1367_s	1349-1367	CAGAUCUUCCAGAAGAAAA	735	UUUUCUUCUGGAAGAUCUG	1304
NM_001735.2_1362-1380_s	1362-1380	AGAAAAUCAGGCCAGGGAA	736	UUCCCUGGCCUGAUUUUCU	1305
NM_001735.2_1371-1389_s	1371-1389	GGCCAGGGAAGGUUACCGA	737	UCGGUAACCUUCCCUGGCC	1306
NM_001735.2_1382-1400_s	1382-1400	GUUACCGAGCAAUAGCAUA	738	UAUGCUAUUGCUCGGUAAC	1307
NM_001735.2_1393-1411_s	1393-1411	AUAGCAUACUCAUCUCUCA	739	UGAGAGAUGAGUAUGCUAU	1308
NM_001735.2_1399-1417_s	1399-1471	UACUCAUCUCUCAGCCAAA	740	UUUGGCUGAGAGAUGAGUA	1309
NM_001735.2_1412-1430_s	1412-1430	GCCAAAGUUACCUUUAUAU	741	AUAUAAAGGUAACUUUGGC	1310
NM_001735.2_1422-1440_s	1422-1440	CCUUUAUAUUGAUUGGACU	742	AGUCCAAUCAAUAUAAAGG	1311
NM_001735.2_1432-1450_s	1432-1450	GAUUGGACUGAUAACCAUA	743	UAUGGUUAUCAGUCCAAUC	1312

NM_001735.2_1439-1457_s	1439-1457	CUGAUAACCAUAAGGCUUU	744	AAAGCCUUAUGGUUAUCAG	1313
NM_001735.2_1451-1469_s	1451-1469	AGGCUUUGCUAGUGGGAGA	745	UCUCCCACUAGCAAAGCCU	1314
NM_001735.2_1462-1480_s	1462-1480	GUGGGAGAACAUCUGAAUA	746	UAUUCAGAUGUUCUCCCAC	1315
NM_001735.2_1471-1489_s	1471-1489	CAUCUGAAUAUUAUUGUUA	747	UAACAAUAAUAUUCAGAUG	1316
NM_001735.2_1479-1497_s	1479-1497	UAUUAUUGUUACCCCCAAA	748	UUUGGGGGUAACAAUAAUA	1317
NM_001735.2_1492-1510_s	1492-1510	CCCAAAAGCCCAUAUAUUG	749	CAAUAUAUGGGCUUUUGGG	1318
NM_001735.2_1493-1511_s	1493-1511	CCAAAAGCCCAUAUAUUGA	750	UCAAUAUAUGGGCUUUUGG	1319
NM_001735.2_1494-1512_s	1494-1512	CAAAAGCCCAUAUAUUGAC	751	GUCAAUAUAUGGGCUUUUG	1320
NM_001735.2_1495-1513_s	1495-1513	AAAAGCCCAUAUAUUGACA	752	UGUCAAUAUAUGGGCUUUU	1321
NM_001735.2_1496-1514_s	1496-1514	AAAGCCCAUAUAUUGACAA	753	UUGUCAAUAUAUGGGCUUU	1322
NM_001735.2_1497-1515_s	1497-1515	AAGCCCAUAUAUUGACAAA	754	UUUGUCAAUAUAUGGGCUU	1323
NM_001735.2_1498-1516_s	1498-1516	AGCCCAUAUAUUGACAAAA	755	UUUUGUCAAUAUAUGGGCU	1324
NM_001735.2_1499-1517_s	1499-1517	GCCCAUAUAUUGACAAAAU	756	AUUUUGUCAAUAUAUGGGC	1325
NM_001735.2_1500-1518_s	1500-1518	CCCAUAUAUUGACAAAAUA	757	UAUUUUGUCAAUAUAUGGG	1326
NM_001735.2_1501-1519_s	1501-1519	CCAUAUAUUGACAAAAUAA	758	UUAUUUUGUCAAUAUAUGG	1327
NM_001735.2_1502-1520_s	1502-1520	CAUAUAUUGACAAAAUAAC	759	GUUAUUUUGUCAAUAUAUG	1328
NM_001735.2_1503-1521_s	1503-1521	AUAUAUUGACAAAAUAACU	760	AGUUAUUUUGUCAAUAUAU	1329
NM_001735.2_1504-1522_s	1504-1522	UAUAUUGACAAAAUAACUC	761	GAGUUAUUUUGUCAAUAUA	1330
NM_001735.2_1505-1523_s	1505-1523	AUAUUGACAAAAUAACUCA	762	UGAGUUAUUUUGUCAAUAU	1331
NM_001735.2_1506-1524_s	1506-1524	UAUUGACAAAAUAACUCAC	763	GUGAGUUAUUUUGUCAAUA	1332
NM_001735.2_1507-1525_s	1507-1525	AUUGACAAAAUAACUCACU	764	AGUGAGUUAUUUUGUCAAU	1333

NM_001735.2_1508-1526_s	1508-1526	UUGACAAAAUAACUCACUA	765	UAGUGAGUUAUUUUGUCAA	1334
NM_001735.2_1509-1527_s	1509-1527	UGACAAAAUAACUCACUAU	766	AUAGUGAGUUAUUUUGUCA	1335
NM_001735.2_1510-1528_s	1510-1528	GACAAAAUAACUCACUAUA	767	UAUAGUGAGUUAUUUUGUC	1336
NM_001735.2_1513-1531_s	1513-1531	AAAAUAACUCACUAUAAUU	768	AAUUAUAGUGAGUUAUUUU	1337
NM_001735.2_1514-1532_s	1514-1532	AAAUAACUCACUAUAAUUA	769	UAAUUAUAGUGAGUUAUUU	1338
NM_001735.2_1515-1533_s	1515-1533	AAUAACUCACUAUAAUUAC	770	GUAAUUAUAGUGAGUUAUU	1339
NM_001735.2_1516-1534_s	1516-1534	AUAACUCACUAUAAUUACU	771	AGUAAUUAUAGUGAGUUAU	1340
NM_001735.2_1518-1536_s	1518-1536	AACUCACUAUAAUUACUUG	772	CAAGUAAUUAUAGUGAGUU	1341
NM_001735.2_1519-1537_s	1519-1537	ACUCACUAUAAUUACUUGA	773	UCAAGUAAUUAUAGUGAGU	1342
NM_001735.2_1520-1538_s	1520-1538	CUCACUAUAAUUACUUGAU	774	AUCAAGUAAUUAUAGUGAG	1343
NM_001735.2_1521-1539_s	1521-1539	UCACUAUAAUUACUUGAUU	775	AAUCAAGUAAUUAUAGUGA	1344
NM_001735.2_1523-1541_s	1523-1541	ACUAUAAUUACUUGAUUUU	776	AAAAUCAAGUAAUUAUAGU	1345
NM_001735.2_1524-1542_s	1524-1542	CUAUAAUUACUUGAUUUUA	777	UAAAAUCAAGUAAUUAUAG	1346
NM_001735.2_1525-1543_s	1525-1543	UAUAAUUACUUGAUUUUAU	778	AUAAAAUCAAGUAAUUAUA	1347
NM_001735.2_1526-1544_s	1526-1544	AUAAUUACUUGAUUUUAUC	779	GAUAAAAUCAAGUAAUUAU	1348
NM_001735.2_1527-1545_s	1527-1545	UAAUUACUUGAUUUUAUCC	780	GGAUAAAAUCAAGUAAUUA	1349
NM_001735.2_1528-1546_s	1528-1546	AAUUACUUGAUUUUAUCCA	781	UGGAUAAAAUCAAGUAAUU	1350
NM_001735.2_1529-1547_s	1529-1547	AUUACUUGAUUUUAUCCAA	782	UUGGAUAAAAUCAAGUAAU	1351
NM_001735.2_1540-1558_s	1540-1558	UUAUCCAAGGGCAAAAUUA	783	UAAUUUUGCCCUUGGAUAA	1352
NM_001735.2_1550-1568_s	1550-1568	GCAAAAUUAUCCACUUUGG	784	CCAAAGUGGAUAAUUUUGC	1353
NM_001735.2_1561-1579_s	1561-1579	CACUUUGGCACGAGGGAGA	785	UCUCCCUCGUGCCAAAGUG	1354

NM_001735.2_1571-1589_s	1571-1589	CGAGGGAGAAAUUUUCAGA	786	UCUGAAAAUUUCUCCCUCG	1355
NM_001735.2_1581-1599_s	1581-1599	AUUUUCAGAUGCAUCUUAU	787	AUAAGAUGCAUCUGAAAAU	1356
NM_001735.2_1591-1609_s	1591-1609	GCAUCUUAUCAAAGUAUAA	788	UUAUACUUUGAUAAGAUGC	1357
NM_001735.2_1600-1618_s	1600-1618	CAAAGUAUAAACAUUCCAG	789	CUGGAAUGUUUAUACUUUG	1358
NM_001735.2_1612-1630_s	1612-1630	AUUCCAGUAACACAGAACA	790	UGUUCUGUGUUACUGGAAU	1359
NM_001735.2_1622-1640_s	1622-1640	CACAGAACAUGGUUCCUUC	791	GAAGGAACCAUGUUCUGUG	1360
NM_001735.2_1632-1650_s	1632-1560	GGUUCCUUCAUCCCGACUU	792	AAGUCGGGAUGAAGGAACC	1361
NM_001735.2_1643-1661_s	1643-1661	CCCGACUUCUGGUCUAUUA	793	UAAUAGACCAGAAGUCGGG	1362
NM_001735.2_1653-1671_s	1653-1671	GGUCUAUUACAUCGUCACA	794	UGUGACGAUGUAAUAGACC	1363
NM_001735.2_1663-1681_s	1663-1681	AUCGUCACAGGAGAACAGA	795	UCUGUUCUCCUGUGACGAU	1364
NM_001735.2_1670-1688_s	1670-1688	CAGGAGAACAGACAGCAGA	796	UCUGCUGUCUGUUCUCCUG	1365
NM_001735.2_1682-1700_s	1682-1700	CAGCAGAAUUAGUGUCUGA	797	UCAGACACUAAUUCUGCUG	1366
NM_001735.2_1693-1711_s	1693-1711	GUGUCUGAUUCAGUCUGGU	798	ACCAGACUGAAUCAGACAC	1367
NM_001735.2_1703-1721_s	1703-1721	CAGUCUGGUUAAAUAUUGA	799	UCAAUAUUUAACCAGACUG	1368
NM_001735.2_1710-1728_s	1710-1728	GUUAAAUAUUGAAGAAAAA	800	UUUUUCUUCAAUAUUUAAC	1369
NM_001735.2_1722-1740_s	1722-1740	AGAAAAAUGUGGCAACCAG	801	CUGGUUGCCACAUUUUUCU	1370
NM_001735.2_1733-1751_s	1733-1751	GCAACCAGCUCCAGGUUCA	802	UGAACCUGGAGCUGGUUGC	1371
NM_001735.2_1740-1758_s	1740-1758	GCUCCAGGUUCAUCUGUCU	803	AGACAGAUGAACCUGGAGC	1372
NM_001735.2_1751-1769_s	1751-1769	AUCUGUCUCCUGAUGCAGA	804	UCUGCAUCAGGAGACAGAU	1373
NM_001735.2_1762-1780_s	1762-1780	GAUGCAGAUGCAUAUUCUC	805	GAGAAUAUGCAUCUGCAUC	1374
NM_001735.2_1771-1789_s	1771-1789	GCAUAUUCUCCAGGCCAAA	806	UUUGGCCUGGAGAAUAUGC	1375

NM_001735.2_1782-1800_s	1782-1800	AGGCCAAACUGUGUCUCUU	807	AAGAGACACAGUUUGGCCU	1376
NM_001735.2_1792-1810_s	1792-1810	GUGUCUCUUAAUAUGGCAA	808	UUGCCAUAUUAAGAGACAC	1377
NM_001735.2_1799-1817_s	1799-1817	UUAAUAUGGCAACUGGAAU	809	AUUCCAGUUGCCAUAUUAA	1378
NM_001735.2_1809-1827_s	1809-1827	AACUGGAAUGGAUUCCUGG	810	CCAGGAAUCCAUUCCAGUU	1379
NM_001735.2_1821-1839_s	1821-1839	UUCCUGGGUGGCAUUAGCA	811	UGCUAAUGCCACCCAGGAA	1380
NM_001735.2_1830-1848_s	1830-1848	GGCAUUAGCAGCAGUGGAC	812	GUCCACUGCUGCUAAUGCC	1381
NM_001735.2_1842-1860_s	1842-1860	AGUGGACAGUGCUGUGUAU	813	AUACACAGCACUGUCCACU	1382
NM_001735.2_1852-1870_s	1852-1870	GCUGUGUAUGGAGUCCAAA	814	UUUGGACUCCAUACACAGC	1383
NM_001735.2_1863-1881_s	1863-1881	AGUCCAAAGAGGAGCCAAA	815	UUUGGCUCCUCUUUGGACU	1384
NM_001735.2_1870-1888_s	1870-1888	AGAGGAGCCAAAAAGCCCU	816	AGGGCUUUUUGGCUCCUCU	1385
NM_001735.2_1883-1901_s	1883-1901	AGCCCUUGGAAAGAGUAUU	817	AAUACUCUUUCCAAGGGCU	1386
NM_001735.2_1893-1911_s	1893-1911	AAGAGUAUUUCAAUUCUUA	818	UAAGAAUUGAAAUACUCUU	1387
NM_001735.2_1900-1918_s	1900-1918	UUUCAAUUCUUAGAGAAGA	819	UCUUCUCUAAGAAUUGAAA	1388
NM_001735.2_1912-1930_s	1912-1930	GAGAAGAGUGAUCUGGGCU	820	AGCCCAGAUCACUCUUCUC	1389
NM_001735.2_1920-1938_s	1920-1938	UGAUCUGGGCUGUGGGGCA	821	UGCCCCACAGCCCAGAUCA	1390
NM_001735.2_1933-1951_s	1933-1951	GGGGCAGGUGGUGGCCUCA	822	UGAGGCCACCACCUGCCCC	1391
NM_001735.2_1943-1961_s	1943-1961	GUGGCCUCAACAAUGCCAA	823	UUGGCAUUGUUGAGGCCAC	1392
NM_001735.2_1950-1968_s	1950-1968	CAACAAUGCCAAUGUGUUC	824	GAACACAUUGGCAUUGUUG	1393
NM_001735.2_1959-1977_s	1959-1977	CAAUGUGUUCCACCUAGCU	825	AGCUAGGUGGAACACAUUG	1394
NM_001735.2_1969-1987_s	1969-1987	CACCUAGCUGGACUUACCU	826	AGGUAAGUCCAGCUAGGUG	1395
NM_001735.2_1979-1997_s	1979-1997	GACUUACCUUCCUCACUAA	827	UUAGUGAGGAAGGUAAGUC	1396

NM_001735.2_1991-2009_s	1991-2009	UCACUAAUGCAAAUGCAGA	828	UCUGCAUUUGCAUUAGUGA	1397
NM_001735.2_2001-2019_s	2001-2019	AAAUGCAGAUGACUCCCAA	829	UUGGGAGUCAUCUGCAUUU	1398
NM_001735.2_2013-2031_s	2013-2013	CUCCCAAGAAAAUGAUGAA	830	UUCAUCAUUUUCUUGGGAG	1399
NM_001735.2_2032-2050_s	2032-2050	CCUUGUAAAGAAAUUCUCA	831	UGAGAAUUUCUUUACAAGG	1400
NM_001735.2_2043-2061_s	2043-2061	AAUUCUCAGGCCAAGAAGA	832	UCUUCUUGGCCUGAGAAUU	1401
NM_001735.2_2053-2071_s	2053-2071	CCAAGAAGAACGCUGCAAA	833	UUUGCAGCGUUCUUCUUGG	1402
NM_001735.2_2063-2081_s	2063-2081	CGCUGCAAAAGAAGAUAGA	834	UCUAUCUUCUUUUGCAGCG	1403
NM_001735.2_2070-2088_s	2070-2088	AAAGAAGAUAGAAGAAAUA	835	UAUUUCUUCUAUCUUCUUU	1404
NM_001735.2_2082-2100_s	2082-2100	AGAAAUAGCUGCUAAAUAU	836	AUAUUUAGCAGCUAUUUCU	1405
NM_001735.2_2089-2107_s	2089-2107	GCUGCUAAAUAUAAACAUU	837	AAUGUUUAUAUUUAGCAGC	1406
NM_001735.2_2103-2121_s	2103-2121	ACAUUCAGUAGUGAAGAAA	838	UUUCUUCACUACUGAAUGU	1407
NM_001735.2_2110-2128_s	2110-2128	GUAGUGAAGAAAUGUUGUU	839	AACAACAUUUCUUCACUAC	1408
NM_001735.2_2119-2137_s	2119-2137	AAAUGUUGUUACGAUGGAG	840	CUCCAUCGUAACAACAUUU	1409
NM_001735.2_2130-2148_s	2130-2148	CGAUGGAGCCUGCGUUAAU	841	AUUAACGCAGGCUCCAUCG	1410
NM_001735.2_2142-2160_s	2142-2160	CGUUAAUAAUGAUGAAACC	842	GGUUUCAUCAUUAUUAACG	1411
NM_001735.2_2150-2168_s	2150-2168	AUGAUGAAACCUGUGAGCA	843	UGCUCACAGGUUUCAUCAU	1412
NM_001735.2_2160-2178_s	2160-2178	CUGUGAGCAGCGAGCUGCA	844	UGCAGCUCGCUGCUCACAG	1413
NM_001735.2_2170-2188_s	2170-2188	CGAGCUGCACGGAUUAGUU	845	AACUAAUCCGUGCAGCUCG	1414
NM_001735.2_2180-2198_s	2180-2198	GGAUUAGUUUAGGGCCAAG	846	CUUGGCCCUAAACUAAUCC	1415
NM_001735.2_2191-2209_s	2191-2209	GGGCCAAGAUGCAUCAAAG	847	CUUUGAUGCAUCUUGGCCC	1416
NM_001735.2_2202-2220_s	2202-2220	CAUCAAAGCUUUCACUGAA	848	UUCAGUGAAAGCUUUGAUG	1417

NM_001735.2_2209-2227_s	2209-2227	GCUUUCACUGAAUGUUGUG	849	CACAACAUUCAGUGAAAGC	1418
NM_001735.2_2219-2237_s	2219-2237	AAUGUUGUGUCGUCGCAAG	850	CUUGCGACGACACAACAUU	1419
NM_001735.2_2229-2247_s	2229-2247	CGUCGCAAGCCAGCUCCGU	851	ACGGAGCUGGCUUGCGACG	1420
NM_001735.2_2241-2259_s	2241-2259	GCUCCGUGCUAAUAUCUCU	852	AGAGAUAUUAGCACGGAGC	1421
NM_001735.2_2249-2267_s	2249-2267	CUAAUAUCUCUCAUAAAGA	853	UCUUUAUGAGAGAUAUUAG	1422
NM_001735.2_2263-2281_s	2263-2281	AAAGACAUGCAAUUGGGAA	854	UUCCCAAUUGCAUGUCUUU	1423
NM_001735.2_2272-2290_s	2272-2290	CAAUUGGGAAGGCUACACA	855	UGUGUAGCCUUCCCAAUUG	1424
NM_001735.2_2283-2301_s	2283-2301	GCUACACAUGAAGACCCUG	856	CAGGGUCUUCAUGUGUAGC	1425
NM_001735.2_2289-2307_s	2289-2307	CAUGAAGACCCUGUUACCA	857	UGGUAACAGGGUCUUCAUG	1426
NM_001735.2_2303-2321_s	2303-2321	UACCAGUAAGCAAGCCAGA	858	UCUGGCUUGCUUACUGGUA	1427
NM_001735.2_2311-2329_s	2311-2329	AGCAAGCCAGAAAUUCGGA	859	UCCGAAUUUCUGGCUUGCU	1428
NM_001735.2_2319-2337_s	2319-2337	AGAAAUUCGGAGUUAUUUU	860	AAAAUAACUCCGAAUUUCU	1429
NM_001735.2_2329-2347_s	2329-2347	AGUUAUUUUCCAGAAAGCU	861	AGCUUUCUGGAAAAUAACU	1430
NM_001735.2_2339-2357_s	2339-2357	CAGAAAGCUGGUUGUGGGA	862	UCCCACAACCAGCUUUCUG	1431
NM_001735.2_2352-2370_s	2352-2370	GUGGGAAGUUCAUCUUGUU	863	AACAAGAUGAACUUCCCAC	1432
NM_001735.2_2361-2379_s	2361-2379	UCAUCUUGUUCCCAGAAGA	864	UCUUCUGGGAACAAGAUGA	1433
NM_001735.2_2372-2390_s	2372-2390	CCAGAAGAAAACAGUUGCA	865	UGCAACUGUUUUCUUCUGG	1434
NM_001735.2_2383-2401_s	2383-2401	CAGUUGCAGUUUGCCCUAC	866	GUAGGGCAAACUGCAACUG	1435
NM_001735.2_2389-2407_s	2389-2407	CAGUUUGCCCUACCUGAUU	867	AAUCAGGUAGGGCAAACUG	1436
NM_001735.2_2401-2419_s	2401-2419	CCUGAUUCUCUAACCACCU	868	AGGUGGUUAGAGAAUCAGG	1437
NM_001735.2_2413-2431_s	2413-2431	ACCACCUGGGAAAUUCAAG	869	CUUGAAUUUCCCAGGUGGU	1438

NM_001735.2_2422-2440_s	2422-2440	GAAAUUCAAGGCGUUGGCA	870	UGCCAACGCCUUGAAUUUC	1439
NM_001735.2_2433-2451_s	2433-2451	CGUUGGCAUUUCAAACACU	871	AGUGUUUGAAAUGCCAACG	1440
NM_001735.2_2439-2457_s	2439-2457	CAUUUCAAACACUGGUAUA	872	UAUACCAGUGUUUGAAAUG	1441
NM_001735.2_2453-2471_s	2453-2471	GUAUAUGUGUUGCUGAUAC	873	GUAUCAGCAACACAUAUAC	1442
NM_001735.2_2463-2481_s	2463-2481	UGCUGAUACUGUCAAGGCA	874	UGCCUUGACAGUAUCAGCA	1443
NM_001735.2_2471-2489_s	2471-2489	CUGUCAAGGCAAAGGUGUU	875	AACACCUUUGCCUUGACAG	1444
NM_001735.2_2483-2501_s	2483-2501	AGGUGUUCAAAGAUGUCUU	876	AAGACAUCUUUGAACACCU	1445
NM_001735.2_2490-2508_s	2490-2508	CAAAGAUGUCUUCCUGGAA	877	UUCCAGGAAGACAUCUUUG	1446
NM_001735.2_2499-2517_s	2499-2517	CUUCCUGGAAAUGAAUAUA	878	UAUAUUCAUUUCCAGGAAG	1447
NM_001735.2_2511-2529_s	2511-2529	GAAUAUACCAUAUUCUGUU	879	AACAGAAUAUGGUAUAUUC	1448
NM_001735.2_2520-2538_s	2520-2538	AUAUUCUGUUGUACGAGGA	880	UCCUCGUACAACAGAAUAU	1449
NM_001735.2_2533-2551_s	2533-2551	CGAGGAGAACAGAUCCAAU	881	AUUGGAUCUGUUCUCCUCG	1450
NM_001735.2_2539-2557_s	2539-2557	GAACAGAUCCAAUUGAAAG	882	CUUUCAAUUGGAUCUGUUC	1451
NM_001735.2_2553-2571_s	2553-2571	GAAAGGAACUGUUUACAAC	883	GUUGUAAACAGUUCCUUUC	1452
NM_001735.2_2560-2578_s	2560-2578	ACUGUUUACAACUAUAGGA	884	UCCUAUAGUUGUAAACAGU	1453
NM_001735.2_2569-2587_s	2569-2587	AACUAUAGGACUUCUGGGA	885	UCCCAGAAGUCCUAUAGUU	1454
NM_001735.2_2583-2601_s	2583-2601	UGGGAUGCAGUUCUGUGUU	886	AACACAGAACUGCAUCCCA	1455
NM_001735.2_2592-2610_s	2592-2610	GUUCUGUGUUAAAAUGUCU	887	AGACAUUUUAACACAGAAC	1456
NM_001735.2_2600-2618_s	2600-2618	UUAAAAUGUCUGCUGUGGA	888	UCCACAGCAGACAUUUUAA	1457
NM_001735.2_2612-2630_s	2612-2630	CUGUGGAGGGAAUCUGCAC	889	GUGCAGAUUCCCUCCACAG	1458
NM_001735.2_2620-2638_s	2620-2638	GGAAUCUGCACUUCGGAAA	890	UUUCCGAAGUGCAGAUUCC	1459

NM_001735.2_2633-2651_s	2633-2651	CGGAAAGCCCAGUCAUUGA	891	UCAAUGACUGGGCUUUCCG	1460
NM_001735.2_2641-2659_s	2641-2659	CCAGUCAUUGAUCAUCAGG	892	CCUGAUGAUCAAUGACUGG	1461
NM_001735.2_2653-2671_s	2653-2671	CAUCAGGGCACAAAGUCCU	893	AGGACUUUGUGCCCUGAUG	1462
NM_001735.2_2659-2677_s	2659-2677	GGCACAAAGUCCUCCAAAU	894	AUUUGGAGGACUUUGUGCC	1463
NM_001735.2_2673-2691_s	2673-2691	CAAAUGUGUGCGCCAGAAA	895	UUUCUGGCGCACACAUUUG	1464
NM_001735.2_2682-2700_s	2682-2700	GCGCCAGAAAGUAGAGGGC	896	GCCCUCUACUUUCUGGCGC	1465
NM_001735.2_2691-2709_s	2691-2709	AGUAGAGGGCUCCUCCAGU	897	ACUGGAGGAGCCCUCUACU	1466
NM_001735.2_2702-2720_s	2702-2720	CCUCCAGUCACUUGGUGAC	898	GUCACCAAGUGACUGGAGG	1467
NM_001735.2_2709-2727_s	2709-2727	UCACUUGGUGACAUUCACU	899	AGUGAAUGUCACCAAGUGA	1468
NM_001735.2_2720-2738_s	2720-2738	CAUUCACUGUGCUUCCUCU	900	AGAGGAAGCACAGUGAAUG	1469
NM_001735.2_2739-2757_s	2739-2757	GGAAAUUGGCCUUCACAAC	901	GUUGUGAAGGCCAAUUUCC	1470
NM_001735.2_2749-2767_s	2749-2767	CUUCACAACAUCAAUUUUU	902	AAAAAUUGAUGUUGUGAAG	1471
NM_001735.2_2761-2779_s	2761-2779	AAUUUUUCACUGGAGACUU	903	AAGUCUCCAGUGAAAAAUU	1472
NM_001735.2_2770-2788_s	2770-2788	CUGGAGACUUGGUUUGGAA	904	UUCCAAACCAAGUCUCCAG	1473
NM_001735.2_2780-2798_s	2780-2798	GGUUUGGAAAAGAAAUCUU	905	AAGAUUUCUUUUCCAAACC	1474
NM_001735.2_2793-2811_s	2793-2811	AAUCUUAGUAAAAACAUUA	906	UAAUGUUUUUACUAAGAUU	1475
NM_001735.2_2802-2820_s	2802-2820	AAAAACAUUACGAGUGGUG	907	CACCACUCGUAAUGUUUUU	1476
NM_001735.2_2813-2831_s	2813-2831	GAGUGGUGCCAGAAGGUGU	908	ACACCUUCUGGCACCACUC	1477
NM_001735.2_2823-2841_s	2823-2841	AGAAGGUGUCAAAAGGGAA	909	UUCCCUUUUGACACCUUCU	1478
NM_001735.2_2829-2847_s	2829-2847	UGUCAAAAGGGAAAGCUAU	910	AUAGCUUUCCCUUUUGACA	1479
NM_001735.2_2843-2861_s	2843-2861	GCUAUUCUGGUGUUACUUU	911	AAAGUAACACCAGAAUAGC	1480

NM_001735.2_2852-2870_s	2852-2870	GUGUUACUUUGGAUCCUAG	912	CUAGGAUCCAAAGUAACAC	1481
NM_001735.2_2862-2880_s	2862-2880	GGAUCCUAGGGGUAUUUAU	913	AUAAAUACCCCUAGGAUCC	1482
NM_001735.2_2872-2890_s	2872-2890	GGUAUUUAUGGUACCAUUA	914	UAAUGGUACCAUAAAUACC	1483
NM_001735.2_2882-2900_s	2882-2900	GUACCAUUAGCAGACGAAA	915	UUUCGUCUGCUAAUGGUAC	1484
NM_001735.2_2892-2910_s	2892-2910	CAGACGAAAGGAGUUCCCA	916	UGGGAACUCCUUUCGUCUG	1485
NM_001735.2_2900-2918_s	2900-2918	AGGAGUUCCCAUACAGGAU	917	AUCCUGUAUGGGAACUCCU	1486
NM_001735.2_2909-2927_s	2909-2927	CAUACAGGAUACCCUUAGA	918	UCUAAGGGUAUCCUGUAUG	1487
NM_001735.2_2922-2940_s	2922-2940	CUUAGAUUUGGUCCCCAAA	919	UUUGGGGACCAAAUCUAAG	1488
NM_001735.2_2933-2951_s	2933-2951	UCCCCAAAACAGAAAUCAA	920	UUGAUUUCUGUUUUGGGGA	1489
NM_001735.2_2941-2959_s	2941-2959	ACAGAAAUCAAAAGGAUUU	921	AAAUCCUUUUGAUUUCUGU	1490
NM_001735.2_2951-2969_s	2951-2969	AAAGGAUUUUGAGUGUAAA	922	UUUACACUCAAAAUCCUUU	1491
NM_001735.2_2962-2980_s	2962-2980	AGUGUAAAAGGACUGCUUG	923	CAAGCAGUCCUUUUACACU	1492
NM_001735.2_2969-2987_s	2969-2987	AAGGACUGCUUGUAGGUGA	924	UCACCUACAAGCAGUCCUU	1493
NM_001735.2_2980-2998_s	2980-2998	GUAGGUGAGAUCUUGUCUG	925	CAGACAAGAUCUCACCUAC	1494
NM_001735.2_2989-3007_s	2989-3007	AUCUUGUCUGCAGUUCUAA	926	UUAGAACUGCAGACAAGAU	1495
NM_001735.2_3001-3019_s	3001-3019	GUUCUAAGUCAGGAAGGCA	927	UGCCUUCCUGACUUAGAAC	1496
NM_001735.2_3013-3031_s	3013-3031	GAAGGCAUCAAUAUCCUAA	928	UUAGGAUAUUGAUGCCUUC	1497
NM_001735.2_3020-3038_s	3020-3038	UCAAUAUCCUAACCCACCU	929	AGGUGGGUUAGGAUAUUGA	1498
NM_001735.2_3033-3051_s	3033-3051	CCACCUCCCCAAAGGGAGU	930	ACUCCCUUUGGGGAGGUGG	1499
NM_001735.2_3039-3057_s	3039-3057	CCCCAAAGGGAGUGCAGAG	931	CUCUGCACUCCCUUUGGGG	1500
NM_001735.2_3050-3068_s	3050-3068	GUGCAGAGGCGGAGCUGAU	932	AUCAGCUCCGCCUCUGCAC	1501

NM_001735.2_3060-3078_s	3060-3078	GGAGCUGAUGAGCGUUGUC	933	GACAACGCUCAUCAGCUCC	1502
NM_001735.2_3072-3090_s	3072-3090	CGUUGUCCCAGUAUUCUAU	934	AUAGAAUACUGGGACAACG	1503
NM_001735.2_3079-3097_s	3079-3097	CCAGUAUUCUAUGUUUUUC	935	GAAAAACAUAGAAUACUGG	1504
NM_001735.2_3091-3109_s	3091-3109	GUUUUUCACUACCUGGAAA	936	UUUCCAGGUAGUGAAAAAC	1505
NM_001735.2_3102-3120_s	3102-3120	CCUGGAAACAGGAAAUCAU	937	AUGAUUUCCUGUUUCCAGG	1506
NM_001735.2_3122-3140_s	3122-3140	GGAACAUUUUUCAUUCUGA	938	UCAGAAUGAAAAAUGUUCC	1507
NM_001735.2_3133-3151_s	3133-3151	CAUUCUGACCCAUUAAUUG	939	CAAUUAAUGGGUCAGAAUG	1508
NM_001735.2_3142-3160_s	3142-3160	CCAUUAAUUGAAAAGCAGA	940	UCUGCUUUUCAAUUAAUGG	1509
NM_001735.2_3153-3171_s	3153-3171	AAAGCAGAAACUGAAGAAA	941	UUUCUUCAGUUUCUGCUUU	1510
NM_001735.2_3161-3179_s	3161-3179	AACUGAAGAAAAAAUUAAA	942	UUUAAUUUUUUUCUUCAGUU	1511
NM_001735.2_3169-3187_s	3169-3187	AAAAAAUUAAAAGAAGGGA	943	UCCCUUCUUUUUAAUUUUUU	1512
NM_001735.2_3183-3201_s	3183-3201	AGGGAUGUUGAGCAUUAUG	944	CAUAAUGCUCAACAUCCCU	1513
NM_001735.2_3192-3210_s	3192-3210	GAGCAUUAUGUCCUACAGA	945	UCUGUAGGACAUAAUGCUC	1514
NM_001735.2_3200-3218_s	3200-3218	UGUCCUACAGAAAUGCUGA	946	UCAGCAUUUCUGUAGGACA	1515
NM_001735.2_3211-3229_s	3211-3229	AAUGCUGACUACUCUUACA	947	UGUAAGAGUAGUCAGCAUU	1516
NM_001735.2_3220-3238_s	3220-3238	UACUCUUACAGUGUGUGGA	948	UCCACACACUGUAAGAGUA	1517
NM_001735.2_3229-3247_s	3229-3247	AGUGUGUGGAAGGGUGGAA	949	UUCCACCCUUCCACACACU	1518
NM_001735.2_3240-3258_s	3240-3258	GGGUGGAAGUGCUAGCACU	950	AGUGCUAGCACUUCCACCC	1519
NM_001735.2_3250-3268_s	3250-3268	GCUAGCACUUGGUUAACAG	951	CUGUUAACCAAGUGCUAGC	1520
NM_001735.2_3260-3278_s	3260-3278	GGUUAACAGCUUUUGCUUU	952	AAAGCAAAAGCUGUUAACC	1521
NM_001735.2_3273-3291_s	3273-3291	UGCUUUAAGAGUACUUGGA	953	UCCAAGUACUCUUAAAGCA	1522

NM_001735.2_3283-3301_s	3283-3301	GUACUUGGACAAGUAAAUA	954	UAUUUACUUGUCCAAGUAC	1523
NM_001735.2_3292-3310_s	3292-3317	CAAGUAAAUAAAUACGUAG	955	CUACGUAUUUAUUUACUUG	1524
NM_001735.2_3299-3317_s	3299-3317	AUAAAUACGUAGAGCAGAA	956	UUCUGCUCUACGUAUUUAU	1525
NM_001735.2_3310-3328_s	3310-3328	GAGCAGAACCAAAAUUCAA	957	UUGAAUUUUGGUUCUGCUC	1526
NM_001735.2_3322-3340_s	3322-3340	AAUUCAAUUUGUAAUUCUU	958	AAGAAUUACAAAUUGAAUU	1527
NM_001735.2_3332-3350_s	3332-3350	GUAAUUCUUUAUUGUGGCU	959	AGCCACAAUAAAGAAUUAC	1528
NM_001735.2_3342-3360_s	3342-3360	AUUGUGGCUAGUUGAGAAU	960	AUUCUCAACUAGCCACAAU	1529
NM_001735.2_3349-3367_s	3349-3367	CUAGUUGAGAAUUAUCAAU	961	AUUGAUAAUUCUCAACUAG	1530
NM_001735.2_3360-3378_s	3360-3378	UUAUCAAUUAGAUAAUGGA	962	UCCAUUAUCUAAUUGAUAA	1531
NM_001735.2_3373-3391_s	3373-3391	AAUGGAUCUUUCAAGGAAA	963	UUUCCUUGAAAGAUCCAUU	1532
NM_001735.2_3380-3398_s	3380-3398	CUUUCAAGGAAAAUUCACA	964	UGUGAAUUUUCCUUGAAAG	1533
NM_001735.2_3391-3409_s	3391-3409	AAUUCACAGUAUCAACCAA	965	UUGGUUGAUACUGUGAAUU	1534
NM_001735.2_3399-3417_s	3399-3417	GUAUCAACCAAUAAAAUUA	966	UAAUUUUAUUGGUUGAUAC	1535
NM_001735.2_3411-3429_s	3411-3429	AAAAUUACAGGGUACCUUG	967	CAAGGUACCCUGUAAUUUU	1536
NM_001735.2_3419-3437_s	3419-3437	AGGGUACCUUGCCUGUUGA	968	UCAACAGGCAAGGUACCCU	1537
NM_001735.2_3433-3451_s	3433-3451	GUUGAAGCCCGAGAGAACA	969	UGUUCUCUCGGGCUUCAAC	1538
NM_001735.2_3441-3459_s	3441-3559	CCGAGAGAACAGCUUAUAU	970	AUAUAAGCUGUUCUCUCGG	1539
NM_001735.2_3452-3470_s	3452-3470	GCUUAUAUCUUACAGCCUU	971	AAGGCUGUAAGAUAUAAGC	1540
NM_001735.2_3460-3478_s	3460-3478	CUUACAGCCUUUACUGUGA	972	UCACAGUAAAGGCUGUAAG	1541
NM_001735.2_3482-3500_s	3482-3500	GAAUUAGAAAGGCUUUCGA	973	UCGAAAGCCUUUCUAAUUC	1542
NM_001735.2_3492-3510_s	3492-3510	GGCUUUCGAUAUAUGCCCC	974	GGGGCAUAUAUCGAAAGCC	1543

NM_001735.2_3499-3517_s	3499-3517	GAUAUAUGCCCCCUGGUGA	975	UCACCAGGGGGCAUAUAUC	1544
NM_001735.2_3513-3531_s	3513-3531	GGUGAAAAUCGACACAGCU	976	AGCUGUGUCGAUUUUCACC	1545
NM_001735.2_3522-3540_s	3522-3540	CGACACAGCUCUAAUUAAA	977	UUUAAUUAGAGCUGUGUCG	1546
NM_001735.2_3529-3547_s	3529-3547	GCUCUAAUUAAAGCUGACA	978	UGUCAGCUUUAAUUAGAGC	1547
NM_001735.2_3542-3560_s	3542-3560	CUGACAACUUUCUGCUUGA	979	UCAAGCAGAAAGUUGUCAG	1548
NM_001735.2_3549-3567_s	3549-3567	CUUUCUGCUUGAAAAUACA	980	UGUAUUUUCAAGCAGAAAG	1549
NM_001735.2_3560-3578_s	3560-3578	AAAAUACACUGCCAGCCCA	981	UGGGCUGGCAGUGUAUUUU	1550
NM_001735.2_3573-3591_s	3573-3591	AGCCCAGAGCACCUUUACA	982	UGUAAAGGUGCUCUGGGCU	1551
NM_001735.2_3581-3599_s	3581-3599	GCACCUUUACAUUGGCCAU	983	AUGGCCAAUGUAAAGGUGC	1552
NM_001735.2_3589-3607_s	3589-3607	ACAUUGGCCAUUUCUGCGU	984	ACGCAGAAAUGGCCAAUGU	1553
NM_001735.2_3602-3620_s	3602-3620	CUGCGUAUGCUCUUUCCCU	985	AGGGAAAGAGCAUACGCAG	1554
NM_001735.2_3613-3631_s	3613-3631	CUUUCCCUGGGAGAUAAAA	986	UUUUAUCUCCCAGGGAAAG	1555
NM_001735.2_3623-3641_s	3623-3641	GAGAUAAAACUCACCCACA	987	UGUGGGUGAGUUUUAUCUC	1556
NM_001735.2_3631-3649_s	3631-3649	ACUCACCCACAGUUUCGUU	988	AACGAAACUGUGGGUGAGU	1557
NM_001735.2_3640-3658_s	3640-3658	CAGUUUCGUUCAAUUGUUU	989	AAACAAUUGAACGAAACUG	1558
NM_001735.2_3650-3668_s	3650-3668	CAAUUGUUUCAGCUUUGAA	990	UUCAAAGCUGAAACAAUUG	1559
NM_001735.2_3662-3680_s	3662-3680	CUUUGAAGAGAGAAGCUUU	991	AAAGCUUCUCUCUUCAAAG	1560
NM_001735.2_3669-3687_s	3669-3687	GAGAGAAGCUUUGGUUAAA	992	UUUAACCAAAGCUUCUCUC	1561
NM_001735.2_3682-3700_s	3682-3700	GUUAAAGGUAAUCCACCCA	993	UGGGUGGAUUACCUUUAAC	1562
NM_001735.2_3691-3709_s	3691-3709	AAUCCACCCAUUUAUCGUU	994	AACGAUAAAUGGGUGGAUU	1563
NM_001735.2_3699-3717_s	3699-3717	CAUUUAUCGUUUUUGGAAA	995	UUUCCAAAAACGAUAAAUG	1564

NM_001735.2_3710-3728_s	3710-3728	UUUGGAAAGACAAUCUUCA	996	UGAAGAUUGUCUUUCCAAA	1565
NM_001735.2_3721-3739_s	3721-3739	AAUCUUCAGCAUAAAGACA	997	UGUCUUUAUGCUGAAGAUU	1566
NM_001735.2_3730-3748_s	3730-3748	CAUAAAGACAGCUCUGUAC	998	GUACAGAGCUGUCUUUAUG	1567
NM_001735.2_3741-3759_s	3741-3759	CUCUGUACCUAACACUGGU	999	ACCAGUGUUAGGUACAGAG	1568
NM_001735.2_3752-3770_s	3752-3770	ACACUGGUACGGCACGUAU	1000	AUACGUGCCGUACCAGUGU	1569
NM_001735.2_3762-3780_s	3762-3780	GGCACGUAUGGUAGAAACA	1001	UGUUUCUACCAUACGUGCC	1570
NM_001735.2_3771-3789_s	3771-3789	GGUAGAAACAACUGCCUAU	1002	AUAGGCAGUUGUUUCUACC	1571
NM_001735.2_3779-3797_s	3779-3797	CAACUGCCUAUGCUUUACU	1003	AGUAAAGCAUAGGCAGUUG	1572
NM_001735.2_3791-3809_s	3791-3809	CUUUACUCACCAGUCUGAA	1004	UUCAGACUGGUGAGUAAAG	1573
NM_001735.2_3803-3821_s	3803-3821	GUCUGAACUUGAAAGAUAU	1005	AUAUCUUUCAAGUUCAGAC	1574
NM_001735.2_3809-3827_s	3809-3827	ACUUGAAAGAUAUAAAUUA	1006	UAAUUUAUAUCUUUCAAGU	1575
NM_001735.2_3819-3837_s	3819-3837	UAUAAAUUAUGUUAACCCA	1007	UGGGUUAACAUAAUUUAUA	1576
NM_001735.2_3829-3847_s	3829-3847	GUUAACCCAGUCAUCAAAU	1008	AUUUGAUGACUGGGUUAAC	1577
NM_001735.2_3839-3857_s	3839-3857	UCAUCAAAUGGCUAUCAGA	1009	UCUGAUAGCCAUUUGAUGA	1578
NM_001735.2_3851-3869_s	3851-3869	UAUCAGAAGAGCAGAGGUA	1010	UACCUCUGCUCUUCUGAUA	1579
NM_001735.2_3863-3881_s	3863-3881	AGAGGUAUGGAGGUGGCUU	1011	AAGCCACCUCCAUACCUCU	1580
NM_001735.2_3872-3890_s	3872-3890	GAGGUGGCUUUUAUUCAAC	1012	GUUGAAUAAAAGCCACCUC	1581
NM_001735.2_3883-3901_s	3883-3901	UAUUCAACCCAGGACACAA	1013	UUGUGUCCUGGGUUGAAUA	1582
NM_001735.2_3893-3911_s	3893-3911	AGGACACAAUCAAUGCCAU	1014	AUGGCAUUGAUUGUGUCCU	1583
NM_001735.2_3899-3917_s	3899-3917	CAAUCAAUGCCAUUGAGGG	1015	CCCUCAAUGGCAUUGAUUG	1584
NM_001735.2_3909-3927_s	3909-3927	CAUUGAGGGCCUGACGGAA	1016	UUCCGUCAGGCCCUCAAUG	1585

NM_001735.2_3922-3940_s	3922-3940	ACGGAAUAUUCACUCCUGG	1017	CCAGGAGUGAAUAUUCCGU	1586
NM_001735.2_3930-3948_s	3930-3948	UUCACUCCUGGUUAAACAA	1018	UUGUUUAACCAGGAGUGAA	1587
NM_001735.2_3939-3957_s	3939-3957	GGUUAAACAACUCCGCUUG	1019	CAAGCGGAGUUGUUUAACC	1588
NM_001735.2_3951-3969_s	3951-3969	CCGCUUGAGUAUGGACAUC	1020	GAUGUCCAUACUCAAGCGG	1589
NM_001735.2_3963-3981_s	3963-3981	GGACAUCGAUGUUUCUUAC	1021	GUAAGAAACAUCGAUGUCC	1590
NM_001735.2_3969-3987_s	3969-3987	CGAUGUUUCUUACAAGCAU	1022	AUGCUUGUAAGAAACAUCG	1591
NM_001735.2_3981-3999_s	3981-3999	CAAGCAUAAAGGUGCCUUA	1023	UAAGGCACCUUUAUGCUUG	1592
NM_001735.2_3992-4010_s	3992-4010	GUGCCUUACAUAAUUAUAA	1024	UUAUAAUUAUGUAAGGCAC	1593
NM_001735.2_3999-4017_s	3999-4017	ACAUAAUUAUAAAAUGACA	1025	UGUCAUUUUAUAAUUAUGU	1594
NM_001735.2_4009-4027_s	4009-4027	AAAAUGACAGACAAGAAUU	1026	AAUUCUUGUCUGUCAUUUU	1595
NM_001735.2_4020-4038_s	4020-4038	CAAGAAUUUCCUUGGGAGG	1027	CCUCCCAAGGAAAUUCUUG	1596
NM_001735.2_4029-4047_s	4029-4047	CCUUGGGAGGCCAGUAGAG	1028	CUCUACUGGCCUCCCAAGG	1597
NM_001735.2_4041-4059_s	4041-4059	AGUAGAGGUGCUUCUCAAU	1029	AUUGAGAAGCACCUCUACU	1598
NM_001735.2_4051-4069_s	4051-4069	CUUCUCAAUGAUGACCUCA	1030	UGAGGUCAUCAUUGAGAAG	1599
NM_001735.2_4062-4080_s	4062-4080	UGACCUCAUUGUCAGUACA	1031	UGUACUGACAAUGAGGUCA	1600
NM_001735.2_4072-4090_s	4072-4090	GUCAGUACAGGAUUUGGCA	1032	UGCCAAAUCCUGUACUGAC	1601
NM_001735.2_4080-4098_s	4080-4098	AGGAUUUGGCAGUGGCUUG	1033	CAAGCCACUGCCAAAUCCU	1602
NM_001735.2_4092-4110_s	4092-4110	UGGCUUGGCUACAGUACAU	1034	AUGUACUGUAGCCAAGCCA	1603
NM_001735.2_4099-4117_s	4099-4117	GCUACAGUACAUGUAACAA	1035	UUGUUACAUGUACUGUAGC	1604
NM_001735.2_4113-4131_s	4113-4131	AACAACUGUAGUUCACAAA	1036	UUUGUGAACUACAGUUGUU	1605
NM_001735.2_4120-4138_s	4120-4138	GUAGUUCACAAAACCAGUA	1037	UACUGGUUUUGUGAACUAC	1606

NM_001735.2_4130-4148_s	4130-4148	AAACCAGUACCUCUGAGGA	1038	UCCUCAGAGGUACUGGUUU	1607
NM_001735.2_4143-4161_s	4143-4161	UGAGGAAGUUUGCAGCUUU	1039	AAAGCUGCAAACUUCCUCA	1608
NM_001735.2_4153-4171_s	4153-4171	UGCAGCUUUUAUUUGAAAA	1040	UUUUCAAAUAAAAGCUGCA	1609
NM_001735.2_4163-4181_s	4163-4181	AUUUGAAAAUCGAUACUCA	1041	UGAGUAUCGAUUUUCAAAU	1610
NM_001735.2_4173-4191_s	4173-4191	CGAUACUCAGGAUAUUGAA	1042	UUCAAUAUCCUGAGUAUCG	1611
NM_001735.2_4182-4200_s	4182-4200	GGAUAUUGAAGCAUCCCAC	1043	GUGGGAUGCUUCAAUAUCC	1612
NM_001735.2_4189-4207_s	4189-4207	GAAGCAUCCCACUACAGAG	1044	CUCUGUAGUGGGAUGCUUC	1613
NM_001735.2_4199-4217_s	4199-4217	ACUACAGAGGCUACGGAAA	1045	UUUCCGUAGCCUCUGUAGU	1614
NM_001735.2_4212-4230_s	4212-4230	CGGAAACUCUGAUUACAAA	1046	UUUGUAAUCAGAGUUUCCG	1615
NM_001735.2_4221-4239_s	4221-4239	UGAUUACAAACGCAUAGUA	1047	UACUAUGCGUUUGUAAUCA	1616
NM_001735.2_4232-4250_s	4232-4250	GCAUAGUAGCAUGUGCCAG	1048	CUGGCACAUGCUACUAUGC	1617
NM_001735.2_4240-4258_s	4240-4258	GCAUGUGCCAGCUACAAGC	1049	GCUUGUAGCUGGCACAUGC	1618
NM_001735.2_4251-4269_s	4251-4269	CUACAAGCCCAGCAGGGAA	1050	UUCCCUGCUGGGCUUGUAG	1619
NM_001735.2_4260-4278_s	4260-4278	CAGCAGGGAAGAAUCAUCA	1051	UGAUGAUUCUUCCCUGCUG	1620
NM_001735.2_4270-4288_s	4270-4288	GAAUCAUCAUCUGGAUCCU	1052	AGGAUCCAGAUGAUGAUUC	1621
NM_001735.2_4283-4301_s	4283-4301	GAUCCUCUCAUGCGGUGAU	1053	AUCACCGCAUGAGAGGAUC	1622
NM_001735.2_4289-4307_s	4289-4307	CUCAUGCGGUGAUGGACAU	1054	AUGUCCAUCACCGCAUGAG	1623
NM_001735.2_4299-4317_s	4299-4317	GAUGGACAUCUCCUUGCCU	1055	AGGCAAGGAGAUGUCCAUC	1624
NM_001735.2_4311-4329_s	4311-4329	CUUGCCUACUGGAAUCAGU	1056	ACUGAUUCCAGUAGGCAAG	1625
NM_001735.2_4322-4340_s	4322-4340	GAAUCAGUGCAAAUGAAGA	1057	UCUUCAUUUGCACUGAUUC	1626
NM_001735.2_4332-4350_s	4332-4350	AAAUGAAGAAGACUUAAAA	1058	UUUUAAGUCUUCUUCAUUU	1627

NM_001735.2_4339-4357_s	4339-4357	GAAGACUUAAAAGCCCUUG	1059	CAAGGGCUUUUAAGUCUUC	1628
NM_001735.2_4353-4371_s	4353-4371	CCUUGUGGAAGGGGUGGAU	1060	AUCCACCCCUUCCACAAGG	1629
NM_001735.2_4360-4378_s	4360-4378	GAAGGGGUGGAUCAACUAU	1061	AUAGUUGAUCCACCCCUUC	1630
NM_001735.2_4370-4388_s	4370-4388	AUCAACUAUUCACUGAUUA	1062	UAAUCAGUGAAUAGUUGAU	1631
NM_001735.2_4380-4398_s	4380-4398	CACUGAUUACCAAAUCAAA	1063	UUUGAUUUGGUAAUCAGUG	1632
NM_001735.2_4393-4411_s	4393-4411	AUCAAAGAUGGACAUGUUA	1064	UAACAUGUCCAUCUUUGAU	1633
NM_001735.2_4402-4420_s	4402-4420	GGACAUGUUAUUCUGCAAC	1065	GUUGCAGAAUAACAUGUCC	1634
NM_001735.2_4413-4431_s	4413-4431	UCUGCAACUGAAUUCGAUU	1066	AAUCGAAUUCAGUUGCAGA	1635
NM_001735.2_4422-4440_s	4422-4440	GAAUUCGAUUCCCUCCAGU	1067	ACUGGAGGGAAUCGAAUUC	1636
NM_001735.2_4432-4450_s	4432-4450	CCCUCCAGUGAUUUCCUUU	1068	AAAGGAAAUCACUGGAGGG	1637
NM_001735.2_4441-4459_s	4441-4459	GAUUUCCUUUGUGUACGAU	1069	AUCGUACACAAAGGAAAUC	1638
NM_001735.2_4453-4471_s	4453-4471	GUACGAUUCCGGAUAUUUG	1070	CAAAUAUCCGGAAUCGUAC	1639
NM_001735.2_4462-4480_s	4462-4480	CGGAUAUUUGAACUCUUUG	1071	CAAAGAGUUCAAAUAUCCG	1640
NM_001735.2_4473-4491_s	4473-4491	ACUCUUUGAAGUUGGGUUU	1072	AAACCCAACUUCAAAGAGU	1641
NM_001735.2_4482-4500_s	4482-4500	AGUUGGGUUUCUCAGUCCU	1073	AGGACUGAGAAACCCAACU	1642
NM_001735.2_4490-4508_s	4490-4508	UUCUCAGUCCUGCCACUUU	1074	AAAGUGGCAGGACUGAGAA	1643
NM_001735.2_4503-4521_s	4503-4521	CACUUUCACAGUGUACGAA	1075	UUCGUACACUGUGAAAGUG	1644
NM_001735.2_4509-4527_s	4509-4527	CACAGUGUACGAAUACCAC	1076	GUGGUAUUCGUACACUGUG	1645
NM_001735.2_4523-4541_s	4523-4541	ACCACAGACCAGAUAAACA	1077	UGUUUAUCUGGUCUGUGGU	1646
NM_001735.2_4531-4549_s	4531-4549	CCAGAUAAACAGUGUACCA	1078	UGGUACACUGUUUAUCUGG	1647
NM_001735.2_4540-4558_s	4540-4558	CAGUGUACCAUGUUUUAUA	1079	UAUAAAACAUGGUACACUG	1648

NM_001735.2_4551-4569_s	4551-4569	GUUUUAUAGCACUUCCAAU	1080	AUUGGAAGUGCUAUAAAAC	1649
NM_001735.2_4562-4580_s	4562-4580	CUUCCAAUAUCAAAAUUCA	1081	UGAAUUUUGAUAUUGGAAG	1650
NM_001735.2_4570-4588_s	4570-4588	AUCAAAAUUCAGAAAGUCU	1082	AGACUUUCUGAAUUUUGAU	1651
NM_001735.2_4581-4599_s	4581-4599	GAAAGUCUGUGAAGGAGCC	1083	GGCUCCUUCACAGACUUUC	1652
NM_001735.2_4591-4609_s	4591-4609	GAAGGAGCCGCGUGCAAGU	1084	ACUUGCACGCGGCUCCUUC	1653
NM_001735.2_4601-4619_s	4601-4619	CGUGCAAGUGUGUAGAAGC	1085	GCUUCUACACACUUGCACG	1654
NM_001735.2_4612-4630_s	4612-4630	GUAGAAGCUGAUUGUGGGC	1086	GCCCACAAUCAGCUUCUAC	1655
NM_001735.2_4619-4637_s	4619-4637	CUGAUUGUGGGCAAAUGCA	1087	UGCAUUUGCCCACAAUCAG	1656
NM_001735.2_4629-4647_s	4629-4647	GCAAAUGCAGGAAGAAUUG	1088	CAAUUCUUCCUGCAUUUGC	1657
NM_001735.2_4639-4657_s	4639-4657	GAAGAAUUGGAUCUGACAA	1089	UUGUCAGAUCCAAUUCUUC	1658
NM_001735.2_4651-4669_s	4651-4669	CUGACAAUCUCUGCAGAGA	1090	UCUCUGCAGAGAUUGUCAG	1659
NM_001735.2_4663-4681_s	4663-4681	GCAGAGACAAGAAAACAAA	1091	UUUGUUUUCUUGUCUCUGC	1660
NM_001735.2_4670-4688_s	4670-4688	CAAGAAAACAAACAGCAUG	1092	CAUGCUGUUUGUUUUCUUG	1661
NM_001735.2_4681-4699_s	4681-4699	ACAGCAUGUAAACCAGAGA	1093	UCUCUGGUUUACAUGCUGU	1662
NM_001735.2_4693-4711_s	4693-4711	CCAGAGAUUGCAUAUGCUU	1094	AAGCAUAUGCAAUCUCUGG	1663
NM_001735.2_4702-4720_s	4702-4720	GCAUAUGCUUAUAAAGUUA	1095	UAACUUUAUAAGCAUAUGC	1664
NM_001735.2_4710-4728_s	4710-4728	UUAUAAAGUUAGCAUCACA	1096	UGUGAUGCUAACUUUAUAA	1665
NM_001735.2_4722-4740_s	4722-4740	CAUCACAUCCAUCACUGUA	1097	UACAGUGAUGGAUGUGAUG	1666
NM_001735.2_4733-4751_s	4733-4751	UCACUGUAGAAAAUGUUUU	1098	AAAACAUUUUCUACAGUGA	1667
NM_001735.2_4740-4758_s	4740-4758	AGAAAAUGUUUUUGUCAAG	1099	CUUGACAAAAACAUUUUCU	1668
NM_001735.2_4750-4768_s	4750-4768	UUUGUCAAGUACAAGGCAA	1100	UUGCCUUGUACUUGACAAA	1669

NM_001735.2_4763-4781_s	4763-4781	AGGCAACCCUUCUGGAUAU	1101	AUAUCCAGAAGGGUUGCCU	1670
NM_001735.2_4770-4788_s	4770-4788	CCUUCUGGAUAUCUACAAA	1102	UUUGUAGAUAUCCAGAAGG	1671
NM_001735.2_4779-4797_s	4779-4797	UAUCUACAAAACUGGGGAA	1103	UUCCCCAGUUUUGUAGAUA	1672
NM_001735.2_4790-4808_s	4790-4808	CUGGGGAAGCUGUUGCUGA	1104	UCAGCAACAGCUUCCCCAG	1673
NM_001735.2_4799-4817_s	4799-4817	CUGUUGCUGAGAAAGACUC	1105	GAGUCUUUCUCAGCAACAG	1674
NM_001735.2_4813-4831_s	4813-4831	GACUCUGAGAUUACCUUCA	1106	UGAAGGUAAUCUCAGAGUC	1675
NM_001735.2_4819-4837_s	4819-4837	GAGAUUACCUUCAUUAAAA	1107	UUUUAAUGAAGGUAAUCUC	1676
NM_001735.2_4831-4849_s	4831-4849	AUUAAAAAGGUAACCUGUA	1108	UACAGGUUACCUUUUUAAU	1677
NM_001735.2_4841-4859_s	4841-4859	UAACCUGUACUAACGCUGA	1109	UCAGCGUUAGUACAGGUUA	1678
NM_001735.2_4850-4868_s	4850-4868	CUAACGCUGAGCUGGUAAA	1110	UUUACCAGCUCAGCGUUAG	1679
NM_001735.2_4863-4881_s	4863-4881	GGUAAAAGGAAGACAGUAC	1111	GUACUGUCUUCCUUUUACC	1680
NM_001735.2_4871-4889_s	4871-4889	GAAGACAGUACUUAAUUAU	1112	AUAAUUAAGUACUGUCUUC	1681
NM_001735.2_4881-4899_s	4881-4899	CUUAAUUAUGGGUAAAGAA	1113	UUCUUUACCCAUAAUUAAG	1682
NM_001735.2_4893-4911_s	4893-4911	UAAAGAAGCCCUCCAGAUA	1114	UAUCUGGAGGGCUUCUUUA	1683
NM_001735.2_4902-4920_s	4902-4920	CCUCCAGAUAAAAUACAAU	1115	AUUGUAUUUUAUCUGGAGG	1684
NM_001735.2_4912-4930_s	4912-4930	AAAUACAAUUUCAGUUUCA	1116	UGAAACUGAAAUUGUAUUU	1685
NM_001735.2_4923-4941_s	4923-4941	CAGUUUCAGGUACAUCUAC	1117	GUAGAUGUACCUGAAACUG	1686
NM_001735.2_4931-4949_s	4931-4949	GGUACAUCUACCCUUUAGA	1118	UCUAAAGGGUAGAUGUACC	1687
NM_001735.2_4942-4960_s	4942-4960	CCUUUAGAUUCCUUGACCU	1119	AGGUCAAGGAAUCUAAAGG	1688
NM_001735.2_4952-4970_s	4952-4970	CCUUGACCUGGAUUGAAUA	1120	UAUUCAAUCCAGGUCAAGG	1689
NM_001735.2_4961-4979_s	4961-4979	GGAUUGAAUACUGGCCUAG	1121	CUAGGCCAGUAUUCAAUCC	1690

NM_001735.2_4971-4989_s	4971-4989	CUGGCCUAGAGACACAACA	1122	UGUUGUGUCUCUAGGCCAG	1691
NM_001735.2_4979-4997_s	4979-4997	GAGACACAACAUGUUCAUC	1123	GAUGAACAUGUUGUGUCUC	1692
NM_001735.2_4991-5009_s	4991-5009	GUUCAUCGUGUCAAGCAUU	1124	AAUGCUUGACACGAUGAAC	1693
NM_001735.2_5000-5018_s	5000-5018	GUCAAGCAUUUUUAGCUAA	1125	UUAGCUAAAAAUGCUUGAC	1694
NM_001735.2_5013-5031_s	5013-5031	AGCUAAUUUAGAUGAAUUU	1126	AAAUUCAUCUAAAUUAGCU	1695
NM_001735.2_5022-5040_s	5022-5040	AGAUGAAUUUGCCGAAGAU	1127	AUCUUCGGCAAAUUCAUCU	1696
NM_001735.2_5033-5051_s	5033-5051	CCGAAGAUAUCUUUUUAAA	1128	UUUAAAAAGAUAUCUUCGG	1697
NM_001735.2_5043-5061_s	5043-5061	CUUUUUAAAUGGAUGCUAA	1129	UUAGCAUCCAUUUAAAAAG	1698
NM_001735.2_5053-5071_s	5053-5071	GGAUGCUAAAAUUCCUGAA	1130	UUCAGGAAUUUUAGCAUCC	1699
NM_001735.2_5059-5077_s	5059-5077	UAAAAUUCCUGAAGUUCAG	1131	CUGAACUUCAGGAAUUUUA	1700
NM_001735.2_5071-5089_s	5071-5089	AGUUCAGCUGCAUACAGUU	1132	AACUGUAUGCAGCUGAACU	1701
NM_001735.2_5080-5098_s	5080-5098	GCAUACAGUUUGCACUUAU	1133	AUAAGUGCAAACUGUAUGC	1702
NM_001735.2_5093-5111_s	5093-5111	ACUUAUGGACUCCUGUUGU	1134	ACAACAGGAGUCCAUAAGU	1703
NM_001735.2_5099-5117_s	5099-5117	GGACUCCUGUUGUUGAAGU	1135	ACUUCAACAACAGGAGUCC	1704
NM_001735.2_5109-5127_s	5109-5127	UGUUGAAGUUCGUUUUUUU	1136	AAAAAAACGAACUUCAACA	1705
NM_001735.2_5122-5140_s	5122-5140	UUUUUUGUUUUCUUCUUUU	1137	AAAAGAAGAAAACAAAAAA	1706
NM_001735.2_5132-5150_s	5132-5150	UCUUCUUUUUUUAAACAUU	1138	AAUGUUUAAAAAAAGAAGA	1707
NM_001735.2_5139-5157_s	5139-5157	UUUUUAAACAUUCAUAGCU	1139	AGCUAUGAAUGUUUAAAAA	1708
NM_001735.2_5152-5170_s	5152-5170	AUAGCUGGUCUUAUUUGUA	1140	UACAAAUAAGACCAGCUAU	1709
NM_001735.2_5159-5177_s	5159-5177	GUCUUAUUUGUAAAGCUCA	1141	UGAGCUUUACAAAUAAGAC	1710
NM_001735.2_5170-5188_s	5170-5188	AAAGCUCACUUUACUUAGA	1142	UCUAAGUAAAGUGAGCUUU	1711

NM_001735.2_5182-5200_s	5182-5200	ACUUAGAAUUAGUGGCACU	1143	AGUGCCACUAAUUCUAAGU	1712
NM_001735.2_5192-5210_s	5192-5210	AGUGGCACUUGCUUUUAUU	1144	AAUAAAAGCAAGUGCCACU	1713
NM_001735.2_5202-5220_s	5202-5220	GCUUUUAUUAGAGAAUGAU	1145	AUCAUUCUCUAAUAAAAGC	1714
NM_001735.2_5212-5230_s	5212-5230	GAGAAUGAUUUCAAAUGCU	1146	AGCAUUUGAAAUCAUUCUC	1715
NM_001735.2_5220-5238_s	5220-5238	UUUCAAAUGCUGUAACUUU	1147	AAAGUUACAGCAUUUGAAA	1716
NM_001735.2_5231-5249_s	5231-5249	GUAACUUUCUGAAAUAACA	1148	UGUUAUUUCAGAAAGUUAC	1717
NM_001735.2_5241-5259_s	5241-5259	GAAAUAACAUGGCCUUGGA	1149	UCCAAGGCCAUGUUAUUUC	1718
NM_001735.2_5253-5271_s	5253-5271	CCUUGGAGGGCAUGAAGAC	1150	GUCUUCAUGCCCUCCAAGG	1719
NM_001735.2_5259-5277_s	5259-5277	AGGGCAUGAAGACAGAUAC	1151	GUAUCUGUCUUCAUGCCCU	1720
NM_001735.2_5273-5291_s	5273-5291	GAUACUCCUCCAAGGUUAU	1152	AUAACCUUGGAGGAGUAUC	1721
NM_001735.2_5279-5297_s	5279-5297	CCUCCAAGGUUAUUGGACA	1153	UGUCCAAUAACCUUGGAGG	1722
NM_001735.2_5293-5311_s	5293-5311	GGACACCGGAAACAAUAAA	1154	UUUAUUGUUUCCGGUGUCC	1723
NM_001735.2_5301-5319_s	5301-5319	GAAACAAUAAAUUGGAACA	1155	UGUUCCAAUUUAUUGUUUC	1724
NM_001735.2_5311-5329_s	5311-5329	AUUGGAACACCUCCUCAAA	1156	UUUGAGGAGGUGUUCCAAU	1725
NM_001735.2_5322-5340_s	5322-5340	UCCUCAAACCUACCACUCA	1157	UGAGUGGUAGGUUUGAGGA	1726
NM_001735.2_5331-5349_s	5331-5349	CUACCACUCAGGAAUGUUU	1158	AAACAUUCCUGAGUGGUAG	1727
NM_001735.2_5343-5361_s	5343-5361	AAUGUUUGCUGGGGCCGAA	1159	UUCGGCCCCAGCAAACAUU	1728
NM_001735.2_5349-5367_s	5349-5367	UGCUGGGGCCGAAAGAACA	1160	UGUUCUUUCGGCCCCAGCA	1729
NM_001735.2_5360-5378_s	5360-5378	AAAGAACAGUCCAUUGAAA	1161	UUUCAAUGGACUGUUCUUU	1730
NM_001735.2_5371-5389_s	5371-5389	CAUUGAAAGGGAGUAUUAC	1162	GUAAUACUCCCUUUCAAUG	1731
NM_001735.2_5380-5398_s	5380-5398	GGAGUAUUACAAAAACAUG	1163	CAUGUUUUUGUAAUACUCC	1732

NM_001735.2_5391-5409_s	5391-5409	AAAACAUGGCCUUUGCUUG	1164	CAAGCAAAGGCCAUGUUUU	1733
NM_001735.2_5399-5417_s	5399-5417	GCCUUUGCUUGAAAGAAAA	1165	UUUUCUUUCAAGCAAAGGC	1734
NM_001735.2_5409-5427_s	5409-5427	GAAAGAAAAUACCAAGGAA	1166	UUCCUUGGUAUUUUCUUUC	1735
NM_001735.2_5420-5438_s	5420-5438	CCAAGGAACAGGAAACUGA	1167	UCAGUUUCCUGUUCCUUGG	1736
NM_001735.2_5433-5451_s	5433-5451	AACUGAUCAUUAAAGCCUG	1168	CAGGCUUUAAUGAUCAGUU	1737
NM_001735.2_5441-5459_s	5441-5459	AUUAAAGCCUGAGUUUGCU	1169	AGCAAACUCAGGCUUUAAU	1738

Example 5: *In Vivo* C5 Silencing

Groups of three female cynomolgus macaques were treated with C5-siRNA AD-58641 subcutaneously in the scapular and mid-dorsal areas of the back at 2.5 mg/kg or 5 mg/kg doses or a vehicle control. Two rounds of dosing were administered with eight doses in each round given every third day. Serum C5 was collected and evaluated using an ELISA assay specific for C5 detection (Abcam) at the indicated time points (Figure 13). C5 levels were normalized to the average of three pre-dose samples. Samples collected prior to dosing, and on day 23 (24 hours after the last dose administered in the first round of treatment) were analyzed by complete serum chemistry, hematology and coagulation panels.

Analysis of serum C5 protein levels relative to pre-treatment serum C5 protein levels demonstrated that the 5 mg/kg AD-58641 dosing regimen reduced serum C5 protein levels up to 98% (Figure 12). The average serum C5 levels were reduced by 97% at the nadir, indicating that the majority of circulating C5 is hepatic in origin. There was potent, dose-dependent and durable knock-down of serum C5 protein levels with subcutaneous administration of AD-58641. No changes in hematology, serum chemistry or coagulation parameters were identified 24 hours after the first round of dosing.

Serum hemolytic activity was also analyzed using a sensitized sheep erythrocyte assay to measure classical pathway activity. The percent hemolysis was calculated relative to maximal hemolysis and to background hemolysis in control samples. Mean hemolysis values +/- the SEM for three animals were calculated and analyzed (Figure 13). Hemolysis was reduced up to 94% in the 5 mg/kg dosing regimen with an average inhibition of 92% at the nadir. The reduction in hemolysis was maintained for greater than two weeks following the last dose.

Example 6: *In Vitro* Screening of Additional siRNAs

The C5 sense and antisense strand sequences shown in Table 20 were modified at the 3'-terminus with a short sequence of deoxy-thymine nucleotides (dT) (Table 21). The *in vitro* efficacy of duplexes comprising the sense and antisense sequences listed in Table 21 was determined using the following methods.

Cell culture and transfections

Hep3B cells (ATCC, Manassas, VA) were grown to near confluence at 37°C in an atmosphere of 5% CO_2 in EMEM (ATCC) supplemented with 10% FBS, before being released from the plate by trypsinization. Transfection was carried out by adding 5µl of Opti-MEM plus 0.1µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad CA. cat # 13778-150) to 5µl of siRNA duplexes per well into a 384-well plate and incubated at room temperature for 15 minutes. 40µl of complete growth media containing ~5 x10^3 Hep3B cells were then added to the siRNA mixture. Cells were incubated for 24 hours prior to RNA purification. Experiments were performed at 10nM final duplex concentration.

Total RNA isolation using DYNABEADS mRNA Isolation Kit (Invitrogen, part #: 610-12)

RNA isolation was performed using a semi-automated process of a Biotek EL 405 washer. Briefly, cells were lysed in 75µl of Lysis/Binding Buffer containing 2ul of Dynabeads, then mixed for 10 minutes on setting 7 of an electromagnetic shaker (Union Scientific). Magnetic beads were captured using magnetic stand and the supernatant was removed. After removing supernatant, magnetic beads were washed with 90µl Wash Buffer A, followed by 90µl of Wash buffer B. Beads were then washed twice with 100ul of Elution buffer which was then aspirated and cDNA generated directly on bead bound RNA in the 384 well plate.

cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813)

A master mix of 2µl 10X Buffer, 0.8µl 25X dNTPs, 2µl Random primers, 1µl Reverse Transcriptase, 1µl RNase inhibitor and 3.2µl of H_2O per reaction were added directly to the bead bound RNA in the 384 well plates used for RNA isolation. Plates were then shaken on an electromagnetic shaker for 10 minutes and then placed in a 37°C incubator for 2 hours. Following this incubation, plates were place on a shake in an 80°C incubator for 7 minutes to inactivate the enzyme and elute the RNA/cDNA from the beads.

Real time PCR

2µl of cDNA were added to a master mix containing 0.5µl GAPDH TaqMan Probe (Applied Biosystems Cat #4326317E), 0.5µl C5 TaqMan probe (Applied Biosystems cat #

Hs00156197_M1) and 5µl Lightcycler 480 probe master mix (Roche Cat #04887301001) per well in a 384 well plates (Roche cat # 04887301001). Real time PCR was done in a Roche LC480 Real Time PCR system (Roche). Each duplex was tested in in at least two independent transfections and each transfection was assayed in duplicate.

To calculate relative fold change, real time data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10nM AD-1955, or mock transfected cells.

Table 22 shows the results of a single dose screen in Hep3B cells transfected with the indicated dT modified iRNAs. Data are expressed as percent of message remaining relative to untreated cells.

Table 21. dT Modified C5 iRNAs

Duplex ID	Sense Sequence	SEQ ID NO:	Position in NM_001735.2	Antisense Sequence	SEQ ID NO:
AD-61779.2	UAUCCGUGGUUUCCUGCUAdTdT	1739	3-21	UAGCAGGAAACCACGGAUAdTdT	2306
AD-61785.2	GGUUUCCUGCUACCUCCAAdTdT	1740	10-28	UUGGAGGUAGCAGGAAACCdTdT	2307
AD-61791.2	CCUCCAACCAUGGGCCUUUdTdT	1741	22-40	AAAGGCCCAUGGUUGGAGGdTdT	2308
AD-61797.2	GGGCCUUUUGGGAAUACUUdTdT	1742	33-51	AAGUAUUCCCAAAAGGCCCdTdT	2309
AD-61803.2	GGAAUACUUUGUUUUUUAAdTdT	1743	43-61	UUAAAAAACAAAGUAUUCCdTdT	2310
AD-61809.2	CUUUGUUUUUUAAUCUUCCdTdT	1744	49-67	GGAAGAUUAAAAAACAAAGdTdT	2311
AD-61815.2	CUUCCUGGGGAAAACCUGGdTdT	1745	63-81	CCAGGUUUUCCCCAGGAAGdTdT	2312
AD-61821.2	GGAAAACCUGGGGACAGGAdTdT	1746	71-89	UCCUGUCCCCAGGUUUUCCdTdT	2313
AD-61780.2	GGGACAGGAGCAAACAUAUdTdT	1747	81-99	AUAUGUUUGCUCCUGUCCCdTdT	2314
AD-61786.2	CAAACAUAUGUCAUUUCAGdTdT	1748	91-109	CUGAAAUGACAUAUGUUUGdTdT	2315
AD-61792.2	CAUUUCAGCACCAAAAAUAdTdT	1749	102-120	UAUUUUUGGUGCUGAAAUGdTdT	2316
AD-61798.2	GCACCAAAAAUAUUCCGUGdTdT	1750	109-127	CACGGAAUAUUUUUGGUGCdTdT	2317
AD-61804.2	CCGUGUUGGAGCAUCUGAAdTdT	1751	123-141	UUCAGAUGCUCCAACACGGdTdT	2318
AD-61810.2	GGAGCAUCUGAAAAUAUUGdTdT	1752	130-148	CAAUAUUUUCAGAUGCUCCdTdT	2319
AD-61816.2	GAAAAUAUUGUGAUUCAAGdTdT	1753	139-157	CUUGAAUCACAAUAUUUUCdTdT	2320
AD-61822.2	GAUUCAAGUUUAUGGAUACdTdT	1754	150-168	GUAUCCAUAAACUUGAAUCdTdT	2321
AD-61781.2	GGAUACACUGAAGCAUUUGdTdT	1755	163-181	CAAAUGCUUCAGUGUAUCCdTdT	2322
AD-61787.2	GAAGCAUUUGAUGCAACAAdTdT	1756	172-190	UUGUUGCAUCAAAUGCUUCdTdT	2323
AD-61793.2	UGCAACAAUCUCUAUUAAAdTdT	1757	183-201	UUUAAUAGAGAUUGUUGCAdTdT	2324
AD-61799.2	AAUCUCUAUUAAAAGUUAUdTdT	1758	189-207	AUAACUUUUAAUAGAGAUUdTdT	2325
AD-61805.2	AAGUUAUCCUGAUAAAAAAdTdT	1759	201-219	UUUUUUAUCAGGAUAACUUdTdT	2326
AD-61811.2	CUGAUAAAAAAUUUAGUUAdTdT	1760	209-227	UAACUAAAAUUUUUUAUCAGdTdT	2327
AD-61817.2	UUAGUUACUCCUCAGGCCAdTdT	1761	221-239	UGGCCUGAGGAGUAACUAAdTdT	2328
AD-61823.2	CCUCAGGCCAUGUUCAUUUdTdT	1762	230-248	AAAUGAACAUGGCCUGAGGdTdT	2329

AD-61782.2	UUCAUUUAUCCUCAGAGAAdTdT	1763	242-260	UUCUCUGAGGAUAAAUGAAdTdT	2330
AD-61788.2	CUCAGAGAAUAAAUUCCAAdTdT	1764	252-270	UUGGAAUUUAUUCUCUGAGdTdT	2331
AD-61794.2	AAUAAAUUCCAAAACUCUGdTdT	1765	259-277	CAGAGUUUUGGAAUUUAUUdTdT	2332
AD-61800.2	CUCUGCAAUCUUAACAAUAdTdT	1766	273-291	UAUUGUUAAGAUUGCAGAGdTdT	2333
AD-61806.2	CUUAACAAUACAACCAAAAdTdT	1767	282-300	UUUUGGUUGUAUUGUUAAGdTdT	2334
AD-61812.2	CAACCAAAACAAUUGCCUGdTdT	1768	292-310	CAGGCAAUUGUUUUGGUUGdTdT	2335
AD-61818.2	CAAUUGCCUGGAGGACAAAdTdT	1769	301-319	UUUGUCCUCCAGGCAAUUGdTdT	2336
AD-61824.2	GGACAAAACCCAGUUUCUUdTdT	1770	313-331	AAGAAACUGGGUUUUGUCCdTdT	2337
AD-61783.2	CCAGUUUCUUAUGUGUAUUdTdT	1771	322-340	AAUACACAUAAGAAACUGGdTdT	2338
AD-61789.2	AUGUGUAUUUGGAAGUUGUdTdT	1772	332-350	ACAACUUCCAAAUACACAUdTdT	2339
AD-61795.2	GGAAGUUGUAUCAAAGCAUdTdT	1773	342-360	AUGCUUUGAUACAACUUCCdTdT	2340
AD-61801.2	GUAUCAAAGCAUUUUUCAAdTdT	1774	349-367	UUGAAAAAUGCUUUGAUACdTdT	2341
AD-61807.2	UUUUCAAAAUCAAAAAGAAdTdT	1775	361-379	UUCUUUUUGAUUUUGAAAAdTdT	2342
AD-61813.2	CAAAAAGAAUGCCAAUAACdTdT	1776	371-389	GUUAUUGGCAUUCUUUUUGdTdT	2343
AD-61819.2	GCCAAUAACCUAUGACAAUdTdT	1777	381-399	AUUGUCAUAGGUUAUUGGCdTdT	2344
AD-61825.2	CCUAUGACAAUGGAUUUCUdTdT	1778	389-407	AGAAAUCCAUUGUCAUAGGdTdT	2345
AD-61784.2	UGGAUUUCUCUUCAUUCAUdTdT	1779	399-417	AUGAAUGAAGAGAAAUCCAdTdT	2346
AD-61790.2	CAUUCAUACAGACAAACCUdTdT	1780	411-429	AGGUUUGUCUGUAUGAAUGdTdT	2347
AD-61796.2	CAGACAAACCUGUUUAUACdTdT	1781	419-437	GUAUAAACAGGUUUGUCUGdTdT	2348
AD-61802.2	GUUUAUACUCCAGACCAGUdTdT	1782	430-448	ACUGGUCUGGAGUAUAAACdTdT	2349
AD-61808.2	AGACCAGUCAGUAAAAGUUdTdT	1783	441-459	AACUUUUACUGACUGGUCUdTdT	2350
AD-61814.2	AGUAAAAGUUAGAGUUUAUdTdT	1784	450-468	AUAAACUCUAACUUUUACUdTdT	2351
AD-61820.2	AGAGUUUAUUCGUUGAAUGdTdT	1785	460-478	CAUUCAACGAAUAAACUCUdTdT	2352
AD-61826.2	CGUUGAAUGACGACUUGAAdTdT	1786	470-488	UUCAAGUCGUCAUUCAACGdTdT	2353
AD-61832.2	CUUGAAGCCAGCCAAAAGAdTdT	1787	483-501	UCUUUUGGCUGGCUUCAAGdTdT	2354
AD-61838.2	CCAGCCAAAAGAGAAACUGdTdT	1788	490-508	CAGUUUCUCUUUUGGCUGGdTdT	2355
AD-61844.2	AAACUGUCUUAACUUUCAUdTdT	1789	503-521	AUGAAAGUUAAGACAGUUUdTdT	2356

AD-61850.2	AACUUUCAUAGAUCCUGAAdTdT	1790	513-531	UUCAGGAUCUAUGAAAGUUdTdT	2357
AD-61856.2	CAUAGAUCCUGAAGGAUCAdTdT	1791	519-537	UGAUCCUUCAGGAUCUAUGdTdT	2358
AD-61862.2	GAAGGAUCAGAAGUUGACAdTdT	1792	529-547	UGUCAACUUCUGAUCCUUCdTdT	2359
AD-61868.2	UGACAUGGUAGAAGAAAUUdTdT	1793	543-561	AAUUUCUUCUACCAUGUCAdTdT	2360
AD-61827.2	GAAGAAAUUGAUCAUAUUGdTdT	1794	553-571	CAAUAUGAUCAAUUUCUUCdTdT	2361
AD-61833.2	GAUCAUAUUGGAAUUAUCUdTdT	1795	562-580	AGAUAAUUCCAAUAUGAUCdTdT	2362
AD-61839.2	GGAAUUAUCUCUUUUCCUGdTdT	1796	571-589	CAGGAAAAGAGAUAAUUCCdTdT	2363
AD-61845.2	CUCUUUUCCUGACUUCAAGdTdT	1797	579-597	CUUGAAGUCAGGAAAAGAGdTdT	2364
AD-61851.2	ACUUCAAGAUUCCGUCUAAdTdT	1798	590-608	UUAGACGGAAUCUUGAAGUdTdT	2365
AD-61857.2	CCGUCUAAUCCUAGAUAUGdTdT	1799	601-619	CAUAUCUAGGAUUAGACGGdTdT	2366
AD-61863.2	CCUAGAUAUGGUAUGUGGAdTdT	1800	610-628	UCCACAUACCAUAUCUAGGdTdT	2367
AD-61869.2	UGUGGACGAUCAAGGCUAAdTdT	1801	623-641	UUAGCCUUGAUCGUCCACAdTdT	2368
AD-61828.2	CGAUCAAGGCUAAAUAUAAdTdT	1802	629-647	UUAUAUUUAGCCUUGAUCGdTdT	2369
AD-61834.2	AUAUAAAGAGGACUUUUCAdTdT	1803	642-660	UGAAAAGUCCUCUUUAUAUdTdT	2370
AD-61840.2	GAGGACUUUUCAACAACUGdTdT	1804	649-667	CAGUUGUUGAAAAGUCCUCdTdT	2371
AD-61846.2	CAACUGGAACCGCAUAUUUdTdT	1805	662-680	AAAUAUGCGGUUCCAGUUGdTdT	2372
AD-61852.2	CGCAUAUUUUGAAGUUAAAdTdT	1806	672-690	UUUAACUUCAAAAUAUGCGdTdT	2373
AD-61858.2	AAGUUAAAGAAUAUGUCUUdTdT	1807	683-701	AAGACAUAUUCUUUAACUUdTdT	2374
AD-61864.2	GAAUAUGUCUUGCCACAUUdTdT	1808	691-709	AAUGUGGCAAGACAUAUUCdTdT	2375
AD-61870.2	CCACAUUUUUCUGUCUCAAdTdT	1809	703-721	UUGAGACAGAAAAAUGUGGdTdT	2376
AD-61829.2	CUGUCUCAAUCGAGCCAGAdTdT	1810	713-731	UCUGGCUCGAUUGAGACAGdTdT	2377
AD-61835.2	CAAUCGAGCCAGAAUAUAAdTdT	1811	719-737	UUAUAUUCUGGCUCGAUUGdTdT	2378
AD-61841.2	GAAUAUAAUUUCAUUGGUUdTdT	1812	730-748	AACCAAUGAAAUUAUAUUCdTdT	2379
AD-61847.2	AUUGGUUACAAGAACUUUAdTdT	1813	742-760	UAAAGUUCUUGUAACCAAUdTdT	2380
AD-61853.2	AGAACUUUAAGAAUUUUGAdTdT	1814	752-770	UCAAAAUUCUUAAAGUUCUdTdT	2381
AD-61859.2	GAAUUUUGAAAUUACUAUAdTdT	1815	762-780	UAUAGUAAUUUCAAAAUUCdTdT	2382
AD-61865.2	GAAAUUACUAUAAAAGCAAdTdT	1816	769-787	UUGCUUUUAUAGUAAUUUCdTdT	2383

AD-61871.2	AAAGCAAGAUAUUUUUAUAdTdT	1817	781-799	UAUAAAAAUAUCUUGCUUUdTdT	2384
AD-61830.2	AUAUUUUUAUAAUAAAGUAdTdT	1818	789-807	UACUUUAUUAUAAAAAUAUdTdT	2385
AD-61836.2	AAGUAGUCACUGAGGCUGAdTdT	1819	803-821	UCAGCCUCAGUGACUACUUdTdT	2386
AD-61842.2	CACUGAGGCUGACGUUUAUdTdT	1820	810-828	AUAAACGUCAGCCUCAGUGdTdT	2387
AD-61848.2	CGUUUAUAUCACAUUUGGAdTdT	1821	822-840	UCCAAAUGUGAUAUAAACGdTdT	2388
AD-61854.2	CACAUUUGGAAUAAGAGAAdTdT	1822	831-849	UUCUCUUAUUCCAAAUGUGdTdT	2389
AD-61860.2	AAUAAGAGAAGACUUAAAAdTdT	1823	840-858	UUUUAAGUCUUCUCUUAUUdTdT	2390
AD-61866.2	CUUAAAAGAUGAUCAAAAAdTdT	1824	852-870	UUUUUGAUCAUCUUUUAAGdTdT	2391
AD-61872.2	GAUGAUCAAAAAGAAAUGAdTdT	1825	859-877	UCAUUUCUUUUUGAUCAUCdTdT	2392
AD-61831.2	AAAUGAUGCAAACAGCAAUdTdT	1826	872-890	AUUGCUGUUUGCAUCAUUUdTdT	2393
AD-61837.2	ACAGCAAUGCAAAACACAAdTdT	1827	883-901	UUGUGUUUUGCAUUGCUGUdTdT	2394
AD-61843.2	AAAACACAAUGUUGAUAAAdTdT	1828	893-911	UUUAUCAACAUUGUGUUUUdTdT	2395
AD-61849.2	CAAUGUUGAUAAAUGGAAUdTdT	1829	899-917	AUUCCAUUUAUCAACAUUGdTdT	2396
AD-61855.2	GGAAUUGCUCAAGUCACAUdTdT	1830	913-931	AUGUGACUUGAGCAAUUCCdTdT	2397
AD-61861.2	GCUCAAGUCACAUUUGAUUdTdT	1831	919-937	AAUCAAAUGUGACUUGAGCdTdT	2398
AD-61867.2	AUUUGAUUCUGAAACAGCAdTdT	1832	930-948	UGCUGUUUCAGAAUCAAAUdTdT	2399
AD-62062.1	UGAAACAGCAGUCAAAGAAdTdT	1833	939-957	UUCUUUGACUGCUGUUUCAdTdT	2400
AD-62068.1	CAAAGAACUGUCAUACUACdTdT	1834	951-969	GUAGUAUGACAGUUCUUUGdTdT	2401
AD-62074.1	CAUACUACAGUUUAGAAGAdTdT	1835	962-980	UCUUCUAAACUGUAGUAUGdTdT	2402
AD-62080.1	CAGUUUAGAAGAUUUAAACdTdT	1836	969-987	GUUUAAAUCUUCUAAACUGdTdT	2403
AD-62086.1	UAAACAACAAGUACCUUUAdTdT	1837	983-1001	UAAAGGUACUUGUUGUUUAdTdT	2404
AD-62092.1	CAAGUACCUUUAUAUUGCUdTdT	1838	990-1008	AGCAAUAUAAAGGUACUUGdTdT	2405
AD-62098.1	UAUUGCUGUAACAGUCAUAdTdT	1839	1002-1020	UAUGACUGUUACAGCAAUAdTdT	2406
AD-62104.1	AACAGUCAUAGAGUCUACAdTdT	1840	1011-1029	UGUAGACUCUAUGACUGUUdTdT	2407
AD-62063.1	AGAGUCUACAGGUGGAUUUdTdT	1841	1020-1038	AAAUCCACCUGUAGACUCUdTdT	2408
AD-62069.1	GGAUUUUCUGAAGAGGCAGdTdT	1842	1033-1051	CUGCCUCUUCAGAAAAUCCdTdT	2409
AD-62075.1	GAAGAGGCAGAAAUACCUGdTdT	1843	1042-1060	CAGGUAUUUCUGCCUCUUCdTdT	2410

AD-62081.1	AGAAAUACCUGGCAUCAAAdTdT	1844	1050-1068	UUUGAUGCCAGGUAUUUCUdTdT	2411
AD-62087.1	GCAUCAAAUAUGUCCUCUCdTdT	1845	1061-1079	GAGAGGACAUAUUUGAUGCdTdT	2412
AD-62093.1	UGUCCUCUCUCCCUACAAAdTdT	1846	1071-1089	UUUGUAGGGAGAGAGGACAdTdT	2413
AD-62099.1	GAAUUUGGUUGCUACUCCUdTdT	1847	1092-1110	AGGAGUAGCAACCAAAUUCdTdT	2414
AD-62105.1	GCUACUCCUCUUUUCCUGAdTdT	1848	1102-1120	UCAGGAAAAGAGGAGUAGCdTdT	2415
AD-62064.1	CUCUUUUCCUGAAGCCUGGdTdT	1849	1109-1127	CCAGGCUUCAGGAAAAGAGdTdT	2416
AD-62070.1	CCUGGGAUUCCAUAUCCCAdTdT	1850	1123-1141	UGGGAUAUGGAAUCCCAGGdTdT	2417
AD-62076.1	CAUAUCCCAUCAAGGUGCAdTdT	1851	1133-1151	UGCACCUUGAUGGGAUAUGdTdT	2418
AD-62082.1	CCAUCAAGGUGCAGGUUAAdTdT	1852	1139-1157	UUAACCUGCACCUUGAUGGdTdT	2419
AD-62088.1	CAGGUUAAAGAUUCGCUUGdTdT	1853	1150-1168	CAAGCGAAUCUUUAACCUGdTdT	2420
AD-62094.1	UUCGCUUGACCAGUUGGUAdTdT	1854	1161-1179	UACCAACUGGUCAAGCGAAdTdT	2421
AD-62100.1	CCAGUUGGUAGGAGGAGUCdTdT	1855	1170-1188	GACUCCUCCUACCAACUGGdTdT	2422
AD-62106.1	GGAGGAGUCCCAGUAACACdTdT	1856	1180-1198	GUGUUACUGGGACUCCUCCdTdT	2423
AD-62065.1	CAGUAACACUGAAUGCACAdTdT	1857	1190-1208	UGUGCAUUCAGUGUUACUGdTdT	2424
AD-62071.1	GAAUGCACAAACAAUUGAUdTdT	1858	1200-1218	AUCAAUUGUUUGUGCAUUCdTdT	2425
AD-62077.1	AACAAUUGAUGUAAACCAAdTdT	1859	1209-1227	UUGGUUUACAUCAAUUGUUdTdT	2426
AD-62083.1	UAAACCAAGAGACAUCUGAdTdT	1860	1220-1238	UCAGAUGUCUCUUGGUUUAdTdT	2427
AD-62089.1	CAUCUGACUUGGAUCCAAGdTdT	1861	1232-1250	CUUGGAUCCAAGUCAGAUGdTdT	2428
AD-62095.1	GAUCCAAGCAAAAGUGUAAdTdT	1862	1243-1261	UUACACUUUUGCUUGGAUCdTdT	2429
AD-62101.1	CAAAAGUGUAACACGUGUUdTdT	1863	1251-1269	AACACGUGUUACACUUUUGdTdT	2430
AD-62107.1	AACACGUGUUGAUGAUGGAdTdT	1864	1260-1278	UCCAUCAUCAACACGUGUUdTdT	2431
AD-62066.1	UGAUGGAGUAGCUUCCUUUdTdT	1865	1272-1290	AAAGGAAGCUACUCCAUCAdTdT	2432
AD-62072.1	GUAGCUUCCUUUGUGCUUAdTdT	1866	1279-1297	UAAGCACAAAGGAAGCUACdTdT	2433
AD-62078.1	GCUUAAUCUCCCAUCUGGAdTdT	1867	1293-1311	UCCAGAUGGGAGAUUAAGCdTdT	2434
AD-62084.1	CCAUCUGGAGUGACGGUGCdTdT	1868	1303-1321	GCACCGUCACUCCAGAUGGdTdT	2435
AD-62090.1	UGACGGUGCUGGAGUUUAAdTdT	1869	1313-1331	UUAAACUCCAGCACCGUCAdTdT	2436
AD-62096.1	GCUGGAGUUUAAUGUCAAAdTdT	1870	1320-1338	UUUGACAUUAAACUCCAGCdTdT	2437

AD-62102.1	UGUCAAAACUGAUGCUCCAdTdT	1871	1332-1350	UGGAGCAUCAGUUUUGACAdTdT	2438
AD-62108.1	GAUGCUCCAGAUCUUCCAGdTdT	1872	1342-1360	CUGGAAGAUCUGGAGCAUCdTdT	2439
AD-62067.1	CAGAUCUUCCAGAAGAAAAdTdT	1873	1349-1367	UUUUCUUCUGGAAGAUCUGdTdT	2440
AD-62073.1	AGAAAAUCAGGCCAGGGAAdTdT	1874	1362-1380	UUCCCUGGCCUGAUUUUCUdTdT	2441
AD-62079.1	GGCCAGGGAAGGUUACCGAdTdT	1875	1371-1389	UCGGUAACCUUCCCUGGCCdTdT	2442
AD-62085.1	GUUACCGAGCAAUAGCAUAdTdT	1876	1382-1400	UAUGCUAUUGCUCGGUAACdTdT	2443
AD-62091.1	AUAGCAUACUCAUCUCUCAdTdT	1877	1393-1411	UGAGAGAUGAGUAUGCUAUdTdT	2444
AD-62097.1	UACUCAUCUCUCAGCCAAAdTdT	1878	1399-1417	UUUGGCUGAGAGAUGAGUAdTdT	2445
AD-62103.1	GCCAAAGUUACCUUUAUAUdTdT	1879	1412-1430	AUAUAAAGGUAACUUUGGCdTdT	2446
AD-62109.1	CCUUUAUAUUGAUUGGACUdTdT	1880	1422-1440	AGUCCAAUCAAUAUAAAGGdTdT	2447
AD-62115.1	GAUUGGACUGAUAACCAUAdTdT	1881	1432-1450	UAUGGUUAUCAGUCCAAUCdTdT	2448
AD-62121.1	CUGAUAACCAUAAGGCUUUdTdT	1882	1439-1457	AAAGCCUUAUGGUUAUCAGdTdT	2449
AD-62127.1	AGGCUUUGCUAGUGGGAGAdTdT	1883	1451-1469	UCUCCCACUAGCAAAGCCUdTdT	2450
AD-62133.1	GUGGGAGAACAUCUGAAUAdTdT	1884	1462-1480	UAUUCAGAUGUUCUCCCACdTdT	2451
AD-62139.1	CAUCUGAAUAUUAUUGUUAdTdT	1885	1471-1489	UAACAAUAAUAUUCAGAUGdTdT	2452
AD-62145.1	UAUUAUUGUUACCCCCAAAdTdT	1886	1479-1497	UUUGGGGGUAACAAUAAUAdTdT	2453
AD-62151.1	CCCAAAAGCCCAUAUAUUGdTdT	1887	1492-1510	CAAUAUAUGGGCUUUUGGGdTdT	2454
AD-62110.1	CCAAAAGCCCAUAUAUUGAdTdT	1888	1493-1511	UCAAUAUAUGGGCUUUUGGdTdT	2455
AD-62116.1	CAAAAGCCCAUAUAUUGACdTdT	1889	1494-1512	GUCAAUAUAUGGGCUUUUGdTdT	2456
AD-62122.1	AAAAGCCCAUAUAUUGACAdTdT	1890	1495-1513	UGUCAAUAUAUGGGCUUUUdTdT	2457
AD-62128.1	AAAGCCCAUAUAUUGACAAdTdT	1891	1496-1514	UUGUCAAUAUAUGGGCUUUdTdT	2458
AD-62134.1	AAGCCCAUAUAUUGACAAAdTdT	1892	1497-1515	UUUGUCAAUAUAUGGGCUUdTdT	2459
AD-62140.1	AGCCCAUAUAUUGACAAAAdTdT	1893	1498-1516	UUUUGUCAAUAUAUGGGCUdTdT	2460
AD-62146.1	GCCCAUAUAUUGACAAAAUdTdT	1894	1499-1517	AUUUUGUCAAUAUAUGGGCdTdT	2461
AD-62152.1	CCCAUAUAUUGACAAAAUAdTdT	1895	1500-1518	UAUUUUGUCAAUAUAUGGGdTdT	2462
AD-62111.1	CCAUAUAUUGACAAAAUAAdTdT	1896	1501-1519	UUAUUUUGUCAAUAUAUGGdTdT	2463
AD-62117.1	CAUAUAUUGACAAAAUAACdTdT	1897	1502-1520	GUUAUUUUGUCAAUAUAUGdTdT	2464

AD-62123.1	AUAUAUUGACAAAAUAACUdTdT	1898	1503-1521	AGUUAUUUUGUCAAUAUAUdTdT	2465
AD-62129.1	UAUAUUGACAAAAUAACUCdTdT	1899	1504-1522	GAGUUAUUUUGUCAAUAUAdTdT	2466
AD-62135.1	AUAUUGACAAAAUAACUCAdTdT	1900	1505-1523	UGAGUUAUUUUGUCAAUAUdTdT	2467
AD-62141.1	UAUUGACAAAAUAACUCACdTdT	1901	1506-1524	GUGAGUUAUUUUGUCAAUAdTdT	2468
AD-62147.1	AUUGACAAAAUAACUCACUdTdT	1902	1507-1525	AGUGAGUUAUUUUGUCAAUdTdT	2469
AD-62153.1	UUGACAAAAUAACUCACUAdTdT	1903	1508-1526	UAGUGAGUUAUUUUGUCAAdTdT	2470
AD-62112.1	UGACAAAAUAACUCACUAUdTdT	1904	1509-1527	AUAGUGAGUUAUUUUGUCAdTdT	2471
AD-62118.1	GACAAAAUAACUCACUAUAdTdT	1905	1510-1528	UAUAGUGAGUUAUUUUGUCdTdT	2472
AD-62124.1	AAAAUAACUCACUAUAAUUdTdT	1906	1513-1531	AAUUAUAGUGAGUUAUUUUdTdT	2473
AD-62130.1	AAAUAACUCACUAUAAUUAdTdT	1907	1514-1532	UAAUUAUAGUGAGUUAUUUUdTdT	2474
AD-62136.1	AAUAACUCACUAUAAUUACdTdT	1908	1515-1533	GUAAUUAUAGUGAGUUAUUUdTdT	2475
AD-62142.1	AUAACUCACUAUAAUUACUdTdT	1909	1516-1534	AGUAAUUAUAGUGAGUUAUUdTdT	2476
AD-62148.1	AACUCACUAUAAUUACUUGdTdT	1910	1518-1536	CAAGUAAUUAUAGUGAGUUUdTdT	2477
AD-62154.1	ACUCACUAUAAUUACUUGAdTdT	1911	1519-1537	UCAAGUAAUUAUAGUGAGUdTdT	2478
AD-62113.1	CUCACUAUAAUUACUUGAUdTdT	1912	1520-1538	AUCAAGUAAUUAUAGUGAGdTdT	2479
AD-62119.1	UCACUAUAAUUACUUGAUUdTdT	1913	1521-1539	AAUCAAGUAAUUAUAGUGAdTdT	2480
AD-62125.1	ACUAUAAUUACUUGAUUUUdTdT	1914	1523-1541	AAAAUCAAGUAAUUAUAGUdTdT	2481
AD-62131.1	CUAUAAUUACUUGAUUUUAdTdT	1915	1524-1542	UAAAAUCAAGUAAUUAUAGdTdT	2482
AD-62137.1	UAUAAUUACUUGAUUUUAUdTdT	1916	1525-1543	AUAAAAUCAAGUAAUUAUAdTdT	2483
AD-62143.1	AUAAUUACUUGAUUUUAUCdTdT	1917	1526-1544	GAUAAAAUCAAGUAAUUAUdTdT	2484
AD-62149.1	UAAUUACUUGAUUUUAUCCdTdT	1918	1527-1545	GGAUAAAAUCAAGUAAUUAdTdT	2485
AD-62155.1	AAUUACUUGAUUUUAUCCAdTdT	1919	1528-1546	UGGAUAAAAUCAAGUAAUUdTdT	2486
AD-62114.1	AUUACUUGAUUUUAUCCAAdTdT	1920	1529-1547	UUGGAUAAAAUCAAGUAAUdTdT	2487
AD-62120.1	UUAUCCAAGGGCAAAAUUAdTdT	1921	1540-1558	UAAUUUUGCCCUUGGAUAAdTdT	2488
AD-62126.1	GCAAAAUUAUCCACUUUGGdTdT	1922	1550-1568	CCAAAGUGGAUAAUUUUGCdTdT	2489
AD-62132.1	CACUUUGGCACGAGGGAGAdTdT	1923	1561-1579	UCUCCCUCGUGCCAAAGUGdTdT	2490
AD-62138.1	CGAGGGAGAAAUUUUCAGAdTdT	1924	1571-1589	UCUGAAAAUUUCUCCCUCGdTdT	2491

AD-62144.1	AUUUUCAGAUGCAUCUUAUdTdT	1925	1581-1599	AUAAGAUGCAUCUGAAAAUdTdT	2492
AD-62150.1	GCAUCUUAUCAAAGUAUAAdTdT	1926	1591-1609	UUAUACUUUGAUAAGAUGCdTdT	2493
AD-62156.1	CAAAGUAUAAACAUUCCAGdTdT	1927	1600-1618	CUGGAAUGUUUAUACUUUGdTdT	2494
AD-62162.1	AUUCCAGUAACACAGAACAdTdT	1928	1612-1630	UGUUCUGUGUUACUGGAAUdTdT	2495
AD-62168.1	CACAGAACAUGGUUCCUUCdTdT	1929	1622-1640	GAAGGAACCAUGUUCUGUGdTdT	2496
AD-62174.1	GGUUCCUUCAUCCCGACUUdTdT	1930	1632-1650	AAGUCGGGAUGAAGGAACCdTdT	2497
AD-62180.1	CCCGACUUCUGGUCUAUUAdTdT	1931	1643-1661	UAAUAGACCAGAAGUCGGGdTdT	2498
AD-62186.1	GGUCUAUUACAUCGUCACAdTdT	1932	1653-1671	UGUGACGAUGUAAUAGACCdTdT	2499
AD-62192.1	AUCGUCACAGGAGAACAGAdTdT	1933	1663-1681	UCUGUUCUCCUGUGACGAUdTdT	2500
AD-62198.1	CAGGAGAACAGACAGCAGAdTdT	1934	1670-1688	UCUGCUGUCUGUUCUCCUGdTdT	2501
AD-62157.1	CAGCAGAAUUAGUGUCUGAdTdT	1935	1682-1700	UCAGACACUAAUUCUGCUGdTdT	2502
AD-62163.1	GUGUCUGAUUCAGUCUGGUdTdT	1936	1693-1711	ACCAGACUGAAUCAGACACdTdT	2503
AD-62169.1	CAGUCUGGUUAAAUAUUGAdTdT	1937	1703-1721	UCAAUAUUUAACCAGACUGdTdT	2504
AD-62175.1	GUUAAAUAUUGAAGAAAAAdTdT	1938	1710-1728	UUUUUCUUCAAUAUUUAACdTdT	2505
AD-62181.1	AGAAAAAUGUGGCAACCAGdTdT	1939	1722-1740	CUGGUUGCCACAUUUUUCUdTdT	2506
AD-62187.1	GCAACCAGCUCCAGGUUCAdTdT	1940	1733-1751	UGAACCUGGAGCUGGUUGCdTdT	2507
AD-62193.1	GCUCCAGGUUCAUCUGUCUdTdT	1941	1740-1758	AGACAGAUGAACCUGGAGCdTdT	2508
AD-62199.1	AUCUGUCUCCUGAUGCAGAdTdT	1942	1751-1769	UCUGCAUCAGGAGACAGAUdTdT	2509
AD-62158.1	GAUGCAGAUGCAUAUUCUCdTdT	1943	1762-1780	GAGAAUAUGCAUCUGCAUCdTdT	2510
AD-62164.1	GCAUAUUCUCCAGGCCAAAdTdT	1944	1771-1789	UUUGGCCUGGAGAAUAUGCdTdT	2511
AD-62170.1	AGGCCAAACUGUGUCUCUUdTdT	1945	1782-1800	AAGAGACACAGUUUGGCCUdTdT	2512
AD-62176.1	GUGUCUCUUAAUAUGGCAAdTdT	1946	1792-1810	UUGCCAUAUUAAGAGACACdTdT	2513
AD-62182.1	UUAAUAUGGCAACUGGAAUdTdT	1947	1799-1817	AUUCCAGUUGCCAUAUUAAdTdT	2514
AD-62188.1	AACUGGAAUGGAUUCCUGGdTdT	1948	1809-1827	CCAGGAAUCCAUUCCAGUUdTdT	2515
AD-62194.1	UUCCUGGGUGGCAUUAGCAdTdT	1949	1821-1839	UGCUAAUGCCACCCAGGAAdTdT	2516
AD-62200.1	GGCAUUAGCAGCAGUGGACdTdT	1950	1830-1848	GUCCACUGCUGCUAAUGCCdTdT	2517
AD-62159.1	AGUGGACAGUGCUGUGUAUdTdT	1951	1842-1860	AUACACAGCACUGUCCACUdTdT	2518

AD-62165.1	GCUGUGUAUGGAGUCCAAAdTdT	1952	1852-1870	UUUGGACUCCAUACACAGCdTdT	2519
AD-62171.1	AGUCCAAAGAGGAGCCAAAdTdT	1953	1863-1881	UUUGGCUCCUCUUUGGACUdTdT	2520
AD-62177.1	AGAGGAGCCAAAAAGCCCUdTdT	1954	1870-1888	AGGGCUUUUUGGCUCCUCUdTdT	2521
AD-62183.1	AGCCCUUGGAAAGAGUAUUdTdT	1955	1883-1901	AAUACUCUUUCCAAGGGCUdTdT	2522
AD-62189.1	AAGAGUAUUUCAAUUCUUAdTdT	1956	1893-1911	UAAGAAUUGAAAUACUCUUdTdT	2523
AD-62195.1	UUUCAAUUCUUAGAGAAGAdTdT	1957	1900-1918	UCUUCUCUAAGAAUUGAAAdTdT	2524
AD-62201.1	GAGAAGAGUGAUCUGGGCUdTdT	1958	1912-1930	AGCCCAGAUCACUCUUCUCdTdT	2525
AD-62160.1	UGAUCUGGGCUGUGGGGCAdTdT	1959	1920-1938	UGCCCCACAGCCCAGAUCAdTdT	2526
AD-62166.1	GGGGCAGGUGGUGGCCUCAdTdT	1960	1933-1951	UGAGGCCACCACCUGCCCCdTdT	2527
AD-62172.1	GUGGCCUCAACAAUGCCAAdTdT	1961	1943-1961	UUGGCAUUGUUGAGGCCACdTdT	2528
AD-62178.1	CAACAAUGCCAAUGUGUUCdTdT	1962	1950-1968	GAACACAUUGGCAUUGUUGdTdT	2529
AD-62184.1	CAAUGUGUUCCACCUAGCUdTdT	1963	1959-1977	AGCUAGGUGGAACACAUUGdTdT	2530
AD-62190.1	CACCUAGCUGGACUUACCUdTdT	1964	1969-1987	AGGUAAGUCCAGCUAGGUGdTdT	2531
AD-62196.1	GACUUACCUUCCUCACUAAdTdT	1965	1979-1997	UUAGUGAGGAAGGUAAGUCdTdT	2532
AD-62202.1	UCACUAAUGCAAAUGCAGAdTdT	1966	1991-2009	UCUGCAUUUGCAUUAGUGAdTdT	2533
AD-62161.1	AAAUGCAGAUGACUCCCAAdTdT	1967	2001-2019	UUGGGAGUCAUCUGCAUUUdTdT	2534
AD-62167.1	CUCCCAAGAAAAUGAUGAAdTdT	1968	2013-2031	UUCAUCAUUUUCUUGGGAGdTdT	2535
AD-62173.1	CCUUGUAAAGAAAUUCUCAdTdT	1969	2032-2050	UGAGAAUUUCUUUACAAGGdTdT	2536
AD-62179.1	AAUUCUCAGGCCAAGAAGAdTdT	1970	2043-2061	UCUUCUUGGCCUGAGAAUUdTdT	2537
AD-62185.1	CCAAGAAGAACGCUGCAAAdTdT	1971	2053-2071	UUUGCAGCGUUCUUCUUGGdTdT	2538
AD-62191.1	CGCUGCAAAAGAAGAUAGAdTdT	1972	2063-2081	UCUAUCUUCUUUUGCAGCGdTdT	2539
AD-62197.1	AAAGAAGAUAGAAGAAAUAdTdT	1973	2070-2088	UAUUUCUUCUAUCUUCUUUdTdT	2540
AD-62203.1	AGAAAUAGCUGCUAAAUAUdTdT	1974	2082-2100	AUAUUUAGCAGCUAUUUCUdTdT	2541
AD-62209.1	GCUGCUAAAUAUAAACAUUdTdT	1975	2089-2107	AAUGUUUAUAUUUAGCAGCdTdT	2542
AD-62215.1	ACAUUCAGUAGUGAAGAAAdTdT	1976	2103-2121	UUUCUUCACUACUGAAUGUdTdT	2543
AD-62221.1	GUAGUGAAGAAAUGUUGUUdTdT	1977	2110-2128	AACAACAUUUCUUCACUACdTdT	2544
AD-62227.1	AAAUGUUGUUACGAUGGAGdTdT	1978	2119-2137	CUCCAUCGUAACAACAUUUdTdT	2545

AD-62233.1	CGAUGGAGCCUGCGUUAAUdTdT	1979	2130-2148	AUUAACGCAGGCUCCAUCGdTdT	2546
AD-62239.1	CGUUAAUAAUGAUGAAACCdTdT	1980	2142-2160	GGUUUCAUCAUUAUUAACGdTdT	2547
AD-62245.1	AUGAUGAAACCUGUGAGCAdTdT	1981	2150-2168	UGCUCACAGGUUUCAUCAUdTdT	2548
AD-62204.1	CUGUGAGCAGCGAGCUGCAdTdT	1982	2160-2178	UGCAGCUCGCUGCUCACAGdTdT	2549
AD-62210.1	CGAGCUGCACGGAUUAGUUdTdT	1983	2170-2188	AACUAAUCCGUGCAGCUCGdTdT	2550
AD-62216.1	GGAUUAGUUUAGGGCCAAGdTdT	1984	2180-2198	CUUGGCCCUAAACUAAUCCdTdT	2551
AD-62222.1	GGGCCAAGAUGCAUCAAAGdTdT	1985	2191-2209	CUUUGAUGCAUCUUGGCCCdTdT	2552
AD-62228.1	CAUCAAAGCUUUCACUGAAdTdT	1986	2202-2220	UUCAGUGAAAGCUUUGAUGdTdT	2553
AD-62234.1	GCUUUCACUGAAUGUUGUGdTdT	1987	2209-2227	CACAACAUUCAGUGAAAGCdTdT	2554
AD-62240.1	AAUGUUGUGUCGUCGCAAGdTdT	1988	2219-2237	CUUGCGACGACACAACAUUdTdT	2555
AD-62246.1	CGUCGCAAGCCAGCUCCGUdTdT	1989	2229-2247	ACGGAGCUGGCUUGCGACGdTdT	2556
AD-62205.1	GCUCCGUGCUAAUAUCUCUdTdT	1990	2241-2259	AGAGAUAUUAGCACGGAGCdTdT	2557
AD-62211.1	CUAAUAUCUCUCAUAAAGAdTdT	1991	2249-2267	UCUUUAUGAGAGAUAUUAGdTdT	2558
AD-62217.1	AAAGACAUGCAAUUGGGAAdTdT	1992	2263-2281	UUCCCAAUUGCAUGUCUUUdTdT	2559
AD-62223.1	CAAUUGGGAAGGCUACACAdTdT	1993	2272-2290	UGUGUAGCCUUCCCAAUUGdTdT	2560
AD-62229.1	GCUACACAUGAAGACCCUGdTdT	1994	2283-2301	CAGGGUCUUCAUGUGUAGCdTdT	2561
AD-62235.1	CAUGAAGACCCUGUUACCAdTdT	1995	2289-2307	UGGUAACAGGGUCUUCAUGdTdT	2562
AD-62241.1	UACCAGUAAGCAAGCCAGAdTdT	1996	2303-2321	UCUGGCUUGCUUACUGGUAdTdT	2563
AD-62247.1	AGCAAGCCAGAAAUUCGGAdTdT	1997	2311-2329	UCCGAAUUUCUGGCUUGCUdTdT	2564
AD-62206.1	AGAAAUUCGGAGUUAUUUUdTdT	1998	2319-2337	AAAAUAACUCCGAAUUUCUdTdT	2565
AD-62212.1	AGUUAUUUUCCAGAAAGCUdTdT	1999	2329-2347	AGCUUUCUGGAAAAUAACUdTdT	2566
AD-62218.1	CAGAAAGCUGGUUGUGGGAdTdT	2000	2339-2357	UCCCACAACCAGCUUUCUGdTdT	2567
AD-62224.1	GUGGGAAGUUCAUCUUGUUdTdT	2001	2352-2370	AACAAGAUGAACUUCCCACdTdT	2568
AD-62230.1	UCAUCUUGUUCCCAGAAGAdTdT	2002	2361-2379	UCUUCUGGGAACAAGAUGAdTdT	2569
AD-62236.1	CCAGAAGAAAACAGUUGCAdTdT	2003	2372-2390	UGCAACUGUUUUCUUCUGGdTdT	2570
AD-62242.1	CAGUUGCAGUUUGCCCUACdTdT	2004	2383-2401	GUAGGGCAAACUGCAACUGdTdT	2571
AD-62248.1	CAGUUUGCCCUACCUGAUUdTdT	2005	2389-2407	AAUCAGGUAGGGCAAACUGdTdT	2572

AD-62207.1	CCUGAUUCUCUAACCACCUdTdT	2006	2401-2419	AGGUGGUUAGAGAAUCAGGdTdT	2573
AD-62213.1	ACCACCUGGGAAAUUCAAGdTdT	2007	2413-2431	CUUGAAUUUCCCAGGUGGUdTdT	2574
AD-62219.1	GAAAUUCAAGGCGUUGGCAdTdT	2008	2422-2440	UGCCAACGCCUUGAAUUUCdTdT	2575
AD-62225.1	CGUUGGCAUUUCAAACACUdTdT	2009	2433-2451	AGUGUUUGAAAUGCCAACGdTdT	2576
AD-62231.1	CAUUUCAAACACUGGUAUAdTdT	2010	2439-2457	UAUACCAGUGUUUGAAAUGdTdT	2577
AD-62237.1	GUAUAUGUGUUGCUGAUACdTdT	2011	2453-2471	GUAUCAGCAACACAUAUACdTdT	2578
AD-62243.1	UGCUGAUACUGUCAAGGCAdTdT	2012	2463-2481	UGCCUUGACAGUAUCAGCAdTdT	2579
AD-62249.1	CUGUCAAGGCAAAGGUGUUdTdT	2013	2471-2489	AACACCUUUGCCUUGACAGdTdT	2580
AD-62208.1	AGGUGUUCAAAGAUGUCUUdTdT	2014	2483-2501	AAGACAUCUUUGAACACCUdTdT	2581
AD-62214.1	CAAAGAUGUCUUCCUGGAAdTdT	2015	2490-2508	UUCCAGGAAGACAUCUUUGdTdT	2582
AD-62220.1	CUUCCUGGAAAUGAAUAUAdTdT	2016	2499-2517	UAUAUUCAUUUCCAGGAAGdTdT	2583
AD-62226.1	GAAUAUACCAUAUUCUGUUdTdT	2017	2511-2529	AACAGAAUAUGGUAUAUUCdTdT	2584
AD-62232.1	AUAUUCUGUUGUACGAGGAdTdT	2018	2520-2538	UCCUCGUACAACAGAAUAUdTdT	2585
AD-62238.1	CGAGGAGAACAGAUCCAAUdTdT	2019	2533-2551	AUUGGAUCUGUUCUCCUCGdTdT	2586
AD-62244.1	GAACAGAUCCAAUUGAAAGdTdT	2020	2539-2557	CUUUCAAUUGGAUCUGUUCdTdT	2587
AD-61874.1	GAAAGGAACUGUUUACAACdTdT	2021	2553-2571	GUUGUAAACAGUUCCUUUCdTdT	2588
AD-61880.1	ACUGUUUACAACUAUAGGAdTdT	2022	2560-2578	UCCUAUAGUUGUAAACAGUdTdT	2589
AD-61886.1	AACUAUAGGACUUCUGGGAdTdT	2023	2569-2587	UCCCAGAAGUCCUAUAGUUdTdT	2590
AD-61892.1	UGGGAUGCAGUUCUGUGUUdTdT	2024	2583-2601	AACACAGAACUGCAUCCCAdTdT	2591
AD-61898.1	GUUCUGUGUUAAAAUGUCUdTdT	2025	2592-2610	AGACAUUUUAACACAGAACdTdT	2592
AD-61904.1	UUAAAAUGUCUGCUGUGGAdTdT	2026	2600-2618	UCCACAGCAGACAUUUUAAdTdT	2593
AD-61910.1	CUGUGGAGGGAAUCUGCACdTdT	2027	2612-2630	GUGCAGAUUCCCUCCACAGdTdT	2594
AD-61916.1	GGAAUCUGCACUUCGGAAAdTdT	2028	2620-2638	UUUCCGAAGUGCAGAUUCCdTdT	2595
AD-61875.1	CGGAAAGCCCAGUCAUUGAdTdT	2029	2633-2651	UCAAUGACUGGGCUUUCCGdTdT	2596
AD-61881.1	CCAGUCAUUGAUCAUCAGGdTdT	2030	2641-2659	CCUGAUGAUCAAUGACUGGdTdT	2597
AD-61887.1	CAUCAGGGCACAAAGUCCUdTdT	2031	2653-2671	AGGACUUUGUGCCCUGAUGdTdT	2598
AD-61893.1	GGCACAAAGUCCUCCAAAUdTdT	2032	2659-2677	AUUUGGAGGACUUUGUGCCdTdT	2599

AD-61899.1	CAAAUGUGUGCGCCAGAAAdTdT	2033	2673-2691	UUUCUGGCGCACACAUUUGdTdT	2600
AD-61905.1	GCGCCAGAAAGUAGAGGGCdTdT	2034	2682-2700	GCCCUCUACUUUCUGGCGCdTdT	2601
AD-61911.1	AGUAGAGGGCUCCUCCAGUdTdT	2035	2691-2709	ACUGGAGGAGCCCUCUACUdTdT	2602
AD-61917.1	CCUCCAGUCACUUGGUGACdTdT	2036	2702-2720	GUCACCAAGUGACUGGAGGdTdT	2603
AD-61876.1	UCACUUGGUGACAUUCACUdTdT	2037	2709-2727	AGUGAAUGUCACCAAGUGAdTdT	2604
AD-61882.1	CAUUCACUGUGCUUCCUCUdTdT	2038	2720-2738	AGAGGAAGCACAGUGAAUGdTdT	2605
AD-61888.1	GGAAAUUGGCCUUCACAACdTdT	2039	2739-2757	GUUGUGAAGGCCAAUUUCCdTdT	2606
AD-61894.1	CUUCACAACAUCAAUUUUUUdTdT	2040	2749-2767	AAAAAUUGAUGUUGUGAAGdTdT	2607
AD-61900.1	AAUUUUUCACUGGAGACUUdTdT	2041	2761-2779	AAGUCUCCAGUGAAAAAUUdTdT	2608
AD-61906.1	CUGGAGACUUGGUUUGGAAdTdT	2042	2770-2788	UUCCAAACCAAGUCUCCAGdTdT	2609
AD-61912.1	GGUUUGGAAAAGAAAUCUUdTdT	2043	2780-2798	AAGAUUUCUUUUCCAAACCdTdT	2610
AD-61918.1	AAUCUUAGUAAAAAACAUUAdTdT	2044	2793-2811	UAAUGUUUUUACUAAGAUUdTdT	2611
AD-61877.1	AAAAACAUUACGAGUGGUGdTdT	2045	2802-2820	CACCACUCGUAAUGUUUUUdTdT	2612
AD-61883.1	GAGUGGUGCCAGAAGGUGUdTdT	2046	2813-2831	ACACCUUCUGGCACCACUCdTdT	2613
AD-61889.1	AGAAGGUGUCAAAAGGGAAdTdT	2047	2823-2841	UUCCCUUUUGACACCUUCUdTdT	2614
AD-61895.1	UGUCAAAAGGGAAAGCUAUdTdT	2048	2829-2847	AUAGCUUUCCCUUUUGACAdTdT	2615
AD-61901.1	GCUAUUCUGGUGUUACUUUdTdT	2049	2843-2861	AAAGUAACACCAGAAUAGCdTdT	2616
AD-61907.1	GUGUUACUUUGGAUCCUAGdTdT	2050	2852-2870	CUAGGAUCCAAAGUAACACdTdT	2617
AD-61913.1	GGAUCCUAGGGGUAUUUAUdTdT	2051	2862-2880	AUAAAUACCCCUAGGAUCCdTdT	2618
AD-61919.1	GGUAUUUAUGGUACCAUUAdTdT	2052	2872-2890	UAAUGGUACCAUAAAUACCdTdT	2619
AD-61878.1	GUACCAUUAGCAGACGAAAdTdT	2053	2882-2900	UUUCGUCUGCUAAUGGUACdTdT	2620
AD-61884.1	CAGACGAAAGGAGUUCCCAdTdT	2054	2892-2910	UGGGAACUCCUUUCGUCUGdTdT	2621
AD-61890.1	AGGAGUUCCCAUACAGGAUdTdT	2055	2900-2918	AUCCUGUAUGGGAACUCCUdTdT	2622
AD-61896.1	CAUACAGGAUACCCUUAGAdTdT	2056	2909-2927	UCUAAGGGUAUCCUGUAUGdTdT	2623
AD-61902.1	CUUAGAUUUGGUCCCCAAAdTdT	2057	2922-2940	UUUGGGGACCAAAUCUAAGdTdT	2624
AD-61908.1	UCCCCAAAACAGAAAUCAAdTdT	2058	2933-2951	UUGAUUUCUGUUUUGGGGAdTdT	2625
AD-61914.1	ACAGAAAUCAAAAGGAUUUdTdT	2059	2941-2959	AAAUCCUUUUGAUUUCUGUdTdT	2626

AD-61920.1	AAAGGAUUUUGAGUGUAAAdTdT	2060	2951-2969	UUUACACUCAAAAUCCUUUdTdT	2627
AD-61879.1	AGUGUAAAAGGACUGCUUGdTdT	2061	2962-2980	CAAGCAGUCCUUUUACACUdTdT	2628
AD-61885.1	AAGGACUGCUUGUAGGUGAdTdT	2062	2969-2987	UCACCUACAAGCAGUCCUUdTdT	2629
AD-61891.1	GUAGGUGAGAUCUUGUCUGdTdT	2063	2980-2998	CAGACAAGAUCUCACCUACdTdT	2630
AD-61897.1	AUCUUGUCUGCAGUUCUAAdTdT	2064	2989-3007	UUAGAACUGCAGACAAGAUdTdT	2631
AD-61903.1	GUUCUAAGUCAGGAAGGCAdTdT	2065	3001-3019	UGCCUUCCUGACUUAGAACdTdT	2632
AD-61909.1	GAAGGCAUCAAUAUCCUAAdTdT	2066	3013-3031	UUAGGAUAUUGAUGCCUUCdTdT	2633
AD-61915.1	UCAAUAUCCUAACCCACCUdTdT	2067	3020-3038	AGGUGGGUUAGGAUAUUGAdTdT	2634
AD-61921.1	CCACCUCCCCAAAGGGAGUdTdT	2068	3033-3051	ACUCCCUUUGGGGAGGUGGdTdT	2635
AD-61927.1	CCCCAAAGGGAGUGCAGAGdTdT	2069	3039-3057	CUCUGCACUCCCUUUGGGGdTdT	2636
AD-61933.1	GUGCAGAGGCGGAGCUGAUdTdT	2070	3050-3068	AUCAGCUCCGCCUCUGCACdTdT	2637
AD-61939.1	GGAGCUGAUGAGCGUUGUCdTdT	2071	3060-3078	GACAACGCUCAUCAGCUCCdTdT	2638
AD-61945.1	CGUUGUCCCAGUAUUCUAUdTdT	2072	3072-3090	AUAGAAUACUGGGACAACGdTdT	2639
AD-61951.1	CCAGUAUUCUAUGUUUUUCdTdT	2073	3079-3097	GAAAAACAUAGAAUACUGGdTdT	2640
AD-61957.1	GUUUUUCACUACCUGGAAAdTdT	2074	3091-3109	UUUCCAGGUAGUGAAAAACdTdT	2641
AD-61963.1	CCUGGAAACAGGAAAUCAUdTdT	2075	3102-3120	AUGAUUUCCUGUUUCCAGGdTdT	2642
AD-61922.1	GGAACAUUUUUCAUUCUGAdTdT	2076	3122-3140	UCAGAAUGAAAAAUGUUCCdTdT	2643
AD-61928.1	CAUUCUGACCCAUUAAUUGdTdT	2077	3133-3151	CAAUUAAUGGGUCAGAAUGdTdT	2644
AD-61934.1	CCAUUAAUUGAAAAGCAGAdTdT	2078	3142-3160	UCUGCUUUUCAAUUAAUGGdTdT	2645
AD-61940.1	AAAGCAGAAACUGAAGAAAdTdT	2079	3153-3171	UUUCUUCAGUUUCUGCUUUdTdT	2646
AD-61946.1	AACUGAAGAAAAAAUUAAAdTdT	2080	3161-3179	UUUAAUUUUUUCUUCAGUUdTdT	2647
AD-61952.1	AAAAAAUUAAAAGAAGGGAdTdT	2081	3169-3187	UCCCUUCUUUUAAUUUUUUdTdT	2648
AD-61958.1	AGGGAUGUUGAGCAUUAUGdTdT	2082	3183-3201	CAUAAUGCUCAACAUCCCUdTdT	2649
AD-61964.1	GAGCAUUAUGUCCUACAGAdTdT	2083	3192-3210	UCUGUAGGACAUAAUGCUCdTdT	2650
AD-61923.1	UGUCCUACAGAAAUGCUGAdTdT	2084	3200-3218	UCAGCAUUUCUGUAGGACAdTdT	2651
AD-61929.1	AAUGCUGACUACUCUUACAdTdT	2085	3211-3229	UGUAAGAGUAGUCAGCAUUdTdT	2652
AD-61935.1	UACUCUUACAGUGUGUGGAdTdT	2086	3220-3238	UCCACACACUGUAAGAGUAdTdT	2653

AD-61941.1	AGUGUGUGGAAGGGUGGAAdTdT	2087	3229-3247	UUCCACCCUUCCACACACUdTdT	2654
AD-61947.1	GGGUGGAAGUGCUAGCACUdTdT	2088	3240-3258	AGUGCUAGCACUUCCACCCdTdT	2655
AD-61953.1	GCUAGCACUUGGUUAACAGdTdT	2089	3250-3268	CUGUUAACCAAGUGCUAGCdTdT	2656
AD-61959.1	GGUUAACAGCUUUUGCUUUdTdT	2090	3260-3278	AAAGCAAAAGCUGUUAACCdTdT	2657
AD-61965.1	UGCUUUAAGAGUACUUGGAdTdT	2091	3273-3291	UCCAAGUACUCUUAAAGCAdTdT	2658
AD-61924.1	GUACUUGGACAAGUAAAUAdTdT	2092	3283-3301	UAUUUACUUGUCCAAGUACdTdT	2659
AD-61930.1	CAAGUAAAUAAAAUACGUAGdTdT	2093	3292-3310	CUACGUAUUUAUUUACUUGdTdT	2660
AD-61936.1	AUAAAUACGUAGAGCAGAAdTdT	2094	3299-3317	UUCUGCUCUACGUAUUUAUdTdT	2661
AD-61942.1	GAGCAGAACCAAAAUUCAAdTdT	2095	3310-3328	UUGAAUUUUGGUUCUGCUCdTdT	2662
AD-61948.1	AAUUCAAUUUGUAAUUCUUdTdT	2096	3322-3340	AAGAAUUACAAAUUGAAUUdTdT	2663
AD-61954.1	GUAAUUCUUUAUUGUGGCUdTdT	2097	3332-3350	AGCCACAAUAAAGAAUUACdTdT	2664
AD-61960.1	AUUGUGGCUAGUUGAGAAUdTdT	2098	3342-3360	AUUCUCAACUAGCCACAAUdTdT	2665
AD-61966.1	CUAGUUGAGAAUUAUCAAUdTdT	2099	3349-3367	AUUGAUAAUUCUCAACUAGdTdT	2666
AD-61925.1	UUAUCAAUUAGAUAAUGGAdTdT	2100	3360-3378	UCCAUUAUCUAAUUGAUAAdTdT	2667
AD-61931.1	AAUGGAUCUUUCAAGGAAAdTdT	2101	3373-3391	UUUCCUUGAAAGAUCCAUUdTdT	2668
AD-61937.1	CUUUCAAGGAAAAUUCACAdTdT	2102	3380-3398	UGUGAAUUUUCCUUGAAAGdTdT	2669
AD-61943.1	AAUUCACAGUAUCAACCAAdTdT	2103	3391-3409	UUGGUUGAUACUGUGAAUUdTdT	2670
AD-61949.1	GUAUCAACCAAUAAAAUUAdTdT	2104	3399-3417	UAAUUUUAUUGGUUGAUACdTdT	2671
AD-61955.1	AAAAUUACAGGGUACCUUGdTdT	2105	3411-3429	CAAGGUACCCUGUAAUUUUdTdT	2672
AD-61961.1	AGGGUACCUUGCCUGUUGAdTdT	2106	3419-3437	UCAACAGGCAAGGUACCCUdTdT	2673
AD-61967.1	GUUGAAGCCCGAGAGAACAdTdT	2107	3433-3451	UGUUCUCUCGGGCUUCAACdTdT	2674
AD-61926.1	CCGAGAGAACAGCUUAUAUdTdT	2108	3441-3459	AUAUAAGCUGUUCUCUCGGdTdT	2675
AD-61932.1	GCUUAUAUCUUACAGCCUUdTdT	2109	3452-3470	AAGGCUGUAAGAUAUAAGCdTdT	2676
AD-61938.1	CUUACAGCCUUUACUGUGAdTdT	2110	3460-3478	UCACAGUAAAGGCUGUAAGdTdT	2677
AD-61944.1	GAAUUAGAAAGGCUUUCGAdTdT	2111	3482-3500	UCGAAAGCCUUUCUAAUUCdTdT	2678
AD-61950.1	GGCUUUCGAUAUAUGCCCCdTdT	2112	3492-3510	GGGGCAUAUAUCGAAAGCCdTdT	2679
AD-61956.1	GAUAUAUGCCCCCUGGUGAdTdT	2113	3499-3517	UCACCAGGGGGCAUAUAUCdTdT	2680

AD-61962.1	GGUGAAAAUCGACACAGCUdTdT	2114	3513-3531	AGCUGUGUCGAUUUUCACCdTdT	2681
AD-61968.1	CGACACAGCUCUAAUUAAAdTdT	2115	3522-3540	UUUAAUUAGAGCUGUGUCGdTdT	2682
AD-61974.1	GCUCUAAUUAAAGCUGACAdTdT	2116	3529-3547	UGUCAGCUUUAAUUAGAGCdTdT	2683
AD-61980.1	CUGACAACUUUCUGCUUGAdTdT	2117	3542-3560	UCAAGCAGAAAGUUGUCAGdTdT	2684
AD-61986.1	CUUUCUGCUUGAAAAUACAdTdT	2118	3549-3567	UGUAUUUUCAAGCAGAAAGdTdT	2685
AD-61992.1	AAAAUACACUGCCAGCCCAdTdT	2119	3560-3578	UGGGCUGGCAGUGUAUUUUdTdT	2686
AD-61998.1	AGCCCAGAGCACCUUUACAdTdT	2120	3573-3591	UGUAAAGGUGCUCUGGGCUdTdT	2687
AD-62004.1	GCACCUUUACAUUGGCCAUdTdT	2121	3581-3599	AUGGCCAAUGUAAAGGUGCdTdT	2688
AD-62010.1	ACAUUGGCCAUUUCUGCGUdTdT	2122	3589-3607	ACGCAGAAAUGGCCAAUGUdTdT	2689
AD-61969.1	CUGCGUAUGCUCUUUCCCUdTdT	2123	3602-3620	AGGGAAAGAGCAUACGCAGdTdT	2690
AD-61975.1	CUUUCCCUGGGAGAUAAAAdTdT	2124	3613-3631	UUUUAUCUCCCAGGGAAAGdTdT	2691
AD-61981.1	GAGAUAAAACUCACCCACAdTdT	2125	3623-3641	UGUGGGUGAGUUUUAUCUCdTdT	2692
AD-61987.1	ACUCACCCACAGUUUCGUUdTdT	2126	3631-3649	AACGAAACUGUGGGUGAGUdTdT	2693
AD-61993.1	CAGUUUCGUUCAAUUGUUUdTdT	2127	3640-3658	AAACAAUUGAACGAAACUGdTdT	2694
AD-61999.1	CAAUUGUUUCAGCUUUGAAdTdT	2128	3650-3668	UUCAAAGCUGAAACAAUUGdTdT	2695
AD-62005.1	CUUUGAAGAGAGAAGCUUUdTdT	2129	3662-3680	AAAGCUUCUCUCUUCAAAGdTdT	2696
AD-62011.1	GAGAGAAGCUUUGGUUAAAdTdT	2130	3669-3687	UUUAACCAAAGCUUCUCUCdTdT	2697
AD-61970.1	GUUAAAGGUAAUCCACCCAdTdT	2131	3682-3700	UGGGUGGAUUACCUUUAACdTdT	2698
AD-61976.1	AAUCCACCCAUUUAUCGUUdTdT	2132	3691-3709	AACGAUAAAUGGGUGGAUUdTdT	2699
AD-61982.1	CAUUUAUCGUUUUUGGAAAdTdT	2133	3699-3717	UUUCCAAAAACGAUAAAUGdTdT	2700
AD-61988.1	UUUGGAAAGACAAUCUUCAdTdT	2134	3710-3728	UGAAGAUUGUCUUUCCAAAdTdT	2701
AD-61994.1	AAUCUUCAGCAUAAAGACAdTdT	2135	3721-3739	UGUCUUUAUGCUGAAGAUUdTdT	2702
AD-62006.1	CUCUGUACCUAACACUGGUdTdT	2136	3741-3759	ACCAGUGUUAGGUACAGAGdTdT	2703
AD-62012.1	ACACUGGUACGGCACGUAUdTdT	2137	3752-3770	AUACGUGCCGUACCAGUGUdTdT	2704
AD-61971.1	GGCACGUAUGGUAGAAACAdTdT	2138	3762-3780	UGUUUCUACCAUACGUGCCdTdT	2705
AD-61977.1	GGUAGAAACAACUGCCUAUdTdT	2139	3771-3789	AUAGGCAGUUGUUUCUACCdTdT	2706
AD-61983.1	CAACUGCCUAUGCUUUACUdTdT	2140	3779-3797	AGUAAAGCAUAGGCAGUUGdTdT	2707

AD-61989.1	CUUUACUCACCAGUCUGAAdTdT	2141	3791-3809	UUCAGACUGGUGAGUAAAGdTdT	2708
AD-61995.1	GUCUGAACUUGAAAGAUAUdTdT	2142	3803-3821	AUAUCUUUCAAGUUCAGACdTdT	2709
AD-62001.1	ACUUGAAAGAUAUAAAUUAdTdT	2143	3809-3827	UAAUUUAUAUCUUUCAAGUdTdT	2710
AD-62007.1	UAUAAAUUAUGUUAACCCAdTdT	2144	3819-3837	UGGGUUAACAUAAUUUAUAdTdT	2711
AD-62013.1	GUUAACCCAGUCAUCAAAUdTdT	2145	3829-3847	AUUUGAUGACUGGGUUAACdTdT	2712
AD-61972.1	UCAUCAAAUGGCUAUCAGAdTdT	2146	3839-3857	UCUGAUAGCCAUUUGAUGAdTdT	2713
AD-61978.1	UAUCAGAAGAGCAGAGGUAdTdT	2147	3851-3869	UACCUCUGCUCUUCUGAUAdTdT	2714
AD-61984.1	AGAGGUAUGGAGGUGGCUUdTdT	2148	3863-3881	AAGCCACCUCCAUACCUCUdTdT	2715
AD-61990.1	GAGGUGGCUUUUAUUCAACdTdT	2149	3872-3890	GUUGAAUAAAAGCCACCUCdTdT	2716
AD-61996.1	UAUUCAACCCAGGACACAAdTdT	2150	3883-3901	UUGUGUCCUGGGUUGAAUAdTdT	2717
AD-62002.1	AGGACACAAUCAAUGCCAUdTdT	2151	3893-3911	AUGGCAUUGAUUGUGUCCUdTdT	2718
AD-62008.1	CAAUCAAUGCCAUUGAGGGdTdT	2152	3899-3917	CCCUCAAUGGCAUUGAUUGdTdT	2719
AD-62014.1	CAUUGAGGGCCUGACGGAAdTdT	2153	3909-3927	UUCCGUCAGGCCCUCAAUGdTdT	2720
AD-61973.1	ACGGAAUAUUCACUCCUGGdTdT	2154	3922-3940	CCAGGAGUGAAUAUUCCGUdTdT	2721
AD-61979.1	UUCACUCCUGGUUAAACAAdTdT	2155	3930-3948	UUGUUUAACCAGGAGUGAAdTdT	2722
AD-61985.1	GGUUAAACAACUCCGCUUGdTdT	2156	3939-3957	CAAGCGGAGUUGUUUAACCdTdT	2723
AD-61991.1	CCGCUUGAGUAUGGACAUCdTdT	2157	3951-3969	GAUGUCCAUACUCAAGCGGdTdT	2724
AD-61997.1	GGACAUCGAUGUUUCUUACdTdT	2158	3963-3981	GUAAGAAACAUCGAUGUCCdTdT	2725
AD-62003.1	CGAUGUUUCUUACAAGCAUdTdT	2159	3969-3987	AUGCUUGUAAGAAACAUCGdTdT	2726
AD-62009.1	CAAGCAUAAAGGUGCCUUAdTdT	2160	3981-3999	UAAGGCACCUUUAUGCUUGdTdT	2727
AD-62056.1	GUGCCUUACAUAAUUAUAAdTdT	2161	3992-4010	UUAUAAUUAUGUAAGGCACdTdT	2728
AD-62015.1	ACAUAAUUAUAAAAUGACAdTdT	2162	3999-4017	UGUCAUUUUAUAAUUAUGUdTdT	2729
AD-62021.1	AAAAUGACAGACAAGAAUUdTdT	2163	4009-4027	AAUUCUUGUCUGUCAUUUUdTdT	2730
AD-62027.1	CAAGAAUUUCCUUGGGAGGdTdT	2164	4020-4038	CCUCCCAAGGAAAUUCUUGdTdT	2731
AD-62033.1	CCUUGGGAGGCCAGUAGAGdTdT	2165	4029-4047	CUCUACUGGCCUCCCAAGGdTdT	2732
AD-62039.1	AGUAGAGGUGCUUCUCAAUdTdT	2166	4041-4059	AUUGAGAAGCACCUCUACUdTdT	2733
AD-62045.1	CUUCUCAAUGAUGACCUCAdTdT	2167	4051-4069	UGAGGUCAUCAUUGAGAAGdTdT	2734

AD-62051.1	UGACCUCAUUGUCAGUACAdTdT	2168	4062-4080	UGUACUGACAAUGAGGUCAdTdT	2735
AD-62057.1	GUCAGUACAGGAUUUGGCAdTdT	2169	4072-4090	UGCCAAAUCCUGUACUGACdTdT	2736
AD-62016.1	AGGAUUUGGCAGUGGCUUGdTdT	2170	4080-4098	CAAGCCACUGCCAAAUCCUdTdT	2737
AD-62022.1	UGGCUUGGCUACAGUACAUdTdT	2171	4092-4110	AUGUACUGUAGCCAAGCCAdTdT	2738
AD-62028.1	GCUACAGUACAUGUAACAAdTdT	2172	4099-4117	UUGUUACAUGUACUGUAGCdTdT	2739
AD-62034.1	AACAACUGUAGUUCACAAAdTdT	2173	4113-4131	UUUGUGAACUACAGUUGUUdTdT	2740
AD-62040.1	GUAGUUCACAAAACCAGUAdTdT	2174	4120-4138	UACUGGUUUUGUGAACUACdTdT	2741
AD-62046.1	AAACCAGUACCUCUGAGGAdTdT	2175	4130-4148	UCCUCAGAGGUACUGGUUUdTdT	2742
AD-62052.1	UGAGGAAGUUUGCAGCUUUdTdT	2176	4143-4161	AAAGCUGCAAACUUCCUCAdTdT	2743
AD-62058.1	UGCAGCUUUUAUUUGAAAAdTdT	2177	4153-4171	UUUUCAAAUAAAAGCUGCAdTdT	2744
AD-62017.1	AUUUGAAAAUCGAUACUCAdTdT	2178	4163-4181	UGAGUAUCGAUUUUCAAAUdTdT	2745
AD-62023.1	CGAUACUCAGGAUAUUGAAdTdT	2179	4173-4191	UUCAAUAUCCUGAGUAUCGdTdT	2746
AD-62029.1	GGAUAUUGAAGCAUCCCACdTdT	2180	4182-4200	GUGGGAUGCUUCAAUAUCCdTdT	2747
AD-62035.1	GAAGCAUCCCACUACAGAGdTdT	2181	4189-4207	CUCUGUAGUGGGAUGCUUCdTdT	2748
AD-62041.1	ACUACAGAGGCUACGGAAAdTdT	2182	4199-4217	UUUCCGUAGCCUCUGUAGUdTdT	2749
AD-62047.1	CGGAAACUCUGAUUACAAAdTdT	2183	4212-4230	UUUGUAAUCAGAGUUUCCGdTdT	2750
AD-62053.1	UGAUUACAAACGCAUAGUAdTdT	2184	4221-4239	UACUAUGCGUUUGUAAUCAdTdT	2751
AD-62059.1	GCAUAGUAGCAUGUGCCAGdTdT	2185	4232-4250	CUGGCACAUGCUACUAUGCdTdT	2752
AD-62018.1	GCAUGUGCCAGCUACAAGCdTdT	2186	4240-4258	GCUUGUAGCUGGCACAUGCdTdT	2753
AD-62024.1	CUACAAGCCCAGCAGGGAAdTdT	2187	4251-4269	UUCCCUGCUGGGCUUGUAGdTdT	2754
AD-62030.1	CAGCAGGGAAGAAUCAUCAdTdT	2188	4260-4278	UGAUGAUUCUUCCCUGCUGdTdT	2755
AD-62036.1	GAAUCAUCAUCUGGAUCCUdTdT	2189	4270-4288	AGGAUCCAGAUGAUGAUUCdTdT	2756
AD-62042.1	GAUCCUCUCAUGCGGUGAUdTdT	2190	4283-4301	AUCACCGCAUGAGAGGAUCdTdT	2757
AD-62048.1	CUCAUGCGGUGAUGGACAUdTdT	2191	4289-4307	AUGUCCAUCACCGCAUGAGdTdT	2758
AD-62054.1	GAUGGACAUCUCCUUGCCUdTdT	2192	4299-4317	AGGCAAGGAGAUGUCCAUCdTdT	2759
AD-62060.1	CUUGCCUACUGGAAUCAGUdTdT	2193	4311-4329	ACUGAUUCCAGUAGGCAAGdTdT	2760
AD-62019.1	GAAUCAGUGCAAAUGAAGAdTdT	2194	4322-4340	UCUUCAUUUGCACUGAUUCdTdT	2761

AD-62025.1	AAAUGAAGAAGACUUAAAAdTdT	2195	4332-4350	UUUUAAGUCUUCUUCAUUUdTdT	2762
AD-62031.1	GAAGACUUAAAAGCCCUUGdTdT	2196	4339-4357	CAAGGGCUUUUAAGUCUUCdTdT	2763
AD-62037.1	CCUUGUGGAAGGGGUGGAUdTdT	2197	4353-4371	AUCCACCCCUUCCACAAGGdTdT	2764
AD-62043.1	GAAGGGGUGGAUCAACUAUdTdT	2198	4360-4378	AUAGUUGAUCCACCCCUUCdTdT	2765
AD-62049.1	AUCAACUAUUCACUGAUUAdTdT	2199	4370-4388	UAAUCAGUGAAUAGUUGAUdTdT	2766
AD-62055.1	CACUGAUUACCAAAUCAAAdTdT	2200	4380-4398	UUUGAUUUGGUAAUCAGUGdTdT	2767
AD-62061.1	AUCAAAGAUGGACAUGUUAdTdT	2201	4393-4411	UAACAUGUCCAUCUUUGAUdTdT	2768
AD-62020.1	GGACAUGUUAUUCUGCAACdTdT	2202	4402-4420	GUUGCAGAAUAACAUGUCCdTdT	2769
AD-62026.1	UCUGCAACUGAAUUCGAUUdTdT	2203	4413-4431	AAUCGAAUUCAGUUGCAGAdTdT	2770
AD-62032.1	GAAUUCGAUUCCCUCCAGUdTdT	2204	4422-4440	ACUGGAGGGAAUCGAAUUCdTdT	2771
AD-62038.1	CCCUCCAGUGAUUUCCUUUdTdT	2205	4432-4450	AAAGGAAAUCACUGGAGGGdTdT	2772
AD-62044.1	GAUUUCCUUUGUGUACGAUdTdT	2206	4441-4459	AUCGUACACAAAGGAAAUCdTdT	2773
AD-62050.1	GUACGAUUCCGGAUAUUUGdTdT	2207	4453-4471	CAAAUAUCCGGAAUCGUACdTdT	2774
AD-62320.1	CGGAUAUUUGAACUCUUUGdTdT	2208	4462-4480	CAAAGAGUUCAAAUAUCCGdTdT	2775
AD-62326.1	ACUCUUUGAAGUUGGGUUUdTdT	2209	4473-4491	AAACCCAACUUCAAAGAGUdTdT	2776
AD-62332.1	AGUUGGGUUUCUCAGUCCUdTdT	2210	4482-4500	AGGACUGAGAAACCCAACUdTdT	2777
AD-62338.1	UUCUCAGUCCUGCCACUUUdTdT	2211	4490-4508	AAAGUGGCAGGACUGAGAAdTdT	2778
AD-62344.1	CACUUUCACAGUGUACGAAdTdT	2212	4503-4521	UUCGUACACUGUGAAAGUGdTdT	2779
AD-62350.1	CACAGUGUACGAAUACCACdTdT	2213	4509-4527	GUGGUAUUCGUACACUGUGdTdT	2780
AD-62356.1	ACCACAGACCAGAUAAACAdTdT	2214	4523-4541	UGUUUAUCUGGUCUGUGGUdTdT	2781
AD-62362.1	CCAGAUAAACAGUGUACCAdTdT	2215	4531-4549	UGGUACACUGUUUAUCUGGdTdT	2782
AD-62321.1	CAGUGUACCAUGUUUUAUAdTdT	2216	4540-4558	UAUAAAACAUGGUACACUGdTdT	2783
AD-62327.1	GUUUUAUAGCACUUCCAAUdTdT	2217	4551-4569	AUUGGAAGUGCUAUAAAACdTdT	2784
AD-62333.1	CUUCCAAUAUCAAAAUUCAdTdT	2218	4562-4580	UGAAUUUUGAUAUUGGAAGdTdT	2785
AD-62339.1	AUCAAAAUUCAGAAAGUCUdTdT	2219	4570-4588	AGACUUUCUGAAUUUUGAUdTdT	2786
AD-62345.1	GAAAGUCUGUGAAGGAGCCdTdT	2220	4581-4599	GGCUCCUUCACAGACUUUCdTdT	2787
AD-62351.1	GAAGGAGCCGCGUGCAAGUdTdT	2221	4591-4609	ACUUGCACGCGGCUCCUUCdTdT	2788

AD-62357.1	CGUGCAAGUGUGUAGAAGCdTdT	2222	4601-4619	GCUUCUACACACUUGCACGdTdT	2789
AD-62363.1	GUAGAAGCUGAUUGUGGGCdTdT	2223	4612-4630	GCCCACAAUCAGCUUCUACdTdT	2790
AD-62322.1	CUGAUUGUGGGCAAAUGCAdTdT	2224	4619-4637	UGCAUUUGCCCACAAUCAGdTdT	2791
AD-62328.1	GCAAAUGCAGGAAGAAUUGdTdT	2225	4629-4647	CAAUUCUUCCUGCAUUUGCdTdT	2792
AD-62334.1	GAAGAAUUGGAUCUGACAAdTdT	2226	4639-4657	UUGUCAGAUCCAAUUCUUCdTdT	2793
AD-62340.1	CUGACAAUCUCUGCAGAGAdTdT	2227	4651-4669	UCUCUGCAGAGAUUGUCAGdTdT	2794
AD-62346.1	GCAGAGACAAGAAAACAAAdTdT	2228	4663-4681	UUUGUUUUCUUGUCUCUGCdTdT	2795
AD-62352.1	CAAGAAAACAAACAGCAUGdTdT	2229	4670-4688	CAUGCUGUUUGUUUUCUUGdTdT	2796
AD-62358.1	ACAGCAUGUAAACCAGAGAdTdT	2230	4681-4699	UCUCUGGUUUACAUGCUGUdTdT	2797
AD-62364.1	CCAGAGAUUGCAUAUGCUUdTdT	2231	4693-4711	AAGCAUAUGCAAUCUCUGGdTdT	2798
AD-62323.1	GCAUAUGCUUAUAAAGUUAdTdT	2232	4702-4720	UAACUUUAUAAGCAUAUGCdTdT	2799
AD-62329.1	UUAUAAAGUUAGCAUCACAdTdT	2233	4710-4728	UGUGAUGCUAACUUUAUAAdTdT	2800
AD-62335.1	CAUCACAUCCAUCACUGUAdTdT	2234	4722-4740	UACAGUGAUGGAUGUGAUGdTdT	2801
AD-62341.1	UCACUGUAGAAAAUGUUUUdTdT	2235	4733-4751	AAAACAUUUUCUACAGUGAdTdT	2802
AD-62347.1	AGAAAAUGUUUUUGUCAAGdTdT	2236	4740-4758	CUUGACAAAAACAUUUUCUdTdT	2803
AD-62353.1	UUUGUCAAGUACAAGGCAAdTdT	2237	4750-4768	UUGCCUUGUACUUGACAAAdTdT	2804
AD-62359.1	AGGCAACCCUUCUGGAUAUdTdT	2238	4763-4781	AUAUCCAGAAGGGUUGCCUdTdT	2805
AD-62365.1	CCUUCUGGAUAUCUACAAAdTdT	2239	4770-4788	UUUGUAGAUAUCCAGAAGGdTdT	2806
AD-62324.1	UAUCUACAAAACUGGGGAAdTdT	2240	4779-4797	UUCCCCAGUUUUGUAGAUAdTdT	2807
AD-62330.1	CUGGGGAAGCUGUUGCUGAdTdT	2241	4790-4808	UCAGCAACAGCUUCCCCAGdTdT	2808
AD-62336.1	CUGUUGCUGAGAAAGACUCdTdT	2242	4799-4817	GAGUCUUUCUCAGCAACAGdTdT	2809
AD-62342.1	GACUCUGAGAUUACCUUCAdTdT	2243	4813-4831	UGAAGGUAAUCUCAGAGUCdTdT	2810
AD-62348.1	GAGAUUACCUUCAUUAAAAdTdT	2244	4819-4837	UUUUAAUGAAGGUAAUCUCdTdT	2811
AD-62354.1	AUUAAAAAGGUAACCUGUAdTdT	2245	4831-4849	UACAGGUUACCUUUUUAAUdTdT	2812
AD-62360.1	UAACCUGUACUAACGCUGAdTdT	2246	4841-4859	UCAGCGUUAGUACAGGUUAdTdT	2813
AD-62366.1	CUAACGCUGAGCUGGUAAAdTdT	2247	4850-4868	UUUACCAGCUCAGCGUUAGdTdT	2814
AD-62325.1	GGUAAAAGGAAGACAGUACdTdT	2248	4863-4881	GUACUGUCUUCCUUUUACCdTdT	2815

AD-62331.1	GAAGACAGUACUUAAUUAUdTdT	2249	4871-4889	AUAAUUAAGUACUGUCUUCdTdT	2816
AD-62337.1	CUUAAUUAUGGGUAAAGAAdTdT	2250	4881-4899	UUCUUUACCCAUAAUUAAGdTdT	2817
AD-62343.1	UAAAGAAGCCCUCCAGAUAdTdT	2251	4893-4911	UAUCUGGAGGGCUUCUUUAdTdT	2818
AD-62349.1	CCUCCAGAUAAAAUACAAUdTdT	2252	4902-4920	AUUGUAUUUUAUCUGGAGGdTdT	2819
AD-62355.1	AAAUACAAUUUCAGUUUCAdTdT	2253	4912-4930	UGAAACUGAAAUUGUAUUUdTdT	2820
AD-62361.1	CAGUUUCAGGUACAUCUACdTdT	2254	4923-4941	GUAGAUGUACCUGAAACUGdTdT	2821
AD-62367.1	GGUACAUCUACCCUUUAGAdTdT	2255	4931-4949	UCUAAAGGGUAGAUGUACCdTdT	2822
AD-62373.1	CCUUUAGAUUCCUUGACCUdTdT	2256	4942-4960	AGGUCAAGGAAUCUAAAGGdTdT	2823
AD-62379.1	CCUUGACCUGGAUUGAAUAdTdT	2257	4952-4970	UAUUCAAUCCAGGUCAAGGdTdT	2824
AD-62385.1	GGAUUGAAUACUGGCCUAGdTdT	2258	4961-4979	CUAGGCCAGUAUUCAAUCCdTdT	2825
AD-62391.1	CUGGCCUAGAGACACAACAdTdT	2259	4971-4989	UGUUGUGUCUCUAGGCCAGdTdT	2826
AD-62397.1	GAGACACAACAUGUUCAUCdTdT	2260	4979-4997	GAUGAACAUGUUGUGUCUCdTdT	2827
AD-62403.1	GUUCAUCGUGUCAAGCAUUdTdT	2261	4991-5009	AAUGCUUGACACGAUGAACdTdT	2828
AD-62409.1	GUCAAGCAUUUUUAGCUAAdTdT	2262	5000-5018	UUAGCUAAAAAAUGCUUGACdTdT	2829
AD-62368.1	AGCUAAUUUAGAUGAAUUUdTdT	2263	5013-5031	AAAUUCAUCUAAAUUAGCUdTdT	2830
AD-62374.1	AGAUGAAUUUGCCGAAGAUdTdT	2264	5022-5040	AUCUUCGGCAAAUUCAUCUdTdT	2831
AD-62380.1	CCGAAGAUAUCUUUUUAAAdTdT	2265	5033-5051	UUUAAAAAGAUAUCUUCGGdTdT	2832
AD-62386.1	CUUUUUAAAUGGAUGCUAAdTdT	2266	5043-5061	UUAGCAUCCAUUUAAAAAGdTdT	2833
AD-62392.1	GGAUGCUAAAAUUCCUGAAdTdT	2267	5053-5071	UUCAGGAAUUUUAGCAUCCdTdT	2834
AD-62398.1	UAAAAUUCCUGAAGUUCAGdTdT	2268	5059-5077	CUGAACUUCAGGAAUUUUAdTdT	2835
AD-62404.1	AGUUCAGCUGCAUACAGUUdTdT	2269	5071-5089	AACUGUAUGCAGCUGAACUdTdT	2836
AD-62410.1	GCAUACAGUUUGCACUUAUdTdT	2270	5080-5098	AUAAGUGCAAACUGUAUGCdTdT	2837
AD-62369.1	ACUUAUGGACUCCUGUUGUdTdT	2271	5093-5111	ACAACAGGAGUCCAUAAGUdTdT	2838
AD-62375.1	GGACUCCUGUUGUUGAAGUdTdT	2272	5099-5117	ACUUCAACAACAGGAGUCCdTdT	2839
AD-62381.1	UGUUGAAGUUCGUUUUUUUdTdT	2273	5109-5127	AAAAAAACGAACUUCAACAdTdT	2840
AD-62387.1	UUUUUUGUUUUCUUCUUUUdTdT	2274	5122-5140	AAAAGAAGAAAACAAAAAAdTdT	2841
AD-62393.1	UCUUCUUUUUUUAAACAUUdTdT	2275	5132-5150	AAUGUUUAAAAAAAGAAGAdTdT	2842

AD-62399.1	UUUUUAAACAUUCAUAGCUdTdT	2276	5139-5157	AGCUAUGAAUGUUUAAAAAdTdT	2843
AD-62405.1	AUAGCUGGUCUUAUUUGUAdTdT	2277	5152-5170	UACAAAUAAGACCAGCUAUdTdT	2844
AD-62411.1	GUCUUAUUUGUAAAGCUCAdTdT	2278	5159-5177	UGAGCUUUACAAAUAAGACdTdT	2845
AD-62370.1	AAAGCUCACUUUACUUAGAdTdT	2279	5170-5188	UCUAAGUAAAGUGAGCUUUdTdT	2846
AD-62376.1	ACUUAGAAUUAGUGGCACUdTdT	2280	5182-5200	AGUGCCACUAAUUCUAAGUdTdT	2847
AD-62382.1	AGUGGCACUUGCUUUUAUUdTdT	2281	5192-5210	AAUAAAAGCAAGUGCCACUdTdT	2848
AD-62388.1	GCUUUUAUUAGAGAAUGAUdTdT	2282	5202-5220	AUCAUUCUCUAAUAAAAGCdTdT	2849
AD-62394.1	GAGAAUGAUUUCAAAUGCUdTdT	2283	5212-5230	AGCAUUUGAAAUCAUUCUCdTdT	2850
AD-62400.1	UUUCAAAUGCUGUAACUUUdTdT	2284	5220-5238	AAAGUUACAGCAUUUGAAAdTdT	2851
AD-62406.1	GUAACUUUCUGAAAUAACAdTdT	2285	5231-5249	UGUUAUUUCAGAAAGUUACdTdT	2852
AD-62412.1	GAAAUAACAUGGCCUUGGAdTdT	2286	5241-5259	UCCAAGGCCAUGUUAUUUCdTdT	2853
AD-62371.1	CCUUGGAGGGCAUGAAGACdTdT	2287	5253-5271	GUCUUCAUGCCCUCCAAGGdTdT	2854
AD-62377.1	AGGGCAUGAAGACAGAUACdTdT	2288	5259-5277	GUAUCUGUCUUCAUGCCCUdTdT	2855
AD-62383.1	GAUACUCCUCCAAGGUUAUdTdT	2289	5273-5291	AUAACCUUGGAGGAGUAUCdTdT	2856
AD-62389.1	CCUCCAAGGUUAUUGGACAdTdT	2290	5279-5297	UGUCCAAUAACCUUGGAGGdTdT	2857
AD-62395.1	GGACACCGGAAACAAUAAAdTdT	2291	5293-5311	UUUAUUGUUUCCGGUGUCCdTdT	2858
AD-62401.1	GAAACAAUAAAUUGGAACAdTdT	2292	5301-5319	UGUUCCAAUUUAUUGUUUCdTdT	2859
AD-62407.1	AUUGGAACACCUCCUCAAAdTdT	2293	5311-5329	UUUGAGGAGGUGUUCCAAUdTdT	2860
AD-62413.1	UCCUCAAACCUACCACUCAdTdT	2294	5322-5340	UGAGUGGUAGGUUUGAGGAdTdT	2861
AD-62372.1	CUACCACUCAGGAAUGUUUdTdT	2295	5331-5349	AAACAUUCCUGAGUGGUAGdTdT	2862
AD-62378.1	AAUGUUUGCUGGGGCCGAAdTdT	2296	5343-5361	UUCGGCCCCAGCAAACAUUdTdT	2863
AD-62384.1	UGCUGGGGCCGAAAGAACAdTdT	2297	5349-5367	UGUUCUUUCGGCCCCAGCAdTdT	2864
AD-62390.1	AAAGAACAGUCCAUUGAAAdTdT	2298	5360-5378	UUUCAAUGGACUGUUCUUUdTdT	2865
AD-62396.1	CAUUGAAAGGGAGUAUUACdTdT	2299	5371-5389	GUAAUACUCCCUUUCAAUGdTdT	2866
AD-62402.1	GGAGUAUUACAAAAACAUGdTdT	2300	5380-5398	CAUGUUUUUGUAAUACUCCdTdT	2867
AD-62408.1	AAAACAUGGCCUUUGCUUGdTdT	2301	5391-5409	CAAGCAAAGGCCAUGUUUUdTdT	2868
AD-62414.1	GCCUUUGCUUGAAAGAAAAdTdT	2302	5399-5417	UUUUCUUUCAAGCAAAGGCdTdT	2869

AD-62415.1	GAAAGAAAAUACCAAGGAAdTdT	2303	5409-5427	UUCCUUGGUAUUUUCUUUCdTdT	2870
AD-62416.1	CCAAGGAACAGGAAACUGAdTdT	2304	5420-5438	UCAGUUUCCUGUUCCUUGGdTdT	2871
AD-62417.1	AACUGAUCAUUAAAGCCUGdTdT	2305	5433-5451	CAGGCUUUAAUGAUCAGUUdTdT	2872

Table 22. C5 single dose screen (10mM) in Hep3B cells with dT modified iRNAs

Duplex ID	Avg. % message remaining
AD-61779.2	43.2
AD-61785.2	22.5
AD-61791.2	27.3
AD-61797.2	30.5
AD-61803.2	30.9
AD-61809.2	75.1
AD-61815.2	90.7
AD-61821.2	33.7
AD-61780.2	53.5
AD-61786.2	34.4
AD-61792.2	27.5
AD-61798.2	23.3
AD-61804.2	23.6
AD-61810.2	33.4
AD-61816.2	39.7
AD-61822.2	24.9
AD-61781.2	31.2
AD-61787.2	22.8
AD-61793.2	28.4
AD-61799.2	91
AD-61805.2	22.1
AD-61811.2	90.9
AD-61817.2	26.1
AD-61823.2	41.3
AD-61782.2	42.5
AD-61788.2	28.9
AD-61794.2	133.5
AD-61800.2	27.9
AD-61806.2	42.8
AD-61812.2	26.9
AD-61818.2	30.6

AD-61824.2	29.3
AD-61783.2	61.3
AD-61789.2	25.5
AD-61795.2	34.2
AD-61801.2	24.2
AD-61807.2	42.8
AD-61813.2	31
AD-61819.2	42.2
AD-61825.2	31
AD-61784.2	34.1
AD-61790.2	26.8
AD-61796.2	34.6
AD-61802.2	30
AD-61808.2	23.5
AD-61814.2	45.3
AD-61820.2	56
AD-61826.2	31.6
AD-61832.2	36.2
AD-61838.2	39.7
AD-61844.2	37
AD-61850.2	66.3
AD-61856.2	172.6
AD-61862.2	41.3
AD-61868.2	32.2
AD-61827.2	52.7
AD-61833.2	29.6
AD-61839.2	41.5
AD-61845.2	29.7
AD-61851.2	37
AD-61857.2	34.9
AD-61863.2	33.3
AD-61869.2	38.2
AD-61828.2	30.3
AD-61834.2	27.1

AD-61840.2	64.3
AD-61846.2	42
AD-61852.2	25.2
AD-61858.2	96.7
AD-61864.2	29.6
AD-61870.2	30.5
AD-61829.2	92.7
AD-61835.2	24.8
AD-61841.2	59.2
AD-61847.2	30.9
AD-61853.2	35.2
AD-61859.2	40.1
AD-61865.2	42.3
AD-61871.2	55.8
AD-61830.2	162.9
AD-61836.2	28.8
AD-61842.2	18.2
AD-61848.2	25
AD-61854.2	42.3
AD-61860.2	41.7
AD-61866.2	28.9
AD-61872.2	64.7
AD-61831.2	16.9
AD-61837.2	24.9
AD-61843.2	27.5
AD-61849.2	25.8
AD-61855.2	20
AD-61861.2	28.6
AD-61867.2	18
AD-62062.1	22
AD-62068.1	29.9
AD-62074.1	40.2
AD-62080.1	30.4
AD-62086.1	21

AD-62092.1	20
AD-62098.1	38.4
AD-62104.1	42.7
AD-62063.1	26.6
AD-62069.1	55.6
AD-62075.1	114.4
AD-62081.1	21.2
AD-62087.1	33.8
AD-62093.1	26.3
AD-62099.1	23.9
AD-62105.1	30.1
AD-62064.1	32
AD-62070.1	135.7
AD-62076.1	84.3
AD-62082.1	42.3
AD-62088.1	36.5
AD-62094.1	66
AD-62100.1	66.4
AD-62106.1	33.9
AD-62065.1	33
AD-62071.1	38.4
AD-62077.1	27.8
AD-62083.1	44.7
AD-62089.1	42.7
AD-62095.1	46.6
AD-62101.1	35.3
AD-62107.1	29.9
AD-62066.1	33.5
AD-62072.1	27.5
AD-62078.1	49.9
AD-62084.1	117.6
AD-62090.1	44
AD-62096.1	33.5
AD-62102.1	39.2

AD-62108.1	69.5
AD-62067.1	32.3
AD-62073.1	81.1
AD-62079.1	46.8
AD-62085.1	31.6
AD-62091.1	32
AD-62097.1	35.3
AD-62103.1	35.6
AD-62109.1	24.7
AD-62115.1	25.7
AD-62121.1	23.1
AD-62127.1	36.3
AD-62133.1	50.9
AD-62139.1	84.1
AD-62145.1	90.8
AD-62151.1	56.9
AD-62110.1	26
AD-62116.1	145.5
AD-62122.1	198.7
AD-62128.1	178.4
AD-62134.1	52.4
AD-62140.1	55.6
AD-62146.1	47.2
AD-62152.1	16.4
AD-62111.1	49.3
AD-62117.1	46.2
AD-62123.1	95.1
AD-62129.1	156.2
AD-62135.1	62
AD-62141.1	128.1
AD-62147.1	146.2
AD-62153.1	35.5
AD-62112.1	43
AD-62118.1	32

AD-62124.1	48.4
AD-62130.1	49.4
AD-62136.1	141.9
AD-62142.1	38.7
AD-62148.1	165.2
AD-62154.1	94.7
AD-62113.1	52.5
AD-62119.1	44
AD-62125.1	129.9
AD-62131.1	68.9
AD-62137.1	106
AD-62143.1	176.1
AD-62149.1	201.3
AD-62155.1	143.3
AD-62114.1	22.8
AD-62120.1	34.6
AD-62126.1	44.6
AD-62132.1	39.5
AD-62138.1	34.5
AD-62144.1	28
AD-62150.1	22.1
AD-62156.1	44.1
AD-62162.1	19.8
AD-62168.1	17.3
AD-62174.1	27
AD-62180.1	15.8
AD-62186.1	20.5
AD-62192.1	33.9
AD-62198.1	14
AD-62157.1	19.3
AD-62163.1	15.4
AD-62169.1	23.6
AD-62175.1	29.6
AD-62181.1	26.4

AD-62187.1	28.8
AD-62193.1	22.9
AD-62199.1	16.4
AD-62158.1	18.5
AD-62164.1	19.1
AD-62170.1	15
AD-62176.1	62.7
AD-62182.1	70.8
AD-62188.1	81.1
AD-62194.1	63.6
AD-62200.1	21.6
AD-62159.1	42.8
AD-62165.1	27.7
AD-62171.1	31.9
AD-62177.1	29.6
AD-62183.1	25.2
AD-62189.1	32.7
AD-62195.1	73.1
AD-62201.1	35.6
AD-62160.1	56.5
AD-62166.1	115.1
AD-62172.1	107.4
AD-62178.1	71.3
AD-62184.1	27.2
AD-62190.1	37.2
AD-62196.1	19.5
AD-62202.1	19.4
AD-62161.1	23.7
AD-62167.1	24.4
AD-62173.1	36
AD-62179.1	50.5
AD-62185.1	40.5
AD-62191.1	39.3
AD-62197.1	39.4

AD-62203.1	34.1
AD-62209.1	34.6
AD-62215.1	31
AD-62221.1	16.3
AD-62227.1	68.5
AD-62233.1	34.3
AD-62239.1	37.2
AD-62245.1	31.2
AD-62204.1	33
AD-62210.1	29
AD-62216.1	38.7
AD-62222.1	34.5
AD-62228.1	30.3
AD-62234.1	15.2
AD-62240.1	26.2
AD-62246.1	40.4
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AD-62055.1	24.5
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AD-62026.1	24.9
AD-62032.1	23
AD-62038.1	21.2
AD-62044.1	34.1
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AD-62326.1	16.6
AD-62332.1	15.4
AD-62338.1	41.9

AD-62344.1	19.6
AD-62350.1	32.3
AD-62356.1	20.4
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AD-62321.1	18.7
AD-62327.1	14.8
AD-62333.1	22.2
AD-62339.1	134.5
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AD-62351.1	35.6
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AD-62363.1	28.2
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AD-62328.1	30.1
AD-62334.1	39.1
AD-62340.1	24.3
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AD-62336.1	25.3
AD-62342.1	45.4
AD-62348.1	91.6
AD-62354.1	132.1

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AD-62349.1	37.6
AD-62355.1	38.8
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AD-62383.1	73.8
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AD-62390.1	37.7
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AD-62402.1	31.6
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AD-62415.1	17.6
AD-62416.1	25.3
AD-62417.1	36.3
AD-61779.2	43.2
AD-61785.2	22.5
AD-61791.2	27.3
AD-61797.2	30.5
AD-61803.2	30.9
AD-61809.2	75.1
AD-61815.2	90.7
AD-61821.2	33.7

AD-61780.2	53.5
AD-61786.2	34.4
AD-61792.2	27.5
AD-61798.2	23.3
AD-61804.2	23.6

Example 7: *In Vivo* Screening of Additional siRNAs

Based on the sequence of AD-58643, an additional four sense and three antisense sequences were synthesized and used to prepare twelve, 21/25 mer compounds (Table 23). In general, the antisense strands of these compounds were extended with a dTdT and the duplexes had fewer fluoro-modified nucleotides.

C57BL/6 mice (N=3 per group) were injected subcutaneously with 1 mg/kg of these GalNAc conjugated duplexes, serum was collected on day 0 pre-bleed, and day 5, and the levels of C5 proteins were quantified by ELISA. C5 protein levels were normalized to the day 0 pre-bleed level.

Figure 14 shows the results of an *in vivo* single dose screen with the indicated iRNAs. Data are expressed as percent of C5 protein remaining relative to pre-bleed levels. Those iRNAs having improved efficacy as compared to the parent compound included AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651. These iRNAs also demontsrated similar potencies (IC_{50} of about 23-59 pM).

The efficacy of these iRNAs was also tested in C57Bl/6 mice using a single-dosing administration protocol. Mice were subcutaneously administered AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651 at a 0. 25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, or 2.5 mg/kg dose. Serum was collected at days 0 and 5 and analyzed for C5 protein levels by ELISA. C5 levels were normalized to the day 0 pre-bleed level.

Figure 15 shows that there is a dose response with all of the tested iRNAs and that single-dosing of all of these iRNAs achieved silencing of C5 protein similar to or better than AD-58641.

The duration of silencing of AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651 *in vivo* was determined by administering a single 1.0 mg/kg dose to C57Bl/6 mice and determining the amount of C5 protein present on days 6, 13, 20, 27, and 34 by ELISA. C5 levels were normalized to the day 0 pre-bleed level.

As demonstrated in Figure 16, each of the iRNAs tested has the same recovery kinetics as AD-62643 trending toward the best silencing, but within the error of the assay.

AD-62510, AD-62643, AD-62645, AD-62646, AD-62650, and AD-62651 were further tested for efficacy and to evaluate the cumulative effect of the iRNAs in rats using a repeat administration protocol. Wild-type Sprague Dawley rats were subcutaneously injected with each of the iRNAs at a 5.0 mg/kg/dose on days 0, 4, and 7. Serum was collected on days 0, 4, 7, 11, 14, 18, 25, 28, and 32. Serum hemolytic activity was quantified as described above.

The results depicted in Figure 17 demonstrate that all of the tested iRNAs have a potent and durable decrease in hemolytic activity and a similar recovery of hemolysis to that observed with AD-58641 treatment.

Table 23: Modified Sense and Antisense Strand Sequences of GalNAc-Conjugated C5 dsRNAs.

Duplex ID	sense ID	Sense (5' to 3')	SEQ ID NO:	AS ID	Antisense (5' to 3')	SEQ ID NO:
AD-58643	A-119326.1	AfsasGfcAfaGfaUfAfUfuUfuUfaUfaAfuAfL96	2873	A-119327.1	usAfsuUfaUfaAfaAfauaUfcUfuGfcUfususu	2886
AD-62642	A-125167.7	asasGfcAfaGfaUfAfUfuUfuuAfuAfauaL96	2874	A-125139.1	usAfsuuaUfaAfaAfauaUfcUfuGfcuususudTdT	2887
AD-62510	A-125167.7	asasGfcAfaGfaUfAfUfuUfuuAfuAfauaL96	2875	A-125173.2	usAfsUfuAfuAfAfaAfauaUfcUfuGfcuususudTdT	2888
AD-62643	A-125167.7	asasGfcAfaGfaUfAfUfuUfuuAfuAfauaL96	2876	A-125647.1	usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT	2889
AD-62644	A-125157.17	asasGfcAfaGfaUfAfUfuUfuuAfuaAfuaL96	2877	A-125139.1	usAfsuuaUfaAfaAfauaUfcUfuGfcuususudTdT	2890
AD-62645	A-125157.17	asasGfcAfaGfaUfAfUfuUfuuAfuaAfuaL96	2878	A-125173.2	usAfsUfuAfuAfAfaAfauaUfcUfuGfcuususudTdT	2891
AD-62646	A-125157.17	asasGfcAfaGfaUfAfUfuUfuuAfuaAfuaL96	2879	A-125647.1	usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT	2892
AD-62647	A-125134.1	asasgcaagauaUfuuuua(Tgn)aauaL96	2880	A-125139.1	usAfsuuaUfaAfaAfauaUfcUfuGfcuususudTdT	2893
AD-62648	A-125134.1	asasgcaagauaUfuuuua(Tgn)aauaL96	2881	A-125173.2	usAfsUfuAfuAfAfaAfauaUfcUfuGfcuususudTdT	2894
AD-62649	A-125134.1	asasgcaagauaUfuuuua(Tgn)aauaL96	2882	A-125647.1	usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT	2895
AD-62428	A-125127.2	asasgcaagaUfaUfuuuuauaauaL96	2883	A-125139.1	usAfsuuaUfaAfaAfauaUfcUfuGfcuususudTdT	2896
AD-62650	A-125127.2	asasgcaagaUfaUfuuuuauaauaL96	2884	A-125173.2	usAfsUfuAfuAfAfaAfauaUfcUfuGfcuususudTdT	2897
AD-62651	A-125127.2	asasgcaagaUfaUfuuuuauaauaL96	2885	A-125647.1	usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT	2898

We claim:

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113), and wherein said dsRNA agent comprises at least one modified nucleotide.

2. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 17 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113),

wherein substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, and

wherein said sense strand is conjugated to a ligand attached at the 3'-terminus.

3. The dsRNA agent of claim 2, wherein all of the nucleotides of said sense strand and all of the nucleotides of said antisense strand are modified nucleotides.

4. The dsRNA agent of claim 2, wherein the modified nucleotide is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative or a dodecanoic acid bisdecylamide group.

5. The dsRNA agent of claim 4, wherein the modified nucleotide is a 2'-O-methyl nucleotide or a 2'-fluoro nucleotide.

6. The dsRNA agent of claim 1, wherein the region of complementarity is between 19 and 23 nucleotides in length.

7. The dsRNA agent of claim 1, wherein each strand is no more than 30 nucleotides in length.

8. The dsRNA agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

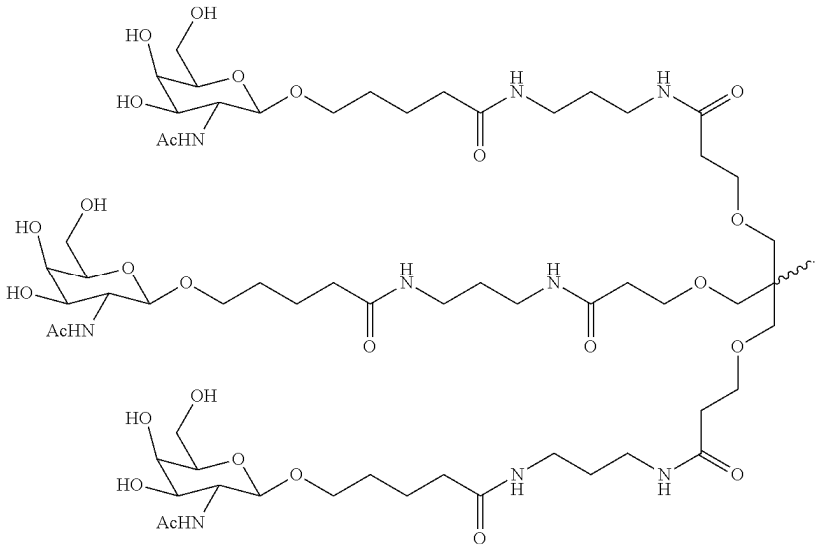
9. The dsRNA agent of claim 1, wherein said agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

10. The dsRNA agent of claim 1, further comprising a ligand.

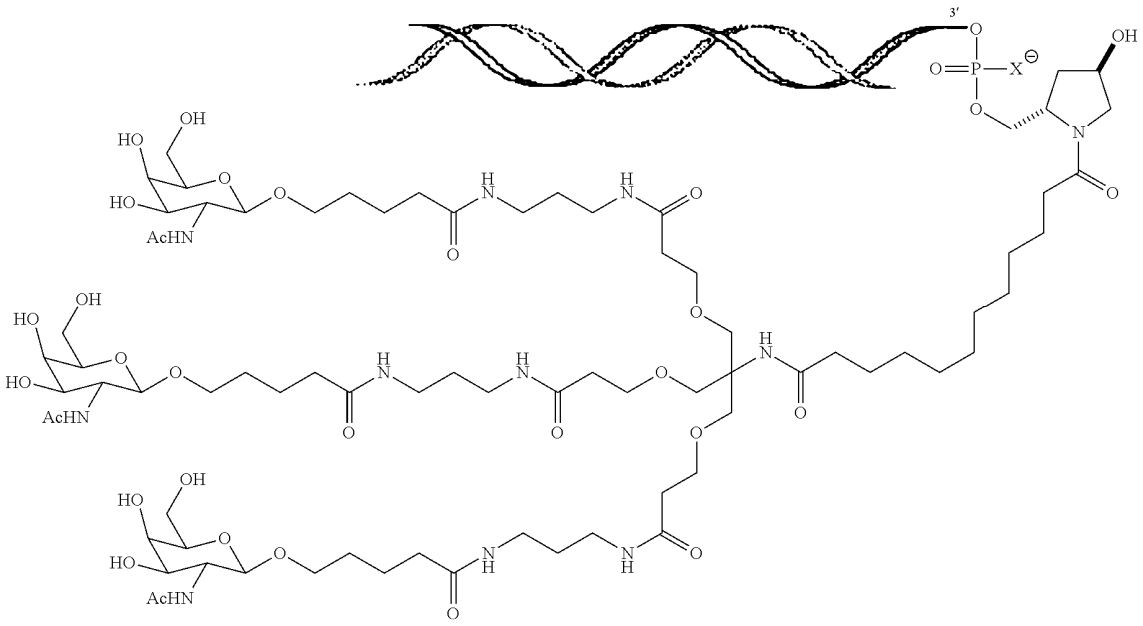
11. The dsRNA agent of claim 10, wherein the ligand is conjugated to the 3' end of the sense strand of the agent.

12. The dsRNA agent of claim 11, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

13. The dsRNA agent of claim 12, wherein the ligand is



14. The dsRNA agent of claim 13, wherein the agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

15. The dsRNA agent of claim 14, wherein the X is O.

16. The dsRNA agent of claim 1, wherein the region of complementarity consists of the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113).

17. The dsRNA agent of claim 1, wherein the agent comprises a sense strand comprising the nucleotide sequence of 5'-AAGCAAGAUAUUUUUAUAAUA-3' (SEQ ID NO:62), and an antisense strand comprising the nucleotide sequence of 5'-UAUUAUAAAAAUAUCUUGCUUUU-3' (SEQ ID NO:113).

18. The dsRNA agent of claim 17, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuususudTdT-3' (SEQ ID NO:2889),

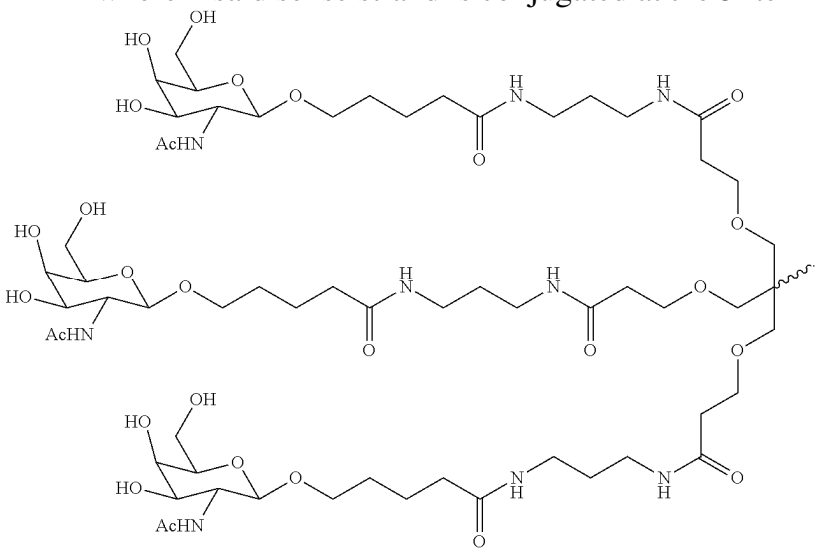
wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage.

19. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement component C5, wherein said dsRNA agent comprises a sense strand and an antisense strand, wherein the sense strand comprises 5'-asasGfcAfaGfaUfAfUfuUfuuAfuAfaua-3' (SEQ ID NO:2876) and the antisense

strand comprises 5'-usAfsUfuAfuaAfaAfauaUfcUfuGfcuusudTdT-3' (SEQ ID NO:2889),

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af, Gf, Cf and Uf are 2'-fluoro A, G, C and U, respectively; dT is a deoxy-thymine nucleotide; and s is a phosphorothioate linkage; and

wherein said sense strand is conjugated at the 3'-terminus to the ligand



20. A cell comprising the dsRNA agent of claim 19.

21. A pharmaceutical composition for inhibiting expression of a complement component C5 gene comprising the dsRNA agent of claim 19.

22. An *in vitro* method of inhibiting complement component C5 expression in a cell, the method comprising: (a) contacting the cell with the dsRNA agent of claim 19; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a complement component C5 gene, thereby inhibiting expression of the complement component C5 gene in the cell.

23. Use of a therapeutically effective amount of the dsRNA agent of claim 19 in the manufacture of a medicament for treating a subject having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

24. The use of claim 23, wherein the disorder is a complement component C5-associated disease.

25. Use of a prophylactically effective amount of the dsRNA agent of claim 19 in

the manufacture of a medicament for preventing at least one symptom in a subject having or prone to having a disease or disorder that would benefit from a reduction in complement component C5 expression, wherein the medicament is to be administered to the subject.

26. The method of claim 22, further comprising contacting the cell with an anti-complement component C5 antibody, or antigen-binding fragment thereof.

27. The use of claim 23, wherein an anti-complement component C5 antibody, or antigen-binding fragment thereof is to be further administered to the subject.

28. The use of claim 25, wherein an anti-complement component C5 antibody, or antigen-binding fragment thereof is to be further administered to the subject.

29. The dsRNA agent of claim 19 for use in therapy.

Abstract

COMPLEMENT COMPONENT C5 IRNA COMPOSITIONS AND METHODS OF USE THEREOF

The invention relates to iRNA, ***e.g.,*** double-stranded ribonucleic acid (dsRNA), compositions targeting the complement component C5 gene, and methods of using such iRNA, ***e.g.,*** dsRNA, compositions to inhibit expression of C5 and to treat subjects having a complement component C5-associated disease, ***e.g.,*** paroxysmal nocturnal hemoglobinuria.

[Figure 1]

<110> ALNYLAM PHARMACEUTICALS, INC.

<120> COMPLEMENT COMPONENT C5 iRNA COMPOSITIONS AND METHODS OF USE THEREOF

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cgcagatagt gccacccatg agtctgcttc agtcaccatg tcaagggaca cagtttggcc 3660

tggagaatac acgtctttat ctggagacag atggacctgg agctggttgc cacacttctc 3720

ctcaatgttt atccagactg cgtcagccac caattctgct gtctgctccc ccgtgactat 3780

gtaatagacc aggagccgcg ctgaaggaac catgtcctgt gtcactggga tgtttatatt 3840

ttgataagat gaatagagaa gtttctcctt tgtgccatac tgtacaattt tgcctttgga 3900

taaaatcaag taattatagt gagttatttt gtcaatatat ggactcttgg gggtgacgat 3960

aatattcaga tattctccca caagcatggg cttgtagttt tcagtccagc caatgtaaat 4020

gtaactctgg ctgagggatg agtatgtaac tgcttcatat tctttgctgg cttgattttc 4080

ttcgggaagt tccggggcat cagttttgac ctcaaacttc agtgatgtca cttctgatgg 4140

gaggttcacc acaaatgaag ccactccatc agcagagtgt gtgatgctcc tctttggttc 4200

caagtcagat gtctcttgat tcacattgac tgtttgtgcc atcagagtta ctgggacccc 4260

tcctaccaac tgctcgagtg aatccttaac ctgtaccttg atggaaaatg gaatcccagg 4320

cttcaggaaa agaggggtag cgaccaaatt cagtgtatag ggagagagga cgtatttgat 4380

gccaggaatt tctgcctctt ccgaaaaccc acctacaagg gcagcaagca ctgagttaat 4440

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<220>
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1 5 10 15

<210> 10
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<212> PRT
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<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 10
Ala Ala Leu Leu Pro Val Leu Leu Ala Ala Pro
1 5 10

<210> 11
<211> 13
<212> PRT
<213> Human immunodeficiency virus

<400> 11
Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 12
<211> 16
<212> PRT
<213> Drosophila sp.

<400> 12
Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

<210> 13
<211> 21
<212> DNA
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<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<220>
<223> Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> 13
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<210> 14
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<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

<220>
<223> Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

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<400> 15
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<210> 16
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<213> Homo sapiens

<400> 16
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<210> 17
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<213> Homo sapiens

<400> 17
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<400> 19
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<400> 26
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<400> 27
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<400> 40
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<400> 47
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<210> 48
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<400> 48
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<210> 49
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<213> Mus musculus

<400> 49
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<210> 50
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<400> 50
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<210> 51
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<400> 51
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<210> 52
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<400> 52
auuuaaacaa caaguaccuu u 21

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<400> 53
auuuaaacaa caaguaccuu u 21

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<400> 57
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<210> 58
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<400> 58
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<210> 59
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<400> 61
ugcagaucaa acacaauuuc a 21

<210> 62
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<400> 62
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<400> 63
aagcaagaua uuuuuauaau a 21

<210> 64
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<400> 64
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<400> 65
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<400> 66
aaguaauuau agugaguuau uuu 23

<210> 67
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<400> 67
uuauagugag uuauuuuguc aau 23

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aaggccaauu uccagaggaa gca 23

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auuauaguga guuauuuugu caa 23

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ugaaggccaa uuuccagagg aag 23

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<400> 71
uauuauaaaa auaucuugcu uuu 23

<210> 72
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<400> 72
uguacuugac aaaaacauuu ucu 23

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<400> 73
aaagguacuu guuguuuaaa ucu 23

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uccuucacag acuuucugaa uuu 23

<210> 75
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<400> 75
uugcaucaaa ugcuucagug uau 23

<210> 76
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<400> 76
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<400> 78
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<400> 79
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<400> 82
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<400> 83
aucaaaugug acuugagcaa uuc 23

<210> 84
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uuuauaagca uaugcaaucu cug 23

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<400> 85
uaaauuuuuu aucaggauaa cuu 23

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uccaauauga ucaauuucuu cua 23

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aacuaaauuu uuuaucagga uaa 23

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<400> 89
uuuacuaaga uuucuuuucc aaa 23

<210> 90
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<400> 90
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<210> 91
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<400> 91
accaaauuca guuuguaggg aga 23

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<400> 94
aaauguucca augauuuccu guu 23

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<400> 95
aguaauuuca aaauucuuaa agu 23

<210> 96
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<400> 96
aucgaauuca guugcagaau aac 23

<210> 97

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<400> 97
ugaaauacuc uuuccaaggg cuu 23

<210> 98
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<400> 98
guaacuaaau uuuuuaucag gau 23

<210> 99
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<400> 99
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<210> 100
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<400> 100
ugaaauugug uuugaucugc aga 23

<210> 101
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<400> 101
acugaaauug uguuugaucu gca 23

<210> 102
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<400> 102
aaaaguucaa auauccggaa ccg 23

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<400> 103
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<210> 104
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<400> 104

aaagguacuu guuguuuaaa ucu 23

<210> 105
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<400> 105
uuauagugag uuauuuuguc aau 23

<210> 106
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<400> 106
uuauagugag uuauuuuguc aau 23

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<400> 107
auuauaguga guuauuuugu caa 23

<210> 108
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<400> 112
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<210> 113
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<400> 113
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<210> 114
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<400> 114
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<210> 115
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<400> 115
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<210> 116
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<400> 116
acugaaauug uguuugaucu gca 23

<210> 117
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<400> 117
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<210> 118
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<210> 119
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<220>
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<400> 119
cuuccucugg aaauuggccu u 21

<210> 120
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<220>
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<400> 120
gacaaaauaa cucacuauaa u 21

<210> 121
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<210> 122
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<400> 122
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<210> 123
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<400> 123
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<210> 124
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<210> 125
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<210> 126
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<220>
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acacugaagc auuugaugca a 21

<210> 127
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<220>
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<400> 127
gcaguucugu guuaaaaugu c 21

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<220>
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<400> 128
aggauuuuga guguaaaagg a 21

<210> 129
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<210> 130
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<210> 131
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<210> 132
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<400> 132
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<210> 133
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<210> 134
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<210> 135
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<220>
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<210> 136
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<220>
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<400> 136
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<210> 137
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<400> 137
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<210> 138
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<400> 138
gaagaaauug aucauauugg a 21

<210> 139
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<400> 139
auccugauaa aaaauuuagu u 21

<210> 140
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<400> 140
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<210> 141
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<220>
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<400> 141
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<210> 142
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<220>
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<400> 142
ucccuacaaa cugaauuugg u 21

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caggagcaaa cauaugucau u 21

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<400> 144
acauguaaca acuguaguuc a 21

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caggaaauca uuggaacauu u 21

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uuuaagaauu uugaaauuac u 21

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<400> 147
uauucugcaa cugaauucga u 21

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<400> 149
ccugauaaaa aauuuaguua c 21

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<210> 1866
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<210> 1867
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<210> 2856
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<400> 2856
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<210> 2862
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<210> 2872
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<400> 2872
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<210> 2873
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<210> 2875
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<210> 2878
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<210> 2879
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