

COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF COMPLEMENT FACTOR B (CFB)

Field of the Invention

5 The invention relates, in part, to compositions and methods that can be used to inhibit a complement factor B (CFB) gene expression.

Background

10 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. The complement system or pathway is part of the innate immune system of host defence against invading pathogens. It mainly consists of more than 30 proteins that are either present as soluble proteins in the blood or are present as membrane-associated proteins.

15 Three main pathways of complement activation have been recognized and are referred to as classical pathway, alternative pathway and lectin pathway. 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
20 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, in maintaining immunologic memory preventing pathogenic reinvasion, and is involved in numerous human pathological states.

25 In functional terms, complement activation occurs inherently at a low level (spontaneous cleavage of C3 to yield C3a and C3b) and is reinforced in the presence of microbes via an enzymatic cascade converting inactive forms of enzymes (zymogenes) into their active counterparts. One type of C3 convertases is a complex of C3b and complement factor B (CFB, Factor B). Once formed, a C3 convertase can convert large amounts of C3 into
30 its cleavage products C3a and C3b within short amount of time. The specific C3 convertase which is a complex of C3b and Factor B has originally been described in the context of the alternative pathway, but may form also in the context of the other two pathways. Within the alternative pathway, Factor B is also a constituent of C5 convertase, a complex which converts C5, a more downstream component of the pathway, into its active form.

35 Complement Factor B (also known as CFB or “factor B”) is involved in activation of the alternative pathway. Binding of CFB to C3b (e.g., on a cell surface) renders CFB susceptible to cleavage by Factor D, forming the serine protease C3Bb, which is itself a C3 convertase, leading to an amplification loop for C3 activation. CFB is primarily synthesised in the liver, as well as in low levels at several extrahepatic sites.

Several diseases are associated with aberrant acquired or genetic activation of the complement pathway as well as with aberrant or over-expression of CFB. for example, C3 glomerulopathy, systemic lupus erythematosus (SLE), Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, rheumatoid arthritis, immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), ischemia/reperfusion injury , antineutrophil cytoplasmic autoantibodies- associated vasculitis (ANCA-AV), dysbiotic periodontal disease, malarial anaemia and hyperlipidemia.

There are currently only few treatments for complement system mediated diseases, disorders and syndromes. The monoclonal humanized antibody Eculizumab is one of them. Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and Myasthenia Gravis, and is currently being evaluated in clinical trials for additional complement component-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a high cost. There is thus a high unmet need for medical treatments of complement mediated or associated diseases. C3 is a pivotal factor in the complement pathway activation. Inhibiting expression of factors such as CFB which are involved in C3 activation therefore presents a promising therapeutic strategy for many complement-mediated diseases. Targeting of CFB expression or activity, e.g., via antisense oligonucleotides, double-stranded siRNAs or small molecule inhibitors targeted to CFB, has been proposed as a potential therapeutic strategy for various complement-mediated conditions.

Accordingly, CFB RNAi agents disclosed herein for for treating diseases, disorders, and conditions associated with complement activation by, for example, activation of complement factor B activity.

Summary of the Invention

In general, the present disclosure features novel CFB gene-specific RNAi agents, compositions that include CFB RNAi agents, and methods for inhibiting expression of a CFB gene in vitro and/or in vivo using the CFB RNAi agents and compositions that include CFB RNAi agents described herein. The CFB RNAi agents described herein can selectively and efficiently decrease, inhibit, or silence expression of a CFB gene in a subject, e.g., a human or animal subject.

According to an aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of

SEQ ID NO: 1, 3 or 5 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 1, 2 or 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, 4 or 6, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

5 In some embodiments, the dsRNA agent includes a sense strand and an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand and
10 an antisense strand forming a double stranded region, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.

In some embodiments, the dsRNA agent including a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand including a region of
15 complementarity to a CFB RNA transcript, wherein the region of complementarity includes at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally including a targeting ligand.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting
20 expression of CFB is provided, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 483-513, 486-516, 491-521, 483-521, 513-543, 987-1017, 989-1019, 1317-1347, 2237-2267, 2439-2469 of SEQ ID NO: 1, and the antisense strand comprises at
25 least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the sense strand comprises at least 15, 16, 17, 18, 19,
30 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 488-508, 491-511, 496-516, 488-516, 518-538, 992-1012, 994-1014, 1322-1342, 2242-2262, 2444-2464 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

35 In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the sense strand comprises at least 15, 16, 17, 18, or

19 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 490-508, 493-511, 498-516, 490-516, 520-538, 994-1012, 996-1014, 1324-1342, 2244-2262, 2446-2464 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In some embodiments, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the sense strand comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 489-507, 492-510, 497-515, 489-515, 519-537, 993-1011, 995-1013, 1323-1341, 2243-2261, 2445-2463 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

In some embodiments, the CFB RNA transcript is SEQ ID NO: 1.

In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the antisense strand of the dsRNA agent is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In certain embodiments, the dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, wherein the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some embodiments, the dsRNA agent includes an antisense strand sequence set forth in any one of Tables 1-3. In some embodiments, the dsRNA agent includes the sequences set forth as a duplex sequence in any of Tables 1-3.

In some embodiments, the dsRNA agent wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

In some embodiments, the dsRNA agent includes at least one modified nucleotide. In certain embodiments, all or substantially all of the nucleotides of the antisense strand are modified nucleotides. In some embodiments, at least one of the modified nucleotides comprises: 2'-O-methyl nucleotide, 2'-fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-Ome nucleotide, inverted 2'-deoxy nucleotide, isomannide nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide including a

5'-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidite, or a non-natural base including nucleotide.

5 In some embodiments, the dsRNA agent includes an E-vinylphosphonate nucleotide at the 5' end of the guide strand.

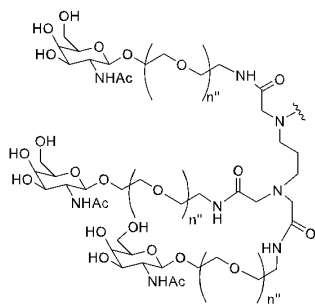
10 In certain embodiments, the dsRNA agent includes at least one phosphorothioate internucleoside linkage. In certain embodiments, the sense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the antisense strand includes at least one phosphorothioate internucleoside linkage. In some embodiments, the sense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand includes 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages. In some embodiments, the 5' end of antisense strand includes 2 phosphorothioate internucleoside linkages. In some embodiments, the 3' end of antisense strand includes 2 phosphorothioate internucleoside linkages. In some embodiments, the 5' end of antisense strand and 3' end of antisense strand includes independently 2 phosphorothioate internucleoside linkages.

15 In some embodiments, all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide, a 2'-fluoro nucleotide and an UNA modified nucleotide, wherein less than 6 modified nucleotides are 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 3 or 5 2'-fluoro nucleotides, preferably, the antisense strand comprises 5 2'-fluoro nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein less than 4 modified nucleotides are 2'-fluoro nucleotides. In certain embodiments, the sense strand comprises 3 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least 14 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 2, 5, 7, 11, 12, 14, 16 and/or 18 counting from the first matching position of the 5' end of the antisense strand are independently a 2'-fluoro nucleotide. In some embodiments, the antisense strand comprises at least one UNA modified nucleotide and 5 2'-fluoro nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 18 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises one UNA modified nucleotide at position 7 and 5 2'-fluoro nucleotides at positions 2, 5, 11, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand

comprises 5 2'-fluoro nucleotides at positions 2, 7, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 7, 11, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 16 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the antisense strand comprises 5 2'-fluoro nucleotides at positions 2, 5, 12, 14 and 18 counting from the first matching position of the 5' end, and the rest 2'-O-methyl nucleotides. In some embodiments, the sense strand comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, preferably, wherein at least 18 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 9, 11 and/or 13 counting from the first matching position of the 3' end of the sense strand are 2'-fluoro nucleotides. In some embodiments, the sense strand comprises at least 18 modified nucleotides are 2'-O-methyl nucleotides and the nucleotides at positions 8, 11 and/or 13 counting from the first matching position of the 3' end of the sense strand are 2'-fluoro nucleotides. In some embodiments, the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3. In some embodiments, the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.

In some embodiments, the dsRNA agent includes at least one modified nucleotide and further includes one or more targeting groups or linking groups. In some embodiments, the one or more targeting groups or linking groups are conjugated to the sense strand. In some embodiments, the targeting group or linking group includes N-acetyl-galactosamine (GalNAc).

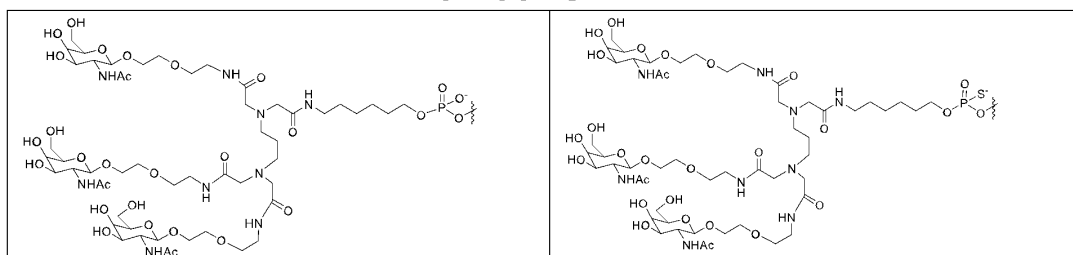
In some embodiments, the targeting group has a structure:



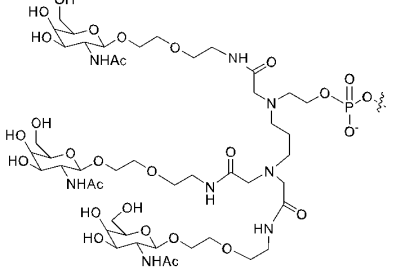
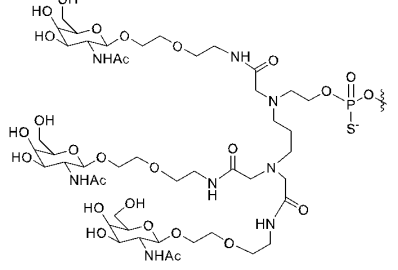
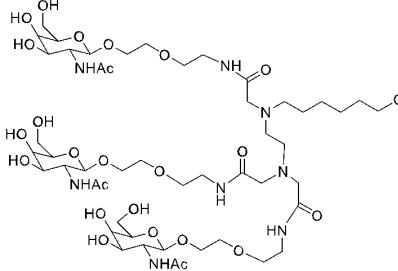
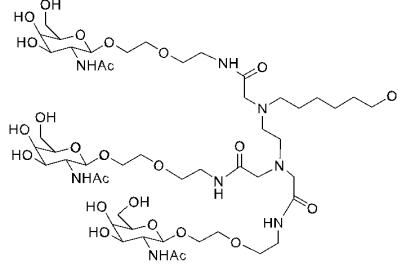
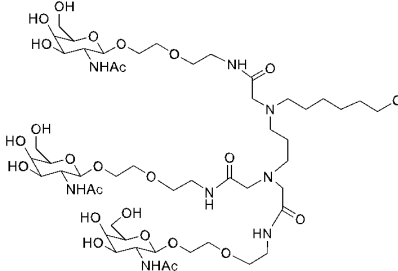
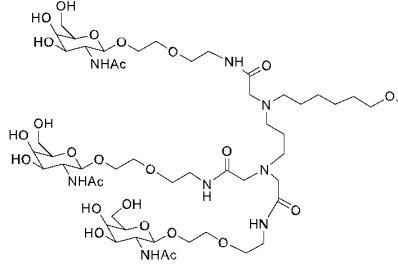
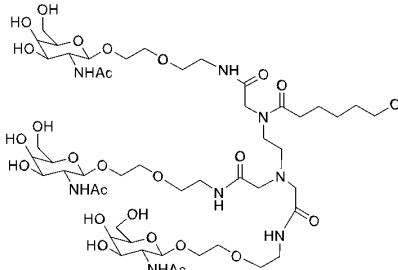
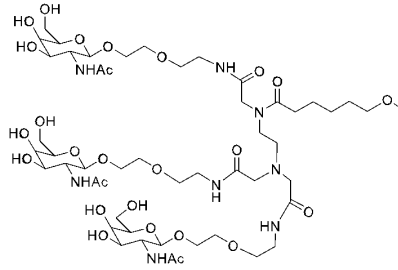
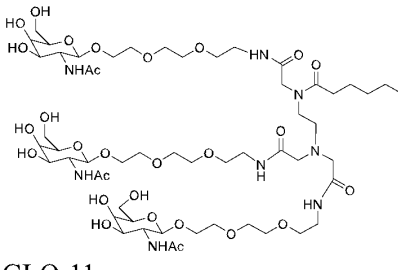
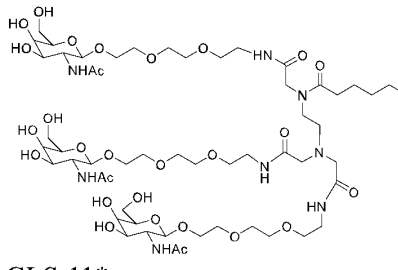
Formula 1

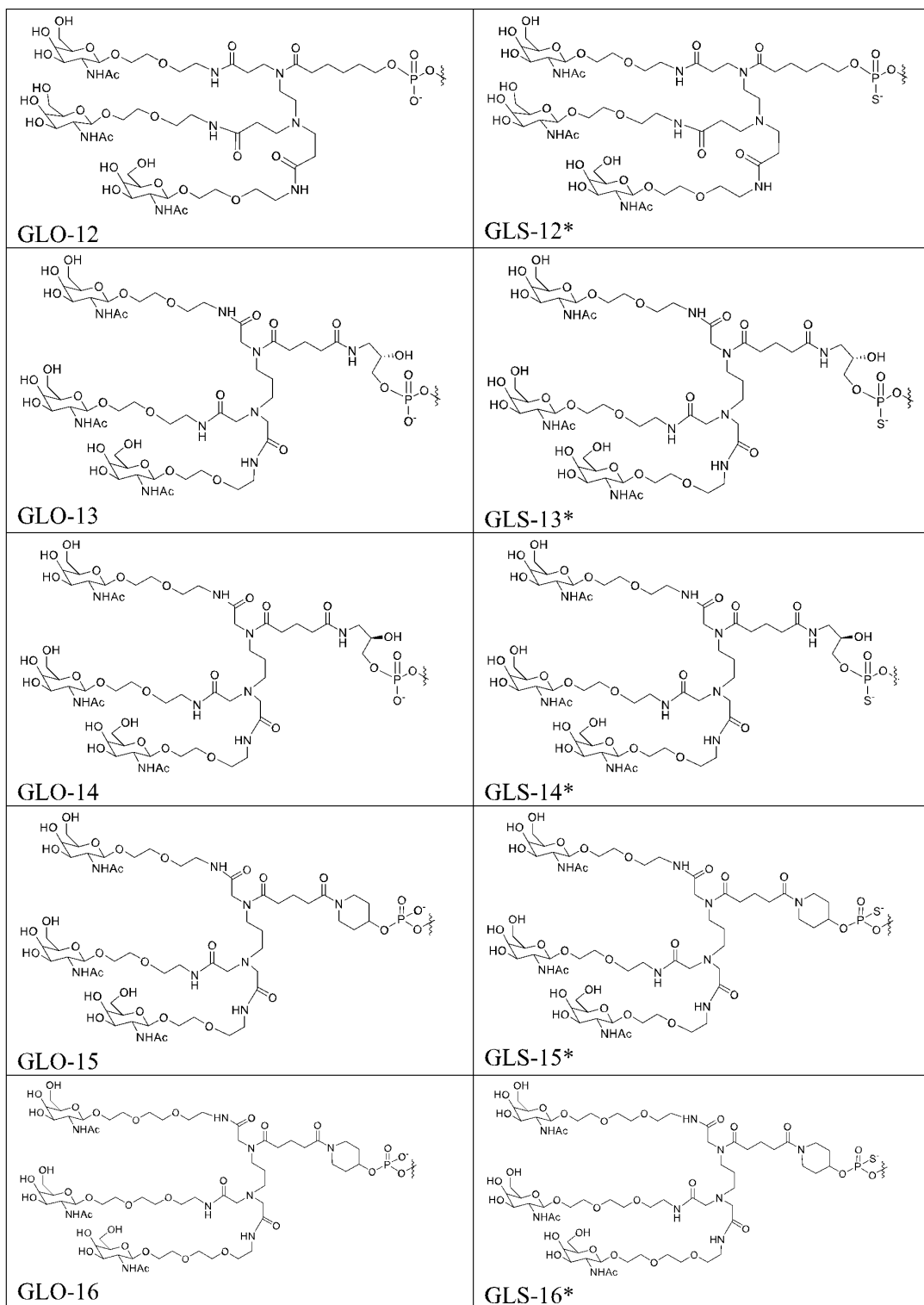
n and n' are independently selected from 1 or 2.

In some embodiments, the targeting group has a structure:



GLO-1 	GLS-1*
GLO-2 	GLS-2*
GLO-3 	GLS-3*
GLO-4 	GLS-4*
GLO-5 	GLS-5*
GLO-6 	GLS-6*

 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*



In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand. In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand.

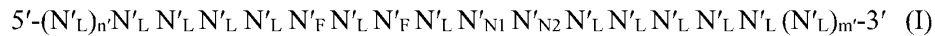
5 In some embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end.

In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each end of the sense strand includes one inverted abasic residue. In certain embodiments, each end of the sense strand includes one imann residue. In certain embodiments, at the 5' terminal end of the sense strand includes one inverted abasic residue or imann residues, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain
10 embodiments, the sense strand further includes targeting group linked to an inverted abasic residue or an imann residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue or imann via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc). In certain embodiments, at the 5' terminal end of the sense strand includes one inverted abasic residue, wherein inverted abasic residue is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain
15 embodiments, the sense strand further includes targeting group linked to an inverted abasic residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc), each strand is independently 21 nucleotides in length.

25 In some embodiments, the dsRNA agent has two blunt ends. In some embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In some embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides.

In certain embodiments, the dsRNA comprises a duplex selected from AV02373, AV02375, AV02379, AV02388, AV02411, AV02464, AV02554, AV02584, AV06327, AV06328, AV06329, and wherein duplex optionally including a targeting ligand. In certain
30 embodiments, the dsRNA comprises a duplex selected from the group consisting of AD01093, AD01093-1, AD01093-2, AD01094, AD01096, AD01393, AD01393-1, AD01396, AD01399, AD01412, AD01420, AD01420-1.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of a CFB RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand comprises sequence may be represented by formula (I):
35



wherein:

each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} and N'_{N2} independently represents a modified or unmodified nucleotide; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' and n' are each independently an integer of 0 to 7.

In some embodiments, N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide.

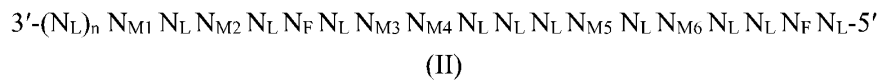
In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, m' is 2 and n' is 4, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2. In some embodiments, m' is 0 and n' is 4, or m' is 0 and n' is 2.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a targeting group that is conjugated to the 3'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, each end of the sense strand includes one inverted abasic residue or imann residues at the 5' terminal end of the sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue or an imann residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue or imann via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc). In certain embodiments, at the 5' terminal end of the sense strand includes one inverted abasic residue, wherein inverted abasic residue is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes

targeting group linked to an inverted abasic residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc), the each strand is independently 21 nucleotides in length. In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to a CFB RNA transcript, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand comprises sequence may be represented by formula (II):



wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} independently represents a modified or unmodified nucleotide; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7.

In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} have only three 2'-fluoro-modified nucleotides.

In some embodiments, N_{M2} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, n is 1, or n is 2, or n is 3, or n is 5. In some embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to another aspect of the invention, a double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA duplex comprises represented by formula (III):

sense: 5'-(N'_L) $_n$ N'_L N'_L N'_L N'_L N'_F N'_L N'_F N'_L N'_{N1} N'_{N2} N'_L N'_L N'_L N'_L N'_L (N'_L) $_{m'}$ -3'

antisense: 3'-(N_L) $_n$ N_{M1} N_L N_{M2} N_L N_F N_L N_{M3} N_{M4} N_L N_L N_L N_{M5} N_L N_{M6} N_L N_L N_F N_L -5'

(III)

wherein:

each strand is about 18 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N_{M6} , N'_{N1} , and N'_{N2} each independently represents a modified or unmodified nucleotide;

each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' , n' and n are each independently an integer of 0 to 7.

In some embodiments, N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} have only three 2'-fluoro-modified nucleotides, N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides.

In some embodiments, m' is 2 and n' is 4, m' is 2 and n' is 6, or m' is 2 and n' is 2. In some embodiments, m' is 1 and n' is 4, or m' is 1 and n' is 2. In some embodiments, m' is 0 and n' is 4, or m' is 0 and n' is 2. In some embodiments, n is 1, or n is 2, or n is 3, or n is 5.

In some embodiments, N'_{N1} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N'_{N2} independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M5} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide.

5 In some embodiments, N_{M1} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, N_{M2} , N_{M3} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

10 In some embodiments, N_{M2} , N_{M4} and N_{M6} each independently represents a 2'-fluoro-modified nucleotide and N_{M5} represents an UNA modified nucleotide.

In some embodiments, the dsRNA agent includes a targeting group that is conjugated to the 5'-terminal end of the sense strand, preferably, the targeting group is any one selected from aforesaid GLO-1 through GLO-16 and GLS-1* through GLS-16*, more preferably, the targeting group is aforesaid GLS-15*. In certain embodiments, the dsRNA agent includes a
15 targeting group that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments, the antisense strand includes one inverted abasic residue at 3'-terminal end. In certain embodiments, the sense strand includes one or two inverted abasic residues and/or one or two imann residues at 3' or/and 5' terminal end. In certain embodiments, each 3' and 5' terminal end of the sense strand independently includes an inverted abasic residue. In certain
20 embodiments, each 3' and 5' terminal end of the sense strand independently includes an imann residue. In certain embodiments, the sense strand includes two inverted abasic residues at 3' and 5' terminal end and either residue at 3' or 5' terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the sense strand includes two imann residues at 3' and 5' terminal end and either residue at 3' or 5'
25 terminal end is further conjugated to a targeting group, which preferably is aforesaid GLS-15*. In certain embodiments, the dsRNA agent has two blunt ends. In certain embodiments, at least one strand includes a 3' overhang of at least 1 nucleotide. In certain embodiments, at least one strand includes a 3' overhang of at least 2 nucleotides. In certain embodiments, each end of the sense strand includes one inverted abasic residue or imann residues at the 5' terminal end of the
30 sense strand, wherein inverted abasic residue or imann residues is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue or an imann residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue or imann via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc).
35 In certain embodiments, at the 5' terminal end of the sense strand includes one inverted abasic

residue, wherein inverted abasic residue is linked to an adjacent nucleotide via a phosphorothioate linkage to the 5' terminal end of the nucleotide sequence of the sense strand. In certain embodiments, the sense strand further includes targeting group linked to an inverted abasic residue at the 5' terminal end of the sense strand, wherein targeting group is linked to an adjacent inverted abasic residue via a phosphorothioate linkage, and optionally targeting group is N-acetyl-galactosamine (GalNAc), the each strand is independently 21 nucleotides in length. In certain embodiments, the antisense strand of the dsRNA agent is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3.

According to an aspect of the invention, a composition is provided that includes any embodiment of the aforementioned dsRNA agent aspect of the invention. In certain embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents. In certain embodiments, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial. In some embodiments, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

According to another aspect of the invention a cell is provided that includes any embodiment of an aforementioned dsRNA agent aspect of the invention. In some embodiments, the cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a CFB gene in a cell, is provided, the method including: (i) preparing a cell including an effective amount of any embodiment of the aforementioned dsRNA agent aspect of the invention or any embodiment of an aforementioned composition of the invention. In certain embodiments, the method also includes: (ii) maintaining the prepared cell for a time sufficient to obtain degradation of the mRNA transcript of a CFB gene, thereby inhibiting expression of the CFB gene in the cell. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously. In some embodiments, the cell is in a subject and the dsRNA agent is administered to the subject by IV administration. In certain embodiments, the method also includes assessing inhibition of the CFB gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of a CFB-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition and/or to a control physiological characteristic of the CFB-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the CFB gene in the subject. In some embodiments, the physiological characteristic is one or more of: the CFB mRNA level and the CFB protein level. A reduction in the expression of CFB may also be assessed indirectly by measuring a decrease in biological activity of CFB, e.g., or

additional pathologies associated with elevated levels of CFB, preferably in the blood or in the kidneys, or over activation of the complement pathway, or additional therapeutic approaches where inhibition of CFB expression is desired. a decrease in one or more of: CFB mRNA level, CFB protein level, CH50 activity (a measure of total hemolytic complement), AH50 (a
5 measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

According to another aspect of the invention, a method of inhibiting expression of a CFB gene in a subject, is provided, the method including administering to the subject an
10 effective amount of an embodiment of the aforementioned dsRNA agent aspect of the invention or an embodiment of an aforementioned composition of the invention. In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration. In some embodiments, the method also includes: assessing inhibition of the CFB gene, following the
15 administration of the dsRNA agent, wherein a means for the assessing comprises: (i) determining one or more physiological characteristics of a CFB-associated disease or condition in the subject and (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition and/or to a control physiological characteristic of the CFB-associated disease or condition, wherein the
20 comparison indicates one or more of a presence or absence of inhibition of expression of the CFB gene in the subject. In some embodiments, expression of the CFB gene can be assessed based on the level or change in level of any variable associated with CFB gene expression, such as CFB mRNA level, CFB protein level. A reduction in the expression of CFB may also be assessed indirectly by measuring a decrease in biological activity of CFB, e.g., or additional
25 pathologies associated with elevated levels of CFB, preferably in the blood or in the kidneys, or over activation of the complement pathway, or additional therapeutic approaches where inhibition of CFB expression is desired. a decrease in one or more of: CFB mRNA level, CFB protein level, CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a
30 measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of CFB protein is provided, the method including:
35 administering to a subject an effective amount of an embodiment of any aforementioned dsRNA agent aspect of the invention or an embodiment of any aforementioned composition of the invention, to inhibit CFB gene expression. In some embodiments, the disease, disorder or condition associated with CFB is selected from the group consisting of: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus erythematosus (SLE), Lupus

Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS), neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies- associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelitis optica (NMO), dense deposit disease, 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), cold agglutinin disease, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis.

In some embodiments, the method also includes: administering an additional therapeutic regimen to the subject. In some embodiments, the additional therapeutic regimen includes a treatment for the CFB-associated disease or condition. In certain embodiments, the additional therapeutic regimen comprises: administering to the subject one or more CFB antisense polynucleotides of the invention, administering to the subject a non-CFB dsRNA therapeutic agent, and a behavioral modification in the subject. In some embodiments, the additional therapeutic agent is selected from the group consisting of an oligonucleotide, a small molecule, a monoclonal antibody, a polyclonal antibody and a peptide. Preferably, the additional therapeutic agent is an inhibitor of C5, such as an anticomplement component C5 antibody, or antigen-binding fragment thereof (e.g., eculizumab, ravulizumab-cwvz, or pozelimab (REGN3918)) or a C5 peptide inhibitor (e.g., zilucoplan). 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. Ravulizumab-cwvz is a humanized IgG2/4 monoclonal 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. Pozelimab (also known as H4H12166P, described in US20170355757) is a fully-human IgG4 monoclonal antibody designed to block complement factor C5. Zilucoplan is a synthetic, macrocyclic peptide that binds complement component 5 (C5) with sub-nanomolar affinity and allosterically inhibits its cleavage into C5a and C5b upon activation of the classical, alternative, or lectin pathways. Preferably, the additional therapeutic is a C3 peptide inhibitor, or analog thereof. In one

embodiment, the C3 peptide inhibitor is compstatin. Compstatin is a cyclic tridecapeptide with potent and selective C3 inhibitory activity.

In some embodiments, the dsRNA agent is administered to the subject subcutaneously. In certain embodiments, the dsRNA agent is administered to the subject by IV administration.

- 5 In some embodiments, the method also includes determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.

In some embodiments, a means of determining an efficacy of the treatment in the subject comprises: (i) determining one or more physiological characteristics of the CFB-associated disease or condition in the subject and (ii) comparing the determined physiological
10 characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

In some embodiments, expression of the CFB gene can be assessed based on the level
15 or change in level of any variable associated with CFB gene expression, such as CFB mRNA level, CFB protein level in the subject, or CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9
20 complex.

According to another aspect of the invention, a method of decreasing a level of CFB protein in a subject compared to a baseline pre-treatment level of CFB protein in the subject, is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any
25 aforementioned composition of the invention, to decrease the level of CFB gene expression. In some embodiments, the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

According to another aspect of the invention, a method of altering a physiological characteristic of a CFB-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition in the subject
30 is provided, the method including administering to the subject an effective amount of an embodiment of any aforementioned dsRNA agent of the invention or an embodiment of any aforementioned composition of the invention, to alter the physiological characteristic of the CFB-associated disease or condition in the subject. In some embodiments, the dsRNA agent is
35 administered to the subject subcutaneously or is administered to the subject by IV administration. In certain embodiments, the physiological characteristic and symptoms are one or more of: CFB mRNA level, CFB protein level in the subject, or CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis),

hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

According to another aspect of the invention, the aforementioned dsRNA agent for use in a method of treating a disease or condition associated with the presence of CFB protein is provided. In some embodiments, the disease or condition is one or more of: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus erythematosus (SLE), Lupus Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS), neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies- associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelitis optica (NMO), dense deposit disease, 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), cold agglutinin disease, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of CFB protein is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1. In some embodiments, the equivalent region is any one of the target regions of SEQ ID NO: 1 and the complementary sequence is one provided in one of Tables 1-3. In certain embodiments, the antisense polynucleotide agent includes one of the antisense sequences provided in one of Tables 1-3.

According to another aspect of the invention, a composition including an embodiment of any aforementioned antisense polynucleotide agents is provided. In some embodiments, the composition also includes a pharmaceutically acceptable carrier. In some embodiments, the composition also includes one or more additional therapeutic agents for treatment of a CFB-associated disease or condition. In certain embodiments, the composition is packaged in a kit,

container, pack, dispenser, pre-filled syringe, or vial. In certain embodiments, the composition is formulated for subcutaneous or IV administration.

According to another aspect of the invention a cell that includes an embodiment of any of the aforementioned antisense polynucleotide agents is provided. In some embodiments, the
5 cell is a mammalian cell, optionally a human cell.

According to another aspect of the invention, a method of inhibiting the expression of a CFB gene in a cell is provided, the method including: (i) preparing a cell including an effective amount of an embodiment of any aforementioned antisense polynucleotide agents. In some
10 embodiments, the method also includes (ii) maintaining the cell prepared in (i) for a time sufficient to obtain degradation of the mRNA transcript of a CFB gene, thereby inhibiting expression of the CFB gene in the cell.

According to another aspect of the invention, a method of inhibiting expression of a CFB gene in a subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide
15 agent.

According to another aspect of the invention, a method of treating a disease or condition associated with the presence of CFB protein, the method including administering to a subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention,
20 to inhibit CFB gene expression. In certain embodiments, the disease or condition is one or more of: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus erythematosus (SLE), Lupus Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy,
25 polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS),
30 neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelitis optica
35 (NMO), dense deposit disease, 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), cold agglutinin disease, humoral and

vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis.

According to another aspect of the invention, a method of decreasing a level of CFB protein in a subject compared to a baseline pre-treatment level of CFB protein in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to decrease the level of CFB gene expression. In certain embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration.

According to another aspect of the invention, an antisense polynucleotide agent for inhibiting expression of CFB gene, is provided, the agent including from 10 to 30 contiguous nucleotides, wherein at least one of the contiguous nucleotides is a modified nucleotide, and wherein the nucleotide sequence of the agent is about 80% or about 85% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NO: 1.

According to another aspect of the invention, a method of altering a physiological characteristic of a CFB-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition in the subject is provided, the method including administering to the subject an effective amount of an embodiment of any of the aforementioned antisense polynucleotide agents or an embodiment of any aforementioned composition of the invention, to alter the physiological characteristic of the CFB disease or condition in the subject. In some embodiments, the antisense polynucleotide agent is administered to the subject subcutaneously or by IV administration. In certain embodiments, the physiological characteristic and symptoms are one or more of: CFB mRNA level, CFB protein level in the subject, or CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

Brief Description of the Sequences

SEQ ID NO: 1 and SEQ ID NO: 2 (reverse complement) are Homo sapiens CFB mRNA [NCBI Reference Sequence: NM_001710.6].

SEQ ID NO: 3 and SEQ ID NO: 4 (reverse complement) are Macaca mulatta (Rhesus monkey) CFB mRNA [NCBI Reference Sequence: XM_015136029.2].

SEQ ID NO: 5 and SEQ ID NO: 6 (reverse complement) are Mus musculus (isoform 1) CFB mRNA [NCBI Reference Sequence: NM_008198.3].

SEQ ID NOs: 7-468,1489-1595 are shown in Table 1 and are sense strand sequences.

SEQ ID NOs: 469-930,1596-1702 are shown in Table 1 and are antisense strand sequences.

5 SEQ ID NOs: 931-1392,1703-1810 are shown in Table 2 with chemical modifications.

SEQ ID NOs: 1393-1488,1811-1879, 1882-1950 are shown in Table 3. A delivery molecule is indicated as "GLX-__" at the 3' end or 5' end of each sense strand.

10 Detailed Description

The invention in part, includes RNAi agents, for example, though not limited to double stranded (ds) RNAi agents, which are capable of inhibiting CFB gene expression. The invention, in part also includes compositions comprising CFB RNAi agents and methods of use of the compositions. CFB RNAi agents disclosed herein may be attached to delivery compounds for delivery to cells, including to hepatocytes. Pharmaceutical compositions of the invention may include at least one dsRNA CFB agent and a delivery compound. In some embodiments of compositions and methods of the invention, the delivery compound is a GalNAc-containing delivery compound. CFB RNAi agents delivered to cells are capable of inhibiting CFB gene expression, thereby reducing activity in the cell of the CFB protein product of the gene. dsRNAi agents of the invention can be used to treat CFB-associated diseases and conditions.

In some embodiments of the invention reducing CFB expression in a cell or subject treats a disease or condition associated with CFB expression in the cell or subject, respectively. Non-limiting examples of diseases and conditions that may be treated by reducing CFB activity are: alleviation or amelioration of one or more symptoms associated with unwanted or excessive CFB expression, CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

As used herein, "G," "C," "A" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, 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. The skilled person understands that guanine, cytosine, adenine, and uracil may 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 may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the

nucleotide sequences of the invention by a nucleotide containing, for example, inosine. Sequences comprising such replacement moieties are embodiments of the invention.

As used herein, " Complement Factor B " used interchangeably with the term "factor B" or "CFB" refers to the naturally occurring gene that encodes a Complement Factor B protein from any vertebrate or mammalian source, including, but not limited to, human, bovine, chicken, rodent, mouse, rat, porcine, ovine, primate, monkey, and guinea pig, unless specified otherwise. The term also refers to fragments and variants of native CFB that maintain at least one in vivo or in vitro activity of a native CFB. The amino acid and complete coding sequences of the reference sequence of the human CFB gene may be found in, for example, GenBank Ref Seq Accession No. NM_001710.6 (SEQ ID NO: 1 and SEQ ID NO:2). *Macaca mulatta* (Rhesus monkey) CFB mRNA GenBank Ref Seq Accession No. XM_015136029.2 (SEQ ID NO:3 and SEQ ID NO:4), *Mus musculus* (isoform 1) NM_008198.3 (SEQ ID NO:5 and SEQ ID NO:6). Additional examples of CFB mRNA sequences are readily available using publicly available databases, e.g., GenBank, UniProt, Ensembl and OMIM.

The following describes how to make and use compositions comprising CFB single-stranded (ssRNA) and dsRNA agents to inhibit CFB gene expression, as well as compositions and methods for treating diseases and conditions caused by or modulated by CFB gene expression. The term "RNAi" is also known in the art, and may be referred to as "siRNA".

As used herein, the term "RNAi" refers to an agent that comprises RNA and mediates targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. As is known in the art, an RNAi target region refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a gene, including messenger RNA (mRNA) that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion. A target sequence may be from 8-30 nucleotides long (inclusive), from 10 - 30 nucleotides long (inclusive), from 12 - 25 nucleotides long (inclusive), from 15 - 23 nucleotides long (inclusive), from 16 -23 nucleotides long (inclusive), or from 18 – 23 nucleotides long (inclusive), including all shorter lengths within each stated range. In some embodiments of the invention, a target sequence is 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 nucleotides long. In certain embodiment a target sequence is between 9 and 26 nucleotides long (inclusive), including all sub-ranges and integers there between. For example, though not intended to be limiting, in certain embodiments of the invention a target sequence is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides long, with the sequence fully or at least substantially complementary to at least part of an RNA transcript of a CFB gene. Some aspects of the invention include pharmaceutical compositions comprising one or more CFB dsRNA agents and a pharmaceutically acceptable carrier. In certain embodiments of the invention, a CFB RNAi as described herein inhibits expression of CFB protein.

As used herein, a “dsRNA agent” means a composition that contains an RNA or RNA-like (e.g., chemically modified RNA) oligonucleotide molecule that is capable of degrading or inhibiting translation of messenger RNA (mRNA) transcripts of a target mRNA in a sequence specific manner. Although not wishing to be limited to a particular theory, dsRNA agents of the invention may operate through the RNA interference mechanism (i.e., inducing RNA interference through interaction with the RNA interference pathway machinery (RNA-induced silencing complex or RISC) of mammalian cells), or by any alternative mechanism(s) or pathway(s). Methods for silencing genes in plant, invertebrate, and vertebrate cells are well known in the art [see, for example, (Sharp et al., *Genes Dev.* 2001, 15:485; Bernstein, et al., (2001) *Nature* 409:363; Nykanen, et al., (2001) *Cell* 107:309; and Elbashir, et al., (2001) *Genes Dev.* 15:188)], the disclosure of each of which is incorporated herein by reference in its entirety.]. Art-known gene silencing procedures can be used in conjunction with the disclosure provided herein to inhibit expression of CFB.

DsRNA agents disclosed herein are comprised of a sense strand and an antisense strand, and include, but are not limited to: short interfering RNAs (siRNAs), RNAi agents, micro RNAs (miRNAs), short hairpin RNAs (shRNA), and dicer substrates. The antisense strand of the dsRNA agents described herein is at least partially complementary to the mRNA being targeted. It is understood in the art that different lengths of dsRNA duplex structure can be used to inhibit target gene expression. For example, dsRNAs having a duplex structure of 19, 20, 21, 22, and 23 base pairs are known to be effective to induce RNA interference (Elbashir et al., *EMBO* 2001, 20:6877-6888). It is also known in the art that shorter or longer RNA duplex structures are also effective to induce RNA interference. In some embodiments, the sense strand and the antisense strand may be the same length or different lengths. In some embodiments, each strand is no more than 40 nucleotides in length. In some embodiments, each strand is no more than 30 nucleotides in length. In some embodiments, each strand is no more than 25 nucleotides in length. In some embodiments, each strand is no more than 23 nucleotides in length. In some embodiments, each strand is no more than 21 nucleotides in length. In some embodiments, the sense and antisense strands of the RNAi agents can each be 15 to 49 nucleotides in length. In some embodiments, the antisense strand is independently 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the length of the sense strand is independently 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, or 49 nucleotides. In some embodiments, the sense strand and the antisense strand are both 21 nucleotides in length. In some embodiments, the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 15 and 23 nucleotides in length. In some embodiments, the region of complementarity is 19-21 nucleotides in length. In some embodiments, the region of complementarity is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. CFB dsRNAs in certain embodiments of the invention can include at least one strand of a length of minimally

21 nt or may have shorter duplexes based on one of the sequences set forth in any one of Tables 1-3, but minus 1, 2, 3, or 4 nucleotides on one or both ends may also be effective as compared to the dsRNAs set forth in Tables 1-3, respectively. In some embodiments of the invention, CFB dsRNA agents may have a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one or more sequences of Tables 1-3, and differ in their ability to inhibit the expression of a CFB gene by not more than 5%, 10%, 15%, 20%, 25%, or 30% from the level of inhibition resulting from a dsRNA comprising the full sequence. A sense sequence, an antisense sequence and a duplex disclosed in Tables 1-3 may be referred to herein as a “parent” sequence, meaning that the sequences disclosed in Tables 1-3 may be modified, shorten, lengthened, include substitutions, etc. as set forth herein, with the resulting sequences retaining all or at least a portion of the efficacy of their parent sequences in methods and compositions of the invention. Sense and antisense strands included in a dsRNA of the invention are independently selected. As used herein the term “independently selected” means each of two or more like elements can be selected independent of the selection of the other elements. For example, though not intended to be limiting, in preparing a dsRNA of the invention, one may select the “elements” of the two strands to include in the duplex. One selected element, the sense sequence may be SEQ ID NO: 932 (shown in Table 2) and the other selected element, the antisense sequence, may be SEQ ID NO: 1163, or may be SEQ ID NO: 1163 that is modified, shortened, lengthened, and/or includes 1, 2, or 3 substitutions as compared to its parent sequence SEQ ID NO: 1163. It will be understood that a duplex of the invention need not include both sense and antisense sequences shown as paired in duplexes in Tables 1-3. Each sense and antisense strand sequence in the tables is immediately followed by its SEQ ID NO.

Certain embodiments of compositions and methods of the invention comprise a single-strand RNA in a composition and/or administered to a subject. For example, an antisense strand such as one listed in any one of Tables 1-3 may be a composition or in a composition administered to a subject to reduce CFB polypeptide activity and/or expression of CFB gene in the subject. Tables 1 shows certain CFB dsRNA agent antisense strand and sense strand core stretch base sequences. A single-strand antisense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand antisense agent” or an “antisense polynucleotide agent”. A single-strand sense molecule that may be included in certain compositions and/or administered in certain methods of the invention are referred to herein as a “single-strand sense agent” or a “sense polynucleotide agent”. The term “base sequence” is used herein in reference to a polynucleotide sequence without chemical modifications or delivery compounds. For example, the sense strand GACAAUGUGAGUGAUGAGAU (SEQ ID NO: 22) shown in Table 1 is the base sequence for SEQ ID NO: 946 in Table 2 and for SEQ ID NO: 1393 in Table 3, with SEQ ID NO: 946 and SEQ ID NO: 1393 shown with their chemical modifications and a delivery compound. Sequences disclosed herein may be assigned identifiers. For example, a

single-stranded sense sequence may be identified with a “Sense strand SS#”; a single stranded antisense sequence may be identified with an “Antisense strand AS#” and a duplex that includes a sense strand and an antisense strand may be identified with a “Duplex AD#/AV#”.

Table 1 includes sense and antisense strands and provides the identification number of duplexes formed from the sense and antisense strand on the same line in Table 1. In certain embodiments of the invention an antisense sequence includes nucleobase u or nucleobase a in position 1 of the antisense sequence. In certain embodiments of the invention an antisense sequence includes nucleobase u in position 1 of the antisense sequence. As used herein, the term “matching position” in a sense and an antisense strand are the positions in each strand that “pair” when the two strands are duplexed strands. For example, in a 21 nucleobases sense strand and a 21 nucleobases antisense strand, nucleobase in position 1 of the sense strand and position 21 in the antisense strand are in “matching positions”. In yet another non-limiting example in a 23 nucleobases sense strand and a 23 nucleobases antisense strand, nucleobase 2 of the sense strand and position 22 of the antisense strand are in matching positions. In another non-limiting example, in an 18 nucleobases sense strand and an 18 nucleobases antisense strand, nucleobase in position 1 of the sense strand and nucleobase 18 in the antisense strand are in matching positions, and nucleobase 4 in the sense strand and nucleobase 15 in the antisense strand are in matching positions. A skilled artisan will understand how to identify matching positions in sense and antisense strands that are or will be duplexed strands and paired strands.

The final column in Table 1 indicates a Duplex AV# for a duplex that includes the sense and antisense sequences in the same table row. For example, Table 1 discloses the duplex assigned Duplex AV02358.um, which includes sense strand SEQ ID NO: 7 and antisense strand SEQ ID NO: 469. Thus, each row in Table 1 identifies a duplex of the invention, each comprising the sense and antisense sequences shown in the same row, with the assigned identifier for each duplex shown in the final column in the row.

In some embodiments of methods of the invention, an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex comprising at least one of the base sequences set forth in Table 1, including 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 sequence modifications. In some embodiments of methods of the invention an RNAi agent comprising a polynucleotide sequence shown in any one of Tables 1-3 is attached to a delivery molecule, a non-limiting example of which is a delivery compound comprising a GalNAc compound, or a GLS-15* compound.

Table 1: Unmodified CFB RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3' direction. Duplex AV# are the number assigned to the duplex of the two strands in the same row in the table.

Duplex AV#	Sense strand	SEQ NO.	ID	Antisense strand	SEQ NO.	ID
AV02358.µm	GAGGUCUAGGUCUGGAGUUUA	7	UAAACUCCAGACCUAGACCUC	469		
AV02359.µm	GAGGUCUGGAGUUUCAGCUUA	8	UAAAGCUGAAACUCCAGACCUC	470		
AV02360.µm	GGGUCUGGAGUUUCAGCUUGA	9	UCAAGCUGAAACUCCAGACCC	471		
AV02361.µm	CGUCUGGAGUUUCAGCUUGGA	10	UCCAAAGCUGAAACUCCAGACG	472		
AV02362.µm	CGAGUUUCAGCUUGGACACUA	11	UAGUGUCCCAAGCUGAAACUCG	473		
AV02363.µm	CAGUUUCAGCUUGGACACUGA	12	UCAGUGUCCCAAGCUGAAACUG	474		
AV02364.µm	GCCUUCGACUUCUCCAAAGAA	13	UUCUUGGAGAAAGUCCGAAAGGC	475		
AV02365.µm	GCGUGUGUCCUUCUGGCUUCA	14	UGAAAGCCAGAAAGACACACGC	476		
AV02366.µm	CUGUGUCCUUCUGGCUUCUAA	15	UUAGAAGCCAGAAAGACACAG	477		
AV02367.µm	CGAAGGCAGAGUGGCAGAGCAA	16	UUGCUCUGCACUCUGCCUUCG	478		
AV02368.µm	CACUUCGAGAAACGGGAAUAA	17	UUAAUCCCCGULUCUGAAAGUG	479		
AV02369.µm	GCCUACUACAUAUGUGAGUGAA	18	UUCACUCACAUUGUAGUAGGC	480		
AV02370.µm	GUACUACAUAUGUGAGUGAUGA	19	UCAUCCACUACAUAUUGUAGUAC	481		
AV02371.µm	GACUACAUAUGUGAGUGAUGAA	20	UUCAUCCACUACAUAUUGUAGUC	482		
AV02372.µm	GCUACAUAUGUGAGUGAUGAGA	21	UCUCAUCCACUACAUAUUGUAGC	483		
AV02373.µm	GACAUUGUGAGUGAUGAGAUUA	22	UAUUCUAUCCACUACAUAUUGUC	484		
AV02374.µm	GAUUGUGAGUGAUGAGAUUCA	23	UAGAUUCUAUCCACUACAUAUC	485		
AV02375.µm	GAUGUGAGUGAUGAGAUUCA	24	UGAAGAUUCUAUCCACUACAUC	486		
AV02376.µm	GUUGAGUGAUGAGAUUCUCUA	25	UAGAGAUUCUAUCCACUACAAC	487		
AV02377.µm	GGUGAGUGAUGAGAUUCUCUA	26	UAAAGAUUCUAUCCACUACACC	488		
AV02378.µm	GGAGUGAUGAGAUUCUCUUA	27	UGAAAAGAGAUUCUAUCCACUCC	489		
AV02379.µm	CAGUGAUGAGAUUCUUCUUA	28	UGGAAAAGAGAUUCUAUCCACUG	490		
AV02380.µm	GGUGAUGAGAUUCUUCUUA	29	UUGGAAAAGAGAUUCUAUCCACC	491		
AV02381.µm	CUGAUGAGAUUCUUCUUA	30	UGUGGAAAAGAGAUUCUAUCCAG	492		
AV02382.µm	GGAGAUUCUUCUUCUUA	31	UAGCAGUGGAAAAGAGAUUCUCC	493		
AV02383.µm	GGAUUCUUCUUCUUA	32	UAUAGCAGUGGAAAAGAGAUUC	494		
AV02384.µm	GCUCUUUCCACUUGCUAUGACA	33	UGUCAUAAGCAGUGGAAAAGAGGC	495		

AV02385.µm	GUCCACUGCUAUGACGGUUA	34	UUAACCGUCAUAGCAGUGGAC	496
AV02386.µm	GCACUGCUAUGACGGUUAACAA	35	UUGUAACCGUCAUAGCAGUGC	497
AV02387.µm	GCUGCUAUGACGGUUAACACUA	36	UAGUGUAACCGUCAUAGCAGC	498
AV02388.µm	GGCUAUGACGGUUAACACUCUA	37	UAGAGUGUAACCGUCAUAGCC	499
AV02389.µm	CCUAUGACGGUUAACACUCUA	38	UGAGAGUGUAACCGUCAUAGG	500
AV02390.µm	GCAAGCAUCUGUGACAAACGGA	39	UCCGUGUCACAGAUCCGUCG	501
AV02391.µm	GCAGUACCGCCUUGAAGACAA	40	UUGUCUUAAGGCGGUACUGC	502
AV02392.µm	GGAAGACAGCGUCCACCUACCA	41	UGGUAAGUGACGCUUCCUCC	503
AV02393.µm	GCUGCCAAAGACUCCUUAACUA	42	UCAUGAAGGAGUCUUGGCCAGC	504
AV02394.µm	CUGGCCGAAGCUUUCUUGUCA	43	UGACAGGAAAGCUUCCGCCAG	505
AV02395.µm	CACAGAGACCAUAGAAGGAGA	44	UCUCCUUCUAUGGUCUCUGUG	506
AV02396.µm	GGAACCAUAGAAAGGAGUCCGAUA	45	UAUCCGACUCCUUCUAUUGGUCC	507
AV02397.µm	GCCCUUCAGGCUCCCAUUGAACA	46	UGUUCAUUGGAGCCUUGAAGGCG	508
AV02398.µm	GUCAAGGCUCCAUGAACAUCUA	47	UAGAUUGUCCAUGGAAGCCUGAC	509
AV02399.µm	GUCCAUGAACAUCUACCUUGA	48	UCCAGGUAGAUUGUUAUGGAC	510
AV02400.µm	CAACAUUCUACCUUGGUGCUAGA	49	UCUAGCACCAAGGUAGAUUGUUG	511
AV02401.µm	GUACCUUGGUGCUAGAUUGAUA	50	UAUCCAUCUAGCACCAAGGUAC	512
AV02402.µm	GUUGGUCUAGAUUGGALUCAGAA	51	UUCUGAUCCAUUCUAGCACACAC	513
AV02403.µm	CGCCAGCAAACTUUCACAGGAGA	52	UCUCCUGUGAAAGUUGCUUGGCG	514
AV02404.µm	GAACUUCACAGGAGGCCAAAAA	53	UUUUUUGGCUCCUGUGAAAUUC	515
AV02405.µm	GCUUCACAGGAGGCCAAAAAAGA	54	UCUUUUUGGCUCCUGUGAAGC	516
AV02406.µm	GUUCACAGGAGGCCAAAAAAGUA	55	UACUUUUUGGCUCCUGUGAAC	517
AV02407.µm	GAGGAGGCCAAAAAAGUGUCUAA	56	UUAGACACUUUUUUGGCUCCUC	518
AV02408.µm	GGGAGGCCAAAAAAGUGUCUAGA	57	UCUAGACACUUUUUUGGCUCCC	519
AV02409.µm	CAGCCAAAAAAGUGUCUAGUCA	58	UGACUAGACACUUUUUUGGCUUG	520
AV02410.µm	GGCCAAAAAAGUGUCUAGUCAAA	59	UUGACUAGACACUUUUUUGGCC	521
AV02411.µm	CCCAAAAAAGUGUCUAGUCAAAA	60	UUUGACUAGACACUUUUUUGGG	522
AV02412.µm	GAAAAAAGUGUCUAGUCAACUA	61	UAGUUGACUAGACACUUUUUUC	523
AV02413.µm	GAAAAGUGUCUAGUCAACUUAA	62	UUAAAGUUGACUAGACACUUC	524
AV02414.µm	GAAAGUGUCUAGUCAACUUAAA	63	UUUAAAGUUGACUAGACACUUC	525
AV02415.µm	CUGUCUAGUCAACUUAUUGA	64	UCAAUUUAAGUUGACUAGACAG	526

AV02416.µm	GGUCUAGUCAACUUAUUGAA	65	UUCAAUUAAGUUGACUAGACC	527
AV02417.µm	CUCUAGUCAACUUAUUGAGA	66	UCUCAUUAAGUUGACUAGAG	528
AV02418.µm	GCUAGUCAACUUAUUGAGAA	67	UUCUCAUUAAGUUGACUAGC	529
AV02419.µm	GUAGUCAACUUAUUGAGAAA	68	UUCUCAUUAAGUUGACUAC	530
AV02420.µm	CUCAACUUAUUGAGAAAGGUA	69	UACCUUCUCAUUAAGUUGAG	531
AV02421.µm	GCAACUUAUUGAGAAAGGUGA	70	UCACCUUCUCAUUAAGUUGC	532
AV02422.µm	GAUUGAGAAAGGUGGCAAGUUA	71	UAACUUGCCACCCUUCUCAUC	533
AV02423.µm	GUUGAGAAAGGUGGCAAGUUA	72	UUAACUUGCCACCCUUCUAC	534
AV02424.µm	GGAAGAAAGGUGGCAAGUUA	73	UCAUAACTUUGCCACCCUUC	535
AV02425.µm	GAGGUGGCAAGUUAUGGUGUA	74	UACACCAUAACUUGCCACCCU	536
AV02426.µm	GGGUGGCAAGUUAUGGUGUGA	75	UCACACCAUAACUUGCCACCC	537
AV02427.µm	CUGGCAAGUUAUGGUGUGAAA	76	UUUCACACCAUAACUUGCCAAG	538
AV02428.µm	CCAAGUUAUGGUGUGAAGCCA	77	UGGCUUCACACCAUAACUUGG	539
AV02429.µm	GAGUUAUGGUGUGAAGCCAAA	78	UUUGGCUUCACACCAUAACUC	540
AV02430.µm	GAUGGUGUGAAGCCAAAGUAA	79	UUAUCCUUGGCUUCACACCAUC	541
AV02431.µm	GAGAUUAUGGUCUAGUGACAUUA	80	UAUGUCACUAGACCAUAUCUC	542
AV02432.µm	GGAUUAUGGUCUAGUGACAUAA	81	UUAUGUCACUAGACCAUAUCC	543
AV02433.µm	CAUUAUGGUCUAGUGACAUUA	82	UAUUAUGUCACUAGACCAUAUG	544
AV02434.µm	GUUAUGGUCUAGUGACAUUAUGA	83	UCAUUAUGUCACUAGACCAUAC	545
AV02435.µm	GAUGGUCUAGUGACAUUAUGCA	84	UGCAUUAUGUCACUAGACCAUC	546
AV02436.µm	CUCUAGUGACAUUAUGCCACAA	85	UUUGGCAUUAUGUCACUAGAG	547
AV02437.µm	GUAGUGACAUUAUGCCACAUAA	86	UUUAUGUGGCAUUAUGUCACUAC	548
AV02438.µm	GAGUGACAUUAUGCCACAUACA	87	UGUAUGUGGCAUUAUGUCACUC	549
AV02439.µm	GCCAAAUAUUGGUGUCAAAAGUA	88	UACUUUGACCCAAAUAUUUUGGC	550
AV02440.µm	GAAAAUUAUUGGUGCAAAAGUGUA	89	UACACUUUUGACCCAAAUAUUUC	551
AV02441.µm	GAAUGAAAUAUUAUUAUGAAAGA	90	UCCUACAUAUUUGAUUUUCAUUC	552
AV02442.µm	GAUGAAAUAUUAUUAUGAAAGAA	91	UUCCUACAUAUUUGAUUUCAUUC	553
AV02443.µm	GUGAUAUUAUUAUUAUGAAAGACA	92	UGUCUUACAUAUUUGAUUUCAAC	554
AV02444.µm	CAAAUUAUUAUUAUGAAAGACCAA	93	UUUGUCUUACAUAUUUGAUUUUG	555
AV02445.µm	GAUCAAUUAUUAUGAAAGACCACAA	94	UUUGUGUCUUACAUAUUUGAUUC	556
AV02446.µm	GUCAAUUAUUAUGAAAGACCACAAAA	95	UUUGUGGUCUUACAUAUUUGAC	557

AV02447.µm	GAUUUAUGAAGACCACAAGUUA	96	UAACUUGUGGUCUUCAUUAUC	558
AV02448.µm	GUUUGAAGACCACAAGUUGAA	97	UUCAACUUGUGGUCUUCAUUAC	559
AV02449.µm	GAUUGAAGACCACAAGUUGAAA	98	UUUCAACUUGUGGUCUUCAUUC	560
AV02450.µm	GGAAGACCACAAGUUGAAGUA	99	UACUUC AACUUGUGGUCUUC	561
AV02451.µm	GAGACCACAAGUUGAAGUCAA	100	UUGACUUC AACUUGUGGUCUC	562
AV02452.µm	GCAAGUUUGAAGUCAGGGACUA	101	UAGUCCCUGACUUC AACUUGC	563
AV02453.µm	GAAGUUUGAAGUCAGGGACUAA	102	UUAGUCCCUGACUUC AACUUC	564
AV02454.µm	GAGUUUGAAGUCAGGGACUAAA	103	UUUAGUCCCUGACUUC AACUC	565
AV02455.µm	CUUGAAGUCAGGGACUUAACAA	104	UUGUUAGUCCCUGACUUC AAG	566
AV02456.µm	GAGUCAGGGACUUAACACCAAA	105	UUUGGUGUUAGUCCCUGACUC	567
AV02457.µm	CUCAAGGACUUAACACCAAGAA	106	UUCUUUGGUGUUAGUCCCUGAG	568
AV02458.µm	GGACUUGAUGGAUUUGCAACA	107	UGUUUGGCAUUC CAUCCAGUCC	569
AV02459.µm	CACUGAUGGAUUUGCACAACAA	108	UUGUUUGGCAUUC CAUCCAGUG	570
AV02460.µm	CACCCAAUUAUCUGUCAUUGAA	109	UUCAAUUGACAGUAAUUGGGUG	571
AV02461.µm	GCCCAUUAUCUGUCAUUGAGA	110	UCAUCCAUGACAGUAAUUGGC	572
AV02462.µm	GCAAUUAUCUGUCAUUGAGAA	111	UUCAUCCAUGACAGUAAUUGC	573
AV02463.µm	GAUUUAUCUGUCAUUGAGAGAA	112	UUCUCAUCCAUGACAGUAAUUC	574
AV02464.µm	GUUACUGUCAUUGAUAGAGUA	113	UAUUCUCAUCCAUGACAGUAAAC	575
AV02465.µm	GACUGUCAUUGAUAGAGAUCCA	114	UGGAUUCUCAUCCAUGACAGUUC	576
AV02466.µm	GAUUUGCAAGGAUUCGCAAAAA	115	UUUUUUGCGAUUC CUUGCCAAUUC	577
AV02467.µm	GCAAGGAGGAUUUAUCUGGAA	116	UUCCAGAUUAUUC CUUCCUUGC	578
AV02468.µm	GGGGAAGGAUUUAUCUGGAUGUA	117	UACAUCCAGAUUAUUC CUCCCC	579
AV02469.µm	CGGAGGAUUUAUCUGGAUGUCA	118	UGACAUCCAGAUUAUUC CUCCG	580
AV02470.µm	CGAGGAUUUAUCUGGAUGUCCA	119	UAGACAUCCAGAUUAUUC CUCCG	581
AV02471.µm	CAGGAUUUAUCUGGAUGUCUAA	120	UUAGACAUCCAGAUUAUUC CUUG	582
AV02472.µm	GGGAUUUAUCUGGAUGUCUAVUA	121	UUAUAGACAUCCAGAUUAUUC CC	583
AV02473.µm	CGAUUAUCUGGAUGUCUAVUGA	122	UCAUAGACAUCCAGAUUAUUC G	584
AV02474.µm	GUUUCUGGAUGUCUAVUGUUA	123	UACACAUAGACAUUC CAAGAUAC	585
AV02475.µm	GAUUCUGGAUGUCUAVUGUGUUA	124	UAAACAUAUAGACAUUC CAAGAUUC	586
AV02476.µm	GUUCUGGAUGUCUAVUGUGUUUA	125	UAAACACAUAUAGACAUUC CAAGAC	587
AV02477.µm	GUUGGAUGUCUAVUGUGUUUGGA	126	UCCAAACACAUAUAGACAUUC CCAC	588

AV02478.µm	CGUGAACCAAGUGAACAUCAA	127	UUGAUGUUCACUUGGUCACG	589
AV02479.µm	CUGAACCAAGUGAACAUCAAA	128	UUUGAUGUUCACUUGGUCAG	590
AV02480.µm	GGAACCAAGUGAACAUCAUA	129	UAUUGAUGUUCACUUGGDUCC	591
AV02481.µm	CAACCAAGUGAACAUCAUUA	130	UCAUUGAUGUUCACUUGGDUU	592
AV02482.µm	GACCAAGUGAACAUCAUUGCA	131	UGCAUUGAUGUUCACUUGGUC	593
AV02483.µm	GCAAGUGAACAUCAUUGCUUA	132	UAAAGCAUUGAUGUUCACUUGC	594
AV02484.µm	GAAGUGAACAUCAUUGCUUA	133	UAAAGCAUUGAUGUUCACUUC	595
AV02485.µm	GGUGAACAUCAUUGCUUUGA	134	UCCAAAGCAUUGAUGUUCACC	596
AV02486.µm	CUGAACAUCAUUGCUUUGGCA	135	UGCCAAAGCAUUGAUGUUCAG	597
AV02487.µm	CAACAUCAUUGCUUUGGCUUA	136	UAAAGCCAAAGCAUUGAUGUUG	598
AV02488.µm	GACAUCAUUGCUUUGGCUUCA	137	UGAAGCCAAAGCAUUGAUGUUC	599
AV02489.µm	GAAUUGCUUUGGCUUCCAAAGAA	138	UUCUUGGAAAGCCAAAGCAUUC	600
AV02490.µm	GUUGCUUUGGCUUCCAAAGAAAA	139	UUUUUUGGAAAGCCAAAGCAC	601
AV02491.µm	GUUGGCUUCCAAAGAAAGACAA	140	UUUGCUUUUUGGAAAGCCAAC	602
AV02492.µm	CGCUUCCAAAGAAAGACAUUA	141	UCAUUGUUCUUUCUUGGAAGCG	603
AV02493.µm	CCUUBCCAAAGAAAGACAUUGAA	142	UUCAUUGUUCUUUCUUGGAAGG	604
AV02494.µm	GUUCCAAAGAAAGACAUUGAGA	143	UUCUUAUUGUUCUUUCUUGGAAC	605
AV02495.µm	GCCAAGAAAAAGACAUUGAGCAA	144	UUGCUCAUUGUUCUUUCUUGGC	606
AV02496.µm	GCAAGAAAAAGACAUUGAGCAAAA	145	UUUGCUCAUUGUUCUUUCUUGC	607
AV02497.µm	GAGAAAGACAUUGAGCAACAAA	146	UUUGUUCUCAUUGUUCUUUCUC	608
AV02498.µm	CAAGACAUUGAGCAACAUUGA	147	UCAUGUUGCUCAUUGUUCUUUG	609
AV02499.µm	GAAGACAUUGAGCAACAUUGUA	148	UACAUUGUUGCUCAUUGUUCUUC	610
AV02500.µm	GAGACAUUGAGCAACAUUGUA	149	UCACAUUGUUGCUCAUUGUUCUC	611
AV02501.µm	CACAUUGAGCAACAUUGUUVUA	150	UAAACAUUGUUGCUCAUUGUG	612
AV02502.µm	GAAUGAGCAACAUUGUUCAAA	151	UUGAACACAUUGUUGCUCAUUC	613
AV02503.µm	GAUGAGCAACAUUGUUCAAAA	152	UUUGAAACACAUUGUUGCUCAUC	614
AV02504.µm	GUUGAGCAACAUUGUUCAAAA	153	UUUUUGAAACACAUUGUUGCUAC	615
AV02505.µm	GGAGCAACAUUGUUCAAAAAGA	154	UCUUUGAAACACAUUGUUGCUCC	616
AV02506.µm	CAGCAACAUUGUUCAAAAAGUA	155	UACUUUGAAACACAUUGUUGCUUG	617
AV02507.µm	GAGUCAAGGAUUAUGGAAAAACA	156	UGUUUUUCCAUUAUCCUUGACUC	618
AV02508.µm	GGUCAAGGAUUAUGGAAAAACCA	157	UGGUUUUCCAUUAUCCUUGACC	619

AV02509.µm	GAGGAUUAUGGAAAACCTUGAA	158	UCCAGGUTUUCCAUUCCUC	620
AV02510.µm	CAUAUGGAAAACCTUGAAGAA	159	UUCUUCCAGGUTUUCCAUUUG	621
AV02511.µm	CAGCUGCUCCTUGCACAGGAA	160	UUCCTUGGCAGGGAGCAGCUG	622
AV02512.µm	CCACAGGAUAUCAAAGCUCUA	161	UAGAGCUTUGAUUCCUGUGG	623
AV02513.µm	GACAGGAUAUCAAAGCUCUGA	162	UCAGAGCUTUGAUUCCUGUC	624
AV02514.µm	GCAGGAUAUCAAAGCUCUGUA	163	UACAGAGCUTUGAUUCCUGC	625
AV02515.µm	GAGGAUAUCAAAGCUCUGUA	164	UAACAGAGCUTUGAUUCCUC	626
AV02516.µm	GGGAUAUCAAAGCUCUGUUA	165	UAAACAGAGCUTUGAUUCCC	627
AV02517.µm	CGAUUAUCAAAGCUCUGUUUA	166	UCAACAGAGCUTUGAUUCCG	628
AV02518.µm	CAUAUCAAAGCUCUGUUUGUA	167	UACAAACAGAGCUTUGAUUUG	629
AV02519.µm	GUUCAAAGCUCUGUUUGUGA	168	UCACAACAGAGCUTUGAUUAC	630
AV02520.µm	GAUCAAAGCUCUGUUUGUGUA	169	UACACAACAGAGCUTUGAUUC	631
AV02521.µm	GCAAAGCUCUGUUUGUGUCUA	170	UAGACACAACAGAGCUTUUGC	632
AV02522.µm	GAAAAGCUCUGUUUGUGUCUGA	171	UCAGACACAACAGAGCUTUC	633
AV02523.µm	GAAGCUCUGUUUGUGUCUGAA	172	UUCAGACACAACAGAGCUTUC	634
AV02524.µm	GGCUCUGUUUGUGUCUGAGGA	173	UCCUCAGACACAACAGAGGCC	635
AV02525.µm	GUCUGUUUGUGUCUGAGGAGA	174	UCUCCUCAGACACAACAGAGAC	636
AV02526.µm	GGGAAGGAGGUCUACAUCAAA	175	UUBGAUGUAGACCTUCCUCCC	637
AV02527.µm	CGAAGGAGGUCUACAUCAAAGA	176	UCUUGAUGUAGACCTUCCUCCG	638
AV02528.µm	CAAGGAGGUCUACAUCCAAAGAA	177	UUCUUGAUGUAGACCTUCCUG	639
AV02529.µm	CGAGGUCUACAUCAAAGAUUGA	178	UCAUUCUUGAUGUAGACCTCG	640
AV02530.µm	CAGGUCUACAUCAAAGAUUGGA	179	UCCAUUCUUGAUGUAGACCTUG	641
AV02531.µm	GUUGUGAGAGAUUGCUCUAUUA	180	UAUUGAGCAUCUCUCUCACAC	642
AV02532.µm	GGUGAGAGAGAUUGCUCUAUUA	181	UUAUUGAGCAUCUCUCUCACCC	643
AV02533.µm	CUGAGAGAGAUUGCUCUAUUA	182	UAUAUUGAGCAUCUCUCUCACG	644
AV02534.µm	GGAGAGAGAUUGCUCUAUUAUGA	183	UCAUAUUGAGCAUCUCUCUCUCC	645
AV02535.µm	CAGAGAGAUUGCUCUAUUAUGCA	184	UGCAUAUUGAGCAUCUCUCUCUG	646
AV02536.µm	GAGGCUAUAGACAAGGUCAAAGA	185	UCUUGACUUBUGCAUAGCCUC	647
AV02537.µm	GUUAUGACAAGGUCAAAGGACAA	186	UUGUCCUUGACUUBUGCAUAC	648
AV02538.µm	GAUGACAAGGUCAAAGGACAUUA	187	UAUGUCCUUGACUUBUGCAUUC	649
AV02539.µm	GGACAAGGUCAAAGGACAUUCUA	188	UAAGAUUCCUUGACUUBUGUCC	650

AV02540.µm	CUGGUCACCCCUCCGUUCCUA	189	UAGGAACCGAGGGGUGACCAG	651
AV02541.µm	GCCUCGGUUCUUCUUUGUACUGA	190	UCAGUACAAAGGAACCGAGGC	652
AV02542.µm	GCUCGGUUCUUCUUUGUACUGGA	191	UCCAGUACAAAGGAACCGAGC	653
AV02543.µm	GUCCUUUUGUACUGGAGGAGUA	192	UACUCCUCCAGUACAAAGGAC	654
AV02544.µm	CAGUGAGUCCCUAUGCUGACA	193	UGUCAGCAUAGGGACUCACUG	655
AV02545.µm	GCAAVACUUGCAGAGGUGAUA	194	UAUCACCUUCGCAAGUAUUGC	656
AV02546.µm	GUACUUGCAGAGGUGAUAUCUA	195	UAGAAUACACCUUCGCAAGUAC	657
AV02547.µm	GCCCUUGAUAUUCACACAGAA	196	UUCUUUGGAACUAUCAAGGC	658
AV02548.µm	GCCUUGAUAUUCACACAGAGA	197	UCUCUUUGGAACUAUCAAGGC	659
AV02549.µm	GCUUGAUAUUCACACAGAGAA	198	UUCUCUUUGGAACUAUCAAGC	660
AV02550.µm	GGAUAGUUCACACAGAGAGUA	199	UACUUCUCUUUGGAACUAUCC	661
AV02551.µm	GGUUCACACAGAGAGAGUCCGUA	200	UAAACGACUUCUCUUUGGAACC	662
AV02552.µm	CUUCACACAGAGAGAGUCCGUUA	201	UAAACGACUUCUCUUUGGAAG	663
AV02553.µm	GUCCACACAGAGAGAGUCCGUUA	202	UGAAACGACUUCUCUUUGGAC	664
AV02554.µm	GCACACAGAGAGAGUCCGUUCAA	203	UUGAAACGACUUCUCUUUGGC	665
AV02555.µm	GACAAGAGAGAGUCCGUUCAUA	204	UAUGAAACGACUUCUCUUUGUC	666
AV02556.µm	GCAAGAGAGAGUCCGUUCAUUA	205	UAAUGAAACGACUUCUCUUGC	667
AV02557.µm	GAAAGAGAGAGUCCGUUCAUUA	206	UGAAUGAAACGACUUCUCUUC	668
AV02558.µm	GAGAGAGAGAGUCCGUUCAUCAA	207	UUGAAUGAAACGACUUCUCUC	669
AV02559.µm	GGAGAGAGAGUCCGUUCAUCAA	208	UUUGAAUGAAACGACUUCUCC	670
AV02560.µm	CAGAGAGAGUCCGUUCAUCAAAG	209	UCUUGAAUGAAACGACUUCUG	671
AV02561.µm	GGAAGAGAGUCCGUUCAUCAAAGUA	210	UACUUGAAUGAAACGACUUC	672
AV02562.µm	CAAGAGAGUCCGUUCAUCAAAGUUA	211	UAACUUGAAUGAAACGACUUG	673
AV02563.µm	GAGAGAGUCCGUUCAUCAAAGUUGA	212	UCAACUUGAAUGAAACGACUUC	674
AV02564.µm	GGUCGUUCCGUUCAUCAAAGUUGGA	213	UCCAACUUGAAUGAAACGACCC	675
AV02565.µm	CUCGUUCCGUUCAUCAAAGUUGGUA	214	UACCAACUUGAAUGAAACGAG	676
AV02566.µm	GCGUUCCGUUCAUCAAAGUUGGUGA	215	UACCAACUUGAAUGAAACGCG	677
AV02567.µm	GGUUUCCGUUCAUCAAAGUUGGUGUA	216	UACACCAACUUGAAUGAAACCC	678
AV02568.µm	CUGUUAUCCAGUUGGGGAGUUA	217	UUACUCCCCAGCUUGAUUACAG	679
AV02569.µm	GUUGGGAGUAGUGGAGUUGCUA	218	UAGACAUCCACUACUCCCCAC	680
AV02570.µm	GGUAGUGGAGUUGUCCGCAAAAA	219	UUUUUUGCAGACAUCCACUACC	681

AV02571.µm	GAGUGGATUGUCUGCAAAAACA	220	UGUUTUUUCAGACAUCCACUC	682
AV02572.µm	CGAUGUCUGCAAAAACCCAGAA	221	UUCUGGUUUUUGCAGACAUCCG	683
AV02573.µm	CAUGUCUGCAAAAACCCAGAAA	222	UUUCUGGUUUUUGCAGACAUUG	684
AV02574.µm	GUUCUCUGCAAAAACCCAGAGA	223	UUCUUCUGGUUUUUGCAGACAC	685
AV02575.µm	GA AAAACCAAGACGGCAAAAA	224	UUUUUGCCGCUUCUGGUUUUC	686
AV02576.µm	GUGAAGGAGAAAAACUCCAAAGAA	225	UUCUUUGAGUUUCUCCUUCAC	687
AV02577.µm	GGAGAGAGAAAAACUCCAAAGAU	226	UAUCUUUGAGUUUCUCCUUC	688
AV02578.µm	GGGAGAAACUCCCAAGAUAGAGA	227	UCUCAUCUUUGAGUUUCUCC	689
AV02579.µm	CAAAACUCCAAAGAUAGAGAUUA	228	UAAUCCUCAUCUUUGAGUUUG	690
AV02580.µm	GACUCCAAAGAUAGAGAUUUUA	229	UCAAAUCCUCAUCUUUGAGUUC	691
AV02581.µm	GAAGAUAGAGAUUUUGGUUUUA	230	UAAACCCAAAUCCUCAUCUUC	692
AV02582.µm	GGAUGAGGAUUUUGGUUUUCA	231	UGAAAAACCCAAAUCCUCAUCC	693
AV02583.µm	CAUGAGGAUUUUGGUUUUCUA	232	UAGAAAAACCCAAAUCCUCAUG	694
AV02584.µm	CCGUGGGAUUUUGAAUUAAAAACA	233	UGUUUUUAUUCCAAUCCCAAGG	695
AV02585.µm	CUGGGAUUUUGAAUUAAAAACAGA	234	UCUGUUUUUAUUCCAAUCCAG	696
AV02586.µm	GGGGAUUUUGAAUUAAAAACAGCA	235	UGUGUUUUUAUUCCAAUCCCC	697
AV02587.µm	CGGAUUUGAAUUAAAAACAGCUA	236	UAGCUUUUUUAUUCCAAUCCG	698
AV02588.µm	GAUUAAAAACAGCUCCGACAAAA	237	UUUGUCCGACGCUGUUUUUAUUC	699
AV02358-19-1.µm	GGUCUAAGGUCUCUGGAGUUUA	238	UAAAAUCCAGACCUAGACC	700
AV02359-19-1.µm	GGUCUUGAGUUUUCAGCUUA	239	UAAAGCUGAAACUCCAGACC	701
AV02360-19-1.µm	GUUCUGAGUUUUCAGCUUGA	240	UCAAGCUGAAACUCCAGAC	702
AV02361-19-1.µm	UCUGGAGUUUUCAGCUUGGA	241	UCCAAAGCUGAAACUCCAGA	703
AV02362-19-1.µm	AGUUUUCAGCUUUGGACACUA	242	UAGUGUCCAAAGCUGAAACU	704
AV02363-19-1.µm	GUUUUCAGCUUUGGACACUUA	243	UCAUGUCCAAAGCUGAAAC	705
AV02364-19-1.µm	CUUCCGACUUCUCCAAAGAA	244	UUUUUGGAGAAAGUCGGAAG	706
AV02365-19-1.µm	GUUGUCCCUUCUUGGCUUA	245	UGAAAGCCAGAAAGGACACAC	707
AV02366-19-1.µm	GUUCUCCUUCUUGGCUUUA	246	UUAGAAAGCCAGAAAGGACAC	708
AV02367-19-1.µm	AAGGACAGAGUGCAGAGAA	247	UUUCUUCGACUUCUGCCUU	709
AV02368-19-1.µm	CUUCGAGAAACGGGGAUUAA	248	UUUUUUCCCCGCUUCUGGAAG	710
AV02369-19-1.µm	CUACUACAUAUGUGAGUGAA	249	UUCACUCACAUAUUGUAGUAG	711
AV02370-19-1.µm	ACUACAUAUGUGAGUGAUGA	250	UCAUACUCACAUUUGUAGU	712

AV02371-19-1.µm	CUACAUGUGAGUGAUGAA	251	UUCAUCCACUCACAUUGUAG	713
AV02372-19-1.µm	UACA AUGUGAGUGAUGAGA	252	UCUCAUCACUCACAUUGUA	714
AV02373-19-1.µm	CAUUGUGAGUGAUGAGAU	253	UAUCUCAUCACUCACAUUG	715
AV02374-19-1.µm	AUGUGAGUGAUGAGAU	254	UAGAUCCAUCAUCACAU	716
AV02375-19-1.µm	UGUGAGUGAUGAGAU	255	UGAGAUCCAUCAUCACAU	717
AV02376-19-1.µm	GUGAGUGAUGAGAU	256	UAGAGAUCCAUCAUCACAU	718
AV02377-19-1.µm	UGAGUGAUGAGAU	257	UAAAGAUCCAUCAUCACAU	719
AV02378-19-1.µm	AGUGAUGAGAU	258	UGAAAGAGAUCCAUCAUC	720
AV02379-19-1.µm	GUGAUGAGAU	259	UGGAAAGAGAUCCAUCAUC	721
AV02380-19-1.µm	UGAUGAGAU	260	UUGGAAAGAGAUCCAUCAUC	722
AV02381-19-1.µm	GAUGAGAU	261	UGUGGAAAGAGAUCCAUCAUC	723
AV02382-19-1.µm	AGAUCU	262	UAGCAUGGAAAGAGAU	724
AV02383-19-1.µm	AUCUCU	263	UAUAGCAGUGGAAAGAGAU	725
AV02384-19-1.µm	UCUUCU	264	UGUCAUAGCAGUGGAAAGAU	726
AV02385-19-1.µm	CCACU	265	UUAAACCGUCAUAGCAGUG	727
AV02386-19-1.µm	ACU	266	UUGUAACCGUCAUAGCAGU	728
AV02387-19-1.µm	UGCUAUGACGGU	267	UAGUGUAACCGUCAUAGCA	729
AV02388-19-1.µm	CUAUGACGGU	268	UAGAGUGUAACCGUCAUAG	730
AV02389-19-1.µm	UAUGACGGU	269	UGAGAGUGUAACCGUCAUA	731
AV02390-19-1.µm	AGCGAU	270	UCCGUUGUCACAGAU	732
AV02391-19-1.µm	AGUAACCGCU	271	UUGUCCUUAAGCGGU	733
AV02392-19-1.µm	AAGACACCGCU	272	UGGUAAGUGACCGU	734
AV02393-19-1.µm	UGCCAAGACU	273	UCAUGAAGGAGU	735
AV02394-19-1.µm	GGCCGAAGCU	274	UGACAGGAAAGCU	736
AV02395-19-1.µm	CAGAGACCAU	275	UCUCCUUAUGGUCU	737
AV02396-19-1.µm	ACCAUAGAAAGAGU	276	UAUCCAGUCUUAUGGU	738
AV02397-19-1.µm	CCUUCAGGCU	277	UGUUAUGGAGCCU	739
AV02398-19-1.µm	CAGGCU	278	UAGAUUGUUAUGGAGCCU	740
AV02399-19-1.µm	CCAUGAACAU	279	UCCAAGGUAGAU	741
AV02400-19-1.µm	ACAUCU	280	UCUAGCACCGUAGAU	742
AV02401-19-1.µm	ACCUGGUGCU	281	UAUCCAUCUAGCACCGU	743

AV02402-19-1.µm	GGUGCUAGAUUGGAUCAGAA	282	UUCUGAUCCAUUCUAGCACC	744
AV02403-19-1.µm	CCAGCAACUUCACAGAGAGA	283	UCUCCUGUGAAGUUGCUGG	745
AV02404-19-1.µm	ACUUCACAGGAGGCCAAAAA	284	UUUUUGGCUCCUGUGAAGU	746
AV02405-19-1.µm	UUCACAGGAGGCCAAAAAGA	285	UCCUUUUUGGCUCCUGUGAA	747
AV02406-19-1.µm	UCACAGGAGGCCAAAAAGUA	286	UACUUUUUGGCUCCUGUA	748
AV02407-19-1.µm	GGAGCCAAAAAAGUGUCUAAA	287	UUAGACACUUUUUGGCUCC	749
AV02408-19-1.µm	GAGCCAAAAAAGUGUCUAGA	288	UCUAGACACUUUUUGGCUCC	750
AV02409-19-1.µm	GCCAAAAAAGUGUCUAGUCA	289	UGACUAGACACUUUUUGGC	751
AV02410-19-1.µm	CCAAAAAAGUGUCUAGUCA	290	UUGACUAGACACUUUUUGG	752
AV02411-19-1.µm	CAAAAAAGUGUCUAGUCAAA	291	UUUGACUAGACACUUUUUG	753
AV02412-19-1.µm	AAAAAGUGUCUAGUCAACUA	292	UAGUUAGACUAGACACUUUU	754
AV02413-19-1.µm	AAAGUGUCUAGUCAACUUAA	293	UUAAAGUUAGACUAGACACUU	755
AV02414-19-1.µm	AGUGUCUAGUCAACUUA AAA	294	UUUAAAGUUAGACUAGACACU	756
AV02415-19-1.µm	GUUCUAGUCAACUUAUUGA	295	UCAAUUUAAGUUAGACUAGAC	757
AV02416-19-1.µm	UCUAGUCAACUUAUUGAAA	296	UUCAAUUUAAGUUAGACUAGA	758
AV02417-19-1.µm	CUAGUCAACUUAUUGAGA	297	UCUCAAUUAAGUUAGACUAG	759
AV02418-19-1.µm	UAGUCAACUUAUUGAGAAA	298	UUCUCAAUUAAGUUAGACUA	760
AV02419-19-1.µm	AGUCAACUUAUUGAGAAA	299	UUUCUCAAUUAAGUUAGACU	761
AV02420-19-1.µm	CAACUUAUUGAGAGAAAGUA	300	UACCUUUCUCAAUUAAAGUUG	762
AV02421-19-1.µm	AACUUAUUGAGAGAAAGUGA	301	UCACCUUUCUCAAUUAAAGUU	763
AV02422-19-1.µm	UUAGAGAAAGUGGCCAAGUUA	302	UAAACUUUGCCACCUUUCUCAA	764
AV02423-19-1.µm	UGAGAAAGUGGCCAAGUUA	303	UUAAACUUUGCCACCUUUCUA	765
AV02424-19-1.µm	AGAAAGUGGCCAAGUUAUGA	304	UCAUUAACUUUGCCACCUUUCU	766
AV02425-19-1.µm	GGUGGCAAGUUAUUGGUGUA	305	UACACCAUUAACUUUGCCACCC	767
AV02426-19-1.µm	GUUGGCAAGUUAUUGGUGUA	306	UCACACCAUUAACUUUGCCACG	768
AV02427-19-1.µm	GGCAAGUUAUUGGUGUGAAA	307	UUUUCACACCAUUAACUUUGCC	769
AV02428-19-1.µm	AAGUUUAUUGGUGUGAAGCCA	308	UGGCUUUCACACCAUUAACUU	770
AV02429-19-1.µm	GUUAUUGGUGUGAAGCCAAA	309	UUUUGGCUUUCACACCAUUAAC	771
AV02430-19-1.µm	UGGUGUGAAGCCAAAGAUUA	310	UUUAUCCUUUGGCUUUCACACCA	772
AV02431-19-1.µm	GAUAUUGGUCUAGUGACAUUA	311	UAUUGUCACUAGACCAUUAUC	773
AV02432-19-1.µm	AUAUUGGUCUAGUGACAUUAA	312	UUUAUUGUCACUAGACCAUUAU	774

AV02433-19-1.µm	UAUGGUCUAGUGACAUUA	313	UAUAUGUCACUAGACCAUA	775
AV02434-19-1.µm	AUGGUCUAGUGACAUUAUGA	314	UCAUAUGUCACUAGACCAU	776
AV02435-19-1.µm	UGGUCUAGUGACAUUAUGCA	315	UGCAUAUGUCACUAGACCA	777
AV02436-19-1.µm	CUAGUGACAUUAUGCCACAA	316	UUGUGCAUAUGUCACUAG	778
AV02437-19-1.µm	AGUGACAUUAUGCCACAUAA	317	UUAUGUGCAUAUGUCACU	779
AV02438-19-1.µm	GUGACAUUAUGCCACAUACA	318	UGUAUGUGCAUAUGUCAC	780
AV02439-19-1.µm	CAAAAUUUUGGUCAAAGUA	319	UACUUUGACCCCAAUUUUG	781
AV02440-19-1.µm	AAAUUUUGGUCAAAGUGUA	320	UACACUUUGACCCCAAUUU	782
AV02441-19-1.µm	AUGAAAUCAAUUAUGAAGA	321	UCUUCAUAAUUGAUUUCAU	783
AV02442-19-1.µm	UGAAAUUCAAUUAUGAAGAA	322	UUCUUCAUAUUGAUUUCA	784
AV02443-19-1.µm	GAAAUCAAUUAUGAAGACA	323	UGUCUUCAUAUUGAUUUUC	785
AV02444-19-1.µm	AAUCAAUUAUGAAGACCAA	324	UUGGUCUUCAUAAUUGAUU	786
AV02445-19-1.µm	UCAAUUAUGAAGACCACAA	325	UUGUGGUCUUCAUAAUUGA	787
AV02446-19-1.µm	CAAUUAUGAAGACCACAAA	326	UUUGUGGUCUUCAUAAUUG	788
AV02447-19-1.µm	UUAUGAAGACCACAAAGUUA	327	UAACUUUGUGGUCUUCAUAA	789
AV02448-19-1.µm	AUGAAGACCACAAAGUUGAA	328	UUCAACUUUGUGGUCUUCAU	790
AV02449-19-1.µm	UGAAGACCACAAAGUUGAAA	329	UUUCAACUUUGUGGUCUUCA	791
AV02450-19-1.µm	AAGACCACAAAGUUUGAAGUA	330	UACUUCAACUUUGUGGUCUU	792
AV02451-19-1.µm	GACCACAAAGUUUGAAGUCA	331	UUGACUUCAACUUUGUGGUC	793
AV02452-19-1.µm	AAGUUGAAGUCAGGACUUA	332	UAGUCCCUGACUUUCAACUU	794
AV02453-19-1.µm	AGUUUGAAGUCAGGACUAAA	333	UUAGUCCCUGACUUUCAACU	795
AV02454-19-1.µm	GUUGAAGUCAGGACUAAAA	334	UUUAGUCCCUGACUUUCAAC	796
AV02455-19-1.µm	UGAAGUCAGGACUUAACAA	335	UUGUUAGUCCCUGACUUCA	797
AV02456-19-1.µm	GUCAAGGACUUAACACCAAA	336	UUUGGUGUUAGUCCCUGAC	798
AV02457-19-1.µm	CAGGGACUUAACACCAGAAA	337	UUCUUUGUGUUAGUCCCUG	799
AV02458-19-1.µm	ACUGAUUGGAUUUGCACAAACA	338	UGUUUGUGCAUUCCAUUCAGU	800
AV02459-19-1.µm	CUGAUUGGAUUUGCACAACAA	339	UUGUUUGUGCAUUCCAUUCAG	801
AV02460-19-1.µm	CCCAAUUAUCUGUCAUUGAA	340	UUCAAUUGACAGUAAUUGGG	802
AV02461-19-1.µm	CAAUUAUCUGUCAUUGAUGA	341	UCAUCCAUUGACAGUAAUUG	803
AV02462-19-1.µm	AAUUAUCUGUCAUUGAUGAA	342	UUCAUCCAUUGACAGUAAUU	804
AV02463-19-1.µm	UUACUUGUCAUUGAUGAGAA	343	UUCUCAUCCAUUGACAGUAA	805

AV02464-19-1.µm	UACUGUCATUUGAUGAGUA	344	UAUCUCAUCAUAGACAGUA	806
AV02465-19-1.µm	CUGUCATUUGAUGAGAUCCA	345	UGGAUUCUCAUCAUAGACAG	807
AV02466-19-1.µm	UUGGCAAGGAUCCGCAAAAA	346	UUUUUGCGAUUCCUUGCCAA	808
AV02467-19-1.µm	AAGGGAGGAUUAUCUGGAA	347	UUCGAGAUAAUCCUCCCUU	809
AV02468-19-1.µm	GGAAGAUUAUCUGGAGUUA	348	UACAUCCAGAUAAUCCUCC	810
AV02469-19-1.µm	GAGGAUUAUCUGGAGUCCA	349	UGACAUCCAGAUAAUCCUC	811
AV02470-19-1.µm	AGGAUUAUCUGGAGUGCUA	350	UAGACAUCCAGAUAAUCCU	812
AV02471-19-1.µm	GGAUUAUCUGGAGUGUCUAA	351	UUAGACAUCCAGAUAAUCC	813
AV02472-19-1.µm	GAUUAUCUGGAGUGUCUUA	352	UAUAGACAUCCAGAUAAUC	814
AV02473-19-1.µm	AUUAUCUGGAGUGUCUAVGA	353	UCAUAGACAUCCAGAUAAU	815
AV02474-19-1.µm	AUCUGGAGUGUCUAVUGUA	354	UACACAUAAGACAUCCAGAU	816
AV02475-19-1.µm	UCUGGAGUGUCUAVUGUUA	355	UAAACAUAAGACAUCCAGA	817
AV02476-19-1.µm	CUGGAGUGUCUAVUGUUA	356	UAAACACAUAAGACAUCCAG	818
AV02477-19-1.µm	GGAUUGUCUAVUGUUAUGGA	357	UCCAAAACAUAAGACAUC	819
AV02478-19-1.µm	UGAACCAAGUGAACAUCCAA	358	UUGAUUGUUCACUUGGUCA	820
AV02479-19-1.µm	GAACCAAGUGAACAUCAAA	359	UUUGAUUGUUCACUUGGUUC	821
AV02480-19-1.µm	AACCAAGUGAACAUCAUUA	360	UAUUGAUUGUUCACUUGGUU	822
AV02481-19-1.µm	ACCAAGUGAACAUCCAUUGA	361	UCAUUGAUUGUUCACUUGGU	823
AV02482-19-1.µm	CCAAAGUGAACAUCCAUUGCA	362	UGCAUUGAUUGUUCACUUGG	824
AV02483-19-1.µm	AAGUGAACAUCCAUUGCUUA	363	UAAAGCAUUGAUUGUUCACU	825
AV02484-19-1.µm	AGUGAACAUCCAUUGCUUA	364	UAAAAGCAUUGAUUGUUCACU	826
AV02485-19-1.µm	UGAACAUCCAUUGCUUUGGA	365	UCCAAAAGCAUUGAUUGUCA	827
AV02486-19-1.µm	GAACAUCCAUUGCUUUGGCA	366	UGCCAAAAGCAUUGAUUGUUC	828
AV02487-19-1.µm	ACAUCCAUUGCUUUGGCUUA	367	UAAAGCCAAAAGCAUUGAUUGU	829
AV02488-19-1.µm	CAUCAAUUGCUUUGGCUUCA	368	UGAAAGCCAAAAGCAUUGAUUG	830
AV02489-19-1.µm	AUGCUUUGGCUUCCCAAGAAA	369	UUUCUUUGGAAGCCAAAAGCAU	831
AV02490-19-1.µm	GCUUUGGCUUCCCAAGAAAA	370	UUUUUUUGGAAGCCAAAAGC	832
AV02491-19-1.µm	UGGCUUCCCAAGAAAGACAA	371	UUUGCUUUUUGGAAGCCA	833
AV02492-19-1.µm	CUUCCAAAGAAAGACAAUGA	372	UCAUUGUUCUUUUGGAAG	834
AV02493-19-1.µm	UUCCAAGAAAGACAAUGAA	373	UUCAUUGUUCUUUUGGAAG	835
AV02494-19-1.µm	UCCAAGAAAGACAAUUGAGA	374	UUCUUAUUGUUCUUUUGGA	836

AV02495-19-1.µm	CAAGAAAGACAUAUGAGCAA	375	UUGCUCAUUGUCUUCUUG	837
AV02496-19-1.µm	AAGAAAGACAUAUGAGCAAA	376	UUUGCUCAUUGUCUUCUU	838
AV02497-19-1.µm	GAAAGACAUAUGAGCAACAA	377	UUUGUGCUCAUUGUCUUUC	839
AV02498-19-1.µm	AAGACAUAUGAGCAACAUUGA	378	UCAUGUUUGCUCAUUGUCUU	840
AV02499-19-1.µm	AGACAUAUGAGCAACAUUGUA	379	UACAUGUUUGCUCAUUGUCU	841
AV02500-19-1.µm	GACAUAUGAGCAACAUUGUGA	380	UCACAUGUUUGCUCAUUGUC	842
AV02501-19-1.µm	CAAUAGAGCAACAUUGUGUUA	381	UAACACAUGUUUGCUCAUUG	843
AV02502-19-1.µm	AUGAGCAACAUUGUGUUCAA	382	UUGAACACAUGUUUGCUCAU	844
AV02503-19-1.µm	UGAGCAACAUUGUGUUCAAA	383	UUUGAACACAUGUUUGCUC	845
AV02504-19-1.µm	GAGCAACAUUGUGUUCAAAA	384	UUUUUGAACACAUGUUUGCUC	846
AV02505-19-1.µm	AGCAACAUUGUGUUCAAAGA	385	UCUUUUUGAACACAUGUUUGCU	847
AV02506-19-1.µm	GCAACAUGUGUUCAAAGUA	386	UACUUUUUGAACACAUGUUUGC	848
AV02507-19-1.µm	GUCAAGGAUAUGGAAAAACA	387	UGUUUUUCCAUATUCCUUGAC	849
AV02508-19-1.µm	UCAAGGAUAUGGAAAAACCA	388	UGGUUUUCCAUATUCCUUGA	850
AV02509-19-1.µm	GGAUAUUGGAAAAACCUUGAA	389	UUCCAAGUUUUUCCAUATUCC	851
AV02510-19-1.µm	UAUUGAAAAACCUUGAAGAA	390	UUUUUCCAGGUUUUUUCCAUUA	852
AV02511-19-1.µm	GCUGCUCUCCUUGCACAAGGAA	391	UUCCUUGUGCAGGGAGCAGC	853
AV02512-19-1.µm	ACAGGAUAUCAAAAGCUCUA	392	UAGAGCUUUUGAUATUCCUGU	854
AV02513-19-1.µm	CAGGAUAUCAAAAGCUCUGA	393	UCAGAGCUUUUGAUATUCCUG	855
AV02514-19-1.µm	AGGAUAUCAAAAGCUCUGUA	394	UACAGAGCUUUUGAUATUCCU	856
AV02515-19-1.µm	GGAUAUCAAAAGCUCUGUUA	395	UAAACAAGACUUUGAUATUCC	857
AV02516-19-1.µm	GAUAUCAAAAGCUCUGUUUA	396	UAAACAAGAGCUUUUGAUATUC	858
AV02517-19-1.µm	AUAUCAAAAGCUCUGUUUGA	397	UCAAAACAGAGCUUUUGAUATU	859
AV02518-19-1.µm	UAUCAAAAGCUCUGUUUUGUA	398	UACAAACAGAGCUUUUGAUUA	860
AV02519-19-1.µm	AUCAAAAGCUCUGUUUUGUA	399	UCACAACAGAGCUUUUGAUU	861
AV02520-19-1.µm	UCAAAAGCUCUGUUUUGUUA	400	UACACAACAGAGCUUUUGA	862
AV02521-19-1.µm	AAAGCUCUGUUUUGUGUUA	401	UAGACACAACAGAGCUUU	863
AV02522-19-1.µm	AAGCUCUGUUUUGUGUUGA	402	UCAGACACAACAGAGCUU	864
AV02523-19-1.µm	AGCUCUGUUUUGUGUCUGAA	403	UUCAGACACAACAGAGCU	865
AV02524-19-1.µm	CUCUGUUUUGUGUCUGAGGA	404	UCCUCAGACACAACAGAG	866
AV02525-19-1.µm	CUGUUUUGUGUCUGAGGAGA	405	UUCUCCUCAGACACAACACAG	867

AV02526-19-1.µm	GAAAGAGGUCUACAUCAA	406	UUUGAUUGUAGACCUCCU	868
AV02527-19-1.µm	AAGGAGGUCUACAUCAA	407	UCUUGAUUGUAGACCUCCU	869
AV02528-19-1.µm	AGGAGGUCUACAUCAA	408	UUCUUGAUUGUAGACCUCCU	870
AV02529-19-1.µm	AGGUCUACAUCAAAGAU	409	UCAUUCUUGAUUGUAGACCU	871
AV02530-19-1.µm	GGUCUACAUCAAAGAU	410	UCCAUCUUGAUUGUAGACC	872
AV02531-19-1.µm	GUUGAGAGAUUGCUCAU	411	UAUUGAGCAUCCUCUCAC	873
AV02532-19-1.µm	UGAGAGAGAUUGCUCAU	412	UUAUUGAGCAUCCUCUCA	874
AV02533-19-1.µm	GAGAGAGAUUGCUCAU	413	UAUAUUGAGCAUCCUCUC	875
AV02534-19-1.µm	AGAGAGAUUGCUCAU	414	UCAUUAUUGAGCAUCCUCU	876
AV02535-19-1.µm	GAGAGAUUGCUCAU	415	UGCAUUAUUGAGCAUCCUC	877
AV02536-19-1.µm	GGCUAUAGCAAAGUCA	416	UCUUGACUUBUGCAUAGCC	878
AV02537-19-1.µm	AUGACAAAAGUCAAGCA	417	UUGUCCUUGACUUBUGCAU	879
AV02538-19-1.µm	UGACAAAAGUCAAGCAU	418	UAUGUCCUUGACUUBUGCA	880
AV02539-19-1.µm	ACAAAAGUCAAGCAU	419	UAGAUUGUCCUUGACUUBU	881
AV02540-19-1.µm	GGUCAACCCUCCGUUC	420	UAGGAACCGAGGGGUGACC	882
AV02541-19-1.µm	CUCGGUUCUUBUGUACU	421	UCAGUACAAGGAACCGAG	883
AV02542-19-1.µm	UCCGUUCCUUBUGUACU	422	UCCAGUACAAGGAACCGA	884
AV02543-19-1.µm	CCUUBUGUACUUGAGGA	423	UACUCCUCCAGUACAAGG	885
AV02544-19-1.µm	GUAGUCCCUAUUGCU	424	UGUCAUCAUAGGGAACU	886
AV02545-19-1.µm	AAUACUUGCAGAGGU	425	UAUCACCCUCUGCAAGU	887
AV02546-19-1.µm	ACUUGCAGAGGUU	426	UAGAAUCCACCCUCGCA	888
AV02547-19-1.µm	CCUUGAUAGUUCACA	427	UUCUUGUGAACUUAUCA	889
AV02548-19-1.µm	CUUGAUAGUUCACA	428	UCUCUUGUGAACUUA	890
AV02549-19-1.µm	UUGAUAGUUCACA	429	UUCUCUUGUGAACUUA	891
AV02550-19-1.µm	AUAGUUCACAAGGA	430	UACUUCUCUUGUGAACU	892
AV02551-19-1.µm	UUCACAAGAGAAUGU	431	UAAACGACUUCUCUUG	893
AV02552-19-1.µm	UCACAAGAGAAUGU	432	UAAACGACUUCUCUUG	894
AV02553-19-1.µm	CACAAGAGAAUGU	433	UGAAACGACUUCUCUUG	895
AV02554-19-1.µm	ACAAGAGAAUGU	434	UUGAAACGACUUCUCUUG	896
AV02555-19-1.µm	CAAGAGAAUGU	435	UAUGAAACGACUUCUCUUG	897
AV02556-19-1.µm	AAGAGAAUGU	436	UAAUGAAACGACUUCUCU	898

AV02557-19-1.µm	AGAGAAGUCGUUUCAUUCA	437	UGAAUUGAAACGACUUCUCU	899
AV02558-19-1.µm	GAGAAGUCGUUUCAUUCAA	438	UGAAUUGAAACGACUUCUC	900
AV02559-19-1.µm	AGAAGUCGUUUCAUUCAA	439	UUUGAAUGAAACGACUUCU	901
AV02560-19-1.µm	GAAUCGUUUCAUUCAAGA	440	UCUUGAAUGAAACGACUUC	902
AV02561-19-1.µm	AAGUCGUUUCAUUCAAGUA	441	UACUUGAAUGAAACGACUU	903
AV02562-19-1.µm	AGUCGUUUCAUUCAAGUUA	442	UAAACUUGAAUGAAACGACU	904
AV02563-19-1.µm	GUUCGUUUCAUUCAAGUGA	443	UCAACUUGAAUGAAACGAC	905
AV02564-19-1.µm	UCGUUUCAUUCAAGUUGGA	444	UCCAACUUGAAUGAAACGA	906
AV02565-19-1.µm	CGUUUUCAUUCAAGUUGGUA	445	UACCAACUUGAAUGAAACG	907
AV02566-19-1.µm	GUUUCAUUCAAGUUGGUGA	446	UCACCAACUUGAAUGAAAC	908
AV02567-19-1.µm	UUUCAUUCAAGUUUGGUGUA	447	UACACCAACUUGAAUGAAA	909
AV02568-19-1.µm	GUAAUUCAGCUGGGGAGUAA	448	UUACUCCCCAGCUGAUUAC	910
AV02569-19-1.µm	GGGAGUAGUGGAGUGUCUA	449	UAGACAUCCACUACUCCCC	911
AV02570-19-1.µm	UAGUGGAGUGUCUGCAAAAA	450	UUUUUUGCAGACAUCCACUA	912
AV02571-19-1.µm	GUUGGAGUGUCUGCAAAAA	451	UGUUUUUGCAGACAUCCAC	913
AV02572-19-1.µm	AUGUCUGCAAAAAACGAGAA	452	UUCUGGUUUUUUGCAGACAU	914
AV02573-19-1.µm	UGUCUGCAAAAAACGAGAAA	453	UUUCUGGUUUUUUGCAGACA	915
AV02574-19-1.µm	GUUCUGCAAAAAACGAGAGA	454	UCUUCUGGUUUUUUGCAGAC	916
AV02575-19-1.µm	AAACCGAAAGCGGCAAAAA	455	UUUUUUGCCGCUUCUGGUUU	917
AV02576-19-1.µm	GAAAGAGAAACUCCAGAAGAA	456	UUCUUUGAGUUUUCUCCUUC	918
AV02577-19-1.µm	AAGGAGAAAACUCCAGAUA	457	UAUCUUUGGAGUUUUCUCCU	919
AV02578-19-1.µm	GAGAAACUCCAAAGAUUGAGA	458	UCUCAUCUUUGGAGUUUCUC	920
AV02579-19-1.µm	AACUCCAAAGAUUGAGAUUA	459	UAAUCCUCAUCCUUGGAGUU	921
AV02580-19-1.µm	CUCCAAGAUUGAGAUUUUGA	460	UCAAAUCCUCAUCCUUGGAG	922
AV02581-19-1.µm	AGAUUGAGAUUUUGGUAUA	461	UAAAACCCAAAUCCUCAUCU	923
AV02582-19-1.µm	AUGAGGAAUUUGGGUUUCA	462	UGAAAAACCCAAAUCCUCAU	924
AV02583-19-1.µm	UGAGGAUUUUUGGUUUUCUA	463	UAGAAAAACCCAAAUCCUCA	925
AV02584-19-1.µm	GUUGGAUUUGAAUUAAAAACA	464	UGUUUUUAUUUCAAUCCAC	926
AV02585-19-1.µm	GGGAUUUGAAUUAAAAACAGA	465	UCUGUUUUUAUUUCAAUCCC	927
AV02586-19-1.µm	GGAUUUGAAUUAAAAACAGCA	466	UGCUUUUUUAUUUCAAUCC	928
AV02587-19-1.µm	GAUUUGAAUUAAAAACAGCUA	467	UAGCUUUUUUAUUUCAAUCC	929

AV02588-19-1.µm	UUAAACAGCUGCGACAA	468	UUUGUGCGACGCUUUUAA	930
AV02022.µm	GACUUCACAUCAACCCUUU	1489	AAAGAGGUUGAUUGUAAAGUC	1596
AV02023.µm	CUGAAGCAGACAGCAGUAAUU	1490	AAUUAUCUGCUGUCUGCUUCAG	1597
AV02024.µm	UCCUUCCGACUUCUCCAAGAU	1491	AUCCUUGGAGAAAGUCGGAAGGA	1598
AV02025.µm	UCGGUUCUUUUUUAUCUGGAGU	1492	ACUCCAGUACAAAGGAACCGA	1599
AV02026.µm	ACUUGCUAUACAUUGGCAAGU	1493	ACUUGCCAAUGUAUAGCAAGU	1600
AV02027.µm	AUGAGCUGGCCAGAUAGACGUU	1494	AACGUCAUCUGGCCAGCUCAU	1601
AV05135.µm	GACGUUGUCCUUCUGGCUUA	1495	UAAGCCAGAAGGACACACGUC	1602
AV05136.µm	GCCCUACUACAUAUGUGAGUGA	1496	UCACUCACAUUUGUAGUAGGGC	1603
AV05137.µm	GUACAUAUGAGUGAUAGAGAA	1497	UUCUCAUCACUCACAUUUGUAC	1604
AV05138.µm	GCAUUGUGAGUGAUAGAGAUCA	1498	UGAUUCUCAUCCACUCACAUUGC	1605
AV05139.µm	GUCUUUCCACUCGUUAUGACGA	1499	UCCGUCAUAGCAGUGGAAAAGAC	1606
AV05140.µm	GACUUGCUAUGACGGUUAACACA	1500	UGUGUAAACCGUCAUAGCAGUC	1607
AV05141.µm	GUUCUCCGGGCGUCUGCCAUAUA	1501	UAUUGGCAGAGCCCCGGAGAC	1608
AV05142.µm	GCCGGGGCUCUGCCAUUCGCA	1502	UGCGAUUUGGCAGAGCCCCGGC	1609
AV05143.µm	GGACAGCGAUCUGUGACACA	1503	UGUUGUCCACAGAUCCGUGUC	1610
AV05144.µm	CCCAAGACTUCCUUCAUUGUACA	1504	UGUACAUGAAGGAGUCUUGGG	1611
AV05145.µm	GCAAGACTUCCUUCAUUGUACGA	1505	UCCGUACAUGAAGGAGUCUUGC	1612
AV05146.µm	GGACUCCUUCAUUGUACGACAA	1506	UUUGUCGUACAUGAAAGGAGUCC	1613
AV05147.µm	GAUCUACCUUGUGCUVAGAUUA	1507	UCAUCUAGCACCCAGGUAGAUU	1614
AV05148.µm	GGAUUGGAUUCAGACAGCAUUGA	1508	UCAAUUGCUGUCUGAUUCCAUCC	1615
AV05149.µm	GCACAGGAGCCAAAAAGUGUA	1509	UACACUUUUUUGGCUCUGUGC	1616
AV05150.µm	GACAGGAGGCCAAAAAGUGUCA	1510	UGACACUUUUUUGGCUCUGUC	1617
AV05151.µm	GCAGGAGGCCAAAAAGUGUCUA	1511	UAGACACUUUUUUGGCUCUGC	1618
AV05152.µm	GCAAAAAAGUGUCUAGUCAACA	1512	UGUUGACUAGACACUUUUUGC	1619
AV05153.µm	GAGUGUCUAGUCAACUUAUAUA	1513	UAUUAAGUUGACTUAGACACUUC	1620
AV05154.µm	GGUGUCUAGUCAACUUAUAUA	1514	UAAUUAAGUUGACUAGACACCC	1621
AV05155.µm	GAGUCAACUUAUUGAGAGAAGA	1515	UCUUUCUCAAUUUAAGUUGACUC	1622
AV05156.µm	GGUCAACUUAAUUGAGAAAGGA	1516	UCCUUUCUCAAUUAAGUUGACC	1623
AV05157.µm	GUUUGGUGUGAAGGCCAAGAUUA	1517	UAUUCUUUGGCUUCACACCAUAC	1624
AV05158.µm	GCCAGGCGAGUGUACAGCAUGA	1518	UCAUUGCUGUACACTUGCCUGGC	1625

AV05159.µm	CCAGUGUACAGCAUGAGAG	1519	UCUCAUCAUGCCUGUACACUGG	1626
AV05160.µm	GCUGAUGGAUUGCACAACAUA	1520	UAUGUUGUGCAAUCCAUCCAGC	1627
AV05161.µm	GUGAUGGAUUGCACAACAUGA	1521	UCAUGUUGUGCAAUCCAUCCAC	1628
AV05162.µm	GCCCAUUAUCUGUCAUUGAUA	1522	UAUCAUUGACAGUAUUGGGGC	1629
AV05163.µm	GAAAGGAGGAUUAUCUGGAUA	1523	UAUCCAGAUAAUCCUCCCUUC	1630
AV05164.µm	GCCAAUGUAACAUCAAUUGCUA	1524	UAGCAUUGAUGUUCACUUGGC	1631
AV05165.µm	GGAAAGACAUAUGAGCAACAUA	1525	UAUGUUGCUCAUUGUCUUC	1632
AV05166.µm	GACAUCAGAUAUGGGGAUAAA	1526	UUUAUCCCCAUUCUUGAUGUC	1633
AV05167.µm	GCAUCAAGAUAUGGGGAUAAAG	1527	UCUUAUCCCCAUUCUUGAUGC	1634
AV05168.µm	GAUCCAAGAUAUGGGGAUAAAG	1528	UUCUUAUCCCCAUUCUUGAUC	1635
AV05169.µm	GUCAAGAUAUGGGGAUAAAGAAA	1529	UUUCUUAUCCCCAUUCUUGAC	1636
AV05170.µm	GCAAGAUAUGGGGAUAAAGAAAA	1530	UUUUUUAUCCCCCAUUCUUGC	1637
AV05171.µm	GAAGAUAUGGGGAUAAAGAAAGA	1531	UCUUUUUAUCCCCCAUUCUUC	1638
AV05172.µm	GAGAUUGGGGAUAAAGAAAAGGA	1532	UCCUUUUUAUCCCCCAUUCUC	1639
AV05173.µm	CGCUAUGACAAAAGUCCAAGGAA	1533	UUCUUUGACUUUGUCAUAGCG	1640
AV05174.µm	GAUGCUGACCCCAUUAUUAUUA	1534	UCAAGUAUUGGGGUCAGCAUC	1641
AV05175.µm	CGAGUAUGGGAUUGUCUCGAAA	1535	UUUGCAGACAUCCACUUAUCUG	1642
AV05176.µm	CUGGAUUGUCUGCAAAAACCAA	1536	UUUGUUUUUGCAGACAUUCCAG	1643
AV05177.µm	GCAAGAUAGGAUUAUUGGGUUA	1537	UAAACCCAAAUCCUCAUUCUUGC	1644
AV05178.µm	GAGGGUUUUCCUUGCUGACAAA	1538	UUGUCCAGCAGGAAACCCCUUC	1645
AV06327.µm	CAAUUGUAGUGAUGAGAUU	1539	AAUUCUAUCCAUCCACAUUG	1646
AV06328.µm	GACCAUUGUGAUGAUGAUAU	1540	AAUUCUAUCCAUCCACAUUGUC	1647
AV06329.µm	GAAAAAGUGUCUAAGUCAACUA	1541	UAGUUAGACUAGACACUUUUUC	1648
AV06330.µm	CCGCGGGAUUGGAUUAUAAACA	1542	UGUUUUAAUUAUCAAUCCCGCGG	1649
AV02022-19-1.µm	CUUUCACAUCAACCUUCUU	1543	AAAAGAGGUUGAUGUGAAAG	1650
AV02023-19-1.µm	GAAAGCAGACAGCAAGUAUUAU	1544	AAUUUAUUGUCUGUCUUGCUC	1651
AV02024-19-1.µm	CUUCCGACUUCUCCCAAGAU	1545	AUUCUUUGAGAAAGUCGGAAG	1652
AV02025-19-1.µm	GGUUCCCUUUUUAUUGGAGAU	1546	ACUCCAGUACAAGGAACC	1653
AV02026-19-1.µm	UUUCUUAUACAUAUUGGCAAGU	1547	ACUUGCCAAUUGUAUAGCAA	1654
AV02027-19-1.µm	GAGCUUGGCCAGAUUGACGUU	1548	AACGUCAUCUUGGCCAGCUC	1655
AV05135-19-1.µm	CGUGUGUCCUUCUUGGCUUA	1549	UAAGCCAGAAAGGACACACG	1656

AV05136-19-1.µm	CCUACUACAUAUGUGAGUGA	1550	UCACUCACACUUGUAGUAGG	1657
AV05137-19-1.µm	ACAAUUGUGAGUGAUGAGAA	1551	UUCUCAUCACUCACACAUUGU	1658
AV05138-19-1.µm	AAUUGUGAGUGAUGAGAUCA	1552	UGAUUCUCAUUCACUCACAUU	1659
AV05139-19-1.µm	CUUUCACUCUGUAUGACGA	1553	UCCGUCAUAGCAGUGGAAAG	1660
AV05140-19-1.µm	CUGCUAUGACGGUUAACACA	1554	UGUGUAACCGUCAUAGCAG	1661
AV05141-19-1.µm	CUCCGGGGCUCUCGCCAAUA	1555	UAUUGGCAGAGCCCCGGAG	1662
AV05142-19-1.µm	CGGGGUCUCUGCCAUCGCA	1556	UGCGAUUGGCAGAGCCCCG	1663
AV05143-19-1.µm	ACAGCGAUCUGUGACAACA	1557	UGUUGUCACAGAUCCGCUU	1664
AV05144-19-1.µm	CAAGACUCCUUCAUUGUACA	1558	UGUACAUGAAGGAAGUCUUG	1665
AV05145-19-1.µm	AAGACUCCUUCAUUGUACGA	1559	UCGUACAUGAAGGAGUCU	1666
AV05146-19-1.µm	ACUCCUUCAUUGUACGACAA	1560	UUGUCGUACAUGAAGGAGU	1667
AV05147-19-1.µm	UCUACCUGGUGCUAGAUGA	1561	UCAUCUAGCACCAAGGUAGA	1668
AV05148-19-1.µm	AUUGAUCAGACAGCAUUGA	1562	UCAAUUGCUGUCUGAUCCAU	1669
AV05149-19-1.µm	ACAGGAGCCAAAAAGUGUA	1563	UACACUUUUUGGCUCCUGU	1670
AV05150-19-1.µm	CAGGAGCCAAAAAGUGUCA	1564	UGACACUUUUUGGCUCCUG	1671
AV05151-19-1.µm	AGGAGCCAAAAAGUGUCUA	1565	UAGACACUUUUUGGCUCCU	1672
AV05152-19-1.µm	AAAAAGUGUCUAGUCAACA	1566	UGUUGACUAGACACUUUUU	1673
AV05153-19-1.µm	GUGUCUAGUCAACUUAUUA	1567	UAUUAAGUUGACUAGACAC	1674
AV05154-19-1.µm	UGUCUAAGUCAACUUAUUA	1568	UAAUUAAGUUGACUAGACA	1675
AV05155-19-1.µm	GUCAACUUAUUGAGAAGA	1569	UCUUCUCAUUAAGUUGAC	1676
AV05156-19-1.µm	UCAACUUAUUGAGAAGGA	1570	UCCUUCUCAUUAAGUUGA	1677
AV05157-19-1.µm	AUGGUGUGAAGCCAAAGUA	1571	UAUCUUUGGCUUCACACCAU	1678
AV05158-19-1.µm	CAGGCAGUGUACAGCAUGA	1572	UCAUGCUGUACACTGCCUG	1679
AV05159-19-1.µm	AGUGUACAGCAUGAUGAGA	1573	UCTUCAUCAUGCTUGUACACU	1680
AV05160-19-1.µm	UGAUGGAUUGCACAACAUA	1574	UAUGUUGUGCAAUCCAUCA	1681
AV05161-19-1.µm	GAUGGAUUGCACAACAUGA	1575	UCAUGUUGUGCAAUCCAUC	1682
AV05162-19-1.µm	CCAUAUACUGUCAUUGAUA	1576	UAUCCAUGACAGUAUUGG	1683
AV05163-19-1.µm	AGGAGGAUUAUCUGGAUA	1577	UAUCCAGAUUAUCCUCCU	1684
AV05164-19-1.µm	CAAGUGAACAUAUUGCUA	1578	UAGCAUUGAUGUUCACUUG	1685
AV05165-19-1.µm	AAAGACAUAUGACAACAUA	1579	UAUGUUGCUCAUUGUCUU	1686
AV05166-19-1.µm	CAUCAAGAUAUGGGGAUAAA	1580	UUUUAUCCCCCAUUCUUGAUG	1687

AV05167-19-1.µm	AUCAAGAATUGGGGAUAAGA	1581	UCUUAUCCCCAUUCUUGAU	1688
AV05168-19-1.µm	UCAAGAAUUGGGGAUAAGAA	1582	UUCUUAUCCCCAUUCUUGA	1689
AV05169-19-1.µm	CAAGAATUGGGGAUAAGAAA	1583	UUUCUUAUCCCCAUUCUUG	1690
AV05170-19-1.µm	AAGAATUGGGGAUAAGAAA	1584	UUUUUUUAUCCCCAUUCUU	1691
AV05171-19-1.µm	AGAAUUGGGGAUAAGAAA	1585	UCUUUUUAUCCCCAUUCU	1692
AV05172-19-1.µm	GAAUUGGGGAUAAGAAA	1586	UCCUUUUUAUCCCCAUUC	1693
AV05173-19-1.µm	CUAUGACAAAGUCAAGGAA	1587	UUCUUUAGACUUUGUCAUAG	1694
AV05174-19-1.µm	UGCUGACCCCAAUACUUGA	1588	UCAAGUAUUUGGGGUCAGCA	1695
AV05175-19-1.µm	AGUAGUGGAUUGUCUCGCAA	1589	UUUGCAGACAUCCACUACU	1696
AV05176-19-1.µm	GGAUUGUCUGCAAAAACCAA	1590	UUUGUUUUUGCAGACAUCC	1697
AV05177-19-1.µm	AAGAUGAGGAUUUUGGUUA	1591	UAAACCAAAUCCUCAUCUU	1698
AV05178-19-1.µm	GGGGUUUCCUCUGGACAA	1592	UUGUCCAGCAGGAAAACCC	1699
AV06328-19-1.µm	CAUUGUGAGUGAUGAGAUU	1593	AAUCUCAUCACUCACAUUG	1700
AV06329-19-1.µm	AAAAGUUGUCUAGUCCAACUA	1594	UAGUUGACUAGACACUUUU	1701
AV06330-19-1.µm	GCGGGAUUGAAUUUAAACA	1595	UGUUUUUAUUCAAUCCCCGC	1702

Sense strand sequences of AV02373.µm, AV02375.µm, AV02379.µm, AV02388.µm, AV02554.µm, and AV02584.µm are shown in table1, corresponding respectively position of 488-508, 491-511, 496-516, 518-538, 2242-2262, 2444-2464 of SEQ ID NO: 1.

Table 2 shows certain chemically modified CFB RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, an RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 2 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises is a duplex identified in a row in Table 2, column one and includes the sequence modifications show in the sense and antisense strand sequences in the same row in Table 2, columns three and six, respectively. In some embodiments of methods of the invention, a sequence shown in Table 2 may be attached to (also referred to herein as “conjugated to”) a compound capable of delivering the RNAi agent to a cell and/or tissue in a subject. A non-limiting example of a delivery compound that may be used in certain embodiments of the invention is a GalNAc-containing compound or a GLS-15*-containing compound. In Table 2, the first column indicates the Duplex AV# of the base sequences as shown in Table 1. Table 2 discloses Duplex AV# and also shows

chemical modifications included in sense and antisense sequence of the duplexes. For example, Table 1 shows base single-strand sequences SEQ ID NO: 7 (sense) and SEQ ID NO: 469 (antisense), which together are the double-stranded duplex identified as: Duplex AV# AV02358.un and Table 2 lists Duplex AV# AV02358, which indicates that the duplex of SEQ ID NO: 931 and SEQ ID NO: 1162 includes base sequences of SEQ ID NO: 7 and SEQ ID NO: 469, respectively, but with the chemical modifications shown in the sense and antisense sequences shown in columns three and six, respectively. The “Sense strand SS#” in Table 2 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 2 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six.

Table 2: provides chemically modified CFB RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. These sequences were used in certain *in vitro* testing studies described herein.

Duplex AV#	Sense strand SS#	Sense Sequence	SEQ ID NO.	Antisense strand AS#	Antisense Sequence	SEQ ID NO.
AV02358	AV02358-SS	g*a*ggucuaGfgUfcUfggauu*u*a	931	AV02358-AS	u*Af*aacuCfagaGfcUfaGfacc*u*c	1162
AV02359	AV02359-SS	g*a*ggucugGfaGfuUfucagcu*u*a	932	AV02359-AS	u*Af*aagcuGfaaacUfCfaGfacc*u*c	1163
AV02360	AV02360-SS	g*g*ggucugGfgUfuUfagcuu*g*a	933	AV02360-AS	u*CF*aagGfc(uUNA)gaaCfuCfaGfacc*c*c	1164
AV02361	AV02361-SS	c*g*ucuggaGfuUfuCfagcuu*g*a	934	AV02361-AS	u*CF*caAfg(cUNA)uggaaAfcUfcCfaga*c*g	1165
AV02362	AV02362-SS	c*g*aguuuicAfgCfuUfggacu*u*a	935	AV02362-AS	u*Af*guGfu(cUNA)caagCfuGfaAfacu*c*g	1166
AV02363	AV02363-SS	c*a*guuuecaGfcUfuGfagacac*u*a	936	AV02363-AS	u*CF*agUfg(uUNA)ccaaGfcUfgAfaac*u*g	1167
AV02364	AV02364-SS	g*c*c*cuuecgAfcUfuCfuccaag*a*a	937	AV02364-AS	u*Uf*f*cuugGfagaaGfuCfGfagag*u*c	1168
AV02365	AV02365-SS	g*c*ggugugCfcUfuCfugcuu*c*a	938	AV02365-AS	u*Gf*aagGfc(cUNA)agaaGfgAfcAfcac*u*g	1169
AV02366	AV02366-SS	c*u*ggugucUfuCfuGfugcuu*c*a	939	AV02366-AS	u*Uf*f*agaaGfcccagAfaGfgAfcac*a*g	1170
AV02367	AV02367-SS	c*g*aaugcaGfaGfuGfcaagc*a*a	940	AV02367-AS	u*Uf*gcUfc(uUNA)gcaacUfclUfgCfcuu*c*g	1171
AV02368	AV02368-SS	c*a*cuuecaGfaAfcGfuggauu*a*a	941	AV02368-AS	u*Uf*f*auucCfcccguUfclUfgGfagag*u*g	1172
AV02369	AV02369-SS	g*c*c*cuacuaCfaAfuGfugauu*a*a	942	AV02369-AS	u*Uf*f*caucCfacaUfclUfaGfuagag*u*c	1173
AV02370	AV02370-SS	g*u*acuacaAfuGfuGfagauu*g*a	943	AV02370-AS	u*CF*aucaCfucacAfuUfclUfaGfuagag*u*c	1174
AV02371	AV02371-SS	g*c*a*cuacaaUfgUfgAfgugauu*g*a	944	AV02371-AS	u*Uf*f*caucAfcucaCfaUfuGfuagag*u*c	1175
AV02372	AV02372-SS	g*c*c*uaacaauGfuGfaGfugauu*g*a	945	AV02372-AS	u*CF*ucauCFacucAfcAfuUfguaa*g*c	1176
AV02373	AV02373-SS	g*a*a*caauuGfaGfuGfauagaa*u*a	946	AV02373-AS	u*Af*ucucAfucauUfclUfaAfcAfuagag*u*c	1177
AV02374	AV02374-SS	g*a*a*augugaGfuGfaUfagauu*c*a	947	AV02374-AS	u*Af*gaucUfcaucAfcUfclUfaAfcuau*u*c	1178

AV02375	AV02375-SS	g*a*ugugagUfgAfuGfagaucuc*a*a	948	AV02375-AS	u*Gf*agauCfucauCfaCfuCfaac*a*u*c	1179
AV02376	AV02376-SS	g*u*ugugagUfgAfuGfauuc*u*a	949	AV02376-AS	u*Af*agagUfcauUfcaUfcau*c*a*c	1180
AV02377	AV02377-SS	g*g*ugugagAfuGfaGfauucuu*a*a	950	AV02377-AS	u*Af*agagAfucauAfuCfaCfuca*c*c	1181
AV02378	AV02378-SS	g*g*ugugagGfaGfaUfucuuu*a*a	951	AV02378-AS	u*Gf*aaagAfgaucUfcafuCfaCu*c*c	1182
AV02379	AV02379-SS	c*a*ugugagAfgAfuCfuuuu*c*a	952	AV02379-AS	u*Gf*gaagGfagauCfuCfaUfcau*c*u*g	1183
AV02380	AV02380-SS	g*g*ugugagGfaUfcaUfcauuc*a*a	953	AV02380-AS	u*Uf*ggaaAfgagUfcaUfcau*c*c	1184
AV02381	AV02381-SS	c*u*ugugagAfuCfuCfuuaac*a*a	954	AV02381-AS	u*Gf*ugagAfgagAfuCfuCfauc*a*g	1185
AV02382	AV02382-SS	g*g*agauucUfuCfuCfaucuc*a*a	955	AV02382-AS	u*Af*gcAfg(uUNa)ggaaAfgAfgAfuCu*c*c	1186
AV02383	AV02383-SS	g*g*auucUfuCfuCfaucuc*a*a	956	AV02383-AS	u*Af*uaagAfgagAfaAfgAfgau*c*c	1187
AV02384	AV02384-SS	g*c*ucuuuUfuCfuCfaucuc*a*a	957	AV02384-AS	u*Gf*uaauAfgagUfgGfaAfga*g*c	1188
AV02385	AV02385-SS	g*u*ccaucGfuAfuGfagucuu*a*a	958	AV02385-AS	u*Uf*aaccGfucauAfgCfaGfuag*a*c	1189
AV02386	AV02386-SS	g*c*acugcuAfuGfaCfagucuu*a*a	959	AV02386-AS	u*Uf*guacCfagucAfuAfgCfaguu*g*c	1190
AV02387	AV02387-SS	g*c*ugcuuGfaCfagfuuaac*a*a	960	AV02387-AS	u*Af*guuAfaccgUfcafuAfga*g*c	1191
AV02388	AV02388-SS	g*g*cuuagCfagfuUfcaucuc*a*a	961	AV02388-AS	u*Af*guuGfuacCfagUfcafuag*a*c	1192
AV02389	AV02389-SS	g*c*uaugagCfagfuUfcaucuc*a*a	962	AV02389-AS	u*Gf*agAfg(uUNa)guacCfagfuCfaa*g*g	1193
AV02390	AV02390-SS	g*c*agcagCfuGfuGfagucuu*a*a	963	AV02390-AS	u*Cf*cgUfu(uUNa)uacaAfgAfuCfaguu*g*c	1194
AV02391	AV02391-SS	g*c*agauccGfagfuUfgaaguc*a*a	964	AV02391-AS	u*Uf*guuUfcaagGfagfuUfcau*g*c	1195
AV02392	AV02392-SS	g*g*aagagCfagfuCfuCfaucuu*a*a	965	AV02392-AS	u*Gf*guAfg(uUNa)ugacGfagfuUfcau*c*c	1196
AV02393	AV02393-SS	g*c*ugcagGfaCfuCfuuaucuu*a*a	966	AV02393-AS	u*Cf*auagAfgagUfcafuGfaguc*a*c	1197
AV02394	AV02394-SS	c*u*ggcagAfgCfuUfcaucuu*a*a	967	AV02394-AS	u*Gf*agCfag(uUNa)aaagCfuUfcaGfaguc*a*g	1198
AV02395	AV02395-SS	g*g*acagagGfaAfgGfagucuu*a*a	968	AV02395-AS	u*Cf*ucCfu(uUNa)uauGfagUfcauGfuag*a*g	1199
AV02396	AV02396-SS	g*g*acagagGfagfuUfcaucuu*a*a	969	AV02396-AS	u*Af*ucagCfucauUfcauUfguu*c*c	1200
AV02397	AV02397-SS	g*u*ccuucGfagCfuCfauagaa*c*a	970	AV02397-AS	u*Gf*uucaUfgagCfagfuUfcauUfguu*c*c	1201
AV02398	AV02398-SS	g*u*ccuucGfagCfuCfauagaa*c*a	971	AV02398-AS	u*Af*guuUfcauGfagCfagfuUfcauUfguu*c*c	1202
AV02399	AV02399-SS	g*u*ccuucGfagCfuCfauagaa*c*a	972	AV02399-AS	u*Cf*caGfag(uUNa)agagCfuUfcauUfguu*c*c	1203
AV02400	AV02400-SS	c*a*acauuAfgCfuGfagucuu*a*a	973	AV02400-AS	u*Cf*uaGfag(uUNa)ccagGfuAfgAfuaguu*a*g	1204
AV02401	AV02401-SS	g*u*acucgUfagCfuAfgauaguu*a*a	974	AV02401-AS	u*Af*uccaUfcauGfagCfagfuUfcauUfguu*c*c	1205
AV02402	AV02402-SS	g*u*ggugcuAfgAfuGfagucuu*a*a	975	AV02402-AS	u*Uf*cuuUfcauGfagCfagfuUfcauUfguu*c*c	1206
AV02403	AV02403-SS	c*g*agagcuAfgAfuGfagucuu*a*a	976	AV02403-AS	u*Cf*ucCfu(uUNa)ugagGfuUfcauUfguu*c*c	1207
AV02404	AV02404-SS	g*a*acuuuGfagCfagfuUfcauUfguu*c*c	977	AV02404-AS	u*Uf*uuuGfagCfagfuUfcauUfguu*c*c	1208
AV02405	AV02405-SS	g*c*uuuGfagCfagfuUfcauUfguu*c*c	978	AV02405-AS	u*Cf*uuuUfagCfagfuUfcauUfguu*c*c	1209
AV02406	AV02406-SS	g*u*uaagGfagCfagfuUfcauUfguu*c*c	979	AV02406-AS	u*Af*cuuUfagCfagfuUfcauUfguu*c*c	1210
AV02407	AV02407-SS	g*a*ggagcuAfgAfgauaguu*a*a	980	AV02407-AS	u*Uf*agagCfaguuUfcauUfguu*c*c	1211

AV02408	AV02408-SS	g*g*gggccaAfaAfaGfugucua*g*a	981	AV02408-AS	u*Cf*uaagcCfaacuuUfuUfgGfecu*c*c	1212
AV02409	AV02409-SS	c*a*ggccaaaAfaGfuGfucuaigu*c*a	982	AV02409-AS	u*Gf*acuaGfaccuUfuUfuUfggc*u*g	1213
AV02410	AV02410-SS	g*g*ggccaaaAfgUfgUfcuaigu*c*a	983	AV02410-AS	u*Uf*ggacuAfgacaCfuUfuUfuug*c*c	1214
AV02411	AV02411-SS	c*c*cacaaaGfuCfuCfuaguca*a*a	984	AV02411-AS	u*Uf*ugacUfagacAfcUfuUfuug*g*g	1215
AV02412	AV02412-SS	g*a*aaagucGfuCfuAfgucac*u*a	985	AV02412-AS	u*Af*guugAfcuagAfcAfcUfuuu*u*c	1216
AV02413	AV02413-SS	g*a*aaagucCfuAfgUfcaacuu*a*a	986	AV02413-AS	u*Uf*aaquUfagacUfagAfcAfcuu*u*c	1217
AV02414	AV02414-SS	g*a*agugucUfaGfuCfacaaua*a*a	987	AV02414-AS	u*Uf*uaagUfugacUfagAfcAfcuu*u*c	1218
AV02415	AV02415-SS	c*u*guucugUfcAfaCfuuaauu*g*a	988	AV02415-AS	u*Cf*aaauAfguuGfaccfuAfgac*a*g	1219
AV02416	AV02416-SS	g*g*ucuaagUfaAfcUfuuaauu*g*a	989	AV02416-AS	u*Uf*caauUfaaguUfgAfcUfagac*a*g	1220
AV02417	AV02417-SS	c*u*cuagucAfaCfuUfaauuug*a*a	990	AV02417-AS	u*Cf*ucauUfaaguUfuGfaccfuag*c*c	1221
AV02418	AV02418-SS	g*c*uaagucAfcUfuAfuugag*a*a	991	AV02418-AS	u*Uf*cucaAfuuaGfuUfgAfcua*g*c	1222
AV02419	AV02419-SS	g*u*agucacAfuUfuAfuugag*a*a	992	AV02419-AS	u*Uf*ucuaAfuuaGfuUfuGfaccu*a*c	1223
AV02420	AV02420-SS	c*u*caacuAfaUfuGfagagug*a*a	993	AV02420-AS	u*Af*ccuuCfuaaUfuAfaGfuug*a*g	1224
AV02421	AV02421-SS	g*c*aacuuAfuUfgAfgaagug*a*a	994	AV02421-AS	u*Cf*accCfu(UfNA)cucaAfuUfaAfguu*g*c	1225
AV02422	AV02422-SS	g*a*uuagagAfgGfuGfcaagug*a*a	995	AV02422-AS	u*Af*acuuGfaccacCfuUfcUfcau*u*c	1226
AV02423	AV02423-SS	g*u*ugagagAfgUfgGfcaagug*a*a	996	AV02423-AS	u*Uf*aacuUfgcacCfcUfuCfuaa*a*c	1227
AV02424	AV02424-SS	g*g*agagagUfgGfcAfaaguuu*g*a	997	AV02424-AS	u*Cf*auaaCfuugcCfaCfcUfuuc*c*c	1228
AV02425	AV02425-SS	g*a*ggugagAfaCfuUfaugugug*a*a	998	AV02425-AS	u*Af*caacAfaaacUfuGfaccfuacc*u*c	1229
AV02426	AV02426-SS	g*g*guugagAfgUfuAfuugugug*a*a	999	AV02426-AS	u*Cf*acAfc(cUNa)auaaCfuUfgCfacc*c*c	1230
AV02427	AV02427-SS	c*u*ggcaagUfuAfuGfugugug*a*a	1000	AV02427-AS	u*Uf*ucaacAfcacuAfaCfuUfgCfacc*c*c	1231
AV02428	AV02428-SS	c*c*aaguuAfgGfuGfugaag*c*a	1001	AV02428-AS	u*Gf*gcUfu(cUNa)acacCfaUfaAfcuu*g*g	1232
AV02429	AV02429-SS	g*a*guuaugGfuGfuGfagaag*c*a	1002	AV02429-AS	u*Uf*uggcUfuacAfcCfaUfaac*u*c	1233
AV02430	AV02430-SS	g*a*guuaugGfuGfuGfagaag*c*a	1003	AV02430-AS	u*Uf*aucuUfggcUfcaAfcAfcu*u*c	1234
AV02431	AV02431-SS	g*g*auaugCfuAfgUfagaca*u*a	1004	AV02431-AS	u*Af*uaugUfcauAfgAfcCfauu*u*g	1235
AV02432	AV02432-SS	g*g*auaugUfcUfaGfugaaua*a*a	1005	AV02432-AS	u*Uf*auguUfcauAfgAfcCfauu*u*c	1236
AV02433	AV02433-SS	c*a*uaugucCfuAfgUfagaca*u*a	1006	AV02433-AS	u*Af*uaugUfcauAfgAfcCfauu*u*c	1237
AV02434	AV02434-SS	g*u*auugucUfaGfuGfacaauu*g*a	1007	AV02434-AS	u*Cf*auaaGfuaaUfaGfaccfaaua*a*c	1238
AV02435	AV02435-SS	g*a*ugugucAfgUfgAfaauug*c*a	1008	AV02435-AS	u*Gf*cauuUfgucaCfuAfgAfcu*u*c	1239
AV02436	AV02436-SS	c*u*cuagucAfcAfuAfuagacac*a*a	1009	AV02436-AS	u*Uf*guGfg(cUNa)auaaGfuCfaccfuag*a*g	1240
AV02437	AV02437-SS	g*u*agugacAfuAfuGfaccacua*a*a	1010	AV02437-AS	u*Uf*auguGfgcauAfuGfuCfaccu*a*c	1241
AV02438	AV02438-SS	g*a*guagacUfaUfgCfaccacua*c*a	1011	AV02438-AS	u*Gf*uaugUfgcaUfaUfgUfaccu*u*c	1242
AV02439	AV02439-SS	g*c*cacaaauUfuCfugGfucacaaug*u*a	1012	AV02439-AS	u*Af*cuuuGfaccacAfaAfuUfuugug*c*c	1243
AV02440	AV02440-SS	g*a*aaauuGfgGfuCfaagugug*u*a	1013	AV02440-AS	u*Af*cauuUfgacCfcaAfaAfuuu*u*c	1244

AV02441	AV02441-SS	g*a*augaaUfcaUfaUfaugaa* ^g a	1014	AV02441-AS	u*CF*uucaUfaauGfaUfuUfcau* ^u c	1245
AV02442	AV02442-SS	g*a*ugaaauCfaAfuUfaugaa* ^g a	1015	AV02442-AS	u*Uf*cuucAfuauUfgAfuUfuca* ^u c	1246
AV02443	AV02443-SS	g*u*ugaaucAfaUfuAfuuga* ^c a	1016	AV02443-AS	u*Gf*ueucAfuauAfuGfaUfuuc* ^a c	1247
AV02444	AV02444-SS	c*a*aaucuaUfuAfuGfaagc* ^a a	1017	AV02444-AS	u*Uf*ggucUfucauAfaUfuGfaau* ^u g	1248
AV02445	AV02445-SS	g*a*uaauuAfuGfaAfgaac* ^a a	1018	AV02445-AS	u*Uf*guGfg(uUNA)cuucafuAfaUfuga* ^u c	1249
AV02446	AV02446-SS	g*u*cauuuUfgAfaGfaacca* ^a a	1019	AV02446-AS	u*Uf*ugugGfuucCfaUfaAfuug* ^a c	1250
AV02447	AV02447-SS	g*a*uaaugAfgAfcCfaacagu* ^u a	1020	AV02447-AS	u*Af*acuGfugucCfuUfcafuua* ^u c	1251
AV02448	AV02448-SS	g*u*auagagAfcCfaCfaagug* ^a a	1021	AV02448-AS	u*Uf*caacUfugugGfuCfuUfcau* ^a c	1252
AV02449	AV02449-SS	g*a*ugaaagCfcaAfcAfaugaa* ^a a	1022	AV02449-AS	u*Uf*ucaacAfaucUfugUfcaUfcau* ^u c	1253
AV02450	AV02450-SS	g* ^g a*aaagacAfcAfaGfuugaa* ^u a	1023	AV02450-AS	u*Af*cuucAfaucUfugUfcaUfcau* ^c c	1254
AV02451	AV02451-SS	g*a*ggaccAfaGfuUfgaaguc* ^a a	1024	AV02451-AS	u*Uf*ggacuUfcaacUfuGfuGfuuc* ^u c	1255
AV02452	AV02452-SS	g*c*aaugagAfaGfuCfaagagc* ^u a	1025	AV02452-AS	u*Af*guCfc(cUNA)ugacUfuCfaAfcuu* ^g c	1256
AV02453	AV02453-SS	g*a*aguuagAfuUfcaAfggagc* ^a a	1026	AV02453-AS	u*Uf*agUf(cUNA)cuagCfuUfcaAfcu* ^u c	1257
AV02454	AV02454-SS	g*a*guugagGfuCfaGfgagaa* ^a a	1027	AV02454-AS	u*Uf*uaugUfcuagAfcUfuCfaac* ^u c	1258
AV02455	AV02455-SS	c*u*ugaaugCfaGfgGfaucua* ^a a	1028	AV02455-AS	u*Uf*guuaGfuuccUfgAfcUfuca* ^a g	1259
AV02456	AV02456-SS	g*a*guacagGfaCfuAfaacac* ^a a	1029	AV02456-AS	u*Uf*ugugGfuugUfcaUfcau* ^u c	1260
AV02457	AV02457-SS	c* ^u a*caugagCfuAfaCfaacaa* ^a a	1030	AV02457-AS	u*Uf*cuugGfuuuAfgUfcaCfuag* ^a g	1261
AV02458	AV02458-SS	g* ^g a*acuagGfaUfuUfgacaa* ^c a	1031	AV02458-AS	u*Gf*uuGfu(uNA)caucCfaCfuCfuag* ^c c	1262
AV02459	AV02459-SS	c*a*cuagagGfaUfuGfaacac* ^a a	1032	AV02459-AS	u*Uf*guugUfcaUfcaUfcau* ^u g	1263
AV02460	AV02460-SS	c*a*cccauUfaCfuGfucauug* ^a a	1033	AV02460-AS	u*Uf*cauGfaacagUfaAfuUfgg* ^u g	1264
AV02461	AV02461-SS	g*c*cauuacCfuGfuCfaugau* ^g a	1034	AV02461-AS	u*CF*aucaAfuagCfaGfuAfaau* ^g c	1265
AV02462	AV02462-SS	g*c*aauiacUfgUfcaAfuugag* ^a a	1035	AV02462-AS	u*Uf*cucaUfcauGfaCfaGfuua* ^u c	1266
AV02463	AV02463-SS	g*a*uaucugUfcaAfuUfgaag* ^a a	1036	AV02463-AS	u*Uf*ueucAfucaUfcaUfcau* ^u c	1267
AV02464	AV02464-SS	g*u*uaucugUfcaAfuUfgaag* ^u a	1037	AV02464-AS	u*Af*ueucAfucaUfcaUfcau* ^a c	1268
AV02465	AV02465-SS	g*a*uuugagUfuGfaUfgaag* ^c a	1038	AV02465-AS	u*Gf*gaUf(cUNA)caucAfaUfgAfcag* ^u c	1269
AV02466	AV02466-SS	g*a*uuugagUfuGfaUfgaag* ^a a	1039	AV02466-AS	u*Uf*uuugCfgaucCfuUfgCfaa* ^u c	1270
AV02467	AV02467-SS	g*c*aaugagGfaUfuUfaucug* ^a a	1040	AV02467-AS	u*Uf*ccagAfuauCfcaUfcau* ^g c	1271
AV02468	AV02468-SS	g* ^g a*ggagagUfuAfuCfuugag* ^u a	1041	AV02468-AS	u*Af*caucAfaucUfcaUfcau* ^c c	1272
AV02469	AV02469-SS	c* ^g a*ggagagUfuUfcaUfgaag* ^c a	1042	AV02469-AS	u*Gf*acAfu(cUNA)caagUfaAfuCfuuc* ^c g	1273
AV02470	AV02470-SS	c* ^g a*ggagagUfuCfuGfaugag* ^u a	1043	AV02470-AS	u*Af*gaacUfcaagAfuAfuUfcau* ^c g	1274
AV02471	AV02471-SS	c*a*gaauaUfcaUfgGfaugag* ^a a	1044	AV02471-AS	u*Uf*agacAfucaGfaUfaAfuuc* ^u g	1275
AV02472	AV02472-SS	g* ^g a*gaauaCfuGfaUfuugua* ^u a	1045	AV02472-AS	u*Af*uaagCfaucAfgAfuAfauc* ^c c	1276
AV02473	AV02473-SS	c* ^g a*auuacUfgGfaUfguau* ^g a	1046	AV02473-AS	u*CF*auagAfaucCfaGfaUfaau* ^c g	1277

AV02474	AV02474-SS	g* u* a u c u g a A f u G f u C f u a u g u g* u* a	1047	AV02474-AS	u* A f* c a c a U f a g a c A f u C f c A f g a u* a* c	1278
AV02475	AV02475-SS	g* a* u c u g g a U f g U f c U f a u g u g u* u* a	1048	AV02475-AS	u* A f* a c a c A f u a g a C f a U f c C f a g a u* u* c	1279
AV02476	AV02476-SS	g* u* c u g g a u G f u C f u A f u g u g u u* u* a	1049	AV02476-AS	u* A f* a a c a C f a u g a A f c A f u C f e a g* a* c	1280
AV02477	AV02477-SS	g* u* g g a u g u C f u A f u G f u g u u g u g* g* a	1050	AV02477-AS	u* C f* c a a c A f a c a u A f g A f c A f u c c* a* c	1281
AV02478	AV02478-SS	c* g* g* a a c c A f a G f u G f u a c a u c* a* a	1051	AV02478-AS	u* U f* g a u g U f u c a c U f u G f g U f u c a* c* g	1282
AV02479	AV02479-SS	c* u* g* g a c c a A f g U f g A f a c a u c a* a* a	1052	AV02479-AS	u* U f* u g a u G f u u c a C f u U f g G f u u c* a* g	1283
AV02480	AV02480-SS	g* g* a a c c a c A f u G f u A f a c a u c a* u* a	1053	AV02480-AS	u* A f* u u g a U f g u u c A f c U f u G f g u u* c* c	1284
AV02481	AV02481-SS	c* a* a c c a a g U f g A f a C f a u c a u* g* a	1054	AV02481-AS	u* C f* a u u g A f u g u u C f a C f u U f g g u* u* g	1285
AV02482	AV02482-SS	g* a* c c a a g u G f a A f c A f u c a u g u* c* a	1055	AV02482-AS	u* G f* c a u u G f a u g u U f c A f c U f u g g u* u* c	1286
AV02483	AV02483-SS	g* c* a a g u g a A f c A f u C f a u g c u u* u* a	1056	AV02483-AS	u* A f* a g c a U f u g a u G f u U f c A f c u u* g* c	1287
AV02484	AV02484-SS	g* a* a g u g a c A f a U f c A f a u g c u u* u* a	1057	AV02484-AS	u* A f* a a g c A f u g a U f g U f u C f a c u u* u* c	1288
AV02485	AV02485-SS	g* g* u g a a a c A f a f a U f g c u u u g* g* a	1058	AV02485-AS	u* C f* c a A f a (g U N A) c a u u G f a U f g U f u c a* c* c	1289
AV02486	AV02486-SS	c* u* g* g a c a c A f a A f u G f c u u u g* u* a	1059	AV02486-AS	u* G f* c c A f a (a U N A) g c a u U f g A f u G f u u c* a* g	1290
AV02487	AV02487-SS	c* a* a c a u c a A f u G f c U f u u g c u u* c* a	1060	AV02487-AS	u* A f* a g c c A f a g c A f u U f g A f u g u* u* g	1291
AV02488	AV02488-SS	g* a* c a u c a a U f g C f u U f u g g c u u* c* a	1061	AV02488-AS	u* G f* a a G f c (c U N A) a a a g C f a U f u G f a u g* u* c	1292
AV02489	AV02489-SS	g* a* a u g c u u U f g G f c U f u c c a g u* a* a	1062	AV02489-AS	u* U f* c u u g G f a a g c C f a A f a G f c a u* u* c	1293
AV02490	AV02490-SS	g* u* g c u u u g G f c U f u C f c a a g a* a* a	1063	AV02490-AS	u* U f* u u c u U f g g a G f c C f a A f a g c* a* c	1294
AV02491	AV02491-SS	g* u* u g g c u n C f c A f a G f a a a g a* a* a	1064	AV02491-AS	u* U f* g u c u U f u c u u G f g A f a G f c a* a* c	1295
AV02492	AV02492-SS	c* g* c u u c c a A f g A f a A f g a c a u* g* a	1065	AV02492-AS	u* C f* a u u g U f c u u u C f u U f g G f a a g* c* g	1296
AV02493	AV02493-SS	c* c* u u c c a a G f a A f a G f a c a u g* a* a	1066	AV02493-AS	u* U f* c a u u G f u c u u U f c U f u G f a a g* g* g	1297
AV02494	AV02494-SS	g* u* u c c a a g A f a A f c A f a c a u g a* g* a	1067	AV02494-AS	u* C f* u c a u U f g u c U f u C f u U f g g a* a* c	1298
AV02495	AV02495-SS	g* c* c a a g a a A f g A f c A f a u g g c* a* a	1068	AV02495-AS	u* U f* g u c u c A f u g u C f u U f u C f u u g* g* c	1299
AV02496	AV02496-SS	g* c* a a g a a a G f a A f u G f a g a c* a* a	1069	AV02496-AS	u* U f* u g c u C f a u g U f c U f u U f c u u* g* c	1300
AV02497	AV02497-SS	g* a* g a a a g C f a A f u G f a g a c* a* a	1070	AV02497-AS	u* U f* g u u g C f u c a u U f g U f c U f u c* u* c	1301
AV02498	AV02498-SS	c* a* a a g a c a A f u G f a G f a c a c a u* g* a	1071	AV02498-AS	u* C f* a u g u U f g u c A f u U f g U f c u u* u* g	1302
AV02499	AV02499-SS	g* a* a g a c a a U f g A f g C f a a c a u g* u* a	1072	AV02499-AS	u* A f* c a u g U f u g c U f a U f u G f u c u* u* c	1303
AV02500	AV02500-SS	g* a* g c a a u G f a G f c A f a c a u g u* g* a	1073	AV02500-AS	u* C f* a c a u G f u g c U f c A f u U f g u* u* c	1304
AV02501	AV02501-SS	c* a* c a u g a G f c A f a C f a u g u g u* u* a	1074	AV02501-AS	u* A f* a c a c A f u g u u G f c U f c A f u g u* u* g	1305
AV02502	AV02502-SS	g* a* a u g a g c A f a C f a U f g u g u c u* a* a	1075	AV02502-AS	u* U f* g a a c A f c a u g U f u G f c U f c a u* u* c	1306
AV02503	AV02503-SS	g* u* g g g c a c A f a U f g U f g u u c a a* a* a	1076	AV02503-AS	u* U f* u g a a C f a c a u G f u U f g C f u c a* u* c	1307
AV02504	AV02504-SS	g* u* g g g c a c A f a U f g U f g u u c a a* a* a	1077	AV02504-AS	u* U f* u u g a A f c a a U f g U f u G f c u c* a* c	1308
AV02505	AV02505-SS	g* g* g* a g c a c A f u G f u G f u u c a a* g* a	1078	AV02505-AS	u* C f* u u u g A f a c a c A f u G f u U f g c u* c* c	1309
AV02506	AV02506-SS	c* a* g* g a c a a U f g U f g U f u c a a g* u* a	1079	AV02506-AS	u* A f* c u u u C f a a c a C f a U f g U f u g c* u* g	1310

AV02507	AV02507-SS	g*a*gucaagGfaUfaUfaggaaac*c*a	1080	AV02507-AS	u*Gf*uuuuCfcauaUfcCfuUfagc*u*c	1311
AV02508	AV02508-SS	g*g*ucaagGfaUfaUfGfcaaac*c*a	1081	AV02508-AS	u*Gf*guuuUfcauaUfcCfuUfuga*c*c	1312
AV02509	AV02509-SS	g*a*ggauuuGfGfaUfaUfaccugg*a*a	1082	AV02509-AS	u*Uf*ccAfG(eUNNA)uuuuCfcAfuaUfucc*u*c	1313
AV02510	AV02510-SS	c*a*uaugGfaUfaUfcCfuaggag*a*a	1083	AV02510-AS	u*Uf*cuucCfaggauUfuUfcCfaua*u*g	1314
AV02511	AV02511-SS	c*a*guugcUfcCfuGfcaacggg*a*a	1084	AV02511-AS	u*Uf*ccUfG(uUNNA)gcagGfGfAgCfaggc*u*g	1315
AV02512	AV02512-SS	c*c*acaggGfaUfaUfcAfagguc*c*a	1085	AV02512-AS	u*Af*ggagCfuaggauUfaUfcCfuug*u*g	1316
AV02513	AV02513-SS	g*a*caugauAfuaUfaUfagguc*c*a	1086	AV02513-AS	u*Cf*agAfG(eUNNA)uuugAfuaUfuCfcuug*u*c	1317
AV02514	AV02514-SS	g*c*aggauUfaUfaUfAgcucug*u*a	1087	AV02514-AS	u*Af*caGfaG(eUNNA)cuuuGfaUfaUfceu*c*c	1318
AV02515	AV02515-SS	g*a*ggauuuCfaUfaUfAgcucug*u*a	1088	AV02515-AS	u*Af*acagAfGcuuUfGfaUfaUfcu*c*c	1319
AV02516	AV02516-SS	g*g*ggauuacUfaUfGfCfucuguu*u*a	1089	AV02516-AS	u*Af*aacaGfaggauUfuGfaUfauc*c*c	1320
AV02517	AV02517-SS	c*g*auaucaUfaUfCfuCfuguuu*u*a	1090	AV02517-AS	u*Cf*aaacAfaggCfuUfuGfaua*u*g	1321
AV02518	AV02518-SS	c*a*uaucuaAfGfCfuCfuguuu*u*a	1091	AV02518-AS	u*Af*caacCfaggCfuUfuGfaua*u*g	1322
AV02519	AV02519-SS	g*u*aucaaaGfCfuUfcUfguuuug*u*a	1092	AV02519-AS	u*Cf*acaaAfcaagGfCfuUfuGfaua*u*c	1323
AV02520	AV02520-SS	g*a*ucaagCfuCfuGfuuuugg*u*a	1093	AV02520-AS	u*Af*cacaAfcaagAfGfCfuUfuga*u*c	1324
AV02521	AV02521-SS	g*c*aaagcuCfuGfuUfuguguc*u*a	1094	AV02521-AS	u*Af*ggacaCfaaacAfGfCfuuu*u*g	1325
AV02522	AV02522-SS	g*a*aaagcuUfGfuUfuUfguguc*u*a	1095	AV02522-AS	u*Cf*agAfG(eUNNA)caaaCfaGfaGfcauu*u*c	1326
AV02523	AV02523-SS	g*a*agucuuGfuUfuGfuugucg*a*a	1096	AV02523-AS	u*Uf*caggCfaacaAfcaUfAgcu*u*c	1327
AV02524	AV02524-SS	g*g*cuuguuUfuGfuGfucugag*a*a	1097	AV02524-AS	u*Cf*cuCfaG(eUNNA)acacaUfaUfAggag*c*c	1328
AV02525	AV02525-SS	g*u*cuuguuGfuGfuCfuaggag*a*a	1098	AV02525-AS	u*Cf*ucCfuG(eUNNA)aggacaUfaUfagag*a*c	1329
AV02526	AV02526-SS	c*g*aaaggGfCfuUfcUfacaucac*a*a	1099	AV02526-AS	u*Uf*ugauGfuaggCfuUfcCfuuc*c*c	1330
AV02527	AV02527-SS	c*g*aaaggGfCfuCfuAfcaucac*a*a	1100	AV02527-AS	u*Cf*uuagUfguagAfCfuCfcauu*u*c	1331
AV02528	AV02528-SS	c*a*aggagGfCfuUfaUfcaucag*a*a	1101	AV02528-AS	u*Uf*cuugAfhuagGfCfuUfcu*u*g	1332
AV02529	AV02529-SS	c*g*aguguuAfcaUfaUfaggauu*u*a	1102	AV02529-AS	u*Cf*auucUfugauGfuAfGfAfcu*u*g	1333
AV02530	AV02530-SS	c*a*ggucuaCfaUfaUfaggauu*u*a	1103	AV02530-AS	u*Cf*cauuCfuugauUfGfaUfagc*c*c	1334
AV02531	AV02531-SS	g*u*ugagagGfaUfaUfGfcaucac*a*a	1104	AV02531-AS	u*Af*uuagGfcaucUfCfuUfcauc*a*c	1335
AV02532	AV02532-SS	g*g*ugagagAfGfaUfaUfGfcaucac*a*a	1105	AV02532-AS	u*Uf*auugAfGcauUfGfCfuCfcauc*c*c	1336
AV02533	AV02533-SS	c*u*ggagagGfaUfGfCfucauac*u*a	1106	AV02533-AS	u*Af*uaauGfaggauUfCfuUfcUfcu*c*a*g	1337
AV02534	AV02534-SS	g*g*aggagGfaUfGfCfucauauu*u*a	1107	AV02534-AS	u*Cf*auauUfaggGfaUfCfuCfucau*c*c	1338
AV02535	AV02535-SS	c*a*ggagagUfGfCfuCfaauauu*u*a	1108	AV02535-AS	u*Gf*cauaUfaggGfaUfCfuUfcu*c*u*g	1339
AV02536	AV02536-SS	g*a*ggcuuGfaCfaUfaggauu*u*a	1109	AV02536-AS	u*Cf*uuagCfuugUfCfaUfaUfagc*c*c	1340
AV02537	AV02537-SS	g*u*auagacaUfaGfuCfaaggac*a*a	1110	AV02537-AS	u*Uf*guccUfaggCfuUfuGfcauac*a*c	1341
AV02538	AV02538-SS	g*a*ugacaaAfGfuUfaUfaggacac*a*a	1111	AV02538-AS	u*Af*ugucCfuagCfuUfuGfcauac*a*c	1342
AV02539	AV02539-SS	g*g*acaagUfCfaUfaUfaggacac*c*a	1112	AV02539-AS	u*Af*gaugUfcauGfaCfuUfugu*c*c	1343

AV02540	AV02540-SS	c*u*gguaacCfcCfuCfgyuuc*u*a	1113	AV02540-AS	u*Af*ggAfa(cUNA)ccagCfgyGfuGfaec*a*g	1344
AV02541	AV02541-SS	g*c*c*cuugauUfcCfuUfuguauu*u*a	1114	AV02541-AS	u*CF*aguacfaagGfaAfcCfgyg*u*g*c	1345
AV02542	AV02542-SS	g*c*c*ucgguuCfcUfuUfuguauu*u*a	1115	AV02542-AS	u*CF*caGfu(aUNA)caagGfaAfcCfgya*u*g*c	1346
AV02543	AV02543-SS	g*u*ccuuuGfAfcCfuGfgyaggu*u*a	1116	AV02543-AS	u*Af*cuCfc(uUNA)ccagUfAfcAfaAgg*a*c	1347
AV02544	AV02544-SS	c*a*gyagguCfcCfuAfuuggu*u*a	1117	AV02544-AS	u*GF*ucAfg(cUNA)auagGfgyAfcUfcau*u*g	1348
AV02545	AV02545-SS	g*c*c*auauauUfgyCfaGfaggyu*u*a	1118	AV02545-AS	u*Af*ucacCfucugCfaAfgUfauu*u*g*c	1349
AV02546	AV02546-SS	g*u*acuugcAfgAfgGfugauu*u*a	1119	AV02546-AS	u*Af*guauCfaecuCfuCfcAfaagu*u*c	1350
AV02547	AV02547-SS	g*c*c*cuugUfAfcUfuUfcaaggu*a*a	1120	AV02547-AS	u*Uf*cuugUfgyacUfAfcUfcaaggu*a*c	1351
AV02548	AV02548-SS	g*c*c*cuugauAfgUfuUfcaaggu*a*a	1121	AV02548-AS	u*CF*ucuuGfugaacCfuAfuCfaaggu*a*c	1352
AV02549	AV02549-SS	g*c*c*uuugauGfuUfcAfaaggu*a*a	1122	AV02549-AS	u*Uf*cuucUfgyagAfcUfaUfcaaggu*a*c	1353
AV02550	AV02550-SS	g*c*gaugauCfaCfaAfgaggu*u*a	1123	AV02550-AS	u*Af*cuucUfcuugUfgyAfaCfuau*u*c*c	1354
AV02551	AV02551-SS	g*c*guacacaAfgAfgAfgaggu*u*a	1124	AV02551-AS	u*Af*acgaCfuucCfuUfgyUfcaaggu*a*c	1355
AV02552	AV02552-SS	c*u*ucacaaGfaGfaAfguggu*u*a	1125	AV02552-AS	u*Af*aacgaAfcuucUfcUfuGfuga*a*g	1356
AV02553	AV02553-SS	g*u*acaaagAfgAfaGfugguu*u*a	1126	AV02553-AS	u*GF*aaacGfaucCfuCfuUfgyu*a*c	1357
AV02554	AV02554-SS	g*c*c*caaggaGfaAfgUfugguu*c*a	1127	AV02554-AS	u*Uf*gaacCfgyacuUfcUfuUfugu*u*g*c	1358
AV02555	AV02555-SS	g*a*c*caaggaAfaGfuCfgyuuc*a*a	1128	AV02555-AS	u*Af*ugaaAfcgaacCfuCfuCfuuggu*a*c	1359
AV02556	AV02556-SS	g*c*c*aaggaAfgUfcGfugguu*u*a	1129	AV02556-AS	u*Af*augaaAfaaggaCfuUfcUfcu*u*g*c	1360
AV02557	AV02557-SS	g*a*aggaagUfcGfuUfucuuu*c*a	1130	AV02557-AS	u*GF*augAfaaggaAfcUfuCfuuc*u*c	1361
AV02558	AV02558-SS	g*a*aggaagUfcGfuUfucuuu*c*a	1131	AV02558-AS	u*Uf*gaugAfaacGfaCfuUfuc*u*c	1362
AV02559	AV02559-SS	g*c*gaagguCfuUfuUfcauuc*a*a	1132	AV02559-AS	u*Uf*ugaaUfgyaaCfgyAfcUfuc*u*c*c	1363
AV02560	AV02560-SS	c*a*gaagguGfuUfuCfaugaa*u*a	1133	AV02560-AS	u*CF*ungaaAfuugaAfcGfaCfuuc*u*g	1364
AV02561	AV02561-SS	g*c*gaagguUfuUfcAfucaaggu*u*a	1134	AV02561-AS	u*Af*cuugAfaugaAfaCfgyAfcuu*u*c*c	1365
AV02562	AV02562-SS	c*a*agguUfuCfaUfcaaggu*u*a	1135	AV02562-AS	u*Af*acuGfaugAfaAfcGfauc*u*g	1366
AV02563	AV02563-SS	g*a*agguUfuCfaUfcaaggu*u*a	1136	AV02563-AS	u*CF*aacUfgyauGfaAfaCfgyac*u*c	1367
AV02564	AV02564-SS	g*c*ucguuCfaUfuCfaaggu*u*a	1137	AV02564-AS	u*CF*caacUfgyauGfaAfaAfcga*u*c	1368
AV02565	AV02565-SS	c*u*cgguuUfcAfaAfguggu*u*a	1138	AV02565-AS	u*Af*ccaacCfugaAfuGfaAfaaggu*a*g	1369
AV02566	AV02566-SS	g*c*guuauUfuCfaAfguggu*u*a	1139	AV02566-AS	u*CF*acCfa(aUNA)cuugAfaUfgyAfaacgu*c	1370
AV02567	AV02567-SS	g*c*guuauUfuCfaAfguggu*u*a	1140	AV02567-AS	u*Af*caacCfaucGfaAfuGfaa*u*c*c	1371
AV02568	AV02568-SS	c*u*guauuUfcAfaAfguggu*u*a	1141	AV02568-AS	u*Uf*acUfc(cUNA)ccagCfuGfaUfuac*a*g	1372
AV02569	AV02569-SS	g*u*guagguUfAfgUfuGfuggu*u*a	1142	AV02569-AS	u*Af*gaacUfcaacUfAfcCfuCfccc*a*c	1373
AV02570	AV02570-SS	g*c*gaagguAfuCfuCfugaa*a*a	1143	AV02570-AS	u*Uf*uuugCfaggaAfuCfcAfcua*a*c*c	1374
AV02571	AV02571-SS	g*a*guagguCfuCfuGfcaaa*a*c	1144	AV02571-AS	u*GF*uuuuUfgyagAfcAfuCfcau*u*c	1375
AV02572	AV02572-SS	c*u*gaugguCfcAfaAfaacgu*a*a	1145	AV02572-AS	u*Uf*cuugUfuuuGfcaAfgAfcu*a*c*g	1376

AV02573	AV02573-SS	c*a*ugucugCfaAfaAfaaccaga*a*a	1146	AV02573-AS	u*Uf*ucugGfuuuUfjgCfaGfaea*u*g	1377
AV02574	AV02574-SS	g*u*ugucugAfaAfaAfaaccaga*a*a	1147	AV02574-AS	u*CF*uuCfu(gUNNA)guuuUfuGfaAfgac*a*c	1378
AV02575	AV02575-SS	g*a*a*aaaccaGfaAfgCfjgccaad*a*a	1148	AV02575-AS	u*Uf*uuugCfjgcuUfcUfgGfuuu*u*c	1379
AV02576	AV02576-SS	g*u*u*gaagugGfaAfaCfuccaaga*a*a	1149	AV02576-AS	u*Uf*cuugGfaguuUfcUfcCfuuc*a*c	1380
AV02577	AV02577-SS	g*g*gaagugAfaAfaCfuccaaga*a*a	1150	AV02577-AS	u*Af*ucuuGfjaguuUfuCfuCfuuu*c*c	1381
AV02578	AV02578-SS	g*g*gaagaaCfuCfaAfaaguuu*a*a	1151	AV02578-AS	u*CF*ucuuCfuuugAfgUfuUfuUfcu*c*c	1382
AV02579	AV02579-SS	c*a*a*aacucAfaGfaUfjgaguu*u*a	1152	AV02579-AS	u*Af*auccUfcaucUfuGfjgAfguu*u*g	1383
AV02580	AV02580-SS	g*a*a*cucaagAfaUfjgAfuuuu*a*a	1153	AV02580-AS	u*CF*aaauCfcauUfcUfuGfjgag*u*c	1384
AV02581	AV02581-SS	g*a*a*agaaugAfuUfuUfjgguuu*c*a	1154	AV02581-AS	u*Af*aaaccfcaauCfcaUfuUfuUfcu*u*c	1385
AV02582	AV02582-SS	g*g*gaagugAfuUfuUfjgguuu*c*a	1155	AV02582-AS	u*Gf*aaaacCfcauAfuCfcaUfuUfcu*c*c	1386
AV02583	AV02583-SS	c*a*a*ugagugAfuUfjgGfuuuu*c*a	1156	AV02583-AS	u*Af*gaagAfaUfcCfuca*u*g	1387
AV02584	AV02584-SS	c*c*ugugugAfuUfjgAfaaaca*a*a	1157	AV02584-AS	u*Gf*uuuuAfaucAfaUfcCfcau*c*g	1388
AV02585	AV02585-SS	c*u*uggaauGfaAfuUfaaaca*a*a	1158	AV02585-AS	u*CF*uuuuUfaauUfcAfaUfccc*a*g	1389
AV02586	AV02586-SS	g*g*gaagugAfaUfuAfaacaag*c*a	1159	AV02586-AS	u*Gf*uguuUfuuaUfuCfaAfucc*c*c	1390
AV02587	AV02587-SS	c*g*gaagugAfuUfaAfaacaag*c*a	1160	AV02587-AS	u*Af*gcuuUfuuaAfuUfcAfauc*c*g	1391
AV02588	AV02588-SS	g*a*a*uaaaacCfaGfaUfjgagaa*a*a	1161	AV02588-AS	u*Uf*fugUfc(gUNNA)gagUfjgUfuUfuuaa*u*c	1392
AV02022	AV02022-SS	g*a*a*cuuuccCfaUfcAfaaccuu*u*u	1703	AV02022-AS	a*Af*agagGfuugUfjgUfuAfaag*u*c	1757
AV02023	AV02023-SS	c*u*u*gaaggaGfaCfaGfaagaa*u*u	1704	AV02023-AS	a*Af*uaacUfjgcuUfcUfjgCfuuc*a*g	1758
AV02024	AV02024-SS	u*c*c*cuuuccAfuUfjgUfaucaga*a*u	1705	AV02024-AS	a*Uf*cuugGfagaaGfuCfjgAfaag*u*g	1759
AV02025	AV02025-SS	u*c*c*uguuuUfuUfjgUfaucaga*a*a	1706	AV02025-AS	a*CF*uccaGfuuaAfaGfjgAfaac*a*g	1760
AV02026	AV02026-SS	a*c*c*uuugaaUfaCfaUfjgagaa*a*a	1707	AV02026-AS	a*CF*uuugCfcaugUfaUfaGfcau*a*g	1761
AV02027	AV02027-SS	a*u*ugagugGfcaGfaGfaagaa*a*a	1708	AV02027-AS	a*Af*cguaCfaugGfcaGfaGfcau*a*a	1762
AV05135	AV05135-SS	g*a*a*cgugugUfcaUfuUfjgagaa*a*a	1709	AV05135-AS	u*Af*agCfcaUNNA)gaagGfaCfaCfaag*u*c	1763
AV05136	AV05136-SS	g*c*c*cuuuccAfaUfaUfjgagaa*a*a	1710	AV05136-AS	u*CF*acUfcaUNNA)cauuGfuAfgUfagag*a*c	1764
AV05137	AV05137-SS	g*u*u*aaauugUfjgAfgUfjgagaa*a*a	1711	AV05137-AS	u*Uf*cucaUfcauUfcauUfjgagaa*a*c	1765
AV05138	AV05138-SS	g*c*c*aaugugAfuUfjgAfuagaa*a*a	1712	AV05138-AS	u*Gf*auccCfaucAfuCfaCfaauu*a*c	1766
AV05139	AV05139-SS	g*u*u*cuuuccAfuUfjgAfuagaa*a*a	1713	AV05139-AS	u*CF*gucaUfagcaGfuGfjgAfaag*a*c	1767
AV05140	AV05140-SS	g*a*a*cuagaaUfjgAfuCfuagaa*a*a	1714	AV05140-AS	u*Gf*uguaAfaagUfcaUfaUfjgagaa*a*c	1768
AV05141	AV05141-SS	g*u*u*cuagaaUfjgAfuCfuagaa*a*a	1715	AV05141-AS	u*Af*uuugCfagagCfcaUfcaUfjgagaa*a*c	1769
AV05142	AV05142-SS	g*c*c*cuagaaUfcaUfjgCfaaagaa*a*a	1716	AV05142-AS	u*Gf*cgAfu(uUNNA)gagaaGfaGfcaagaa*a*c	1770
AV05143	AV05143-SS	g*g*gaagugAfuCfuGfuagaa*a*a	1717	AV05143-AS	u*Gf*uuuuCfagagAfuCfuGfuagaa*a*c	1771
AV05144	AV05144-SS	c*c*c*caagaaUfcaUfuUfcaagaa*a*a	1718	AV05144-AS	u*Gf*uaacUfjagagGfaGfuCfuagaa*a*c	1772
AV05145	AV05145-SS	g*c*c*aaagaaUfcaUfuCfaagaa*a*a	1719	AV05145-AS	u*CF*guacAfuagaaGfjgAfgUfcau*a*c	1773

AV05146	AV05146-SS	g*a*guacucUfcafuGfuagac*a*a	1720	AV05146-AS	u*Uf*guugUfacaGfaAfgGfagu*c*c	1774
AV05147	AV05147-SS	g*a*ucuaacUfgGfuGfouagau*g*a	1721	AV05147-AS	u*CF*aucuAfgaacCfaGfgUfagau*c*c	1775
AV05148	AV05148-SS	g*a*auggaGfaGfaCfagcau*g*a	1722	AV05148-AS	u*CF*augcUfugcUfgAfuCfcau*c*c	1776
AV05149	AV05149-SS	g*c*acaggaGfcCfaAfaaagug*u*a	1723	AV05149-AS	u*Af*cauUfuuGfUfcCfuugu*g*c	1777
AV05150	AV05150-SS	g*a*aggggCfcaAfaAfaagug*c*a	1724	AV05150-AS	u*Gf*acacUfuuuGfgCfuCfoug*u*c	1778
AV05151	AV05151-SS	g*c*aggggCfaAfaAfaagug*c*a	1725	AV05151-AS	u*Af*gacacUuuUfgGfUfcu*g*c	1779
AV05152	AV05152-SS	g*c*aaaaagUfgUfcUfagucac*c*a	1726	AV05152-AS	u*Gf*uygaCfuagaCfaCfuUfuuu*g*c	1780
AV05153	AV05153-SS	g*a*guucucUfgUfcAfaucuaa*u*a	1727	AV05153-AS	u*Af*uaaGfuagaCfuAfgAfcac*u*c	1781
AV05154	AV05154-SS	g*a*guucuaGfuCfaAfcuaau*u*a	1728	AV05154-AS	u*Af*auuaAfgugAfcUfaGfaca*c*c	1782
AV05155	AV05155-SS	g*a*gucaacUfaAfaUfugagaa*g*a	1729	AV05155-AS	u*CF*uuucUfaauAfaGfuUfgac*u*c	1783
AV05156	AV05156-SS	g*a*ucaacuUfaAfuUfagagaa*g*a	1730	AV05156-AS	u*CF*cuUfc(uUNA)cauUfaAfgUfuga*c*c	1784
AV05157	AV05157-SS	g*u*auggugUfgAfaGfcaagaa*u*a	1731	AV05157-AS	u*Af*ucuuGfgcuCfaCfcau*u*a*c	1785
AV05158	AV05158-SS	g*c*caaggcGfuGfuAfcagcau*g*a	1732	AV05158-AS	u*CF*auGfc(uUNA)guacAfcUfgCfoug*g*c	1786
AV05159	AV05159-SS	c*c*aguguaCfaGfcAfuagaa*g*a	1733	AV05159-AS	u*CF*ucauCfagcUfgUfaCfcau*g*g	1787
AV05160	AV05160-SS	g*c*uguguaAfuUfgCfacaaca*u*a	1734	AV05160-AS	u*Af*uguuGfugcaAfuCfcAfuca*g*c	1788
AV05161	AV05161-SS	g*u*guuggaUfuGfcAfaacaa*g*a	1735	AV05161-AS	u*CF*auguUfgugcaAfuUfcCfauc*a*c	1789
AV05162	AV05162-SS	g*c*ccaauuAfcUfgUfcauuga*u*a	1736	AV05162-AS	u*Af*ucauUfgacaGfuAfaUfugg*g*c	1790
AV05163	AV05163-SS	g*a*aggggGfaUfuAfuugaa*u*a	1737	AV05163-AS	u*Af*uccaGfaauUfcCfuCfcu*u*c	1791
AV05164	AV05164-SS	g*c*caagugAfaCfaUfcauug*c*a	1738	AV05164-AS	u*Af*ggcuUfgaugUfuCfaCfuug*g*c	1792
AV05165	AV05165-SS	g*a*aaaggaAfuUfgAfgcaaca*u*a	1739	AV05165-AS	u*Af*uguuGfucaUfuGfuCfuuu*c*c	1793
AV05166	AV05166-SS	g*a*ucaagaGfaAfuGfggaa*a*a	1740	AV05166-AS	u*Uf*uaucCfcauUfcUfuGaug*u*c	1794
AV05167	AV05167-SS	g*c*aucaagAfaUfgGfggaa*a*a	1741	AV05167-AS	u*CF*uuucUfauccCfaAfuUfcu*g*c	1795
AV05168	AV05168-SS	g*a*ucaagaAfuGfgGfgaauag*a*a	1742	AV05168-AS	u*Uf*cuuaUfccccAfuUfcUfuga*u*c	1796
AV05169	AV05169-SS	g*u*caagauGfgGfgGfaaagaa*a*a	1743	AV05169-AS	u*Uf*ucuuAfucccCfaUfuCfuug*a*c	1797
AV05170	AV05170-SS	g*c*aaagauGfgGfgAfaagaa*g*a	1744	AV05170-AS	u*CF*uuucUfauccCfaAfuUfcu*g*c	1798
AV05171	AV05171-SS	g*a*agaaugGfgGfaUfaagaa*g*a	1745	AV05171-AS	u*CF*cuuucCfuuaCfcccAfuuc*u*c	1799
AV05172	AV05172-SS	g*a*gaugggGfgAfuAfaagaa*g*a	1746	AV05172-AS	u*Uf*cuuGfcauuUfgUfcAfuag*g*c	1800
AV05173	AV05173-SS	c*a*cuangCfaAfaGfuaagaa*g*a	1747	AV05173-AS	u*Uf*cuuGfcauuUfgUfcAfuag*g*c	1801
AV05174	AV05174-SS	g*a*ugcugCfcccAfaucuu*g*a	1748	AV05174-AS	u*Uf*ugcaGfcauUfgUfcAfuac*u*c	1802
AV05175	AV05175-SS	c*a*uguaugGfgAfuGfucugaa*a*a	1749	AV05175-AS	u*Uf*ugcaGfcauUfgUfcAfuac*u*c	1803
AV05176	AV05176-SS	c*u*ggauuGfuGfaAfaaac*a*a	1750	AV05176-AS	u*Uf*gguuUfugcaAfgAfcAfucc*a*g	1804
AV05177	AV05177-SS	g*c*aaagauGfgGfaUfuuugaa*u*a	1751	AV05177-AS	u*Af*accCfaaucCfuCfaUfcuu*g*c	1805
AV05178	AV05178-SS	g*a*gggguuUfcCfuGfougaa*a*a	1752	AV05178-AS	u*Uf*guCfcaUNA)gagGfaAfaCfccc*u*c	1806

AV06327	AV06327-SS	c*a*auguGfAfuGfauagagu* u	1753	AV06327-AS	a* Af*ucucAfucacUfcAfcafu* u* g	1807
AV06328	AV06328-SS	g*a*caanguGfAfuGfauagga* u* u	1754	AV06328-AS	a* Af*ucucAfucacUfcAfcafu* u* c	1808
AV06329	AV06329-SS	g*a*aaanguGfAfuGfauagga* u* a	1755	AV06329-AS	u* Af*guugAfucagAfcafu* u* c	1809
AV06330	AV06330-SS	c*c*gcgggaUfuGfAfuuaaa* c* a	1756	AV06330-AS	u* Gf*uuuuAfauCfauUfcCfegc* g* g	1810

Table 3 shows certain chemically modified CFB RNAi agent antisense strand and sense strand sequences of the invention. In some embodiments of methods of the invention, RNAi agents shown in Table 3 are administered to a cell and/or subject. In some embodiments of methods of the invention, a RNAi agent with a polynucleotide sequence shown in Table 3 is administered to a subject. In some embodiments of the invention an RNAi agent administered to a subject comprises a duplex identified in a row in Table 3, column one and includes the sequence modifications and/or delivery compound show in the sense and antisense strand sequences in the same row in Table 3, columns three and six, respectively. The sequences were used in certain in vivo testing studies described elsewhere herein. In some embodiments of methods of the invention, a sequence shown in Table 3 may be attached to (also referred to herein as “conjugated to”) a compound for delivery, a non-limiting example of which is a GalNAc-containing compound, with a delivery compound identified in Table 3 as “GLX-n” on sense strands in column three. As used herein, “GLX-n” is used to represent either a “GLS-n*” or a GLO-n” delivery compound (“X” can be either “S” or “O”) and GLX-0 can be any of the “GLS-n*” and “GLO-n” delivery compounds that can be attached to 3'-end of oligonucleotide during synthesis. As used herein and shown in Table 3, “GLX-n” is used to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is provided elsewhere herein. One skilled in the art will be able to prepare and use a dsRNA compound of the invention in which the attached delivery compound is one of GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16. Column one of Table 3 provides a Duplex AD# assigned to the duplex of the sense and antisense sequences in that row of the table. For example, Duplex AD# AD01093 is the duplex of sense strand SEQ ID NO: 1393 and

antisense strand SEQ ID NO: 1441. Each line in Table 3 provides a sense strand and an antisense strand, and discloses the duplex of the sense and antisense strands shown. The “Sense strand SS#” in Table 3 column two is the assigned identifier for the Sense Sequence (including modifications) shown column 3 in the same row. The “Antisense strand AS#” in Table 3 column five is the assigned identifier for the Antisense sequence (including modifications) shown in column six. An identifier for certain attached GalNAc-containing “GLO-n” or “GLS-n*” compounds is shown as GLS-5*, GLS-15* or GLX-0, and it will be understood that another of the “GLO-n” or “GLS-n*” compounds may be substituted for the compound shown as GLO-0, with the resulting compound included in an embodiment of a method and/or a composition of the invention.

Table 3 provides chemically modified CFB RNAi agent antisense strand and sense strand sequences. All sequences shown 5' to 3'. The sequences were used in certain in vivo testing studies described elsewhere herein. A delivery molecule used in the *in vivo* studies is indicated as “GLO-n” or “GLS-n*” at the 3'-end or 5'-end of each sense strand.

Duplex AD#	Sense strand SS#	Sense Sequence	SEQ ID NO	Antisense strand AS#	Antisense Sequence	SEQ ID NO
AD01093	AD01093-SS	(GLS-15*)(imann*)gacaauguGfAcfuGfauugagau*a*(imann)	1393	AD01093-AS	u*Af*ucucAfucacUfcAfcaAfung*u*c	1441
AD01094	AD01094-SS	(GLS-15*)(imann*)cccaaaaGfAcfuGfAcfuagucac*a*(imann)	1394	AD01094-AS	u*Uf*ugacUfagacAfcUfuUfung*g*g	1442
AD01095	AD01095-SS	(GLS-15*)(imann*)gcacaaucAcfuGfAcfuauugaug*a*(imann)	1395	AD01095-AS	u*CF*aucaAfugacAfgUfaAfung*g*c	1443
AD01096	AD01096-SS	(GLS-15*)(imann*)guuacuguCfaUfuGfauugagau*a*(imann)	1396	AD01096-AS	u*Af*ucucAfucacUfAgAfcAfuaa*a*c	1444
AD01097	AD01097-SS	(GLS-15*)(imann*)guucugguCfAcfuAfuguguuu*a*(imann)	1397	AD01097-AS	u*Af*aacacAfuaugAfcAfucfcau*g*c	1445
AD01098	AD01098-SS	(GLS-15*)(imann*)gagaaagacAfcAcfuGfagacac*a*(imann)	1398	AD01098-AS	u*Uf*guugCfucacUfGufUfcUfuuc*u*c	1446
AD01099	AD01099-SS	(GLS-15*)(imann*)gauugagacAfcAcfuGfuguuca*a*(imann)	1399	AD01099-AS	u*Uf*ugaaCfacaugGfuUfGcfuca*u*c	1447
AD01100	AD01100-SS	(GLS-15*)(imann*)cauaucaAfcGfAcfuGfuguuu*a*(imann)	1400	AD01100-AS	u*Af*caacCfagagGfAcfuUfuGfaua*u*g	1448
AD01101	AD01101-SS	(GLS-15*)(imann*)gagagagacGfGufUfuUfcauuca*a*(imann)	1401	AD01101-AS	u*Uf*ugaaUfgaacCfGufUfuUfuuc*u*c	1449
AD01102	AD01102-SS	(GLS-15*)(imann*)gaguguguuUfcAcfuUfcaaguuu*a*(imann)	1402	AD01102-AS	u*CF*aacuUfgaauGfaAfacCfagac*u*c	1450
AD01103	AD01103-SS	(GLS-15*)(imann*)gagucguuUfcAcfuUfcaaguuu*a*(imann)	1403	AD01103-AS	u*CF*caacUfugaaUfGufAfaAfcau*c*c	1451
AD01104	AD01104-SS	(GLS-15*)(imann*)gagagagacGfGufUfuUfuguguuu*a*(imann)	1404	AD01104-AS	u*Af*aacacCfacaugCfcUfcAfucuu*u*c	1452
AD01389	AD01389-SS	(GLS-15*)(imann*)gagugucacGfGufUfcUfagaguuu*a*(imann)	1405	AD01389-AS	u*Af*aacucCfcaagAfcUfaGfacc*u*c	1453
AD01390	AD01390-SS	(GLS-15*)(imann*)gagugucugGfAcfuUfcaaguuu*a*(imann)	1406	AD01390-AS	u*Af*agucUfgaacCfucCfAcfacc*u*c	1454

[illegible]

AD01422	AD01422-SS	(GLS-15*)(imann*)gsgggaugAfuUfuAfaacagc*a*(imann)	1438	AD01422-AS	u*Gf*cugguUfuuaAfuuCfaAfucc*c*c	1486
AD01423	AD01423-SS	(GLS-15*)(imann*)gsggaugAfuUfaAfaacagc*a*(imann)	1439	AD01423-AS	u*Af*ggcuUfuuaAfauUfcAfauc*c*g	1487
AD01420-1	AD01420-1-SS	(GLS-15*)(imann*)ccggggaUfuGfaAfuaaac*a*(imann) a*a*gaagaAfgUfcGfuuucauccau(L96)	1440	AD01420-1-AS	u*Gf*uuuuAfauuCFauUfcCfcgc*g*g a*Uf*gaUfAgAfaAcgaCFuUfcuccu*g*u	1488
AD01080	AD01080-SS	(GLS-15*)(imann*)gcuacuaCFaAfufuGfugeugc*a*(imann)	1811	AD01080-AS	u*Uf*gaUfAgAfaAcgaCFuUfcuccu*g*u	1882
AD01696	AD01696-SS	(GLS-15*)(imann*)gcuacuaCFaAfufuGfugeugc*a*(imann)	1812	AD01696-AS	u*Uf*caucCFacuUfugUfaGfug*g*c	1883
AD01697	AD01697-SS	(GLS-15*)(imann*)guacuacAfufuGfuGfagugc*a*(imann)	1813	AD01697-AS	u*CF*aucaCFucaCFauUfGfagu*g*c	1884
AD01698	AD01698-SS	(GLS-15*)(imann*)gcuacauGfuGfaGfugaugc*a*(imann)	1814	AD01698-AS	u*CF*ucauCFacuCFacAfufuUfgua*g*c	1885
AD01699	AD01699-SS	(GLS-15*)(imann*)ggygagugAfufuGfaGfaucucu*a*(imann)	1815	AD01699-AS	u*Af*agagAfucuCfaUCfaCFuca*c*c	1886
AD01700	AD01700-SS	(GLS-15*)(imann*)ggaucucuUfuCFcAfccugcuu*a*(imann)	1816	AD01700-AS	u*Af*ugcAfgyGfaaAfgaUfcau*c*c	1887
AD01701	AD01701-SS	(GLS-15*)(imann*)gcaucguAfufuGfaCFgguuaca*a*(imann)	1817	AD01701-AS	u*Uf*guacCFcguCFauAfGCFagu*g*c	1888
AD01702	AD01702-SS	(GLS-15*)(imann*)gcuycuaCFaCFgGfuacacu*a*(imann)	1818	AD01702-AS	u*Af*gyguAfaccGfucAfuaAfgea*g*c	1889
AD01703	AD01703-SS	(GLS-15*)(imann*)gagccaaAfafuGfuGfuccuagc*a*(imann)	1819	AD01703-AS	u*Gf*acuaGfacaCFuuUfuUfgygc*u*g	1890
AD01704	AD01704-SS	(GLS-15*)(imann*)gaaagguGfuCFuAfgucaacu*a*(imann)	1820	AD01704-AS	u*Af*guugAfcauGfacaCFcUfuUfgygc*u*g	1891
AD01705	AD01705-SS	(GLS-15*)(imann*)gaaagguGfuAfguUfcaacu*a*(imann)	1821	AD01705-AS	u*Uf*aagguUfgaUfagAfcaFcau*u*c	1892
AD01706	AD01706-SS	(GLS-15*)(imann*)gcuacuuAfufuGfagagagc*a*(imann)	1822	AD01706-AS	u*Af*ccuCFucaAfuaAfagGfuge*a*g	1893
AD01707	AD01707-SS	(GLS-15*)(imann*)gguugagAfgGfuGfccaugc*a*(imann)	1823	AD01707-AS	u*Af*acuGfcaCFcuUfcUfcaa*u*c	1894
AD01708	AD01708-SS	(GLS-15*)(imann*)ggaugauGfuCFuAfgygcau*a*(imann)	1824	AD01708-AS	u*Af*ugucAfcauGfcaCFaUfanc*u*c	1895
AD01709	AD01709-SS	(GLS-15*)(imann*)gcuaggaCFaAfufuGfccaaca*a*(imann)	1825	AD01709-AS	u*Uf*anguGfcaUfauGfuCFacu*a*c	1896
AD01710	AD01710-SS	(GLS-15*)(imann*)gcuaggaCFaAfufuGfagagagc*a*(imann)	1826	AD01710-AS	u*Uf*cuucAfuaUfugaAfufuUfcau*u*c	1897
AD01711	AD01711-SS	(GLS-15*)(imann*)gcuacuuUfAgAfafGfaccaca*a*(imann)	1827	AD01711-AS	u*Uf*ugugGfucUfcaUfcaAfugc*a*c	1898
AD01712	AD01712-SS	(GLS-15*)(imann*)gcuaggaCFcAfcaFagugagc*a*(imann)	1828	AD01712-AS	u*Uf*ucaCFuugUfgyUfcUfuca*u*c	1899
AD01713	AD01713-SS	(GLS-15*)(imann*)ggaaccAfafuGfuUfgaguc*a*(imann)	1829	AD01713-AS	u*Uf*gaUfcauCFuGfuGfugc*u*c	1900
AD01714	AD01714-SS	(GLS-15*)(imann*)gcuaggaCFaCFgGfacaaca*a*(imann)	1830	AD01714-AS	u*Uf*guuaGfuccCFugAfcaUfuca*a*g	1901
AD01715	AD01715-SS	(GLS-15*)(imann*)gcuacugUfcaAfufuGfagagagc*a*(imann)	1831	AD01715-AS	u*Uf*cucaUfcaUfgaCFaGfuaa*u*c	1902
AD01716	AD01716-SS	(GLS-15*)(imann*)gcuaggaAfgGfaUfccaaca*a*(imann)	1832	AD01716-AS	u*Uf*uuugCFgaucFcuUfGCFcaa*u*c	1903
AD01717	AD01717-SS	(GLS-15*)(imann*)ggaaggaAfufuCFuGfagugc*a*(imann)	1833	AD01717-AS	u*Af*gaUfcauCFaUfcaUfcaUfcau*c*g	1904
AD01718	AD01718-SS	(GLS-15*)(imann*)ggygagguCFuAfufuGfuuugc*a*(imann)	1834	AD01718-AS	u*CF*caaaCFacuUfagAfcaAfucc*a*c	1905
AD01719	AD01719-SS	(GLS-15*)(imann*)gcaaggaAfcAfufuGfauugc*a*(imann)	1835	AD01719-AS	u*Af*agcaUfugaUfguUfcaFcau*u*c	1906
AD01720	AD01720-SS	(GLS-15*)(imann*)caacaucaAfufuGfufuGfauugc*a*(imann)	1836	AD01720-AS	u*Af*agccAfagCFauUfgaAfugc*u*g	1907
AD01721	AD01721-SS	(GLS-15*)(imann*)ggygguugGfufuCFcaaggaac*a*(imann)	1837	AD01721-AS	u*Uf*uuuUfgygaAfgyCFaAfagc*a*c	1908
AD01722	AD01722-SS	(GLS-15*)(imann*)gaaaggaUfAgAfcaFcaugc*a*(imann)	1838	AD01722-AS	u*Af*caugUfugcUfcaUfufuGfuc*u*c	1909

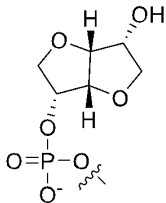
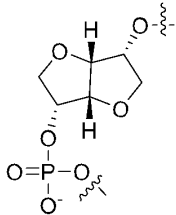
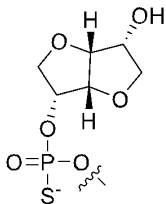
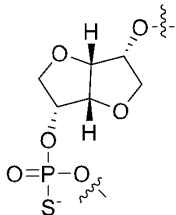
AD01723	AD01723-SS	(GLS-15*)(imann*)jacaauGfCfaCfauGguuuc*a*(imann)	1839	AD01723-AS	u*Af*acaCAfugUfCfCfauGguuuc*a*(imann)	1910
AD01724	AD01724-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1840	AD01724-AS	u*Uf*gaacAfcauGfUuGfCfUfcau*u*c	1911
AD01725	AD01725-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1841	AD01725-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1912
AD01726	AD01726-SS	(GLS-15*)(imann*)jcaGgaacaUfGfUfGfUfGguuuc*a*(imann)	1842	AD01726-AS	u*Af*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1913
AD01727	AD01727-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1843	AD01727-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1914
AD01728	AD01728-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1844	AD01728-AS	u*Af*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1915
AD01729	AD01729-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1845	AD01729-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1916
AD01730	AD01730-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1846	AD01730-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1917
AD01731	AD01731-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1847	AD01731-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1918
AD01732	AD01732-SS	(GLS-15*)(imann*)jgaGgaacaAfUfGfUfGguuuc*a*(imann)	1848	AD01732-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1919
AD01093-1	AD01093-1-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1849	AD01093-1-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1920
AD01393-1	AD01393-1-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1850	AD01393-1-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1921
AD01399-1	AD01399-1-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1851	AD01399-1-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1922
AD02225	AD02225-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1852	AD02225-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1923
AD01704-1	AD01704-1-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1853	AD01704-1-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1924
AD02226	AD02226-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1854	AD02226-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1925
AD02227	AD02227-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1855	AD02227-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1926
AD02228	AD02228-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1856	AD02228-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1927
AD02229	AD02229-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1857	AD02229-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1928
AD02230	AD02230-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1858	AD02230-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1929
AD02231	AD02231-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1859	AD02231-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1930
AD02232	AD02232-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1860	AD02232-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1931
AD02233	AD02233-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1861	AD02233-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1932
AD02234	AD02234-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1862	AD02234-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1933
AD02235	AD02235-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1863	AD02235-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1934
AD02236	AD02236-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1864	AD02236-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1935
AD02237	AD02237-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1865	AD02237-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1936
AD02238	AD02238-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1866	AD02238-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1937
AD02239	AD02239-SS	(GLS-15*)(imann*)jcauGguCfAfaCfUfGguuuc*a*(imann)	1867	AD02239-AS	u*Uf*uuuGfAcaCfUuGfUfGguuuc*a*(imann)	1938

AD02240	AD02240-SS	(GLS-15*)(invab)*ggccuugaUfAfuUfcaacaaga*a*(invab)	1868	AD02240-AS	u*Uf*cuugUfIgaacUfAfuAfagug*g*c	1939
AD02241	AD02241-SS	(GLS-15*)(invab)*gguuuucUfAfAfgfhuugugug*a*(invab)	1869	AD02241-AS	u*Af*cucaAfacuGfAfuGfAa*a*c	1940
AD02339	AD02339-SS	(GLS-15*)(invab)*gucacaugUfIgfUfIgaugugug*a*(invab)	1870	AD02339-AS	u*Uf*cucaUfcaacuCfAfuUfugu*a*c	1941
AD02340	AD02340-SS	(GLS-15*)(invab)*gacugcuUfIgfAfGfIguuacac*a*(invab)	1871	AD02340-AS	u*Gf*uguaAfceguCfAfuUfAfgcag*g*c	1942
AD02341	AD02341-SS	(GLS-15*)(invab)*ggcaaaUfIgfUfIfigugcaac*a*(invab)	1872	AD02341-AS	u*Af*caacuUfuugugfUfCfIguu*g*c	1943
AD02342	AD02342-SS	(GLS-15*)(invab)*ggcuuagUfIgfUfIfigugcaac*a*(invab)	1873	AD02342-AS	u*Gf*uygaCfIgaagCfAfuUfuuu*g*c	1944
AD02343	AD02343-SS	(GLS-15*)(invab)*ggugucuaGfuCfAfcuuauu*a*(invab)	1874	AD02343-AS	u*Af*auuaAfIguugAfUfUfAfgfaca*a*c	1945
AD02344	AD02344-SS	(GLS-15*)(invab)*ggacuacaGfAfuGfIgeguaa*a*(invab)	1875	AD02344-AS	u*Uf*uaucCfccaacuUfUfuGfauug*g*c	1946
AD02345	AD02345-SS	(GLS-15*)(invab)*cguguuugUfIgfAfuCfIucugca*a*(invab)	1876	AD02345-AS	u*Uf*ugcaGfcaacuCfAfUfUfacu*c*g	1947
AD02346	AD02346-SS	(GLS-15*)(invab)*ggcaugauAfIgfAfuUfIugugugug*a*(invab)	1877	AD02346-AS	u*Af*accCAfaucCfIuCfAfuUfcuti*g*c	1948
AD02347	AD02347-SS	(GLS-15*)(invab)*ggaguguuUfCfCfIgfIuggaca*a*(invab)	1878	AD02347-AS	u*Uf*guCfIcfalUNAfgeagGfAfuAfuCfccc*g*c	1949
AD01093-2	AD01093-2-SS	(GLS-15*)(invab)*ggcaacuGfAfuGfIgaugauu*a*(invab)	1879	AD01093-2-AS	a*Af*ucucAfuaacUfCfAfCfAfuuug*u*c	1950

AD01786 comprise nucleotide sequences is consisting of u*Uf*gAfAuFgAfAfAfGfAf*CF*u*Uf*c*Uf*cGfAuUfCfAuUfCf*Af*(L-96) (SEQ ID NO 1880); AD01787 comprise nucleotide sequences is consisting of (GLO-15) (MOE-A*)(MOE-T*)(MOE-m5C*)(MOE-m5C*)(MOE-m5C*)(dA*)(m5dC*)(dG*)(m5dC*)(m5dC*)(dT*)(dG*)(dT*)(MOE-m5C*)(MOE-m5C*)(MOE-A*)(MOE-G*)(MOE-m5C) (SEQ ID NO 1881); L-96 is refers to the compound GalINAc3 in Jayaprakash, et al., (2014) J. Am. Chem. Soc., 136, 16958–16961.

Table 4: 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, and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position of the parent nucleotide (i.e., it is a 2'-deoxy-2'- fluoronucleotide). It will also be understood that the abbreviations correspond to nucleotides which omit the 3'-phosphate when found at the 3'-terminal position (i.e., they are 3'-OH). A skilled artisan will understand that these abbreviations are just identification symbols and are able to determine the linking modes of the nucleotide sequences containing these abbreviations.

Abbreviations	Nucleotide(s)
A	adenosine-3'-phosphate
C	cytidine-3'-phosphate
G	guanosine-3'-phosphate
T	5-methyluridine-3'-phosphate
U	uridine-3'-phosphate
a	2'-O-methyladenosine-3'-phosphate
c	2'-O-methylcytidine-3'-phosphate
g	2'-O-methylguanosine-3'-phosphate
t	2'-O-methyl-5-methyluridine-3'-phosphate
u	2'-O-methyluridine-3'-phosphate
Af	2'-fluoroadenosine-3'-phosphate
Cf	2'-fluorocytidine-3'-phosphate
Gf	2'-fluoroguanosine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Af*	2'-fluoroadenosine-3'-phosphorothioate
Cf*	2'-fluorocytidine-3'-phosphorothioate
Gf*	2'-fluoroguanosine-3'-phosphorothioate
Tf*	2'-fluoro-5-methyluridine-3'-phosphorothioate
Uf*	2'-fluorouridine-3'-phosphorothioate
a*	2'-O-methyladenosine-3'-phosphorothioate
c*	2'-O-methylcytidine-3'-phosphorothioate
g*	2'-O-methylguanosine-3'-phosphorothioate
t*	2'-O-methyl-5-methyluridine-3'-phosphorothioate
u*	2'-O-methyluridine-3'-phosphorothioate
aUNA	2', 3'-seco-adenosine-3'-phosphate
cUNA	2', 3'-seco-cytidine-3'-phosphate
gUNA	2', 3'-seco-guanosine-3'-phosphate
tUNA	2', 3'-seco-5-methyluridine-3'-phosphate
uUNA	2', 3'-seco- uridine-3'-phosphate
Vp	Vinyl-phosphate
invab	inverted abasic-5'-phosphate. linked to adjacent nucleotide via a

	substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strand; linked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab which omit the 5'-phosphate when found at the 3'-terminal position (i.e., they are 5'-OH)	
invab*	inverted abasic-5'-phosphorothioate. linked to adjacent nucleotide via a substituent at its 3' position (a 3'-3' linkage) when on the 3' end of a strandlinked to adjacent nucleotide via a substituent at its 5' position (a 5'-5' internucleotide linkage) when on the 5' end of a strand, It will also be understood that the abbreviations correspond to invab* which omit the 5'-phosphorothioate when found at the 3'-terminal position (i.e., they are 5'-OH);	
imann	imann when at the end of each strand 	imann when in the middle of each strand 
imann*	isomannide residue- phosphorothioate	
	imann* when at the end of each strand 	imann* when in the middle of each strand 
MOE-A*	2'-methoxyxyethyl adenosine-3'-phosphorothioate	
MOE-T*	2'-methoxyxyethyl	
MOE-m5C*	2'-methoxyxyethyl-(5-Me-cytidine)-3'-phosphorothioate	
m5dC*	2'-deoxy-(5-Me-cytidine)-3'-phosphorothioate	
dA*	2'-deoxyadenosine-3'-phosphorothioate	
dG*	2'-deoxyguanosine-3'-phosphorothioate	
dT*	2'-deoxythymidine-3'-phosphorothioate	

In certain embodiments of the invention a dsRNA (also referred to herein as a “duplex”) is one disclosed in one of Tables 1-3. Each row in Tables 1-3 discloses a duplex comprising the sequence of the sense strand and the sequence of the antisense strand in that table row. In addition to the duplexes disclosed in Tables 1-3, it will be understood that in some embodiments, a duplex of the invention may include sense and antisense sequences shown in Tables 1-3, that differ by zero, one, two, or three nucleotides shown in a sequence shown in Tables 1-3. Thus, as non-limiting examples, in some embodiments, an antisense strand in a

duplex of the invention may be SEQ ID NO: 484, 490, 497, 665, or 667 with zero, one, two, or three different nucleotides than those in SEQ ID 484, 490, 497, 665, or 667 respectively.

It will be understood that the sequence of the sense strand and the sequence of the antisense strand in a duplex of the invention may be independently selected. Thus, a dsRNA of the invention may comprise a sense strand and an antisense strand of a duplex disclosed in a row in Tables 1-3. Alternatively, in a dsRNA of the invention, one or both of the selected sense and antisense strand in the dsRNA may include sequences shown in Tables 1-3 but with one or both of the sense and antisense sequences including 1, 2, 3, or more nucleobase substitutions from the parent sequence. The selected sequences may in some embodiments be longer or shorter than their parent sequence. Thus, dsRNA agents included in the invention can but need not include exact sequences of the sense and antisense pairs disclosed as duplexes in Tables 1-3.

In some embodiments, a dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a CFB RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand. In some instances, the region of complementarity to the CFB RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3. In some embodiments of a dsRNA agent of the invention, the antisense strand of the dsRNA is at least substantially complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments, an antisense strand of a dsRNA agent of the invention is fully complementary to any one of a target region of SEQ ID NO: 1 and is provided in any one of Tables 1-3. In some embodiments a dsRNA agent includes a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is at least substantially complementary to the antisense strand sequence in the dsRNA agent. In other embodiments, a dsRNA agent of the invention comprises a sense strand sequence set forth in any one of Tables 1-3, and the sense strand sequence is fully complementary to the antisense strand sequence in the dsRNA agent. In some instances, a dsRNA agent of the invention comprises an antisense strand sequence set forth in any one of Tables 1-3. Some embodiments of a dsRNA agent of the invention comprises the sense and antisense sequences disclosed as duplex in any of Tables 1-3. As described herein, it will be understood that the sense and antisense strands in a duplex of the invention may be independently selected.

Mismatches

It is known to skilled in art, mismatches are tolerated for efficacy in dsRNA, especially the mismatches are within terminal region of dsRNA. Certain mismatches tolerate better, for example mismatches with wobble base pairs G:U and A:C are tolerated better for efficacy (Du

et al., A systematic analysis of the silencing effects of an active siRNA at all single-nucleotide mismatched target sites. *Nucleic Acids Res.* 2005 Mar 21;33(5):1671-7. Doi: 10.1093/nar/gki312. *Nucleic Acids Res.* 2005;33(11):3698). Some embodiments of methods and compounds of the invention a CFB dsRNA agent may contain one or more mismatches to the CFB target sequence. In some embodiments, CFB dsRNA agent of the invention includes no mismatches. In certain embodiments, CFB dsRNA agent of the invention includes no more than 1 mismatch. In some embodiments, CFB dsRNA agent of the invention includes no more than 2 mismatches. In certain embodiments, CFB dsRNA agent of the invention includes no more than 3 mismatches. In some embodiments of the invention, an antisense strand of a CFB dsRNA agent contains mismatches to a CFB target sequence that are not located in the center of the region of complementarity. In some embodiments, the antisense strand of the CFB dsRNA agent includes 1, 2, 3, 4, or more mismatches that are within the last 5, 4, 3, 2, or 1 nucleotide from one or both of the 5' or 3' end of the region of complementarity. Methods described herein and/or methods known in the art can be used to determine whether a CFB dsRNA agent containing a mismatch to a CFB target sequence is effective in inhibiting the expression of the CFB gene.

Complementarity

As used herein, unless otherwise indicated, the term “complementary,” when used to describe a first nucleotide sequence (e.g., CFB dsRNA agent sense strand or targeted CFB mRNA) in relation to a second nucleotide sequence (e.g., CFB dsRNA agent antisense strand or a single-stranded antisense polynucleotide), means the ability of an oligonucleotide or polynucleotide including the first nucleotide sequence to hybridize [form base pair hydrogen bonds under mammalian physiological conditions (or similar conditions *in vitro*)] and form a duplex or double helical structure under certain conditions with an oligonucleotide or polynucleotide including the second nucleotide sequence. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. A skilled artisan 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 include Watson-Crick base pairs or non-Watson-Crick base pairs and include natural or modified nucleotides or nucleotide mimics, at least to the extent that the above hybridization requirements are fulfilled. Sequence identity or complementarity is independent of modification.

Complementary sequences, for example, within a CFB 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. It will be understood that in embodiments when two oligonucleotides are designed to form, upon hybridization, one or

more single stranded overhangs, such overhangs are not regarded herein as mismatches with regard to the determination of complementarity. For example, a CFB dsRNA agent comprising one oligonucleotide 19 nucleotides in length and another oligonucleotide 20 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 19 nucleotides that is fully complementary to the shorter oligonucleotide, can yet be referred to as “fully complementary” for the purposes described herein. Thus, as used herein, “fully complementary” means that all (100%) of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The contiguous sequence may comprise all or a part of a first or second nucleotide sequence.

The term “substantially complementary” as used herein means that in a hybridized pair of nucleobase sequences, at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. The term “substantially complementary” can be used in reference to a first sequence with respect to a second sequence if the two sequences include one or more, for example at least 1, 2, 3, 4, or 5 mismatched base pairs upon hybridization for a duplex up to 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs (bp), while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of CFB gene expression via a RISC pathway.

The term, “partially complementary” may be used herein in reference to a hybridized pair of nucleobase sequences, in which at least 75%, but not all, of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide. In some embodiments, “partially complementary” means at least 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the bases in a contiguous sequence of a first polynucleotide will hybridize with the same number of bases in a contiguous sequence of a second polynucleotide.

The terms “complementary,” “fully complementary,” “substantially complementary,” and “partially complementary” are used herein in reference to the base matching between the sense strand and the antisense strand of a CFB dsRNA agent, between the antisense strand of a CFB dsRNA agent and a sequence of a target CFB mRNA, or between a single-stranded antisense oligonucleotide and a sequence of a target CFB mRNA. It will be understood that the term “antisense strand of a CFB dsRNA agent” may refer to the same sequence of an “CFB antisense polynucleotide agent”.

As used herein, the term “substantially identical” or “substantial identity” used in reference to a nucleic acid sequence means a nucleic acid sequence comprising a sequence with at least about 85% sequence identity or more, preferably at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or

at least 99%, compared to a reference sequence. Percentage of sequence identity is determined by comparing two optimally aligned sequences over a comparison window. The percentage is calculated by determining the number of positions at which the identical nucleic acid base occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity. The inventions disclosed herein encompasses nucleotide sequences substantially identical to those disclosed herein, e.g., in Tables 1-3. In some embodiments, the sequences disclosed herein are exactly identical, or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% percent identical to those disclosed herein, e.g., in Tables 1-3.

As used herein, the term “strand comprising a sequence” means an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature. The term “double-stranded RNA” or “dsRNA,” as used herein, refers to an RNAi that includes an RNA molecule or complex of molecules having a hybridized duplex region comprising two anti-parallel and substantially or fully complementary nucleic acid strands, which are referred to as having “sense” and “antisense” orientations with respect to a target CFB RNA. The duplex region can be of any length that permits specific degradation of a desired target CFB RNA through a RISC pathway but will typically range from 9 to 30 base pairs in length, e.g., 15-30 base pairs in length. Considering a duplex between 9 and 30 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. CFB dsRNA agents generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a CFB dsDNA agent comprises a sequence that is substantially complementary to a region of a target CFB RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a “hairpin loop”) between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. In some embodiments of the invention, a hairpin look comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more unpaired nucleotides. Where the two substantially complementary strands of a CFB

dsRNA agent 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 a hairpin loop, the connecting structure is referred to as a “linker.” The term “siRNA” is also used herein to refer to a dsRNA agent as described herein.

5 In some embodiments of the invention a CFB dsRNA agent may include a sense and antisense sequence that have no-unpaired nucleotides or nucleotide analogs at one or both terminal ends of the dsRNA agent. An end with no unpaired nucleotides is referred to as a “blunt end” and as having no nucleotide overhang. If both ends of a dsRNA agent are blunt, the dsRNA is referred to as “blunt ended.” In some embodiments of the invention, a first end
10 of a dsRNA agent is blunt, in some embodiments a second end of a dsRNA agent is blunt, and in certain embodiments of the invention, both ends of a CFB dsRNA agent are blunt.

In some embodiments of dsRNA agents of the invention, the dsRNA does not have one or two blunt ends. In such instances there is at least one unpaired nucleotide at the end of a strand of a dsRNA agent. For example, when a 3'-end of one strand of a dsRNA extends
15 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 1, 2, 3, 4, 5, 6, or more nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. It will be understood that in some embodiments a nucleotide overhang is on a sense strand of a dsRNA agent, on an antisense strand of a dsRNA agent, or
20 on both ends of a dsRNA agent and 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 certain embodiments of the invention, one or more of the nucleotides in an overhang is replaced with a nucleoside thiophosphate.

As used herein, the term “antisense strand” or “guide strand” refers to the strand of a
25 CFB dsRNA agent that includes a region that is substantially complementary to a CFB target sequence. As used herein the term “sense strand,” or “passenger strand” refers to the strand of a CFB dsRNA agent that includes a region that is substantially complementary to a region of the antisense strand of the CFB dsRNA agent.

30 *Modifications*

In some embodiments of the invention the RNA of a CFB RNAi agent is chemically modified to enhance stability and/or one or more other beneficial characteristics. Nucleic acids in certain embodiments of the invention may be synthesized and/or modified by methods well established in the art, for example, those described in “Current protocols in Nucleic Acid
35 Chemistry,” Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is incorporated herein by reference. Modifications that can be present in certain embodiments of CFB dsRNA agents of the invention include, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, conjugation, inverted linkages, etc.) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) 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, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in certain embodiments of CFB dsRNA agents, CFB antisense polynucleotides, and CFB sense polynucleotides of the invention include, but are not limited to RNAs comprising modified backbones or no natural internucleoside linkages. As a non-limiting example, an RNA having a modified backbone may not have a phosphorus atom in the backbone. RNAs that do not have a phosphorus atom in their internucleoside backbone may be referred to as oligonucleosides. In certain embodiments of the invention, a modified RNA has a phosphorus atom in its internucleoside backbone.

It will be understood that the term “RNA molecule” or “RNA” or “ribonucleic acid molecule” encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. The terms “ribonucleoside” and “ribonucleotide” may be used interchangeably herein. An RNA molecule can be modified in the nucleobase structure or in the ribose-phosphate backbone structure, e.g., as described herein below, and molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. In some embodiments of the invention, an RNA molecule comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or up to the full length of the CFB dsRNA agent molecule's ribonucleosides that are modified ribonucleosides. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule.

DsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention may, in some embodiments comprise one or more independently selected modified nucleotide and/or one or more independently selected non-phosphodiester linkage. As used herein the term “independently selected” used in reference to a selected element, such as a modified nucleotide, non-phosphodiester linkage, etc., means that two or more selected elements can but need not be the same as each other.

As used herein, a “nucleotide base,” “nucleotide,” or “nucleobase” is a heterocyclic pyrimidine or purine compound, which is a standard constituent of all nucleic acids, and includes the bases that form the nucleotides adenine, guanine, cytosine, thymine, and uracil. A

nucleobase may further be modified to include, though not intended to be limiting: universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. The term “ribonucleotide” or “nucleotide” may be used herein to refer to an unmodified nucleotide, a modified nucleotide, or a surrogate replacement moiety. Those in the art will recognize that
5 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.

In one embodiment, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability to form
10 the required duplex structure and that permit or mediate the specific degradation of a target RNA via a RISC pathway. In certain embodiments of the invention, a CFB RNA interference agent includes a single stranded RNA that interacts with a target CFB RNA sequence to direct the cleavage of the target CFB RNA.

Modified RNA backbones can include, for example, phosphorothioates, chiral
15 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
20 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. Means of preparing phosphorus-containing linkages are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents, certain modified CFB antisense polynucleotides, and/or certain modified CFB sense polynucleotides
25 of the invention.

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
30 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 CH₂ component parts. Means of
35 preparing modified RNA backbones that do not include a phosphorus atom are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents, certain modified CFB antisense polynucleotides, and/or certain modified CFB sense polynucleotides of the invention.

In certain embodiments of the invention, RNA mimetics are included in CFB dsRNAs, CFB antisense polynucleotides, and/or CFB sense polynucleotides, such as, but not limited to: replacement of the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units with novel groups. In such embodiments, base units are maintained for hybridization with an appropriate CFB 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. Means of preparing RNA mimetics are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents of the invention.

Some embodiments of the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular $-\text{CH}_2\text{-NH-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-O-CH}_2-$ [known as a methylene (methylimino) or MMI backbone], $-\text{CH}_2\text{-O-N(CH}_3\text{)-CH}_2-$, $-\text{CH}_2\text{-N(CH}_3\text{)-N(CH}_3\text{)-CH}_2-$ and $-\text{N(CH}_3\text{)-CH}_2-$ [wherein the native phosphodiester backbone is represented as $-\text{O-P-O-CH}_2-$]. Means of preparing RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents, certain CFB antisense polynucleotides, and/or certain CFB sense polynucleotides of the invention.

Modified RNAs can also contain one or more substituted sugar moieties. CFB dsRNAs, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention may comprise 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 may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $\text{O}[(\text{CH}_2)_n\text{O}]_m\text{CH}_3$, $\text{O}(\text{CH}_2)_n\text{OCH}_3$, $\text{O}(\text{CH}_2)_n\text{NH}_2$, $\text{O}(\text{CH}_2)_n\text{CH}_3$, $\text{O}(\text{CH}_2)_n\text{ONH}_2$, and $\text{O}(\text{CH}_2)_n\text{ON}[(\text{CH}_2)_n\text{CH}_3]_2$, 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, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of a CFB dsRNA agent, or a group for improving the pharmacodynamic properties of a CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O-CH₂CH₂OCH₃, 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'-dimethylaminoethoxy, i.e., a $\text{O}(\text{CH}_2)_2\text{ON}(\text{CH}_3)_2$ 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-CH₂-O-CH₂-N(CH₂)₂. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents of the invention.

Other modifications include 2'-methoxy (2'-OCH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of a CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide of the invention, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked CFB dsRNAs, CFB antisense polynucleotides, or CFB sense polynucleotides, and the 5' position of 5' terminal nucleotide. CFB dsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Means of preparing modified RNAs such as those described are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention.

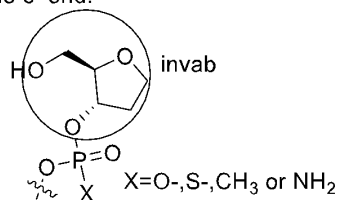
An CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide may, in some embodiments, include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine and guanine, and the pyrimidine bases thymine, cytosine and uracil. Modified nucleobases include other synthetic and natural nucleobases such as 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 and 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. Additional nucleobases that may be included in certain embodiments of CFB dsRNA agents of the invention are known in the art, see for example: Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. Ed. Wiley-VCH, 2008; The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L., Ed. John Wiley & Sons, 1990, English et al., Angewandte Chemie, International Edition, 1991, 30, 613, Sanghvi, Y S., Chapter 15, dsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Means of preparing dsRNAs, CFB antisense strand polynucleotides and/or CFB sense strand polynucleotides that comprise nucleobase modifications and/or substitutions such as those described herein are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents, CFB sense polynucleotides, and/or CFB antisense polynucleotides of the invention.

Certain embodiments of CFB dsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention include RNA modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide with a modified ribose moiety comprising an extra bridge connecting the 2' and 4' carbons. This structure effectively
 5 “locks” the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids in a CFB dsRNA agent, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention may increase stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1):439-447; Mook, O R. et al., (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. et al., (2003) *Nucleic Acids Research* 31(12):3185-3193). Means
 10 of preparing dsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides that comprise locked nucleic acid(s) are routinely practiced in the art and such methods can be used to prepare certain modified CFB dsRNA agents of the invention.

Certain embodiments of CFB dsRNA compounds, sense polynucleotides, and/or antisense polynucleotides of the invention, include at least one modified nucleotide, wherein
 15 the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine- glycol
 20 nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S- Isomer, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'- phosphate, a nucleotide comprising 2'-deoxyadenosine-3'-phosphate, a nucleotide comprising 2'- deoxycytidine-3'- phosphate, a nucleotide comprising 2'-
 25 deoxyuridine-3'- phosphate, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide. In some embodiments, a CFB dsRNA compound includes an E-vinylphosphonate nucleotide at the 5' -end of the antisense strand, also referred to herein as the guide strand.

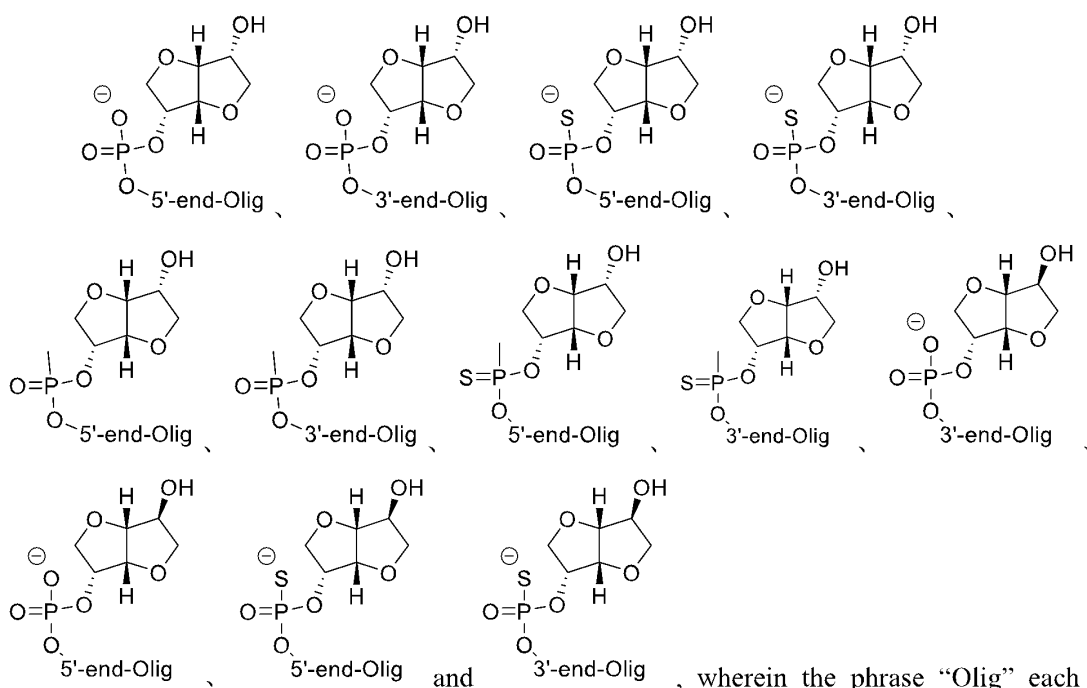
Certain embodiments of CFB dsRNA compounds, 3' and 5' end of sense
 30 polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide. It is known to skilled in art, including an abasic or inverted abasic nucleotide at the end of oligonucleotide enhances stability (Czauderna et al. *Structural*
 35 *variations and stabilizing modifications of synthetic siRNAs in mammalian cells. Nucleic Acids Res.* 2003;31(11):2705-2716. doi:10.1093/nar/gkg393). In some embodiments, a CFB dsRNA compound includes one or more inverted abasic residues (invab) at either 3'-end or 5'-end, or both 3'-end and 5'-end. Exemplified inverted abasic residues (invab) include, but are not limited to the following:

when at the 3'-end:

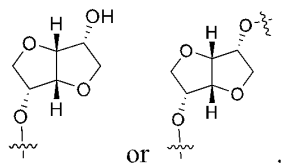


attached to 3'-end of oligonucleotide

- Certain embodiments of CFB dsRNA compounds, 3' and 5' end of sense polynucleotides, and/or 3' end of antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises: isomannide residues or stereoisomer of said isomannide residues. Specific examples of isomannide residues or stereoisomers of said isomannide residues include, but are not limited to:



- wherein the phrase "Olig" each independently represents a polynucleotide moiety. Exemplified isomannide residues (imann) include, but are not limited to, the following:



In certain embodiments, the isomannide nucleotides may further conjugate to one or more targeting groups or delivery molecules, such as GalNAc moieties.

- Certain embodiments of CFB dsRNA compounds, antisense polynucleotides of the invention, include at least one modified nucleotide, wherein the at least one modified nucleotide comprises unlocked nucleic acid nucleotide (UNA) or/and glycol nucleic acid

nucleotide (GNA). It is known to skilled in art, UNA and GNA are thermally destabilizing chemical modifications, can significantly improves the off-target profile of a siRNA compound (Janas, et al., Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity. *Nat Commun.* 2018;9(1):723. doi:10.1038/s41467-018-02989-4; Laursen et al.,
5 Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo. *Mol BioSyst.* 2010;6:862–70).

Another modification that may be included in the RNA of certain embodiments of CFB dsRNA agents, CFB antisense polynucleotides, and/or CFB sense polynucleotides of the invention, comprises chemically linking to the RNA one or more ligands, moieties or
10 conjugates that enhance one or more characteristics of the CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide, respectively. Non-limiting examples of characteristics that may be enhanced are: CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide activity, cellular distribution, delivery of a CFB dsRNA agent, pharmacokinetic properties of a CFB dsRNA agent, and cellular uptake of the CFB
15 dsRNA agent. In some embodiments of the invention, a CFB dsRNA agent comprises one or more targeting groups or linking groups, which in certain embodiments of CFB dsRNA agents of the invention are conjugated to the sense strand. A non-limiting example of a targeting group is a compound comprising N-acetyl-galactosamine (GalNAc). The terms “targeting group”, “targeting agent”, “linking agent”, “targeting compound”, “delivery molecule”,
20 “delivery compound” and “targeting ligand” may be used interchangeably herein. In certain embodiments of the invention a CFB dsRNA agent comprises a targeting compound that is conjugated to the 5'-terminal end of the sense strand. In certain embodiments of the invention a CFB dsRNA agent comprises a targeting compound that is conjugated to the 3'-terminal end of the sense strand. In some embodiments of the invention, a CFB dsRNA agent comprises a
25 targeting group that comprises GalNAc. In certain embodiments of the invention a CFB dsRNA agent does not include a targeting compound conjugated to one or both of the 3'-terminal end and the 5'-terminal end of the sense strand. In certain embodiments of the invention a CFB dsRNA agent does not include a GalNAc containing targeting compound conjugated to one or both of the 5'-terminal end and the 3'-terminal end of the sense strand.

30 Additional targeting and linking agents are well known in the art, for example, targeting and linking agents that may be used in certain embodiments of the invention include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan et al., *Biorg. Med. Chem. Lett.*, 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. Lett.*, 1993, 3:2765-2770), a
35 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).

Certain embodiments of a composition comprising a CFB dsRNA agent, CFB antisense polynucleotide, and/or CFB sense polynucleotide may comprise a ligand that alters distribution, targeting, or etc. of the CFB dsRNA agent. In some embodiments of a composition comprising a CFB dsRNA agent of the invention, the ligand increases 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. A ligand useful in a composition and/or method of the invention may be a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. A ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid or polyamine. Examples of polyamino acids are a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazene. 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.

A ligand included in a composition and/or method of the invention may comprise a targeting group, non-limiting examples of which are 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 or a liver 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-gulucosamine 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.

A ligand included in a composition and/or method of the invention may be a protein, e.g., glycoprotein, or peptide, for example a molecule with a specific affinity for a co-ligand, or an antibody, for example an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, cardiac cell, or bone cell. A ligand useful in an embodiment of a composition and/or method of the invention can be a hormone or hormone receptor. A ligand useful in an embodiment of a composition and/or method of the invention can be a lipid, lectin, carbohydrates, vitamin, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, or multivalent fucose. A ligand useful in an embodiment of a composition and/or method of the invention can be a substance that can increase uptake of the CFB dsRNA 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. Non-limiting examples of this type of agent are: taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, and myoservin.

In some embodiments, a ligand attached to a CFB dsRNA agent of the invention functions as a pharmacokinetic (PK) modulator. An example of a PK modulator that may be used in compositions and methods of the invention includes but is not limited to: a lipophiles, a bile acid, a steroid, a phospholipid analogue, a peptide, a protein binding agent, PEG, a vitamin, cholesterol, a fatty acid, cholic acid, lithocholic acid, dialkylglycerides, diacylglyceride, a phospholipid, a sphingolipid, naproxen, ibuprofen, vitamin E, biotin, an aptamer that binds a serum protein, etc. Oligonucleotides comprising 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 may also be used in compositions and/or methods of the invention as ligands.

CFB dsRNA agent compositions

In some embodiments of the invention, a CFB dsRNA agent is in a composition. A composition of the invention may include one or more CFB dsRNA agent and optionally one or more of a pharmaceutically acceptable carrier, a delivery agent, a targeting agent, detectable label, etc. A non-limiting example of a targeting agent that may be useful according to some

embodiments of methods of the invention is an agent that directs a CFB dsRNA agent of the invention to and/or into a cell to be treated. A targeting agent of choice will depend upon such elements as: the nature of the CFB-associated disease or condition, and on the cell type being targeted. In a non-limiting example, in some embodiments of the invention it may be desirable to target a CFB dsRNA agent to and/or into a liver cell. It will be understood that in some embodiments of methods of the invention, a therapeutic agent comprises a CFB dsRNA agent with only a delivery agent, such as a delivery agent comprising N-Acetylgalactosamine (GalNAc), without any additional attached elements. For example, in some aspects of the invention a CFB dsRNA agent may be attached to a delivery compound comprising GalNAc and included in a composition comprising a pharmaceutically acceptable carrier and administered to a cell or subject without any detectable labels, or targeting agents, etc. attached to the CFB dsRNA agent.

In cases where a CFB dsRNA agent of the invention is administered with and/or attached to one or more delivery agents, targeting agents, labeling agents, etc. a skilled artisan will be aware of and able to select and use suitable agents for use in methods of the invention. Labeling agents may be used in certain methods of the invention to determine the location of a CFB dsRNA agent in cells and tissues and may be used to determine a cell, tissue, or organ location of a treatment composition comprising a CFB dsRNA agent that has been administered in methods of the invention. Procedures for attaching and utilizing labeling agents such as enzymatic labels, dyes, radiolabels, etc. are well known in the art. It will be understood that in some embodiments of compositions and methods of the invention, a labeling agent is attached to one or both of a sense polynucleotide and an antisense polynucleotide included in a CFB dsRNA agent.

Delivery of CFB dsRNA agents and CFB antisense polynucleotide agents

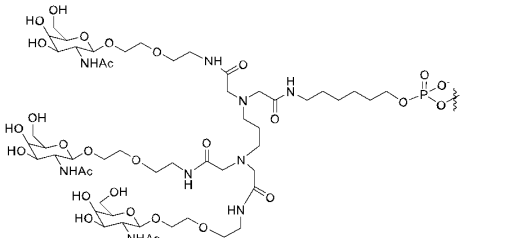
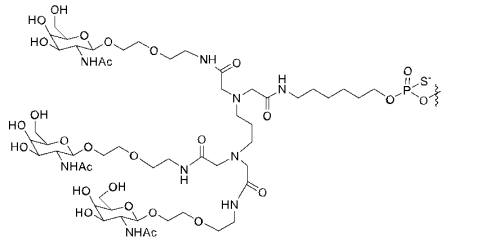
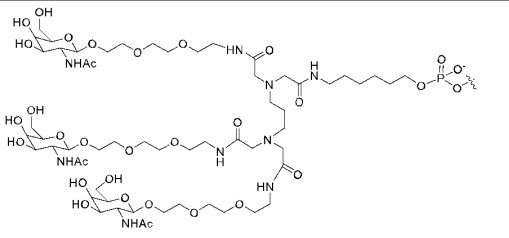
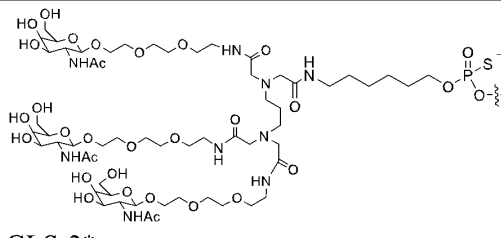
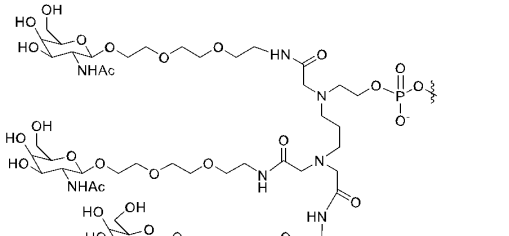
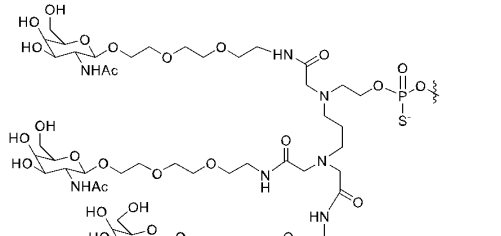
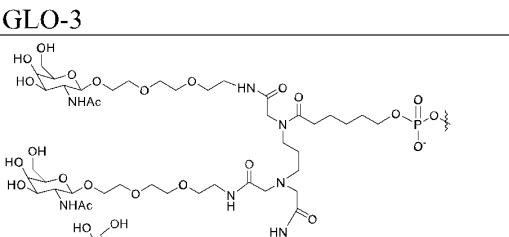
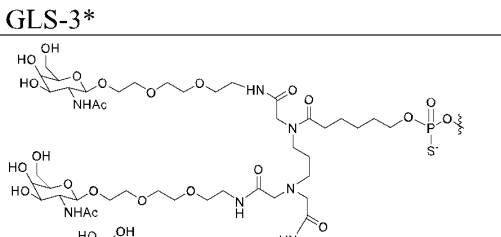
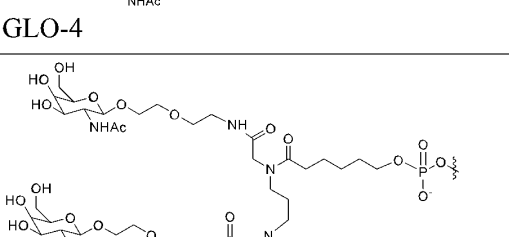
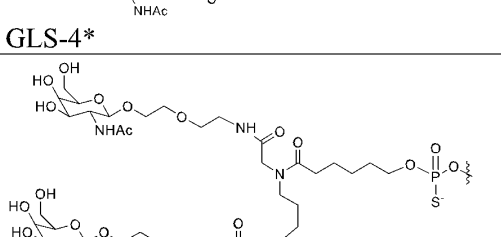
Certain embodiments of methods of the invention, includes delivery of a CFB dsRNA agent into a cell. As used herein the term, "delivery" means facilitating or effecting uptake or absorption into the cell. Absorption or uptake of a CFB dsRNA agent can occur through unaided diffusive or active cellular processes, or by use of delivery agents, targeting agents, etc. that may be associated with a CFB dsRNA agent of the invention. Delivery means that are suitable for use in methods of the invention include, but are not limited to: *in vivo* delivery, in which a CFB dsRNA agent is injected into a tissue site or administered systemically. In some embodiments of the invention, a CFB dsRNA agent is attached to a delivery agent.

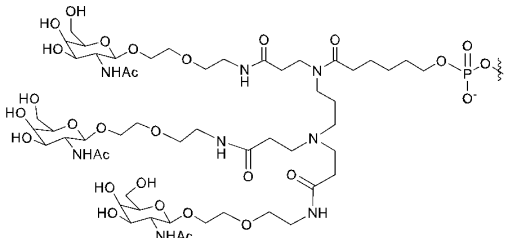
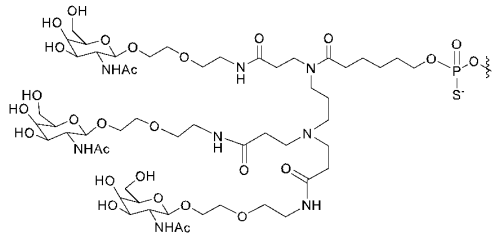
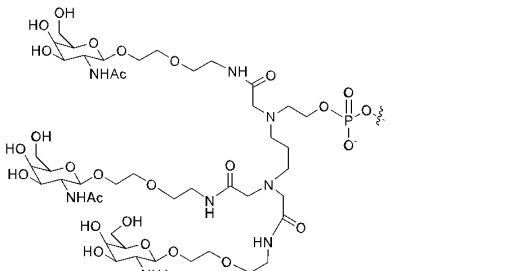
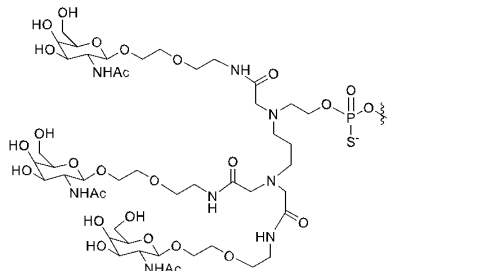
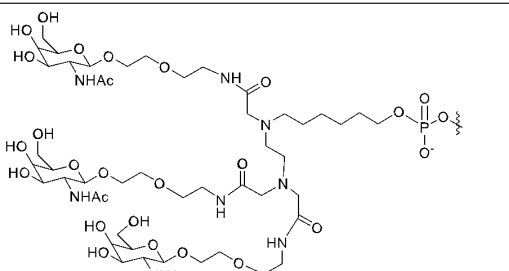
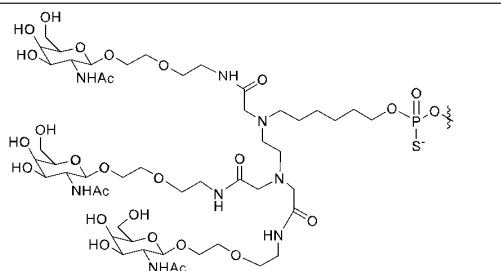
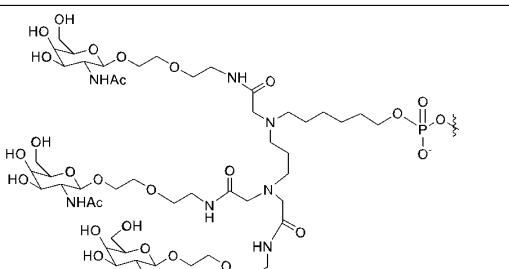
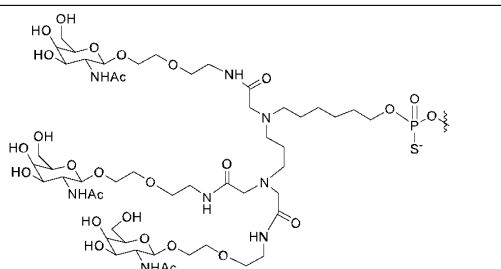
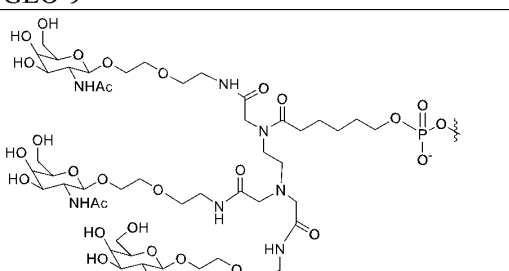
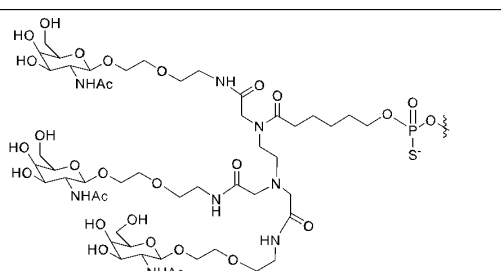
Non-limiting examples of methods that can be used to deliver CFB dsRNA agents to cells, tissues and/or subjects include: CFB dsRNA-GalNAc conjugates, SAMiRNA technology, LNP-based delivery methods, and naked RNA delivery. These and other delivery methods have been used successfully in the art to deliver therapeutic RNAi agents for treatment of various diseases and conditions, such as but not limited to: liver diseases, acute intermittent porphyria (AIP), hemophilia, pulmonary fibrosis, etc. Details of various delivery means are

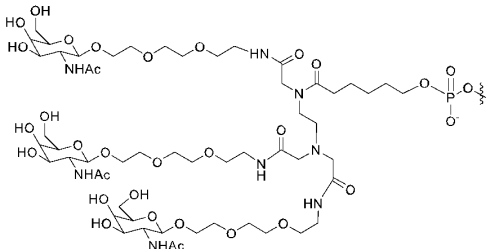
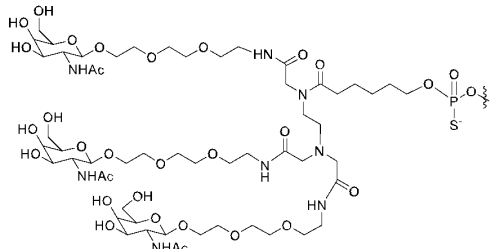
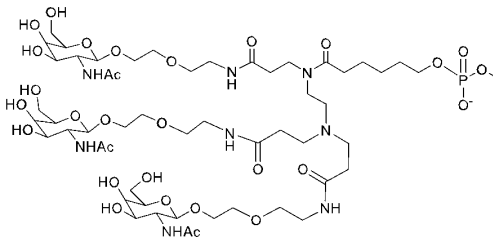
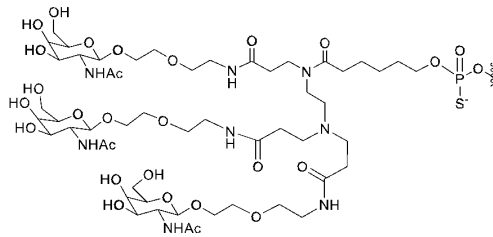
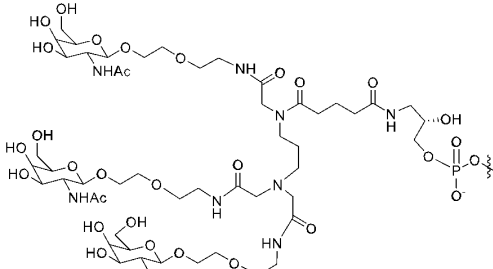
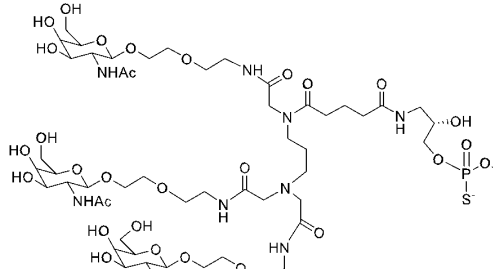
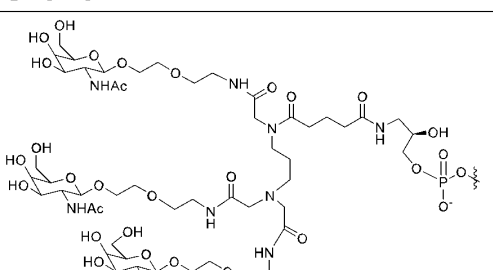
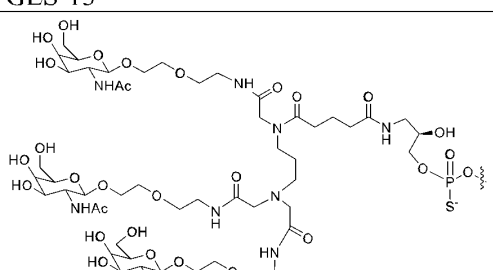
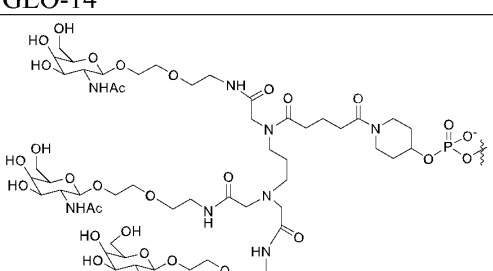
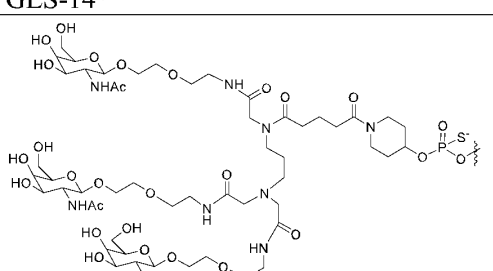
found in publications such as: Nikam, R.R. & K. R. Gore (2018) *Nucleic Acid Ther*, 28 (4), 209-224 Aug 2018; Springer A.D. & S.F. Dowdy (2018) *Nucleic Acid Ther*. Jun 1; 28(3): 109-118; Lee, K. et al., (2018) *Arch Pharm Res*, 41(9), 867-874; and Nair, J.K. et al., (2014) *J. Am. Chem. Soc.* 136:16958-16961, the content each of which is incorporated by reference
 5 herein.

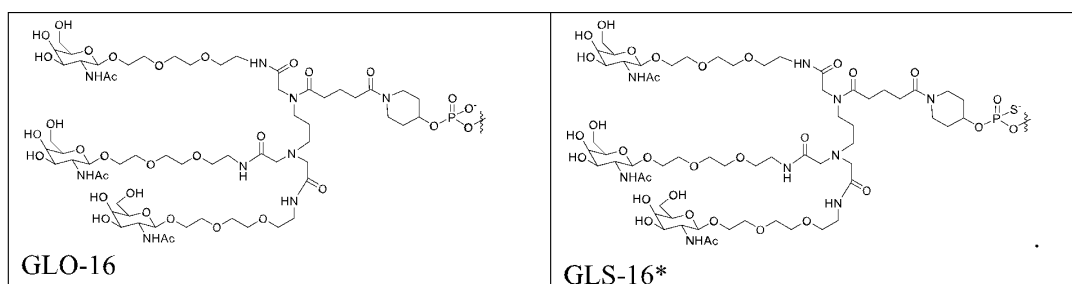
Some embodiments of the invention comprise use of lipid nanoparticles (LNPs) to deliver a CFB dsRNA agent of the invention to a cell, tissue, and/or subject. LNPs are routinely used for *in vivo* delivery of CFB dsRNA agents, including therapeutic CFB dsRNA agents. One benefit of using an LNP or other delivery agent is an increased stability of the
 10 CFB RNA agent when it is delivered to a subject using the LNP or other delivery agent. In some embodiments of the invention an LNP comprises a cationic LNP that is loaded with one or more CFB RNAi molecules of the invention. The LNP comprising the CFB RNAi molecule(s) is administered to a subject, the LNPs and their attached CFB RNAi molecules are taken up by cells via endocytosis, their presence results in release of RNAi trigger molecules,
 15 which mediate RNAi.

Another non-limiting example of a delivery agent that may be used in embodiments of the invention to delivery a CFB dsRNA agent of the invention to a cell, tissue and/or subject is an agent comprising GalNAc that is attached to a CFB dsRNA agent of the invention and delivers the CFB dsRNA agent to a cell, tissue, and/or subject. Examples of certain additional
 20 delivery agents comprising GalNAc that can be used in certain embodiments of methods and composition of the invention are disclosed in PCT Application: WO2020191183A1 (incorporated herein in its entirety). A non-limiting example of a GalNAc targeting ligand that can be used in compositions and methods of the invention to deliver a CFB dsRNA agent to a cell is a targeting ligand cluster. Examples of targeting ligand clusters
 25 that are presented herein are referred to as: GalNAc Ligand with phosphodiester link (GLO) and GalNAc Ligand with phosphorothioate link (GLS). The term "GLX-n" may be used herein to indicate the attached GalNAc-containing compound is any one of compounds GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*, GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4,
 30 GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, the structure of each of which is shown below, with the below with location of attachment of the GalNAc-targeting ligand to an RNAi agent of the invention at far right of each (shown with "§"). It will be understood that any RNAi and dsRNA molecule of the invention can be attached to the GLS-1*, GLS-2*, GLS-3*, GLS-4*, GLS-5*, GLS-6*,
 35 GLS-7*, GLS-8*, GLS-9*, GLS-10*, GLS-11*, GLS-12*, GLS-13*, GLS-14*, GLS-15*, GLS-16*, GLO-1, GLO-2, GLO-3, GLO-4, GLO-5, GLO-6, GLO-7, GLO-8, GLO-9, GLO-10, GLO-11, GLO-12, GLO-13, GLO-14, GLO-15, and GLO-16, GLO-1 through GLO-16 and GLS-1* through GLS-16* structures are shown below.

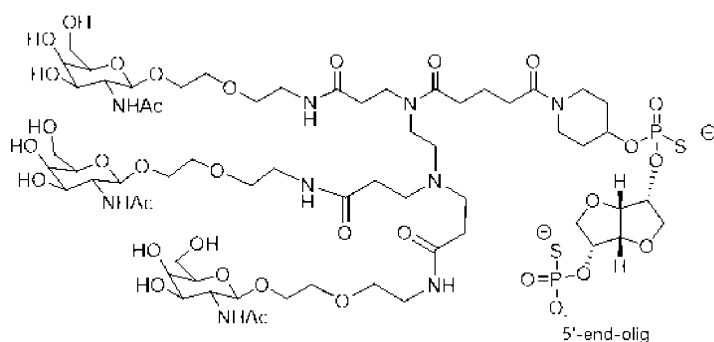
 GLO-1	 GLS-1*
 GLO-2	 GLS-2*
 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*

 GLO-6	 GLS-6*
 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*

 GLO-11	 GLS-11*
 GLO-12	 GLS-12*
 GLO-13	 GLS-13*
 GLO-14	 GLS-14*
 GLO-15	 GLS-15*



In certain embodiments, the aforesaid isomannide nucleotides may further conjugate to one or more GalNAc targeting ligands. Specific examples of isomannide nucleotides conjugated to a GalNAc targeting ligand include, but are not limited to:



, wherein the phrase "olig"

each independently represents a polynucleotide moiety.

In some embodiments of the invention, *in vivo* delivery can also be by a beta-glucan delivery system, such as those described in U.S. Pat. Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. *In vitro* introduction of a CFB RNAi agent into a cell may also be done using art-known methods such as electroporation and lipofection. In certain embodiments of methods of the invention, a CFB dsRNA is delivered without a targeting agent. These RNAs may be delivered as "naked" RNA molecules. As a non-limiting example, a CFB dsRNA of the invention may be administered to a subject to treat a CFB-associated disease or condition in the subject, such as a cardiovascular disease, in a pharmaceutical composition comprising the RNAi agent, but not including a targeting agent such as a GalNAc targeting compound.

In addition to certain delivery means described herein, it will be understood that RNAi delivery means, such as but not limited to those described herein and those used in the art, can be used in conjunction with embodiments of CFB RNAi agents and treatment methods described herein.

CFB dsRNA agents of the invention may be administered to a subject in an amount and manner effective to reduce a level and activity of CFB polypeptide in a cell and/or subject. In some embodiments of methods of the invention one or more CFB dsRNA agents are administered to a cell and/or subject to treat a disease or condition associated with CFB expression and activity. Methods of the invention, in some embodiments, include

administering one or more CFB dsRNA agents to a subject in need of such treatment to reduce a disease or condition associated with CFB expression in the subject. CFB dsRNA agents or CFB antisense polynucleotide agents of the invention can be administered to reduce CFB expression and/or activity in one more of *in vitro*, *ex vivo*, and *in vivo* cells.

- 5 In some embodiments of the invention, a level, and thus an activity, of CFB polypeptide in a cell is reduced by delivering (e.g. introducing) an CFB dsRNA agent or CFB antisense polynucleotide agent into a cell. Targeting agents and methods may be used to aid in delivery of a CFB dsRNA agent or CFB antisense polynucleotide agent to a specific cell type, cell subtype, organ, spatial region within a subject, and/or to a sub-cellular region within a cell.
- 10 An CFB dsRNA agent can be administered in certain methods of the invention singly or in combination with one or more additional CFB dsRNA agents. In some embodiments, 2, 3, 4, or more independently selected CFB dsRNA agents are administered to a subject.

- In certain embodiments of the invention, an CFB dsRNA agent is administered to a subject to treat a CFB-associated disease or condition in conjunction with one or more additional therapeutic regimens for treating the CFB-associate disease or condition. Non-limiting examples of additional therapeutic regimens are: administering one or more CFB antisense polynucleotides of the invention, administering a non-CFB dsRNA therapeutic agent, and a behavioral modification. An additional therapeutic regimen may be administered at a time that is one or more of: prior to, simultaneous with, and following administration of a CFB dsRNA agent of the invention. It will be understood that simultaneous with as used herein, within five minutes of time zero, within 10 minutes of time zero, within 30 minutes of time zero, within 45 minutes of time zero, and within 60 minutes of time zero, with "time zero" the time of administration of the CFB dsRNA agent of the invention to the subject. Non-limiting examples of non-CFB dsRNA therapeutic agents are: an inhibitor of C5, such as an anticomplement component C5 antibody, or antigen-binding fragment thereof (e.g., eculizumab, ravulizumab-cwvz, or pozelimab (REGN3918)) or a C5 peptide inhibitor (e.g., zilucoplan). 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.
- 25 Ravulizumab-cwvz is a humanized IgG2/4 monoclonal 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. Pozelimab (also known as H4H12166P, described in US20170355757) is a fully-human IgG4 monoclonal antibody designed to block complement factor C5. Zilucoplan is a synthetic, macrocyclic peptide that binds complement component 5 (C5) with sub-nanomolar affinity and allosterically inhibits its cleavage into C5a and C5b upon activation of the classical, alternative, or lectin pathways. Preferably, the additional therapeutic is a C3 peptide inhibitor, or analog thereof. In one embodiment, the C3 peptide inhibitor is compstatin. Compstatin is a cyclic tridecapeptide with potent and selective C3 inhibitory activity. These and other therapeutic
- 30
- 35

agents and behavior modifications are known in the art and used to treat a CFB-associated disease or condition in a subject and may be administered to a subject in combination with the administration of one or more CFB dsRNA agents of the invention to treat the CFB-associated disease or condition. A CFB dsRNA agent of the invention administered to a cell or subject to
5 treat a CFB-associated disease or condition may act in a synergistic manner with one or more other therapeutic agents or activities and increase the effectiveness of the one or more therapeutic agents or activities and/or to increase the effectiveness of the CFB dsRNA agent at treating the CFB-associated disease or condition.

Treatment methods of the invention that include administration of a CFB dsRNA agent
10 can be used prior to the onset of a CFB-associated disease or condition and/or when a CFB-associated disease or condition is present, including at an early stage, mid-stage, and late stage of the disease or condition and all times before and after any of these stages. Methods of the invention may also be to treat subjects who have previously been treated for a CFB-associated disease or condition with one or more other therapeutic agents and/or therapeutic activities that
15 were not successful, were minimally successful, and/or are no longer successful at treating the CFB-associated disease or condition in the subject.

Vector Encoded dsRNAs

In certain embodiments of the invention, a CFB dsRNA agent can be delivered into a
20 cell using a vector. CFB dsRNA agent transcription units can be included in a DNA or RNA vector. Prepare and use of such vectors encoding transgenes for delivering sequences into a cell and or subject are well known in the art. Vectors can be used in methods of the invention that result in transient expression of CFB dsRNA, for example for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more weeks. The length of the transient
25 expression can be determined using routine methods based on elements such as, but not limited to the specific vector construct selected and the target cell and/or tissue. Such 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)
30 92:1292).

An individual strand or strands of a CFB dsRNA agent 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 to a cell using means such as transfection or infection. In certain embodiments each individual strand of a
35 CFB dsRNA agent of the invention can be transcribed by promoters that are both included on the same expression vector. In certain embodiments of the invention a CFB dsRNA agent is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the CFB dsRNA agent has a stem and loop structure.

Non-limiting examples of RNA expression vectors are DNA plasmids or viral vectors. Expression vectors useful in embodiments of the invention can be compatible with eukaryotic cells. Eukaryotic cell expression vectors are routinely used in the art and are available from a number of commercial sources. Delivery of CFB dsRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-
5 planted from a subject followed by reintroduction into the subject, or by any other means that allows for introduction into a desired target cell.

Viral vector systems that may be included in an embodiment of a method of the include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to
10 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. Constructs for the recombinant expression of a CFB dsRNA agent may include
15 regulatory elements, such as promoters, enhancers, etc., which may be selected to provide constitutive or regulated/inducible expression. Viral vector systems, and the use of promoters and enhancers, etc. are routine in the art and can be used in conjunction with methods and compositions described herein.

Certain embodiments of the invention include use of viral vectors for delivery of CFB
20 dsRNA agents into cells. Numerous adenovirus-based delivery systems are routinely used in the art for deliver to, for example, lung, liver, the central nervous system, endothelial cells, and muscle. Non-limiting examples of viral vectors that may be used in methods of the invention are: AAV vectors, a pox virus such as a vaccinia virus, a Modified Virus Ankara (MVA), NYVAC, an avipox such as fowl pox or canary pox.

Certain embodiments of the invention include methods of delivering CFB dsRNA
25 agents into cells using a vector and such vectors may be in a pharmaceutically acceptable carrier that may, but need not, include a slow release matrix in which the gene delivery vehicle is imbedded. In some embodiments, a vector for delivering a CFB dsRNA can be produced from a recombinant cell, and a pharmaceutical composition of the invention may include one
30 or more cells that produced the CFB dsRNA delivery system.

Pharmaceutical Compositions Containing CFB dsRNA or ssRNA agents

Certain embodiments of the invention include use of pharmaceutical compositions containing a CFB dsRNA agent or CFB antisense polynucleotide agent and a pharmaceutically
35 acceptable carrier. The pharmaceutical composition containing the CFB dsRNA agent or CFB antisense polynucleotide agent can be used in methods of the invention to reduce CFB gene expression and CFB activity in a cell and is useful to treat a CFB-associated disease or condition. Such pharmaceutical compositions can be formulated based on the mode of delivery. Non-limiting examples of formulations for modes of delivery are: a composition

formulated for subcutaneous delivery, a composition formulated for systemic administration via parenteral delivery, a composition formulated for intravenous (IV) delivery, a composition formulated for intrathecal delivery, a composition formulated for direct delivery into brain, etc. Administration of a pharmaceutical composition of the invention to deliver a CFB dsRNA agent or CFB antisense polynucleotide agent into a cell may be done using one or more means such as: 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. A CFB dsRNA agent or CFB antisense polynucleotide agent can also be delivered directly to a target tissue, for example directly into the liver, directly into a kidney, etc. It will be understood that “delivering a CFB dsRNA agent” or “delivering a CFB antisense polynucleotide agent” into a cell encompasses delivering a CFB dsRNA agent or CFB antisense polynucleotide agent, respectively, directly as well as expressing a CFB dsRNA agent in a cell from an encoding vector that is delivered into a cell, or by any suitable means with which the CFB dsRNA or CFB antisense polynucleotide agent becomes present in a cell. Preparation and use of formulations and means for delivering inhibitory RNAs are well known and routinely used in the art.

As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention and a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

As used herein terms such as: “pharmacologically effective amount,” “therapeutically effective amount” and “effective amount” refers to that amount of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a

disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 10% reduction in that parameter. For example, a therapeutically effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent can reduce CFB polypeptide levels by at least 10%.

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Effective amounts

Methods of the invention, in some aspects comprise contacting a cell with a CFB dsRNA agent or CFB antisense polynucleotide agent in an effective amount to reduce CFB gene expression in the contacted cell. Certain embodiments of methods of the invention

10 comprise administering a CFB dsRNA agent or a CFB antisense polynucleotide agent to a subject in an amount effective to reduce CFB gene expression and treat a CFB-associated disease or condition in the subject. An “effective amount” used in terms of reducing expression of CFB and/or for treating a CFB-associated disease or condition, is an amount necessary or sufficient to realize a desired biologic effect. For example, an effective amount of

15 a CFB dsRNA agent or CFB antisense polynucleotide agent to treat a CFB-associated disease or condition could be that amount necessary to (i) slow or halt progression of the disease or condition; or (ii) reverse, reduce, or eliminate one or more symptoms of the disease or condition. In some aspects of the invention, an effective amount is that amount of a CFB dsRNA agent or CFB antisense polynucleotide agent that when administered to a subject in

20 need of a treatment of a CFB-associated disease or condition, results in a therapeutic response that prevents and/or treats the disease or condition. According to some aspects of the invention, an effective amount is that amount of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention that when combined or co-administered with another therapeutic treatment for a CFB-associated disease or condition, results in a therapeutic response that

25 prevents and/or treats the disease or condition. In some embodiments of the invention, a biologic effect of treating a subject with a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention may be the amelioration and or absolute elimination of symptoms resulting from the CFB-associated disease or condition. In some embodiments of the invention, a biologic effect is the complete abrogation of the CFB-associated disease or condition, as

30 evidenced for example, by a diagnostic test that indicates the subject is free of the CFB-associated disease or condition. A non-limiting example of a physiological symptom that may be detected includes a reduction in CFB level in liver of a subject following administration of an agent of the invention. Additional art-known means of assessing the status of a CFB-associated disease or condition can be used to determine an effect of an agent and/or methods

35 of the invention on a CFB-associated disease or condition.

Typically, an effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent to decrease CFB polypeptide activity to a level to treat a CFB-associated disease or condition will be determined in clinical trials, establishing an effective dose for a test population versus a control population in a blind study. In some embodiments, an effective

amount will be that results in a desired response, e.g., an amount that diminishes a CFB-associated disease or condition in cells, tissues, and/or subjects with the disease or condition. Thus, an effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent to treat a CFB-associated disease or condition that can be treated by reducing CFB polypeptide activity may be the amount that when administered decreases the amount of CFB polypeptide activity in the subject to an amount that is less than the amount that would be present in the cell, tissue, and/or subject without the administration of the CFB dsRNA agent or CFB antisense polynucleotide agent. In certain aspects of the invention the level of CFB polypeptide activity, and/or CFB gene expression present in a cell, tissue, and/or subject that has not been contacted with or administered a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention is referred to as a “control” amount. In some embodiments of methods of the invention a control amount for a subject is a pre-treatment amount for the subject, in other words, a level in a subject before administration of a CFB agent can be a control level for that subject and compared to a level of CFB polypeptide activity and/or CFB gene expression in the subject following siRNA administered to the subject. In the case of treating a CFB-associated disease or condition the desired response may be reducing or eliminating one or more symptoms of the disease or condition in the cell, tissue, and/or subject. The reduction or elimination may be temporary or may be permanent. It will be understood that the status of a CFB-associated disease or condition can be monitored using methods of determining CFB polypeptide activity, CFB gene expression, symptom evaluation, clinical testing, etc. In some aspects of the invention, a desired response to treatment of a CFB-associated disease or condition is delaying the onset or even preventing the onset of the disease or condition.

An effective amount of a compound that decreases CFB polypeptide activity may also be determined by assessing physiological effects of administration of a CFB dsRNA agent or CFB antisense polynucleotide agent on a cell or subject, such as a decrease of a CFB-associated disease or condition following administration. Assays and/or symptomatic monitoring of a subject can be used to determine efficacy of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention, which may be administered in a pharmaceutical compound of the invention, and to determine the presence or absence of a response to the treatment. A non-limiting example, is that one or more art-known tests of CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex. Another non-limiting example, is that one or more art-known tests of liver function can be used to determine the status of the CFB-associated lipid imbalance in a subject before and after treatment of the subject with a CFB dsRNA agent of the invention.

Some embodiments of the invention include methods of determining an efficacy of an dsRNA agent or CFB antisense polynucleotide agent of the invention administered to a subject,

to treat a CFB-associated disease or condition by assessing and/or monitoring one or more “physiological characteristics” of the CFB-associated disease or condition in the subject. Non-limiting examples of physiological characteristics of a CFB-associated disease or condition are the CFB mRNA level, the CFB protein level, or CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex. Standard means of determining such physiological characteristic are known in the art and include, but are not limited to, blood tests, imaging studies, physical examination, etc.

It will be understood that the amount of a CFB dsRNA agent or CFB antisense polynucleotide agent administered to a subject can be modified based, at least in part, on such determinations of disease and/or condition status and/or physiological characteristics determined for a subject. The amount of a treatment may be varied for example by increasing or decreasing the amount of a CFB-dsRNA agent or CFB antisense polynucleotide agent, by changing the composition in which the CFB dsRNA agent or CFB antisense polynucleotide agent, respectively, is administered, by changing the route of administration, by changing the dosage timing and so on. The effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent will vary with the particular condition being treated, the age and physical condition of the subject being treated; the severity of the condition, the duration of the treatment, the nature of the concurrent therapy (if any), the specific route of administration, and additional factors within the knowledge and expertise of the health practitioner. For example, an effective amount may depend upon the desired level of CFB polypeptide activity and or CFB gene expression that is effective to treat the CFB-associated disease or condition. A skilled artisan can empirically determine an effective amount of a particular CFB dsRNA agent or CFB antisense polynucleotide agent of the invention for use in methods of the invention without necessitating undue experimentation. Combined with the teachings provided herein, by selecting from among various CFB dsRNA agents or CFB antisense polynucleotide agents of the invention, and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned that is effective to treat the particular subject. As used in embodiments of the invention, an effective amount of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention can be that amount that when contacted with a cell results in a desired biological effect in the cell.

It will be recognized that CFB gene silencing may be determined in any cell expressing CFB, either constitutively or by genomic engineering, and by any appropriate assay. In some embodiments of the invention, CFB gene expression is reduced by at least 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% by administration of a CFB dsRNA agent of the invention. In some embodiments of the invention, CFB gene expression is reduced by at between 5% and 10%, 5%

and 25%, 10% and 50%, 10% and 75%, 25% and 75%, 25% and 100%, or 50% and 100% by administration of a CFB dsRNA agent of the invention.

Dosing

5 CFB dsRNA agents and CFB antisense polynucleotide agents are delivered in pharmaceutical compositions in dosages sufficient to inhibit expression of CFB genes. In certain embodiments of the invention, a dose of CFB dsRNA agent or CFB antisense polynucleotide agent is in a range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of 1 to 50 mg per kilogram body weight, 5 to 40
10 mg/kg body weight, 10 to 30 mg/kg body weight, 1 to 20 mg/kg body weight, 1 to 10 mg/kg body weight, 4 to 15 mg/kg body weight per day, inclusive. For example, the CFB dsRNA agent or CFB antisense polynucleotide agent can be administered in an amount that is from about 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 1
15 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4 mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8
20 mg/kg, 5.9 mg/kg, 6 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23mg/kg, 24 mg/kg, 25 mg/kg, 26 mg/kg, 27 mg/kg, 28 mg/kg, 29 mg/kg, 30 mg/kg, 31 mg/kg, 32 mg/kg, 33mg/kg, 34 mg/kg, 35 mg/kg, 36 mg/kg, 37 mg/kg, 38 mg/kg, 39 mg/kg, 40 mg/kg, 41 mg/kg, 42 mg/kg, 43mg/kg, 44 mg/kg, 45 mg/kg, 46 mg/kg, 47 mg/kg, 48 mg/kg, 49 mg/kg, through 50 mg/kg body per
30 single dose.

Various factors may be considered in the determination of dosage and timing of delivery of a CFB dsRNA agent of the invention. The absolute amount of a CFB dsRNA agent or CFB antisense polynucleotide agent delivered will depend upon a variety of factors including a concurrent treatment, the number of doses and the individual subject parameters
35 including age, physical condition, size and weight. These are factors well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. In some embodiments, a maximum dose can be used, that is, the highest safe dose according to sound medical judgment.

Methods of the invention may in some embodiments include administering to a subject 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more doses of a CFB dsRNA agent or CFB antisense polynucleotide agent. In some instances, a pharmaceutical compound, (e.g., comprising a CFB dsRNA agent or comprising a CFB antisense polynucleotide agent) can be administered to a subject at least daily, every other day, weekly, every other week, monthly, etc. Doses may be administered once per day or more than once per day, for example, 2, 3, 4, 5, or more times in one 24 hour period. A pharmaceutical composition of the invention may be administered once daily, or the CFB dsRNA agent or CFB antisense polynucleotide agent may 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 some embodiments of methods of the invention, a pharmaceutical composition of the invention is administered to a subject one or more times per day, one or more times per week, one or more times per month, or one or more times per year.

Methods of the invention, in some aspects, include administration of a pharmaceutical compound alone, in combination with one or more other CFB dsRNA agents or CFB antisense polynucleotide agents, and/or in combination with other drug therapies or treatment activities or regimens that are administered to subjects with a CFB-associated disease or condition. Pharmaceutical compounds may be administered in pharmaceutical compositions. Pharmaceutical compositions used in methods of the invention may be sterile and contain an amount of a CFB dsRNA agent or CFB antisense polynucleotide agent that will reduce activity of a CFB polypeptide to a level sufficient to produce the desired response in a unit of weight or volume suitable for administration to a subject. A dose administered to a subject of a pharmaceutical composition that includes a CFB dsRNA agent or CFB antisense polynucleotide agent to reduce CFB protein activity can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

Treatment

As used herein, “CFB-associated disease”, “CFB-associated diseases and conditions” and “diseases and conditions caused and/or modulated by CFB” is intended to include any disease associated with the CFB gene or protein. Such diseases may be caused, for example, by overproduction of CFB protein, by mutation of the CFB gene, by abnormal cleavage of the CFB protein, by abnormal interaction between CFB and other proteins or other endogenous or exogenous substances. Exemplary CFB -associated diseases include, but are not limited to: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus

erythematosus (SLE), Lupus Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS), neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelitis optica (NMO), dense deposit disease, 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), cold agglutinin disease, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis, or lipid imbalance related to CFB.

In certain aspects of the invention, a subject may be administered a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention at a time that is one or more of before or after diagnosis of a CFB-associated disease or condition. In some aspects of the invention, a subject is at risk of having or developing a CFB-associated disease or condition. A subject at risk of developing a CFB-associated disease or condition is one who has an increased probability of developing the CFB-associated disease or condition, compared to a control risk of developing the CFB-associated disease or condition. In some embodiments of the invention, a level of risk may be statistically significant compared to a control level of risk. A subject at risk may include, for instance, a subject who is, or will be, a subject who has a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a CFB-associated disease or condition than a control subject without the preexisting disease or genetic abnormality; a subject having a family and/or personal medical history of the CFB-associated disease or condition; and a subject who has previously been treated for a CFB-associated disease or condition. It will be understood that a preexisting disease and/or a genetic abnormality that makes the subject more susceptible to a CFB-associated disease or condition, may be a disease or genetic abnormality that when present has been previously identified as having a correlative relation to a higher likelihood of developing a CFB-associated disease or condition.

It will be understood that a CFB dsRNA agent or CFB antisense polynucleotide agent may be administered to a subject based on a medical status of the individual subject. For example, a health-care provided for a subject may assess a CFB level measured in a sample

obtained from a subject and determine it is desirable to reduce the subject's CFB level, by administration of a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention. In this example, the CFB level may be considered to be a physiological characteristic of a CFB-associated condition, even if the subject is not diagnosed as having a CFB-associated disease such as one disclosed herein. A healthcare provider may monitor changes in the subject's CFB level, as a measure of efficacy of the administered CFB dsRNA agent or CFB antisense polynucleotide agent of the invention. In a non-limiting example, a biological sample, such as a blood or serum sample may be obtained from a subject and a CFB level for the subject determined in the sample. A CFB dsRNA agent or CFB antisense polynucleotide agent is administered to the subject and a blood sample is obtained from the subject following the administration and the CFB level determined using the sample and the results compared to the results determined in the subject's pre-administration (prior) sample. A reduction in the subject's CFB level in the later sample compared to the pre-administration level indicates the administered CFB dsRNA agent or CFB antisense polynucleotide agent efficacy in reducing the lipid level in the subject.

Certain embodiments of methods of the invention include adjusting a treatment that includes administering a dsRNA agent or a CFB antisense polynucleotide agent of the invention to a subject based at least in part on assessment of a change in one or more of the subject's physiological characteristics of a CFB-associated disease or condition resulting from the treatment. For example, in some embodiments of the invention, an effect of an administered dsRNA agent or CFB antisense polynucleotide agent of the invention may be determined for a subject and used to assist in adjusting an amount of a dsRNA agent or CFB antisense polynucleotide agent of the invention subsequently administered to the subject. In a non-limiting example, a subject is administered a dsRNA agent or CFB antisense polynucleotide agent of the invention, the subject's CFB level is determined after the administration, and based at least in part on the determined level, a greater amount of the dsRNA agent or CFB antisense polynucleotide agent is determined to be desirable in order to increase the physiological effect of the administered agent, for example to reduce or further reduce the subject's CFB level. In another non-limiting example, a subject is administered a dsRNA agent or CFB antisense polynucleotide agent of the invention, the subject's CFB level is determined after the administration and based at least in part on the determined level, a lower amount of the dsRNA agent or CFB antisense polynucleotide agent is desirable to administer to the subject.

Thus, some embodiments of the invention include assessing a change in one or more physiological characteristics of resulting from a subject's previous treatment to adjust an amount of a dsRNA agent or CFB antisense polynucleotide agent of the invention subsequently administered to the subject. Some embodiments of methods of the invention include 1, 2, 3, 4, 5, 6, or more determinations of a physiological characteristic of a CFB-associated disease or condition to assess and/or monitor the efficacy of an administered CFB

dsRNA agent or CFB antisense polynucleotide agent of the invention, and optionally using the determinations to adjust one or more of: a dose, administration regimen, and or administration frequency of a dsRNA agent or CFB antisense polynucleotide agent of the invention to treat a CFB-associated disease or condition in a subject. In some embodiments of methods of the invention, a desired result of administering an effective amount of a dsRNA agent or CFB antisense polynucleotide agent of the invention to a subject is a reduction of the subject's the CFB mRNA level, the CFB protein level in the subject, or CH50 activity (a measure of total hemolytic complement), AH50 (a measure the hemolytic activity of the alternate pathway of complement), lactate dehydrogenase (LDH) (a measure of intravascular hemolysis), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

As used herein, the terms "treat", "treated", or "treating" when used with respect to a CFB-associated disease or condition may refer to a prophylactic treatment that decreases the likelihood of a subject developing the CFB-associated disease or condition, and also may refer to a treatment after the subject has developed a CFB-associated disease or condition in order to eliminate or reduce the level of the CFB-associated disease or condition, prevent the CFB-associated disease or condition from becoming more advanced (e.g., more severe), and/or slow the progression of the CFB-associated disease or condition in a subject compared to the subject in the absence of the therapy to reduce activity in the subject of CFB polypeptide.

Certain embodiments of agents, compositions, and methods of the invention can be used to inhibit CFB gene expression. As used herein in reference to expression of a CFB gene, the terms "inhibit," "silence," "reduce," "down-regulate," and "knockdown" mean the expression of the CFB gene, as measured by one or more of: a level of RNA transcribed from the gene, a level of activity of CFB expressed, and a level of CFB polypeptide, protein or protein subunit translated from the mRNA in a cell, group of cells, tissue, organ, or subject in which the CFB gene is transcribed, is reduced when the cell, group of cells, tissue, organ, or subject is contacted with (e.g., treated with) a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention, compared to a control level of RNA transcribed from the CFB gene, a level of activity of expressed CFB, or a level of CFB translated from the MRNA, respectively. In some embodiments, a control level is a level in a cell, tissue, organ or subject that has not been contacted with (e.g., treated with) the CFB dsRNA agent or CFB antisense polynucleotide agent.

Administration methods

A variety of administration routes for a CFB dsRNA agent or CFB antisense polynucleotide agent are available for use in methods of the invention. The particular delivery mode selected will depend at least in part, upon the particular condition being treated and the dosage required for therapeutic efficacy. Methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode

that produces effective levels of treatment of a CFB-associated disease or condition without causing clinically unacceptable adverse effects. In some embodiments of the invention, a CFB dsRNA agent or CFB antisense polynucleotide agent may be administered via an oral, enteral, mucosal, subcutaneous, and/or parenteral route. The term “parenteral” includes subcutaneous, intravenous, intrathecal, intramuscular, intraperitoneal, and intrasternal injection, or infusion techniques. Other routes include but are not limited to nasal (e.g., via a gastro-nasal tube), dermal, vaginal, rectal, sublingual, and inhalation. Delivery routes of the invention may include intrathecal, intraventricular, or intracranial. In some embodiments of the invention, a CFB dsRNA agent or CFB antisense polynucleotide agent may be placed within a slow-release matrix and administered by placement of the matrix in the subject. In some aspects of the invention, a CFB dsRNA agent or CFB antisense polynucleotide agent may be delivered to a subject cell using nanoparticles coated with a delivery agent that targets a specific cell or organelle. Various delivery means, methods, agents are known in the art. Non-limiting examples of delivery methods and delivery agents are additionally provided elsewhere herein. In some aspects of the invention, the term “delivering” in reference to a CFB dsRNA agent or CFB antisense polynucleotide agent may mean administration to a cell or subject of one or more “naked” CFB dsRNA agent or CFB antisense polynucleotide agent sequences and in certain aspects of the invention “delivering” means administration to a cell or subject via transfection means, delivering a cell comprising a CFB dsRNA agent or CFB antisense polynucleotide agent to a subject, delivering a vector encoding a CFB dsRNA agent or CFB antisense polynucleotide agent into a cell and/or subject, etc. Delivery of a CFB dsRNA agent or CFB antisense polynucleotide agent using a transfection means may include administration of a vector to a cell and/or subject.

In some methods of the invention one or more CFB dsRNA agents or CFB antisense polynucleotide agents may be administered in formulations, which may be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients. In some embodiments of the invention a CFB dsRNA agent or CFB antisense polynucleotide agent may be formulated with another therapeutic agent for simultaneous administration. According to methods of the invention, a CFB dsRNA agent or CFB antisense polynucleotide agent may be administered in a pharmaceutical composition. In general, a pharmaceutical composition comprises a CFB dsRNA agent or CFB antisense polynucleotide agent and optionally, a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those of ordinary skill in the art. As used herein, a pharmaceutically acceptable carrier means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients, e.g., the ability of the CFB dsRNA agent or CFB antisense polynucleotide agent to inhibit CFB gene expression in a cell or subject. Numerous methods to administer and deliver

dsRNA agents or CFB antisense polynucleotide agents for therapeutic use are known in the art and may be utilized in methods of the invention.

Pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers and other materials that are well-known in the art. Exemplary pharmaceutically acceptable carriers are described in U.S. Pat. No. 5,211,657 and others are known by those skilled in the art. Such preparations may routinely contain salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. When used in medicine, the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Some embodiments of methods of the invention include administering one or more CFB dsRNA agents or CFB antisense polynucleotide agents directly to a tissue. In some embodiments, the tissue to which the compound is administered is a tissue in which the CFB-associated disease or condition is present or is likely to arise, non-limiting examples of which are the heart. Direct tissue administration may be achieved by direct injection or other means. Many orally delivered compounds naturally travel to and through the liver and kidneys and some embodiments of treatment methods of the invention include oral administration of one or more CFB dsRNA agents to a subject. CFB dsRNA agents or CFB antisense polynucleotide agents, either alone or in conjunction with other therapeutic agents, may be administered once, or alternatively they may be administered in a plurality of administrations. If administered multiple times, the CFB dsRNA agent or CFB antisense polynucleotide agent may be administered via different routes. For example, though not intended to be limiting, a first (or first several) administrations may be made via subcutaneous means and one or more additional administrations may be oral and/or systemic administrations.

For embodiments of the invention in which it is desirable to administer a CFB dsRNA agent or CFB antisense polynucleotide agent systemically, the CFB dsRNA agent or CFB antisense polynucleotide agent may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with or without an added preservative. CFB dsRNA agent formulations (also referred to as pharmaceutical compositions) may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such

as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Lower doses will result from other forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day may be used as needed to achieve appropriate systemic or local levels of one or more CFB dsRNA agents or CFB antisense polynucleotide agents and to achieve appropriate reduction in CFB protein activity.

In yet other embodiments, methods of the invention include use of a delivery vehicle such as biocompatible microparticle, nanoparticle, or implant suitable for implantation into a recipient, e.g., a subject. Exemplary bioerodible implants that may be useful in accordance with this method are described in PCT Publication No. WO 95/24929 (incorporated by reference herein), which describes a biocompatible, biodegradable polymeric matrix for containing a biological macromolecule.

Both non-biodegradable and biodegradable polymeric matrices can be used in methods of the invention to deliver one or more CFB dsRNA agents or CFB antisense polynucleotide agents to a subject. In some embodiments, a matrix may be biodegradable. Matrix polymers may be natural or synthetic polymers. A polymer can be selected based on the period of time over which release is desired, generally in the order of a few hours to a year or longer. Typically, release over a period ranging from between a few hours and three to twelve months can be used. The polymer optionally is in the form of a hydrogel that can absorb up to about 90% of its weight in water and further, optionally is cross-linked with multivalent ions or other polymers.

In general, CFB dsRNA agents or CFB antisense polynucleotide agents may be delivered in some embodiments of the invention using the bioerodible implant by way of diffusion, or by degradation of the polymeric matrix. Exemplary synthetic polymers for such use are well known in the art. Biodegradable polymers and non-biodegradable polymers can be used for delivery of CFB dsRNA agents or CFB antisense polynucleotide agents using art-known methods. Bioadhesive polymers such as bioerodible hydrogels (see H. S. Sawhney, C. P. Pathak and J. A. Hubell in *Macromolecules*, 1993, 26, 581-587, the teachings of which are incorporated by reference herein) may also be used to deliver CFB dsRNA agents or CFB antisense polynucleotide agents for treatment of a CFB-associated disease or condition. Additional suitable delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of a CFB dsRNA

agent or CFB antisense polynucleotide agent, increasing convenience to the subject and the medical care professional. Many types of release delivery systems are available and known to those of ordinary skill in the art. (See for example: U.S. Pat. Nos. 5,075,109; 4,452,775; 4,675,189; 5,736,152; 3,854,480; 5,133,974; and 5,407,686 (the teaching of each of which is incorporated herein by reference). In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be suitable for prophylactic treatment of subjects and for subjects at risk of developing a recurrent CFB-associated disease or condition. Long-term release, as used herein, means that the implant is constructed and arranged to deliver a therapeutic level of a CFB dsRNA agent or CFB antisense polynucleotide agent for at least up to 10 days, 20 days, 30 days, 60 days, 90 days, six months, a year, or longer. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

Therapeutic formulations of CFB dsRNA agents or CFB antisense polynucleotide agents may be prepared for storage by mixing the molecule or compound having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [Remington's Pharmaceutical Sciences 21st edition, (2006)], in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG).

Cells, Subjects, and Controls

Methods of the invention may be used in conjunction with cells, tissues, organs and/or subjects. In some aspects of the invention a subject is a human or vertebrate mammal including but not limited to a dog, cat, horse, cow, goat, mouse, rat, and primate, e.g., monkey. Thus, the invention can be used to treat CFB-associated diseases or conditions in human and non-human subjects. In some aspects of the invention a subject may be a farm animal, a zoo animal, a domesticated animal or non-domesticated animal and methods of the invention can

be used in veterinary prevention and treatment regimens. In some embodiments of the invention, the subject is a human and methods of the invention can be used in human prevention and treatment regimens.

Non-limiting examples of subjects to which the present invention can be applied are subjects who are diagnosed with, suspected of having, or at risk of having a disease or condition associated with a higher than desirable CFB expression and/or activity, also referred to as “elevated levels of CFB expression”. Non-limiting examples of diseases and conditions associated with a higher than desirable levels of CFB expression and/or activity are described elsewhere herein. Methods of the invention may be applied to a subject who, at the time of treatment, has been diagnosed as having the disease or condition associated with a higher than desirable CFB expression and/or activity, or a subject who is considered to be at risk for having or developing a disease or condition associated with a higher than desirable CFB expression and/or activity. In some aspects of the invention a disease or condition associated with a higher than desirable CFB level of expression and/or activity is an acute disease or condition, and in certain aspects of the invention a disease or condition associated with a higher than desirable CFB level of expression and/or activity is a chronic disease or condition.

In a non-limiting example, a CFB dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, statin resistant hypercholesterolemia, which is a disease in which it is desirable to reduce CFB expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

In another non-limiting example, a CFB dsRNA agent of the invention is administered to a subject diagnosed with, suspected of having, or at risk of having, hyperlipidemia, which is a disease in which it is desirable to reduce CFB expression. Methods of the invention may be applied to the subject who, at the time of treatment, has been diagnosed as having the disease or condition, or a subject who is considered to be at risk for having or developing the disease or condition.

A cell to which methods of the invention may be applied include cells that are *in vitro*, *in vivo*, *ex vivo* cells. Cells may be in a subject, in culture, and/or in suspension, or in any other suitable state or condition. A cell to which a method of the invention may be applied can be a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, kidney cell or other type of vertebrate cell, including human and non-human mammalian cells. In certain aspects of the invention, a cell to which methods of the invention may be applied is a healthy, normal cell that is not known to be a disease cell. In certain embodiments of the invention a cell to which methods and compositions of the invention are applied to a liver cell, a hepatocyte, a cardiac cell, a pancreatic cell, a cardiovascular cell, and/or a kidney cell. In certain aspects of the invention, a control cell is a normal cell, but it will be understood that a cell having a disease or condition may also serve as a control cell in particular circumstances

for example to compare results in a treated cell having a disease or condition versus an untreated cell having the disease or condition, etc.

A level of CFB polypeptide activity can be determined and compared to control level of CFB polypeptide activity, according to methods of the invention. A control may be a predetermined value, which can take a variety of forms. It can be a single cut-off value, such as a median or mean. It can be established based upon comparative groups, such as in groups having normal levels of CFB polypeptide and/or CFB polypeptide activity and groups having increased levels of CFB polypeptide and/or CFB polypeptide activity. Another non-limiting example of comparative groups may be groups having one or more symptoms of or a diagnosis of a CFB-associated disease or condition; groups without having one or more symptoms of or a diagnosis of the disease or condition; groups of subjects to whom an siRNA treatment of the invention has been administered; groups of subjects to whom an siRNA treatment of the invention has not been administered. Typically, a control may be based on apparently healthy normal individuals in an appropriate age bracket or apparently healthy cells. It will be understood that controls according to the invention may be, in addition to predetermined values, samples of materials tested in parallel with the experimental materials. Examples include samples from control populations or control samples generated through manufacture to be tested in parallel with the experimental samples. In some embodiments of the invention, a control may include a cell or subject not contacted or treated with a CFB dsRNA agent of the invention and in such instances, a control level of CFB polypeptide and/or CFB polypeptide activity can be compared to a level of CFB polypeptide and/or CFB polypeptide activity in a cell or subject contacted with a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention.

In some embodiments of the invention a level of CFB polypeptide determined for a subject can be a control level against which a level of CFB polypeptide determined for the same subject at a different time is compared. In a non-limiting example, a level of CFB is determined in a biological sample obtained from a subject who has not been administered a CFB treatment of the invention. In some embodiments, the biological sample is a serum sample. The level of CFB polypeptide determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a CFB dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and the level of CFB polypeptide in the subsequent sample or samples can be compared to the control/baseline level for the subject. Such comparisons can be used to assess onset, progression, or recession of a CFB associated disease or condition in the subject. For example, a level of CFB polypeptide in the baseline sample obtained from the subject that is higher than a level obtained from the same subject after the subject has been administered a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention indicates regression of the CFB-associated disease or condition and

indicates efficacy of the administered CFB dsRNA agent of the invention for treatment of the CFB-associated disease or condition.

In some aspects of the invention, values of one or more of a level of CFB polypeptide and/or CFB polypeptide activity determined for a subject may serve as control values for later comparison of levels of CFB polypeptide and/or CFB activity, in that same subject, thus permitting assessment of changes from a “baseline” CFB polypeptide activity in a subject. Thus, an initial CFB polypeptide level and/or initial CFB polypeptide activity level may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of CFB polypeptide and/or CFB polypeptide activity in the subject, with the initial level serving as a control level for that subject.

Using methods of the invention, CFB dsRNA agents and/or CFB antisense polynucleotide agents of the invention may be administered to a subject. Efficacy of the administration and treatment of the invention can be assessed when a level of CFB polypeptide in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration level of CFB polypeptide in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example a level of CFB polypeptide in a control serum sample. It will be understood that a level of CFB polypeptide and a level of CFB polypeptide activity both correlate with a level of CFB gene expression. Certain embodiments of methods of the invention comprise administering a CFB dsRNA and/or CFB antisense agent of the invention to a subject in an amount effective to inhibit CFB gene expression and thereby reduce a level of CFB polypeptide and reduce a level of CFB polypeptide activity in the subject.

Some embodiments of the invention, include determining presence, absence, and/or an amount (also referred to herein as a level) of CFB polypeptide in one or more biological samples obtained from one or more subjects. The determination can be used to assess efficacy of a treatment method of the invention. For example, methods and compositions of the invention can be used to determine a level of CFB polypeptide in a biological sample obtained from a subject previously treated with administration of a CFB dsRNA agent and/or a CFB antisense agent of the invention. A level of CFB polypeptide determined in a serum sample obtained from the treated subject that is lower by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pretreatment level of CFB polypeptide determined for the subject, or compared to a non-contacted control biological sample level, indicates a level of efficacy of the treatment administered to the subject.

In some embodiments of the invention a physiological characteristic of a CFB-associated disease or condition determined for a subject can be a control determination against which a determination of the physiological characteristic in the same subject at a different time is compared. In a non-limiting example, a physiological characteristic such as the CFB mRNA level, the CFB protein level in the subject, or CH50 activity, AH50, lactate dehydrogenase

(LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex in the plasma or the tissue sample is determined in a biological sample, such as a serum sample, obtained from a subject who has not been administered a CFB treatment of the invention. The CFB mRNA level (and/or other physiological characteristic of a CFB disease or condition) determined in the sample obtained from the subject can serve as a baseline or control value for the subject. After one or more administrations of a CFB dsRNA agent to the subject in a treatment method of the invention, one or more additional serum samples can be obtained from the subject and CFB mRNA level and/or CFB protein level in the subsequent sample or samples are compared to the control/baseline level and/or ratio, respectively, for the subject. Such comparisons can be used to assess onset, progression, or recession of a CFB associated disease or condition in the subject. For example, CFB mRNA level in the baseline sample obtained from the subject that is higher than CFB mRNA level determined in a sample obtained from the same subject after the subject has been administered a CFB dsRNA agent or CFB antisense polynucleotide agent of the invention indicates regression of the CFB-associated disease or condition and indicates efficacy of the administered CFB dsRNA agent of the invention for treatment of the CFB-associated disease or condition.

In some aspects of the invention, values of one or more of a physiological characteristic of a CFB-associated disease or condition determined for a subject may serve as control values for later comparison of the physiological characteristics in that same subject, thus permitting assessment of changes from a “baseline” physiological characteristic in a subject. Thus, an initial physiological characteristic may be present and/or determined in a subject and methods and compounds of the invention may be used to decrease the level of CFB polypeptide and/or CFB polypeptide activity in the subject, with the initial physiological characteristic determination serving as a control for that subject.

Using methods of the invention, CFB dsRNA agents and/or CFB antisense polynucleotide agents of the invention may be administered to a subject in an effective amount to treat a CFB disease or condition. Efficacy of the administration and treatment of the invention can be assessed by determining a change in one or more physiological characteristics of the CFB disease or condition. In a non-limiting example, a CFB mRNA level in a serum sample obtained from a subject is decreased by at least 0.5%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more compared to a pre-administration lipid in a serum sample obtained from the subject at a prior time point, or compared to a non-contacted control level, for example CFB mRNA level in a control serum sample. It will be understood that the CFB mRNA level, the CFB protein level in the subject, or the lipid level, the triglyceride, the cholesterol level, the free fatty acids level in the plasma or the tissue sample each correlates with a level of CFB gene expression. Certain embodiments of methods of the invention comprise administering a CFB dsRNA and/or CFB antisense agent of the invention to a subject in an amount effective to inhibit CFB gene expression and thereby reduce the CFB mRNA

level, the CFB protein level in the subject, or otherwise positively impact a physiological characteristic of a CFB-associated disease or condition in the subject.

Some embodiments of the invention, include determining presence, absence, and/or a change in a physiological characteristic of a CFB-associated disease or condition using methods such as but not limited to: (1) assessing one or more biological samples obtained from one or more subjects for the physiological characteristic; (2) imaging a subject (for example but not limited to obtaining a liver image); and (3) or physical examination of the subject. The determination can be used to assess efficacy of a treatment method of the invention.

10 *Kits*

Also within the scope of the invention are kits that comprise one or more CFB dsRNA agents and/or CFB antisense polynucleotide agents and instructions for its use in methods of the invention. Kits of the invention may include one or more of a CFB dsRNA agent, CFB sense polynucleotide, and CFB antisense polynucleotide agent that may be used to treat a CFB-associated disease or condition. Kits containing one or more CFB dsRNA agents, CFB sense polynucleotides, and CFB antisense polynucleotide agents can be prepared for use in treatment methods of the invention. Components of kits of the invention may be packaged either in aqueous medium or in lyophilized form. A kit of the invention may comprise a carrier being compartmentalized to receive in close confinement therein one or more container means or series of container means such as test tubes, vials, flasks, bottles, syringes, or the like. A first container means or series of container means may contain one or more compounds such as a CFB dsRNA agent and/or CFB sense or antisense polynucleotide agent. A second container means or series of container means may contain a targeting agent, a labelling agent, a delivery agent, etc. that may be included as a portion of a CFB dsRNA agent and/or CFB antisense polynucleotide to be administered in an embodiment of a treatment method of the invention.

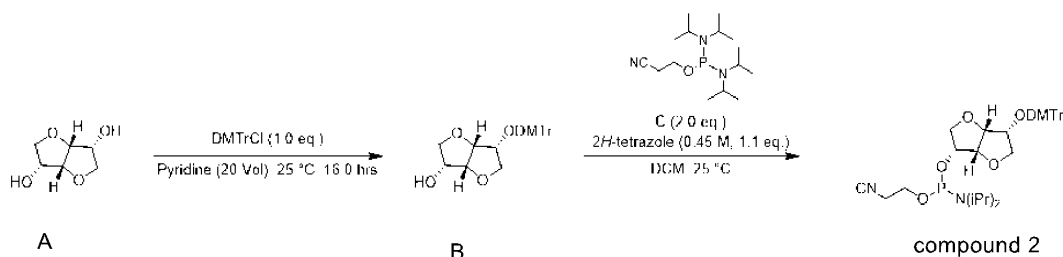
A kit of the invention may also include instructions. Instructions typically will be in written form and will provide guidance for carrying-out a treatment embodied by the kit and for making a determination based upon that treatment.

30 The following examples are provided to illustrate specific instances of the practice of the present invention and are not intended to limit the scope of the invention. As will be apparent to one of ordinary skill in the art, the present invention will find application in a variety of compositions and methods.

35 Examples

Example 1.

Phosphoramidite Compound 2



DMTrCl (232 g, 684 mmol, 1.0 *eq*) in pyridine (400 mL) was added to the solution of isomannide compound **A** (100 g, 684 mmol, 1.0 *eq*) in pyridine (600 mL), and the mixture was stirred at 25 °C for 12 hrs. LC-MS showed compound **A** was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was diluted with water (500 mL), extracted with DCM (500 mL *2), and the combined organic phases were washed with brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue. The residue was purified by column chromatography (DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound **B** (150 g, 48.9% yield) a yellow solid.

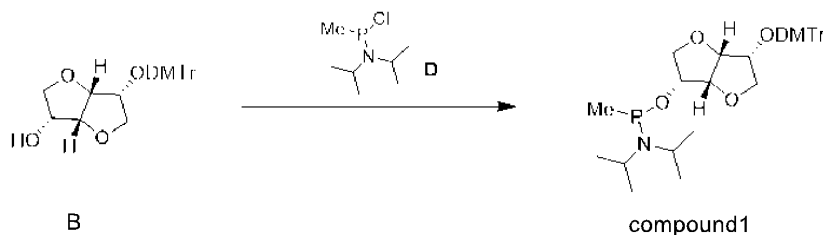
¹H NMR: EC4783-404-P1B1_C (400 MHz, DMSO-*d*₆) δ ppm 7.46 (br d, *J*=7.63 Hz, 2 H) 7.28 - 7.37 (m, 6 H) 7.19 - 7.25 (m, 1 H) 6.90 (br d, *J*=7.88 Hz, 4 H) 4.70 (d, *J*=6.50 Hz, 1 H) 3.99 - 4.09 (m, 6 H) 3.88 - 3.96 (m, 2 H) 3.83 (br dd, *J*=7.82, 6.94 Hz, 1 H) 3.74 (s, 6 H) 3.41 (br t, *J*=8.13 Hz, 1 H) 3.05 (t, *J*=8.44 Hz, 1 H) 2.85 (br t, *J*=7.50 Hz, 1 H).

To a solution of compound **B** (80.0 g, 178 mmol, 1.0 *eq*) in DCM (800 mL) at 25 °C under N₂ atmosphere was added dropwise 2H-tetrazole (0.45 M, 436 mL, 1.1 *eq*), then compound **C** (80.6 g, 267 mmol, 85.0 mL, 1.5 *eq*) in DCM (200 mL) was added dropwise to the mixture. The reaction mixture was stirred at 25 °C under for 1.0 hr. LC-MS showed compound **B** was consumed completely and one main peak with desired mass was detected. The resulting reaction mixture was cooled to -20 °C and poured into ice cold sat.NaHCO₃ (500 mL), extracted with DCM (500 mL *3), the combined organic layers were washed with sat.NaHCO₃/brine=1:1 (300 mL/300 mL), dried over Na₂SO₄ and concentrated in vacuum (35 °C) to get the residue (100 mL). The residue was purified by column chromatography (Al₂O₃, DCM/MeOH=100/1 to 50/1, 0.1% Et₃N) to give compound2 (77 g, 119 mmol, 66.5% yield) as a white solid.

¹H NMR: EC4783-423-P1B1_C (400 MHz, DMSO-*d*₆) δ ppm 7.22 (br d, *J*=7.50 Hz, 2 H) 7.05 - 7.14 (m, 6 H) 6.96 - 7.02 (m, 1 H) 6.67 (br dd, *J*=8.82, 1.81 Hz, 4 H) 3.95 - 4.07 (m, 2 H) 3.73 - 3.83 (m, 1 H) 3.62 - 3.72 (m, 2 H) 3.48 - 3.53 (m, 6 H) 3.27 - 3.37 (m, 3 H) 3.11 (s, 6 H) 2.82 (td, *J*=8.54, 2.31 Hz, 1 H) 2.47 - 2.63 (m, 3 H) 2.28 (br d, *J*=1.63 Hz, 3 H) 0.82 - 1.00 (m, 13 H).

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Phosphoramidite Compound 1



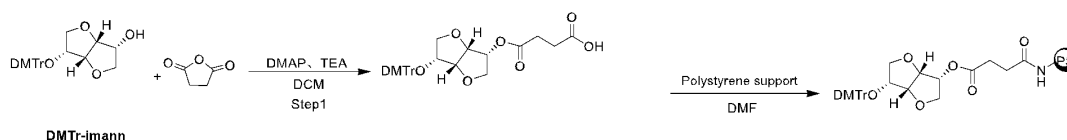
To a solution of compound **B** (500 mg, 1.11 mmol, 1.0 eq) in DCM (5.0 mL) was added compound **D** (607 mg, 3.34 mmol, 3.0 eq) and DIEA (432 mg, 3.34 mmol, 582 μ L, 3.0 eq) under N_2 atmosphere at 0-5 $^{\circ}C$, the mixture was stirred at 25 $^{\circ}C$ for 1.0 hrs. LC-MS showed
 5 Compound **B** was consumed completely, several new peaks were shown on LC-MS and $\sim 70.9\%$ of desired compound was detected. The resulting reaction mixture was cooled to -20 $^{\circ}C$ and poured into cold (0-5 $^{\circ}C$) sat.NaHCO₃ (5.0 mL) solution, extracted with DCM (5.0 mL *2), the combined organic layers were washed with cold (0-5 $^{\circ}C$) sat.NaHCO₃/brine =1:1 (5.0 mL/5.0 mL), dried over Na₂SO₄ and concentrated in vacuum to get the residue (~ 5 mL). The residue
 10 was purified by column chromatography (alkaline Al₂O₃, Petroleum ether/Ethyl acetate=10/1 to 5/1, 0.1% Et₃N) to give compound **1** (280 mg, 471 μ mol, 42.3% yield) was obtained as a white solid.

¹H NMR: EC10615-49-P1N (400 MHz, DMSO-*d*₆) δ ppm 7.44 (br d, $J=7.63$ Hz, 2 H), 7.31 (br t, $J=7.94$ Hz, 6 H), 7.18 - 7.26 (m, 1 H), 6.89 (brd, $J=8.00$ Hz, 4 H), 4.08 - 4.13 (m, 1 H), 3.95 - 4.03 (m, 1 H), 3.84 - 3.93 (m, 1 H), 3.77 - 3.83 (m, 1 H), 3.74 (s, 6 H), 3.43 - 3.53 (m, 3 H), 3.38 (br d, $J=6.75$ Hz, 1 H), 2.94 - 3.04 (m, 1 H), 2.70 - 2.85 (m, 1 H), 1.09 - 1.15 (m, 12 H), 1.07 (br s, 3 H).

Other phosphoramidites may be prepared according to procedures described herein and/or prior arts such as, but are not limited to, US426,220 and WO02/36743.

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Example 2. Preparation of a solid support comprising phosphoramidites monomers of the present invention



25 represents amine methyl polyethylene macroporous resin carrier part

Dichloromethane (19.50kg) was added to the 50 L glass kettle under the protection of nitrogen and started stirring. The temperature was controlled at 20~30 $^{\circ}C$, and DMTr imann (1.47 kg), triethylamine (1.50 kg), 4-dimethylaminopyridine (0.164 kg) and succinic anhydride (1.34 kg) was added to the glass kettle. The system was kept at 20~30 $^{\circ}C$ for 18h, samples

were taken and the reaction was ended. Saturated sodium bicarbonate solution (22.50 kg) was added into the reaction system, stirred for 10-20 min, and allowed to separate into layers. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane, and the organic phase was combined and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to get the residue forming a gray to off-white solid of 1.83 kg.

N, N-dimethylformamide (23.50 kg) was added into a 100L glass kettle and stirred. The temperature was controlled at 20~30 °C. Under the protection of nitrogen, the products of the previous step, O-benzotriazole tetramethylurea hexafluorophosphate (0.33 kg) and N, N-diisopropylethylamine (0.13 kg) were added into the aforesaid 100L glass kettle through the solid feeding funnel and stirred for 10~30 minutes and were discharged into a 50 L zinc barrel for use. Macroporous amine methyl resin (3.25 kg) (purchased from Tianjin Nankai Hecheng Science and Technology Co., Ltd., batch number HA2X1209, load capacity 0.48 mmol/g) were added into the aforesaid 100 L solid phase synthesis reactor through the solid feeding funnel, the temperature was controlled at 20~30 °C, N, N-dimethylformamide (21.00 kg+21.00 kg) and the reaction solution in the zinc barrel of the previous step were add into the solid phase synthesis reactor. The system was subject to thermal insulation reaction, and the solid load was tracked to $\geq 250\mu\text{mol/g}$, and the load detection method was UV. The system was filtered under the pressure of nitrogen, the filter cake was washed with N, N-dimethylformamide for three times (26.00kg+26.10kg+26.00kg), and the filter cake was left in the kettle. CAP.A (50% acetonitrile and 50% acetic anhydride, 4.40kg+4.42kg+4.30kg) and CAP.B (20% pyridine and 30% N-methylimidazole and 50% acetonitrile, 4.40kg+4.40kg+4.47kg) were added into the 80L glass kettle, and stirred for 3~8min before use. This operation was repeated for three times to cap, and acetonitrile (18.00 kg+18.00 kg+18.00 kg+17.50 kg+17.50 kg) was added into the solid phase synthesis kettle. Filter-pressed after nitrogen bubbling for 10~30 min. This operation was repeated for four times, the filter cake was purged in the solid phase synthesis kettle with nitrogen for 2-4 h, and then was transferred to a 50 L filter press tank. The temperature was controlled at 15~30 °C, continued drying, and obtained yellow to white solid product after drying, weight: 3.516 kg.

The isomannide residue can be added to the 5' -end or 3' -end of the oligonucleotide chain by a method well known to those skilled in the art, such as the reverse abasic (invab) method, and further added to the target to the group.

Example 3. Synthesis of CFB RNAi Agents.

CFB RNAi agent duplexes shown in Table 2-3, above, were synthesized in accordance with the following general procedures:

Sense and antisense strand sequences of siRNA were synthesized on oligonucleotide synthesizers using a well-established solid phase synthesis method based on phosphoramidite chemistry. Oligonucleotide chain propagation is achieved through 4-step cycles: a deprotection, a condensation, a capping and an oxidation or a sulfurization step for addition of each

nucleotide. Syntheses were performed on a solid support made of controlled pore glass (CPG, 1000 Å). Monomer phosphoramidites may be purchased from commercial sources or may be the phosphoramidite compounds in example 1. The phosphoramidite compounds herein may be attached to the 3'-end as a monomeric phosphoramidite, and further be attached to the CPG solid support. In the case of attachment at the 5'-end, the phosphoramidite compounds may be used for the final coupling reaction, and can be further conjugated to target ligands if necessary. Phosphoramidites with GalNAc ligand cluster (GLS-5* or GLS-15* Phosphoramidites as non-limiting examples) were public in WO2023/045995A1 (incorporated herein in its entirety). For siRNAs used for *in vitro* screening (Table 2), syntheses were carried out at 2 µmol scale, and for siRNAs used for *in vivo* testing (Table 3), syntheses were carried out at scale of 5 µmol or larger. In the case where the GalNAc ligand (GLO-n Phosphoramidites as non-limiting examples were public in WO2023/045995A1 (incorporated herein in its entirety)) is attached at 3'-end of sense strand, GalNAc ligand attached CPG solid support was used. In the case where the GalNAc ligand (GLS-5* or GLS-15* as non-limiting example are attached at 5'-end of sense strand, GLS-5* or GLS-15* Phosphoramidites with GalNAc ligand cluster were public in WO2023/045995A1 (incorporated herein in its entirety)) are attached at 5'-end of sense strand, a GalNAc phosphoramidite was used for the last coupling reaction. Trichloroacetic acid (TCA) 3% in dichloromethane was used for deprotection of 4,4'-dimethoxytrityl protecting group (DMT). 5-Ethylthio-1H-tetrazole was used as an activator. I₂ in THF/Py/H₂O and phenylacetyl disulfide (PADS) in pyridine/MeCN was used for oxidation and sulfurization reactions, respectively. After the final solid phase synthesis step, solid support bound oligomer was cleaved and protecting groups were removed by treating with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution. For the synthesis of siRNAs used for *in vitro* screening, crude mixture was concentrated. The remaining solid was dissolved in 1.0 M NaOAc, and ice cold EtOH was added to precipitate out the single strand product as the sodium salt, which was used for annealing without further purification. For the synthesis of siRNAs used for *in vivo* testing, crude single strand product was further purified by ion pairing reversed phase HPLC (IP-RP-HPLC). Purified single strand oligonucleotide product from IP-RP-HPLC was converted to sodium salt by dissolving in 1.0 M NaOAc and precipitation by addition of ice cold EtOH. Annealing of equimolar complementary sense strand and antisense strand oligonucleotide in water was performed to form the double strand siRNA product, which was lyophilized to afford a fluffy white solid.

In certain studies, a method used to attach a targeting group comprising GalNAc (also referred to herein as a GalNAc delivery compound) to the 5'-end of a sense strand included use of a GalNAc phosphoramidite (GLS-5* or GLS-15* Phosphoramidites) in the last coupling step in the solid phase synthesis, using a synthetic process such as the process used if oligonucleotide chain propagation of adding a nucleotide to the 5'-end of the sense strand is performed.

In some studies a method of attaching a targeting group comprising GalNAc to the 3'-end of a sense strand comprised use of a solid support (CPG) that included a GLO-n. In some studies, a method of attaching a targeting group comprising GalNAc to the 3'-end of a sense strand comprises attaching a GalNAc targeting group to CPG solid support through an ester bond and using the resulting CPG with the attached GalNAc targeting group when synthesizing the sense strand, which results in the GalNAc targeting group attached at the 3'-end of the sense strand.

The imann residues can be added to the 5' end or 3' end of the oligonucleotide chain by a method well known to those skilled in the art, such as the inverted abasic residues (invab) method, and/or further added to the target to the GalNAc targeting group.

Example 4. *In Vitro* Screening of CFB siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density, mixed with the complexes of psiCHECK(TM)-2 Vector plasmid and Lipofectamine 2000 (Invitrogen-11668-019) and seeded into 96-well plates. Cells were transfected with test siRNAs or a control siRNA using Lipofectamine RNAiMax (Invitrogen -13778-150) at the same time of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at two concentrations (1 nM and 10 nM) in triplicate.

Day 1, psiCHECK(TM)-2 Vector transfection (one plate)

(1) Transfer 2.5 µg psiCHECK(TM)-2 Vector plasmid into an RNASE free Eppendorf tube (solution mix#1)

(2) Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to $1 \times 10^5/\text{ml}$

(3) Transfer 7.5 µL Lipofectamine 2000 (Invitrogen-11668-019) into solution mix#1 tube, mix.

(4) Add solution in Step 3 into cell suspension, mix, and dispense suspension into the 96 well plate (100 µl/well)

Day 2, siRNAs transfection

(1) Dilute Lipofectamine®RNAiMAX Reagent with Opti-MEM® Medium.

(2) Dilute the siRNA with RNA-free water to make 12×stock.

(3) Mix equal volume of diluted RNAiMax and siRNA. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Add 45 µl /well compound Lipofectamine® RNAiMAX(Opti-MEM) mix into 225 µl /well DMEM fresh medium, and discard the supernatants in assay plate, add 120 µl /well compound mix into 96 well plates.

(5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

- (1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.
- 5 (2) Transfer 100 µl cell lysates into a plate, then measure the firefly luminescence.
- (3) Add 50µl of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.
- (4) Calculate the relative expression

Data analysis

- 10 Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

- % inhibition= 100-(Ratio of sample well/ the average Ratio of no compound control)
- 15 ×100%

The duplex sequences used correspond to those shown in Table 5-7.

Table 5 provides experimental results of *in vitro* studies using various CFB RNAi agents to inhibit CFB expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ±SD)	
	10nM	1nM
AV02358	78.85±1.28	73.22±1.51
AV02359	51.86±6.47	33.86±6.33
AV02360	11.90±8.86	29.27±2.25
AV02361	20.43±8.24	18.07±2.59
AV02362	-3.31±13.26	-8.04±12.73
AV02363	12.50±5.21	7.41±7.05
AV02364	19.68±6.72	21.48±2.24
AV02365	16.14±1.38	21.47±3.95
AV02366	-5.31±2.10	-6.22±4.50
AV02367	38.35±7.42	32.70±9.53
AV02368	-10.06±14.23	6.88±3.55
AV02369	29.11±3.89	15.01±10.92
AV02370	44.96±1.52	25.15±4.65
AV02371	50.81±2.65	30.69±11.27
AV02373	62.58±1.82	49.37±1.89
AV02374	64.46±5.00	52.27±4.09
AV02375	65.09±3.06	51.65±3.69
AV02376	53.34±4.13	42.77±6.35
AV02378	56.94±7.39	32.39±7.96
AV02380	50.70±2.96	48.58±2.06

AV02381	46.90 $\pm$ 2.81	43.81 $\pm$ 1.94
AV02382	31.79 $\pm$ 7.71	40.16 $\pm$ 4.66
AV02383	20.41 $\pm$ 1.37	20.90 $\pm$ 5.56
AV02384	4.54 $\pm$ 3.18	0.78 $\pm$ 7.34
AV02385	21.05 $\pm$ 7.43	11.25 $\pm$ 6.36
AV02388	47.96 $\pm$ 8.18	43.77 $\pm$ 6.61
AV02390	2.47 $\pm$ 2.81	-0.01 $\pm$ 7.14
AV02391	15.85 $\pm$ 14.28	6.04 $\pm$ 0.57
AV02392	34.20 $\pm$ 5.92	6.28 $\pm$ 6.65
AV02393	22.20 $\pm$ 8.49	5.88 $\pm$ 3.11
AV02394	16.69 $\pm$ 6.94	1.85 $\pm$ 7.89
AV02396	23.26 $\pm$ 4.61	30.83 $\pm$ 2.27
AV02397	-16.14 $\pm$ 2.13	-5.65 $\pm$ 3.35
AV02398	10.04 $\pm$ 2.64	16.44 $\pm$ 5.84
AV02399	-7.96 $\pm$ 4.32	-11.29 $\pm$ 3.60
AV02400	-20.34 $\pm$ 5.33	-2.13 $\pm$ 7.40
AV02401	21.96 $\pm$ 14.53	15.17 $\pm$ 2.95
AV02402	26.15 $\pm$ 5.27	11.66 $\pm$ 5.49
AV02404	-6.14 $\pm$ 0.74	3.00 $\pm$ 6.73
AV02405	0.39 $\pm$ 5.98	-0.40 $\pm$ 6.66
AV02406	3.56 $\pm$ 5.28	-4.26 $\pm$ 9.93
AV02407	3.44 $\pm$ 6.90	2.47 $\pm$ 0.09
AV02408	12.58 $\pm$ 7.37	20.65 $\pm$ 2.20
AV02410	46.35 $\pm$ 2.68	37.79 $\pm$ 5.28
AV02379	50.65 $\pm$ 4.18	41.39 $\pm$ 4.60
AV02387	5.52 $\pm$ 4.86	0.84 $\pm$ 3.74
AV02395	-4.59 $\pm$ 9.65	-0.53 $\pm$ 9.08
AV02403	15.89 $\pm$ 2.92	5.47 $\pm$ 8.25
AV02411	35.83 $\pm$ 4.25	32.71 $\pm$ 2.81
AV02022	34.15 $\pm$ 8.13	39.43 $\pm$ 9.78

Table 6 provides experimental results of *in vitro* studies using various CFB RNAi agents to inhibit CFB expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean $\pm$ SD)	
	10nM	1nM
AV02414	58.44 $\pm$ 6.34	14.01 $\pm$ 2.05
AV02415	24.48 $\pm$ 14.25	5.58 $\pm$ 1.63
AV02416	31.97 $\pm$ 3.33	7.50 $\pm$ 4.28
AV02417	25.95 $\pm$ 9.30	16.15 $\pm$ 9.01
AV02418	42.97 $\pm$ 5.34	9.02 $\pm$ 5.13
AV02420	35.00 $\pm$ 8.58	8.87 $\pm$ 4.28
AV02421	15.80 $\pm$ 4.08	16.38 $\pm$ 9.91
AV02422	22.05 $\pm$ 1.77	22.55 $\pm$ 0.49
AV02423	18.98 $\pm$ 2.72	7.46 $\pm$ 6.19
AV02424	10.79 $\pm$ 3.59	7.34 $\pm$ 14.42
AV02425	9.79 $\pm$ 3.77	3.03 $\pm$ 6.94

AV02426	26.73 $\pm$ 1.61	9.47 $\pm$ 2.32
AV02428	15.76 $\pm$ 5.82	4.42 $\pm$ 5.52
AV02429	25.81 $\pm$ 7.54	2.14 $\pm$ 6.60
AV02430	7.80 $\pm$ 6.50	-0.10 $\pm$ 6.59
AV02431	30.97 $\pm$ 2.02	3.23 $\pm$ 7.65
AV02432	18.85 $\pm$ 2.49	1.60 $\pm$ 4.93
AV02433	-0.87 $\pm$ 8.80	4.83 $\pm$ 7.06
AV02434	6.22 $\pm$ 9.60	1.87 $\pm$ 3.28
AV02436	47.14 $\pm$ 6.01	28.66 $\pm$ 6.40
AV02437	-3.38 $\pm$ 2.51	2.88 $\pm$ 8.50
AV02438	0.23 $\pm$ 3.45	8.98 $\pm$ 6.91
AV02439	-5.33 $\pm$ 9.10	2.83 $\pm$ 5.65
AV02440	25.25 $\pm$ 5.37	12.04 $\pm$ 2.79
AV02441	32.99 $\pm$ 2.90	10.13 $\pm$ 0.89
AV02442	44.07 $\pm$ 4.87	21.94 $\pm$ 5.53
AV02444	26.93 $\pm$ 3.63	4.89 $\pm$ 7.76
AV02445	7.21 $\pm$ 7.63	3.21 $\pm$ 2.44
AV02446	25.60 $\pm$ 7.35	8.63 $\pm$ 6.73
AV02447	32.67 $\pm$ 3.70	13.49 $\pm$ 7.88
AV02448	30.82 $\pm$ 1.72	13.33 $\pm$ 3.20
AV02449	26.82 $\pm$ 5.54	2.02 $\pm$ 2.10
AV02450	27.15 $\pm$ 3.99	-2.70 $\pm$ 9.88
AV02452	29.20 $\pm$ 3.47	9.78 $\pm$ 0.82
AV02453	14.98 $\pm$ 1.54	15.17 $\pm$ 9.57
AV02454	-4.59 $\pm$ 6.95	1.56 $\pm$ 8.37
AV02455	-8.24 $\pm$ 2.81	-1.08 $\pm$ 2.61
AV02456	-12.98 $\pm$ 2.00	9.01 $\pm$ 2.01
AV02457	1.59 $\pm$ 0.72	0.21 $\pm$ 5.39
AV02458	16.99 $\pm$ 6.20	9.26 $\pm$ 5.64
AV02460	18.68 $\pm$ 3.35	-8.62 $\pm$ 5.70
AV02461	33.01 $\pm$ 2.98	6.27 $\pm$ 1.79
AV02462	29.50 $\pm$ 8.75	7.84 $\pm$ 7.42
AV02463	46.17 $\pm$ 0.32	12.26 $\pm$ 1.92
AV02464	43.54 $\pm$ 9.24	8.36 $\pm$ 3.80
AV02465	47.17 $\pm$ 3.43	4.34 $\pm$ 6.00
AV02466	34.51 $\pm$ 2.99	3.45 $\pm$ 1.12
AV02468	48.39 $\pm$ 1.62	25.37 $\pm$ 9.88
AV02469	29.41 $\pm$ 2.44	2.35 $\pm$ 4.72
AV02470	29.53 $\pm$ 5.19	25.58 $\pm$ 7.58
AV02471	19.66 $\pm$ 7.52	11.06 $\pm$ 4.43
AV02472	8.02 $\pm$ 20.67	13.45 $\pm$ 2.92
AV02473	28.00 $\pm$ 4.28	-5.08 $\pm$ 4.15
AV02474	40.96 $\pm$ 3.32	24.15 $\pm$ 6.94
AV02476	-11.56 $\pm$ 9.62	-3.91 $\pm$ 1.40
AV02477	-3.22 $\pm$ 0.05	-14.83 $\pm$ 5.24
AV02478	11.53 $\pm$ 4.95	-2.01 $\pm$ 1.80
AV02479	-15.10 $\pm$ 6.54	-0.21 $\pm$ 7.74
AV02480	20.71 $\pm$ 6.13	-1.76 $\pm$ 5.20

AV02481	8.20±23.97	-1.31±0.29
AV02482	2.55±11.71	-1.45±2.20
AV02484	6.34±8.71	-5.34±2.44
AV02485	4.41±5.56	-12.45±7.66
AV02486	5.83±6.63	-6.34±3.51
AV02487	6.67±0.27	8.30±4.18
AV02488	2.25±4.72	-1.40±10.49
AV02489	26.38±5.66	1.24±2.50
AV02490	14.37±6.62	4.02±6.19
AV02492	24.87±2.37	11.22±7.54
AV02493	20.77±6.89	9.40±9.19
AV02494	5.73±15.89	9.71±6.95
AV02495	39.54±12.34	13.61±4.16
AV02496	18.72±12.96	14.91±8.47
AV02497	48.94±9.50	14.97±6.14
AV02498	20.15±8.36	5.40±7.22
AV02500	54.19±3.46	44.17±4.37
AV02501	37.54±4.02	26.37±3.64
AV02502	17.66±3.26	15.28±9.48
AV02503	51.59±4.08	33.57±5.52
AV02504	43.22±7.64	34.42±4.85
AV02505	35.67±4.26	21.44±6.64
AV02506	46.52±6.10	24.00±6.32
AV02419	41.18±5.85	21.14±3.65
AV02427	14.12±11.78	11.87±11.61
AV02435	16.82±3.98	7.62±12.34
AV02443	38.13±6.10	12.04±3.81
AV02451	32.60±5.25	11.45±3.55
AV02459	15.67±3.76	0.46±9.10
AV02467	43.70±7.28	11.65±8.20
AV02475	45.37±3.89	22.95±2.67
AV02483	43.19±2.67	26.00±2.35
AV02491	23.95±7.58	17.88±2.71
AV02499	32.18±8.17	19.84±9.53
AV02507	19.18±4.11	10.87±14.36
AV02358	73.38±2.07	72.16±4.50
AV02022	49.01±3.42	37.56±4.02

Table 7 provides experimental results of *in vitro* studies using various CFB RNAi agents to inhibit CFB expression. The duplex sequences used correspond to those shown in

5 Table 2.

Duplex AV#	Average Inhibition % (Mean ±SD)	
	10nM	1nM
AV02508	46.98±8.60	8.98±6.03
AV02509	57.30±10.29	27.29±11.78
AV02510	38.50±7.87	-0.29±2.61

AV02511	16.24±9.63	2.13±1.26
AV02512	38.93±3.64	3.56±7.82
AV02513	16.25±5.01	0.98±3.36
AV02514	46.23±4.52	6.42±6.00
AV02516	22.75±2.01	6.74±7.97
AV02517	-2.74±6.25	-7.02±8.09
AV02518	17.99±5.90	5.81±6.00
AV02519	22.75±12.89	4.97±1.96
AV02520	23.14±9.43	9.77±2.96
AV02521	53.81±4.58	29.86±5.76
AV02522	38.35±3.64	23.49±7.20
AV02524	2.17±0.61	-18.13±12.84
AV02525	-19.35±6.92	-25.56±10.14
AV02526	26.75±6.81	-0.94±4.85
AV02527	8.51±4.55	3.92±4.26
AV02528	28.39±1.57	13.18±1.05
AV02529	33.57±8.04	6.27±2.69
AV02530	2.70±7.71	-14.42±0.47
AV02532	23.49±8.92	-0.92±7.87
AV02533	30.79±0.98	5.18±1.68
AV02534	1.31±8.22	-16.75±2.25
AV02535	18.49±1.44	-11.67±1.48
AV02536	-14.95±14.38	-7.92±9.61
AV02537	28.50±3.60	3.72±3.00
AV02538	49.86±2.64	18.95±1.78
AV02540	-4.42±5.00	-7.62±1.91
AV02541	23.28±2.66	8.74±14.79
AV02542	27.10±2.18	9.35±6.56
AV02543	18.41±3.50	0.81±8.73
AV02544	3.25±6.19	-3.33±16.57
AV02545	32.22±6.44	3.30±10.09
AV02546	11.77±20.59	-4.39±2.08
AV02548	47.07±7.74	12.07±7.68
AV02549	49.44±3.19	18.76±1.09
AV02550	34.08±9.58	1.41±8.47
AV02551	60.99±4.13	47.11±3.68
AV02552	60.91±1.58	39.11±1.69
AV02553	50.40±2.41	24.89±9.46
AV02554	69.01±2.65	52.14±2.99
AV02556	59.17±3.92	27.20±1.71
AV02557	40.99±2.16	4.45±12.04
AV02558	58.47±4.89	18.92±7.16
AV02559	53.78±6.64	30.36±6.98
AV02560	37.82±9.83	1.54±9.12
AV02561	53.81±1.29	19.03±5.71
AV02562	31.89±8.65	8.72±4.33
AV02564	44.98±2.91	12.81±7.17
AV02565	-14.90±13.54	-36.07±2.75

AV02566	33.28 $\pm$ 4.24	2.73 $\pm$ 6.55
AV02567	49.58 $\pm$ 2.60	23.31 $\pm$ 8.41
AV02568	10.54 $\pm$ 5.02	-11.41 $\pm$ 8.68
AV02569	19.85 $\pm$ 8.51	6.18 $\pm$ 8.60
AV02570	26.19 $\pm$ 8.99	11.37 $\pm$ 3.77
AV02572	58.10 $\pm$ 7.29	18.12 $\pm$ 3.45
AV02573	16.83 $\pm$ 8.09	0.37 $\pm$ 1.87
AV02574	10.18 $\pm$ 3.07	-5.82 $\pm$ 5.91
AV02575	29.11 $\pm$ 5.17	11.90 $\pm$ 0.29
AV02576	34.98 $\pm$ 3.90	1.31 $\pm$ 6.38
AV02577	54.14 $\pm$ 3.03	27.99 $\pm$ 9.92
AV02578	9.53 $\pm$ 0.81	5.25 $\pm$ 3.20
AV02580	34.32 $\pm$ 7.66	-2.41 $\pm$ 7.80
AV02581	55.03 $\pm$ 4.37	47.35 $\pm$ 4.41
AV02582	47.06 $\pm$ 2.46	18.61 $\pm$ 6.79
AV02583	46.58 $\pm$ 0.17	31.60 $\pm$ 8.65
AV02584	55.46 $\pm$ 8.50	35.69 $\pm$ 3.75
AV02585	67.49 $\pm$ 0.42	44.66 $\pm$ 4.41
AV02586	62.75 $\pm$ 1.95	24.02 $\pm$ 5.23
AV02515	55.61 $\pm$ 8.28	19.03 $\pm$ 8.63
AV02523	51.73 $\pm$ 3.70	24.01 $\pm$ 7.70
AV02531	26.78 $\pm$ 5.03	11.44 $\pm$ 4.75
AV02539	40.98 $\pm$ 7.01	5.43 $\pm$ 3.15
AV02547	44.10 $\pm$ 9.36	6.12 $\pm$ 8.55
AV02555	58.38 $\pm$ 2.32	38.30 $\pm$ 5.54
AV02563	61.45 $\pm$ 1.58	33.60 $\pm$ 4.01
AV02571	39.49 $\pm$ 5.19	17.90 $\pm$ 0.82
AV02579	23.50 $\pm$ 4.98	8.69 $\pm$ 4.47
AV02587	61.53 $\pm$ 3.23	37.46 $\pm$ 4.95
AV02588	38.50 $\pm$ 3.72	29.29 $\pm$ 3.15
AV02358	80.02 $\pm$ 0.46	65.46 $\pm$ 4.78
AV02022	49.26 $\pm$ 4.33	29.20 $\pm$ 7.17

Example 5. *In Vivo* testing of CFB siRNA Duplexes

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human CFB and luciferase gene. At day 8, mice were subcutaneously administered a single 2 or 3 mg/kg of CFB siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 15, day 22 and day29. Plasma samples were isolated and luciferase activity of plasma samples was measured per manufacturer's recommended protocol. Since expression of human CFB level correlates with expression level of luciferase, percent of remaining CFB was calculated by comparing luciferase activity in samples from siRNA treated groups before and after treatment, normalized by the change of luciferase activity over the same period of time in samples from the control treated group. Results are summarized in Table 8 and Table 9.

Table 8. CFB siRNA single 3 mpk subcutaneous dose screening in AAV- CFB transduced mouse. Percent of reduction of human CFB in mouse serum was normalized to CFB expression pre-dosing of siRNA and to the PBS control group.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD01093	0.18 $\pm$ 0.06	0.03 $\pm$ 0.01	3
AD01094	0.45 $\pm$ 0.25	0.08 $\pm$ 0.02	3
AD01095	0.9 $\pm$ 0.22	0.24 $\pm$ 0.09	3
AD01096	0.36 $\pm$ 0.04	0.1 $\pm$ 0.01	3
AD01097	0.59 $\pm$ 0.07	0.2 $\pm$ 0.06	3
AD01098	0.36 $\pm$ 0.05	0.11 $\pm$ 0.02	3
AD01099	0.6 $\pm$ 0.09	0.23 $\pm$ 0.04	3
AD01100	0.95 $\pm$ 0.11	0.35 $\pm$ 0.02	3
AD01101	0.32 $\pm$ 0.06	0.12 $\pm$ 0.02	3
AD01102	0.6 $\pm$ 0.1	0.14 $\pm$ 0.04	3
AD01103	1.14 $\pm$ 0.13	0.45 $\pm$ 0.15	3
AD01104	0.36 $\pm$ 0.17	0.26 $\pm$ 0.05	3

- 5 Table 9. CFB siRNA single 2mpk subcutaneous dose screening in AAV- CFB transduced mouse. Percent of reduction of human CFB in mouse serum was normalized to CFB expression pre-dosing of siRNA and to the PBS control group.

Duplex AD#	D15 remaining percent relative to D8 (Mean $\pm$ SD)	D22 remaining percent relative to D8 (Mean $\pm$ SD)	D29 remaining percent relative to D8 (Mean $\pm$ SD)	Dosage (mg/kg)
AD01080	0.59 $\pm$ 0.47	0.23 $\pm$ 0.03	0.23 $\pm$ 0.04	2
AD01093	0.28 $\pm$ 0.08	0.23 $\pm$ 0.1	0.19 $\pm$ 0.05	2
AD01094	0.32 $\pm$ 0.06	0.32 $\pm$ 0.1	0.3 $\pm$ 0.1	2
AD01096	0.43 $\pm$ 0.03	0.33 $\pm$ 0.02	0.37 $\pm$ 0.05	2
AD01389	1.07 $\pm$ 0.09	1.05 $\pm$ 0.03	1.02 $\pm$ 0.03	2
AD01390	1.1 $\pm$ 0.16	1.04 $\pm$ 0.08	0.3 $\pm$ 0.1	2
AD01392	0.47 $\pm$ 0.12	0.36 $\pm$ 0.13	0.38 $\pm$ 0.1	2
AD01393	0.37 $\pm$ 0.08	0.23 $\pm$ 0.05	0.28 $\pm$ 0.06	2
AD01394	0.58 $\pm$ 0.13	0.56 $\pm$ 0.06	0.51 $\pm$ 0.08	2
AD01395	0.49 $\pm$ 0.08	0.35 $\pm$ 0.06	0.33 $\pm$ 0.02	2
AD01396	0.33 $\pm$ 0.18	0.24 $\pm$ 0.14	0.22 $\pm$ 0.14	2
AD01397	0.41 $\pm$ 0.08	0.29 $\pm$ 0.14	0.25 $\pm$ 0.06	2
AD01398	0.47 $\pm$ 0.03	0.28 $\pm$ 0.1	0.31 $\pm$ 0.07	2
AD01399	0.3 $\pm$ 0.05	0.16 $\pm$ 0.03	0.19 $\pm$ 0.02	2
AD01401	0.47 $\pm$ 0.14	0.43 $\pm$ 0.05	0.38 $\pm$ 0.07	2
AD01402	0.99 $\pm$ 0.15	1.01 $\pm$ 0.09	0.78 $\pm$ 0.06	2
AD01403	0.59 $\pm$ 0.11	0.65 $\pm$ 0.12	0.53 $\pm$ 0.12	2
AD01404	0.98 $\pm$ 0.28	1.11 $\pm$ 0.32	1.01 $\pm$ 0.26	2
AD01405	1.13 $\pm$ 0.07	1.27 $\pm$ 0.03	1 $\pm$ 0.07	2

AD01406	0.57±0.22	0.63±0.15	0.55±0.05	2
AD01407	0.55±0.08	0.44±0.07	0.42±0.05	2
AD01408	0.61±0.17	0.72±0.22	0.48±0.11	2
AD01409	0.58±0.23	0.53±0.13	0.47±0.12	2
AD01410	0.48±0.31	0.77±0.24	0.6±0.17	2
AD01411	0.8±0.1	0.77±0.06	0.63±0.09	2
AD01412	0.33±0.07	0.32±0.13	0.23±0.06	2
AD01413	1.43±0.48	1.44±0.28	1.2±0.32	2
AD01414	0.79±0.12	0.79±0.02	0.74±0.08	2
AD01415	0.43±0.07	0.3±0.01	0.34±0.02	2
AD01416	0.65±0.09	0.54±0.17	0.45±0.14	2
AD01417	0.68±0.15	0.5±0.05	0.45±0.02	2
AD01418	0.95±0.09	0.8±0.08	0.82±0.09	2
AD01419	1.06±0.13	0.92±0.03	0.9±0.08	2
AD01420	0.17±0.08	0.12±0.04	0.1±0.02	2
AD01421	0.27±0.06	0.23±0.05	0.2±0.03	2
AD01422	0.96±0.19	0.64±0.08	0.58±0.1	2
AD01423	0.64±0.09	0.42±0.06	0.35±0.07	2

Example 6. *In Vivo* testing of CFB siRNA Duplexes

At day 1, female C57BL/6J mice (4 in each group) were infected by intravenous administration of a solution of adeno-associated virus 8 (AAV8) vector encoding human CFB and luciferase gene. At day 8, mice were subcutaneously administered a single 2 mg/kg of CFB siRNA agents or PBS. Blood samples were collected at day 8, before dosing of siRNA, at day 18, day 25 and day32. Plasma samples were isolated and serum samples were collected for quantification protein level through ELISA was measured per manufacturer's recommended protocol. Since expression of human CFB level correlates with expression level of luciferase, percent of remaining CFB was calculated by comparing in samples from siRNA treated groups before and after treatment, normalized by the change of ELISA over the same period of time in samples from the control treated group. Results are summarized in Table 10.

Table 10. CFB siRNA single 2 mpk subcutaneous dose screening in AAV- CFB transduced mouse. Percent of reduction of human CFB in mouse serum was normalized to CFB expression pre-dosing of siRNA and to the PBS control group.

Duplex AD#	remaining relative to D8 (Mean ±SD)			Dosage mg/kg
	D18	D25	D32	
AD01080	0.14±0.04	0.15±0.07	0.21±0.12	2
AD01093	0.12±0	0.11±0	0.11±0.01	2
AD01094	0.15±0.01	0.14±0.02	0.2±0.02	2
AD01096	0.18±0.09	0.16±0.02	0.17±0.03	2
AD01389	0.12±0.03	0.12±0.02	0.12±0.03	2

AD01390	0.2±0.05	0.21±0.07	0.24±0.09	2
AD01391	0.1±0.02	0.1±0.04	0.09±0.03	2
AD01392	0.29±0.04	0.27±0.05	0.29±0.05	2
AD01393	0.42±0.1	0.37±0.02	0.39±0.04	2
AD01394	0.82±0.1	0.8±0.16	0.94±0.12	2
AD01395	0.64±0.06	0.74±0.17	0.8±0.15	2
AD01396	0.24±0.06	0.39±0.1	0.31±0.07	2
AD01397	0.43±0.08	0.88±0.16	0.69±0.07	2
AD01398	0.48±0.07	0.69±0.11	0.56±0.1	2
AD01399	0.24±0.04	0.28±0.05	0.23±0.06	2
AD01400	0.1±0.03	0.12±0.03	0.13±0.02	2
AD01401	0.55±0.07	0.81±0.08	0.73±0.05	2
AD01402	0.48±0.02	0.76±0.04	0.62±0.1	2
AD01403	0.18±0.03	0.29±0.06	0.29±0.06	2
AD01404	0.16±0.03	0.26±0.03	0.24±0.12	2
AD01405	0.46±0.04	0.87±0.06	0.69±0.08	2
AD01406	0.31±0.02	0.47±0.05	0.36±0.02	2
AD01407	0.41±0.2	0.47±0.15	0.42±0.18	2
AD01408	0.27±0.06	0.41±0.09	0.32±0.08	2
AD01409	0.4±0.06	0.52±0.02	0.43±0.03	2
AD01410	0.51±0.1	0.64±0.17	0.59±0.11	2
AD01411	0.34±0.05	0.44±0.08	0.39±0.1	2
AD01412	0.32±0.17	0.63±0.08	0.72±0.17	2
AD01413	0.19±0.04	0.19±0.04	0.23±0.04	2
AD01414	0.65±0.09	0.67±0.08	0.59±0.13	2
AD01415	0.25±0.05	0.26±0.07	0.36±0.05	2
AD01416	0.38±0.05	0.5±0.04	0.68±0.13	2
AD01417	0.56±0.07	0.84±0.09	0.9±0.07	2
AD01418	0.58±0.07	0.75±0.04	0.75±0.11	2
AD01419	0.34±0.03	0.41±0.03	0.39±0.03	2
AD01420	0.52±0.04	0.88±0.1	0.89±0.26	2
AD01421	0.46±0.07	0.65±0.1	0.67±0.06	2
AD01422	0.66±0.18	0.9±0.21	0.8±0.3	2
AD01423	0.38±0.01	0.49±0.07	0.43±0.09	2

Blood samples were collected at day 8, before dosing of siRNA, at day 15, day 22 and day29. Results are summarized in Table 11 and Table 12.

- 5 Table 11. CFB siRNA single 2 mpk subcutaneous dose screening in AAV- CFB transduced mouse. Percent of reduction of human CFB in mouse serum was normalized to CFB expression pre-dosing of siRNA and to the PBS control group.

Duplex AD#	CFB remaining compared to day8 (Mean ±SEM)			Dose(mg/kg)
	Day15	Day22	Day29	
AD01399-1	0.12±0.01	0.08±0.02	0.11±0.02	2
AD01704-1	0.12±0.04	0.07±0.02	0.1±0.03	2
AD01399	0.11±0.01	0.06±0.01	0.09±0.01	2

AD01704	0.12±0.01	0.1±0.03	0.13±0.01	2
AD02226	0.33±0.04	0.26±0.04	0.39±0.02	2
AD02227	0.19±0.02	0.09±0.01	0.16±0.04	2
AD02228	0.29±0.04	0.18±0.03	0.33±0.07	2
AD02229	0.6±0.07	0.41±0.02	0.4±0.01	2
AD02230	1.38±0.38	0.89±0.23	0.95±0.27	2
AD02231	0.71±0.06	0.53±0.03	0.66±0.1	2
AD02232	0.48±0.03	0.37±0.06	0.43±0.05	2
AD02233	0.5±0.08	0.35±0.04	0.38±0.04	2
AD02234	0.32±0.07	0.28±0.05	0.4±0.05	2
AD02235	0.51±0.02	0.3±0.03	0.48±0.06	2
AD02236	0.45±0.01	0.24±0.03	0.37±0.05	2
AD02237	0.27±0.03	0.14±0.01	0.25±0.03	2
AD02238	0.54±0.07	0.38±0.07	0.46±0.07	2
AD02239	0.33±0.04	0.18±0.02	0.22±0.03	2
AD02240	0.42±0.05	0.21±0.02	0.29±0.02	2
AD02241	0.34±0.03	0.25±0.03	0.37±0.06	2

Table 12. CFB siRNA single 2 mpk subcutaneous dose screening in AAV- CFB transduced mouse. Percent of reduction of human CFB in mouse plasma was normalized to CFB expression pre-dosing of siRNA and to the PBS control group.

Duplex AD#	CFB remaining compared to day8 (Mean ±SEM)			Dose(mg/kg)
	Day15	Day22	Day29	
AD02342	0.26±0.02	0.28±0.01	0.34±0.02	2
AD02343	0.17±0.04	0.28±0.06	0.36±0.07	2
AD02344	0.36±0.08	0.47±0.13	0.63±0.21	2
AD02345	0.24±0.04	0.26±0.03	0.34±0.03	2
AD02346	0.29±0.02	0.59±0.1	0.57±0.03	2
AD02347	0.6±0.07	1.16±0.18	0.84±0.08	2

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Example 7. *In Vivo* testing of CFB siRNA Duplexes in NHP PD model

Cynomolgus monkeys (6 years old, 3~6 kg of weights, 3 monkeys in each group) were enrolled in the study. Each monkey was subcutaneously administered a single 6 mg/kg of CFB siRNA agents or PBS at day 1 (pre-dosing of siRNA). After overnight fast, serum were drawn at day -14 (pre-dose), day -7 (pre-dose), 1 (pre-dose), , 8, 15, 22, 29, 35, 43, 50, 57, 64, and 71; CFB protein remaining by Western blotting, the result is shown in table 13.

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Table 13 The results of CFB protein concentration in serum were measured by Western blotting

Duplex AD#	CFB remaining compared to pre-dosing (%) (Mean ±SD)											Dose(mg/kg)
	Day8	Day15	Day22	Day29	Day36	Day43	Day50	Day57	Day64	Day71		
AD0109 3	56.05±6.4 5	24.62±2.26	15.02±5.22	13.34±5.46	14.81±7.95	15.26±2.1	14.02±0.21	12.15±7.97	11.69±8.11	11.28±5		6
AD0139 3	79.98±1.75	38.02±8.03	26.05±2.13	20.79±8.31	27.18±3.61	21.66±7.47	20.06±2.14	28.08±1.57	21.3±1.76	38.4±2.61		6
AD0139 6	70.89±3.58	37.85±3.86	24.03±3.81	24.08±7.18	22.48±4.68	23.5±6.32	25.51±0.06	25.53±1.11	34.92±4.46	46.54±21.87		6
AD0139 9	60.47±6.8	29.19±3.91	18.8±8.44	16.75±8.76	18.28±8.53	20.84±1.75	20.98±4.01	24.26±7.94	18.87±0.36	25.1±2.43		6
AD0141 2	103.1±0.08	88.6±2.31	93.69±8.03	77.76±7.64	89.57±9.04	91.42±3.97	89.76±2.32	100.33±8.62	89.65±3.93	103.81±9.64		6
AD0142 0	90.2±6.43	67.39±8.71	54.22±0.56	51.32±6.92	56.43±8.12	53.71±32.13	62.08±25.97	66.24±33.92	64.32±40.48	72.47±29.78		6
AD0142 0-1	85.11±6.75	43.23±0.92	40.17±4.85	32.15±6.59	53.15±29.9	37.77±8.29	34.21±27.24	38.56±27.52	37.96±32.42	58.27±42.91		6
AD0178 7	120.61±1.32	102.26±9.66	113.15±8.08	115.51±6.64	122.69±1.97	120.12±40.89	110.84±20.59	123.55±33.75	112.63±31.32	129.61±21.11		6

Example 8. *In Vivo* testing of CFB siRNA Duplexes in NHP PD model

Cynomolgus monkeys (6 years old, 3~6 kg of weights, 3 monkeys in each group) were enrolled in the study. Each monkey was subcutaneously administered a single 6 mg/kg of CFB siRNA agents or PBS at day 1 (pre-dosing of siRNA). After overnight fast, serum were drawn at day -14 (pre-dose), day -7 (pre-dose), 1 (pre-dose), all group Sample collection: Day -14, Day -7, 1, 8, 15, 22, 29, 35, 43, 50, 57, 71, and 85; CFB protein remaining by Western blotting (WB), Alternative (C5b-9) and Classical (C5b-9) by WISLAB kit, the result is shown in table 14-16.

Table 14 The results of CFB protein concentration in serum were measured by Western blotting normalized by Transferrin..

Duplex AD#	CFB remaining compared to pre-dosing (%) (Mean ±SEM)										Dose(mg/kg)
	Day8	Day15	Day22	Day29	Day36	Day43	Day50	Day57	Day71	Day85	
AD01093-1	41.63±6.0 ₉	23.21±2.3 ₃	19.73±3.4 ₄	20.95±6.0 ₈	21.95±5.1 ₆	30.21±4.0 ₅	35.19±2.5 ₆	37.53±3.7 ₉	38.88±5.1 ₃	49.86±2.3	6
AD01393-1	53.86±7.4 ₆	24.92±6.9 ₃	18.78±6.4 ₆	17.3±7.68	19.07±8.7 ₆	21.24±9.9 ₂	27.04±3.8 ₈	28.46±0.8 ₁	41.68±6.3 ₃	51.25±5.5 ₃	6
AD01399-1	39.05±8.5 ₁	11.51±2.9 ₈	6.95±4.89	7.32±2.53	8.42±3.65	12.82±6.2 ₆	14.96±7.96	20.59±2.6 ₁	28.91±7.3 ₇	47.7±26.68	6
AD02225	51.86±4.6 ₇	35.12±3.3 ₅	24.95±4.1 ₂	26.14±6.2 ₅	27.53±6.1 ₁	30.08±6.8	36.85±4.94	39.94±7.18	46.59±7.11	49.64±2.89	6
AD01704-1	30.57±4.7	8.09±4.44	4.31±0.85	3.82±0.99	3.83±1.22	4.41±4.83	4.88±2.36	6.02±4.96	9.8±3.61	14.01±4.14	6

Table 15 The results of Alternative (C5b-9) in serum were measured by WISLAB kit.

Duplex AD#	Complement activity(C5b-9) remaining compared to pre-dosing (%) (Mean ±SEM)										Dose(mg/kg)
	Day8	Day15	Day22	Day29	Day36	Day43	Day50	Day57	Day71	Day85	
AD01093-1	6.65±2.36	1±0.81	0.32±0.33	0.42±0.18	0.75±0.19	5.91±5.77	4.42±4.25	3.3±2.57	18.37±4.68	33.39±23.87	6
AD01393-1	28±2.34	2.42±4.41	1±0.46	1.81±0.82	1.31±0.09	3.19±2.37	7.67±6.4	8.8±6.07	25.47±5.94	40.98±2.51	6
AD01399-1	12.9±5.13	0.24±0.15	0.66±0.27	0.38±0.04	0.34±0.54	0.74±0.92	1.47±4.62	5.65±5.61	20.42±5.96	27.92±8.46	6
AD02225	27±0.59	9.86±2.8	1.98±0.6	5.46±2.57	5.5±2.55	9.26±3.65	15.37±5.65	30.3±0.24	53.52±3.49	66.4±5.75	6
AD01704-1	9.18±5.2	0.18±0.6	-0.3±0.23	-0.17±0.2	-	-0.2±0.15	0.03±0.53	0.16±0.52	1.44±4.24	8.29±7.81	6

Table 16 The results of Classical (C5b-9) in serum were measured by WIESLAB kit.

Duplex AD#	Complement activity(C5b-9) remaining compared to pre-dosing (%)(Mean ±SEM)										Dose(mg/k g)
	Day8	Day15	Day22	Day29	Day36	Day43	Day50	Day57	Day71	Day85	
AD0109	110.72±40	115.29±8.	113.23±48.	125.72±48	125.9±44.	128.3±21.	116.67±44.	124.2±41.	137.23±4.1	144.27±45.	6
3-1	.3	17	81	.3	11	07	73	55	1	28	
AD0139	100.03±40.	103.27±4.	96.03±4.63	102.31±4	98.01±4.9	100.87±5.	95.91±2.97	98.78±3.2	115.89±2.7	120.72±3.8	6
3-1	78	25			4	67		1	3	5	
AD0139	103.63±43.	103.67±7.	92.67±3.09	101.4±9.3	103.06±6.	106.33±7.	101.36±4.2	105.28±5.	121.06±48.	119.17±49.	6
9-1	87	35		3	33	53		72	88	36	
AD0222	96.19±3.5	95.5±6.77	96.3±41.44	92.88±5.0	96.02±4.5	98.23±7.6	94.13±5.68	104.92±7.	137.13±3.9	133.59±49.4	6
5	6			5		2		06		5	
AD0170	90.29±3.6	93.52±3.6	92.64±6.06	93.4±3.97	96.05±3.4	90.78±4.2	93.45±4.39	94.17±2.7	117.72±2.9	116.42±4.9	6
4-1	5	6			8	8		5	3		

Example 9. *In Vivo* testing of CFB siRNA Duplexes in NHP PD model

Cynomolgus monkeys (6 years old, 3~6 kg of weights, 3 monkeys in each group) were enrolled in the study. Each monkey was subcutaneously administered a single 3mg/kg of CFB siRNA agents or PBS at day 1 (pre-dosing of siRNA). After overnight fast, serum were drawn at day -14 (pre-dose), day -7 (pre-dose), 1 (pre-dose), all group Sample collection: Day -14, Day -7, 1, 8, 15, 22, 29, 35, 43, 50, and 57; CFB protein remaining by Western blotting (WB). The result is shown in table 17.

Table 17 The results of CFB protein concentration in serum were measured by Western blotting.

Duplex AD#	CFB remaining compared to pre-dosing (%)(Mean $\pm$ SEM)							
	Day8	Day15	Day22	Day29	Day36	Day43	Day50	Day57
AD0109 3-1	73.17 $\pm$ 5.21	46.94 $\pm$ 1.52	41.11 $\pm$ 4.76	38.28 $\pm$ 5.56	42.43 $\pm$ 6.64	45 $\pm$ 6.63	44.08 $\pm$ 9.05	49.95 $\pm$ 1.73
AD0109 3-2	43.57 $\pm$ 4.58	16.8 $\pm$ 5.21	8.55 $\pm$ 2.83	7.93 $\pm$ 3.67	8.21 $\pm$ 2.87	11.47 $\pm$ 3.63	12.84 $\pm$ 3.68	15.42 $\pm$ 2.62

Example 10. *In Vitro* Screening of CFB siRNA Duplexes

Huh7 cells were trypsinized and adjusted to appropriate density seeded into 96-well plates. Cells were transfected with the complexes of psiCHECK(TM)-2 Vector plasmid, blank vector pCNDNA 3.0, siRNAs or a control siRNA using Lipofectamine 2000 (Invitrogen-11668-019) at the next day of seeding following the protocol according to manufacturer's recommendation. The siRNAs were tested at different concentrations (10 nM and 1 nM,) in triplicate.

Day 1, Add trypsin to disassociate Huh7 cells in one flask, and count cells using Vi-Cell counting machine, adjust the cell density to 1×10^5 /ml and culture with DMEM medium.

Day 2, psiCHECK(TM)-2 Vector/blank vector pCDNA3.0/siRNAs/ Lipofectamine 2000 mixture transfection.

(1) Mix appropriate Lipofectamine 2000 (Invitrogen-11668-019) with Opti-MEM® Medium (solution mix#1). Final equal 0.3 μ l Lipofectamine 2000 and Opti-MEM® Medium 4.7 μ l per well.

(2) Mix appropriate psiCHECK(TM)-2 Vector, blank pCNDNA 3.0 vector and siRNAs with Opti-MEM® Medium (solution mix#2).

(3) Mix equal volume of solution mix#1 and mix#2 (mix#3), final 10 μ l per well. Incubate the mixture at RT for 15 min to allow complex formation.

(4) Remove DMEM medium, add 10 μ l mixed solution mix#3 and 90 μ l fresh DMEM medium.

(5) No compound control well was defined as cells transfected with psiCHECK(TM)-2 Vector and blank vector pCNDNA 3.0 and without siRNA treatment; blank control was cell only wells.

Day 3, Dual-Glo® Luciferase Assay

- (1) Add Reagent to assay plate, wait 10 minutes to allow for cell lysis to occur.
- (2) Transfer 100 µl cell lysates into a plate, then measure the firefly luminescence.
- (3) Add 50µl of Dual-Glo® Stop & Glo® Reagent to the assay plates and mix, wait 10 minutes, then measure Renilla luminescence.
- (4) Calculate the relative expression

Data analysis

Ratio of sample well= (sample Renilla luminescence-background blank)/ (sample Fireflyluminescence-background blank)

Ratio of no compound control well= (control Renilla luminescence-background blank)/ (control sample Fireflyluminescence-background blank)

- % inhibition= 100-(Ratio of sample well/ the average Ratio of no compound control) ×100%

Table 18 provides experimental results of *in vitro* studies using various CFB RNAi agents to inhibit CFB expression. The duplex sequences used correspond to those shown in Table 2.

Duplex AV#	Average Inhibition % (Mean ±SD)	
	10nM	1nM
AV05135	51.57±4.83	51.60±2.54
AV05136	32.31±0.69	32.34±1.14
AV05137	71.85±2.09	52.74±2.46
AV05138	53.25±5.26	44.54±3.24
AV05139	16.69±6.03	10.55±5.25
AV05140	72.53±1.26	65.88±1.76
AV05141	3.49±9.89	-0.14±1.35
AV05142	-12.92±10.03	5.19±8.18
AV05143	41.13±6.14	26.59±2.19
AV05144	41.24±2.37	36.04±4.49
AV05145	43.64±1.59	41.60±2.02
AV05146	49.94±5.88	53.33±7.09
AV05147	8.21±6.47	-2.41±5.21
AV05148	15.01±6.01	26.41±2.81
AV05149	57.70±2.98	41.88±4.99
AV05150	53.07±2.20	38.87±5.17
AV05151	23.81±4.60	17.76±4.77
AV05152	71.35±2.10	63.63±3.64
AV05153	36.66±2.35	37.38±2.22
AV05154	55.53±6.50	66.12±2.35

AV05155	13.71 $\pm$ 5.79	-1.37 $\pm$ 6.90
AV05156	33.91 $\pm$ 0.86	27.81 $\pm$ 1.82
AV05157	52.10 $\pm$ 0.61	39.46 $\pm$ 5.46
AV05158	50.62 $\pm$ 1.23	45.44 $\pm$ 6.29
AV05159	1.54 $\pm$ 3.62	1.10 $\pm$ 2.90
AV05160	7.48 $\pm$ 5.49	7.84 $\pm$ 4.84
AV05161	26.98 $\pm$ 3.37	20.49 $\pm$ 2.34
AV05162	43.54 $\pm$ 2.62	31.84 $\pm$ 4.57
AV05163	47.02 $\pm$ 4.48	45.82 $\pm$ 3.45
AV05164	19.99 $\pm$ 6.09	11.83 $\pm$ 6.63
AV05165	33.67 $\pm$ 6.78	34.77 $\pm$ 1.92
AV05166	53.68 $\pm$ 1.72	48.54 $\pm$ 0.94
AV05167	19.24 $\pm$ 4.53	11.36 $\pm$ 5.80
AV05168	29.33 $\pm$ 3.39	22.61 $\pm$ 3.48
AV05169	22.14 $\pm$ 6.96	22.66 $\pm$ 7.16
AV05170	20.93 $\pm$ 0.36	19.60 $\pm$ 5.36
AV05171	30.90 $\pm$ 2.25	31.23 $\pm$ 1.74
AV05172	28.21 $\pm$ 1.88	12.81 $\pm$ 1.58
AV05173	27.28 $\pm$ 9.37	23.23 $\pm$ 5.22
AV05174	49.83 $\pm$ 4.10	40.03 $\pm$ 6.41
AV05175	74.61 $\pm$ 0.55	73.75 $\pm$ 2.06
AV05176	32.49 $\pm$ 2.21	33.65 $\pm$ 4.89
AV05177	71.81 $\pm$ 3.71	72.37 $\pm$ 2.55
AV05178	55.10 $\pm$ 1.40	53.76 $\pm$ 1.89

Equivalents

Although several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto; the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems,

articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

5 All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

10 The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified, unless clearly indicated to the contrary.

15 All references, patents and patent applications and publications that are cited or referred to in this application are incorporated herein in their entirety herein by reference.

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent including 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:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.
2. The dsRNA agent of claim 1, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 483-513, 486-516, 491-521, 483-521, 513-543, 987-1017, 989-1019, 1317-1347, 2237-2267, 2439-2469 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.
3. The dsRNA agent of claim 1-2, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 488-508, 491-511, 496-516, 488-516, 518-538, 992-1012, 994-1014, 1322-1342, 2242-2262, 2444-2464 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.
4. The dsRNA agent of claim 1, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript RNA transcript which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.
5. The dsRNA agent of claim 1, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.
6. The dsRNA agent of claim 1, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a CFB RNA transcript, wherein the region of complementarity comprises

at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand.

5 7. The dsRNA agent of claim 6, wherein the region of complementarity to a CFB RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3.

10 8. The dsRNA agent of any one of claims 1-7, wherein the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and preferably the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3.

15 9. The dsRNA agent of any one of claims 1-8, wherein the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the dsRNA agent, preferably, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3.

20 10. The dsRNA agent of any one of claims 1-9, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

11. The dsRNA of any one of claims 1-10, wherein the dsRNA agent comprises at least one modified nucleotide.

25 12. The dsRNA agent of any one of claims 1-11, wherein all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides.

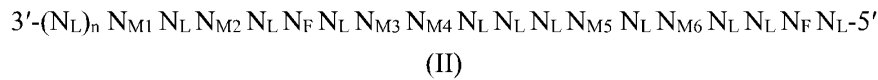
30 13. The dsRNA agent of claim 1-12, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of a CFB RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand comprises sequence may be represented by formula (I):



35 wherein:

each N'_F represents a 2'-fluoro-modified nucleotide; each N'_{N1} and N'_{N2} independently represents a modified or unmodified nucleotide; each N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' and n' are each independently an integer of 0 to 7.

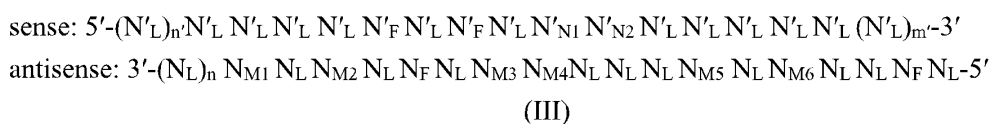
14. The dsRNA agent of claim 1-12, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of a CFB RNA transcript, wherein each strand is about 18 to about 30 nucleotides in length, wherein the antisense strand comprises sequence may be represented by formula (II):



wherein:

each N_F represents a 2'-fluoro-modified nucleotide; each N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} independently represents a modified or unmodified nucleotide; each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7.

15. The dsRNA agent of claim 1-12, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB is provided, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a dsRNA duplex, wherein said sense strand is complementary to the antisense strand, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript, wherein the region of complementarity comprises at least 15 contiguous nucleotides, wherein the dsRNA comprises duplex represented by formula (III):



wherein:

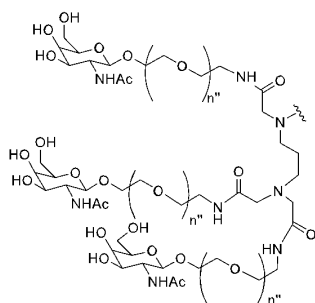
each strand is about 18 to about 30 nucleotides in length;

each N_F and N'_F independently represents a 2'-fluoro-modified nucleotide; N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , N'_{N1} , and N'_{N2} each independently represents a modified or unmodified nucleotide; N'_{N1} and N'_{N2} include only one 2'-Fluorine modified nucleotides; N_{M1} , N_{M2} , N_{M3} , N_{M4} , N_{M5} , and N_{M6} have only three 2'-fluoro-modified nucleotides; each N_L and N'_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and m' , n' and n are each independently an integer of 0 to 7.

16. The dsRNA agent of any one of claims 11-15, wherein the one or more modified nucleotides are independently selected from the group consisting of: a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, a 2'-deoxy nucleotide, a 2'3'-seco nucleotide mimic, a locked

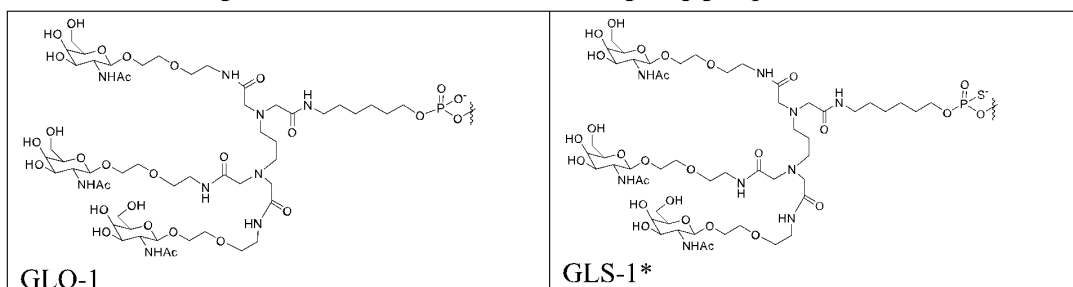
- nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2'-F-Arabino nucleotide, a 2'-methoxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2'-Ome nucleotide, an inverted 2'-deoxy nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesterol derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.
- 10 17. The dsRNA agent of any one of claims 1-16, comprises an E-vinylphosphonate nucleotide at the 5' end of the guide strand.
18. The dsRNA agent of any one of claims 1-17, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage.
- 15 19. The dsRNA agent of any one of claims 1-17 wherein the sense strand comprises at least one phosphorothioate internucleoside linkage.
- 20 20. The dsRNA agent of any one of claims 1-17, wherein the antisense strand comprises at least one phosphorothioate internucleoside linkage.
21. The dsRNA agent of any one of claims 1-17, wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
- 25 22. The dsRNA agent of any one of claims 1-17, wherein the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.
23. The dsRNA agent of any one of claims 1-22, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3.
- 30 24. The dsRNA agent of any one of claims 1-22, wherein the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3.
25. The dsRNA agent of any one of claims 1-24, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length.
- 35 26. The dsRNA agent of any one of claims 1-25, wherein the region of complementarity is 19-21 nucleotides in length.

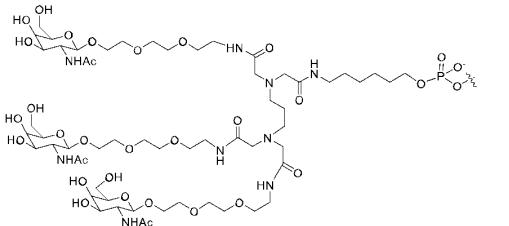
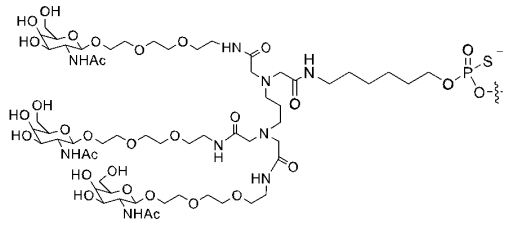
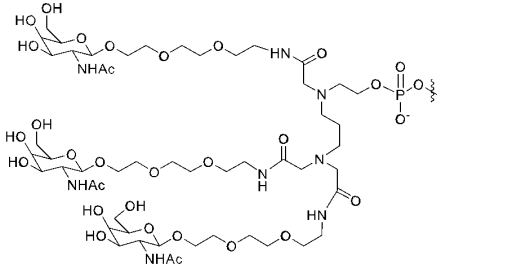
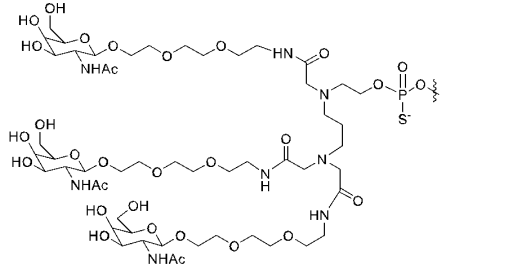
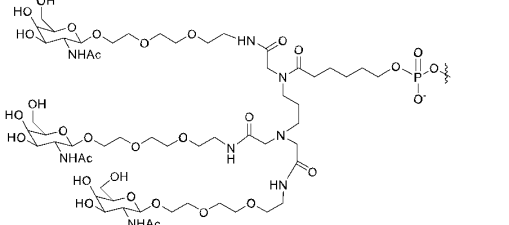
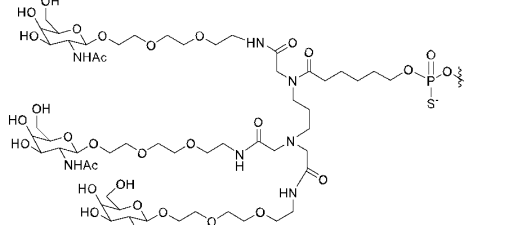
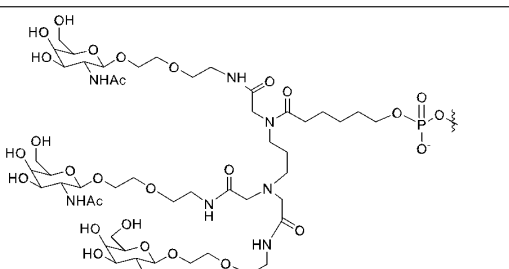
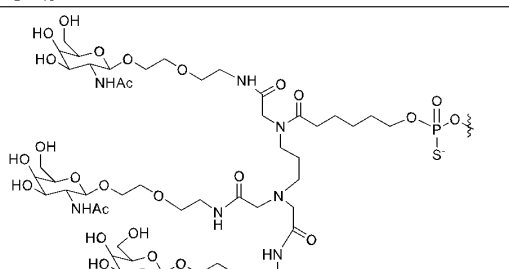
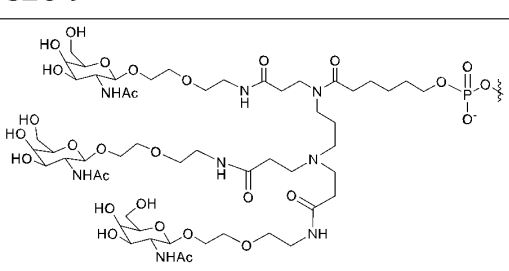
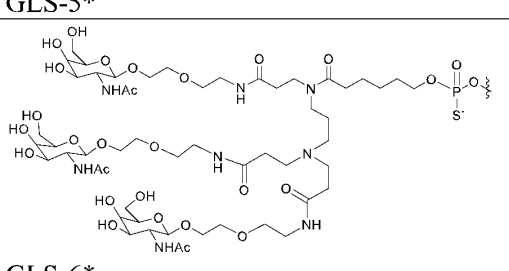
27. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 30 nucleotides in length.
- 5 28. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 25 nucleotides in length.
29. The dsRNA agent of any one of claims 1-26, wherein each strand is no more than 23 nucleotides in length.
- 10 30. The dsRNA agent of any one of claims 1-29, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups.
31. The dsRNA agent of claim 30, wherein the one or more targeting groups or linking groups
- 15 are conjugated to the sense strand.
32. The dsRNA agent of claim 30 or 31, wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc).
- 20 33. The dsRNA agent of claim 30-32, wherein the targeting group has a structure:

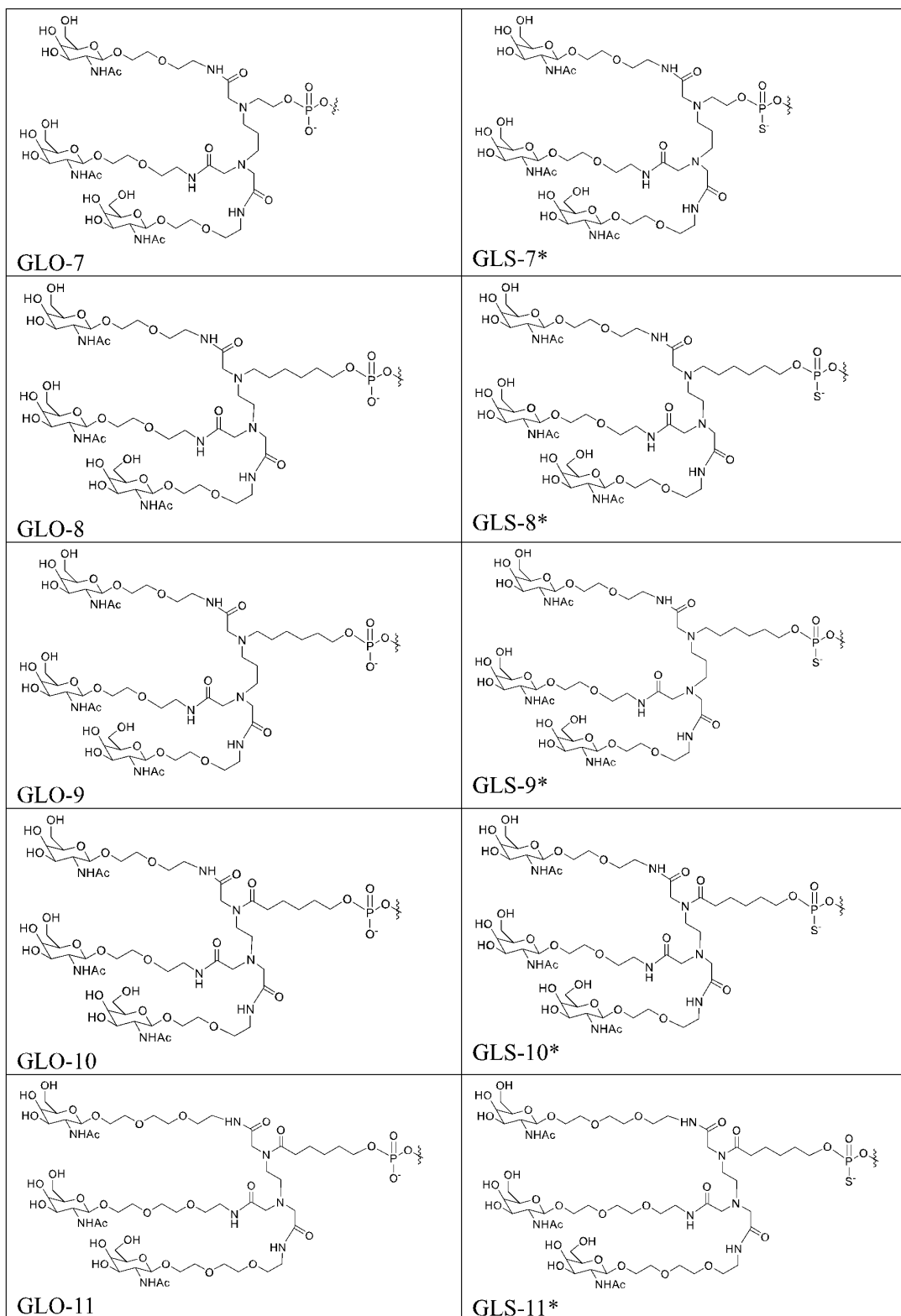


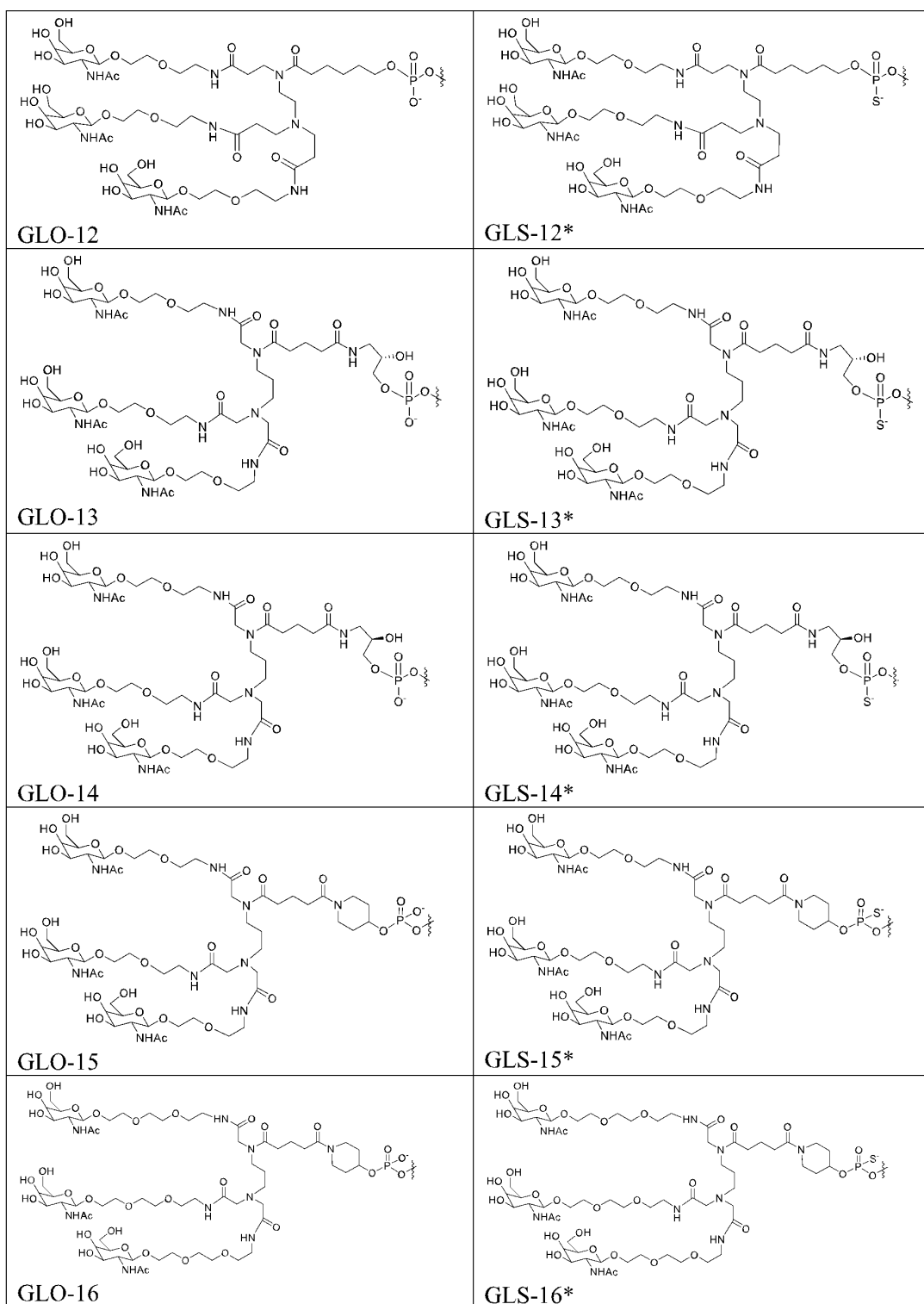
n' are independently selected from 1 or 2.

34. The dsRNA agent of claim 30-33, wherein the targeting group has a structure:



 GLO-2	 GLS-2*
 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*
 GLO-6	 GLS-6*





35. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5'-terminal end of the sense strand.

36. The dsRNA agent of any one of claims 1-34, wherein the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand.
- 5 37. The dsRNA agent of any one of claims 1-34, wherein the antisense strand comprises one inverted abasic residue at 3'-terminal end.
38. The dsRNA agent of any one of claims 1-34, wherein the sense strand comprises one or two inverted abasic residues or imann residues at 3' or/and 5' terminal end.
- 10 39. The dsRNA agent of any one of claims 1-38, wherein the dsRNA agent has two blunt ends.
40. The dsRNA agent of any one of claims 1-38, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
- 15 41. The dsRNA agent of any one of claims 1-38, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
42. The dsRNA agent of any one of claims 1-41 wherein the CFB RNA transcript is SEQ ID NO: 1.
- 20 43. A composition comprising a dsRNA agent of any one of claims 1-42.
44. The composition of claim 43, further comprising a pharmaceutically acceptable carrier.
- 25 45. The composition of claim 44, further comprising one or more additional therapeutic agents.
46. The composition of claim 45, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial.
- 30 47. The composition of any one of claims 43-46, wherein the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.
48. A cell comprising a dsRNA agent of any one of claims 1-42, optionally, the cell is a mammalian cell, optionally a human cell.
- 35 49. A method of inhibiting the expression of a CFB gene in a cell, the method comprising:
(i) preparing a cell comprising an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42 or a composition of any one of claims 43-47.

50. The method of claim 49, further comprising:

(ii) maintaining the cell prepared in claim 49 (i) for a time sufficient to obtain degradation of the mRNA transcript of a CFB gene, thereby inhibiting expression of the CFB gene in the cell.

51. The method of any one of claims 49-50, wherein the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously.

52. The method of any one of claims 49-50, wherein the cell is in a subject and the dsRNA agent is administered to the subject by IV administration.

53. The method of claim 51 or 52, further comprising assessing inhibition of the CFB gene, following the administration of the dsRNA agent to the subject, wherein a means for the assessing comprises:

(i) determining one or more physiological characteristics of a CFB-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition and/or to a control physiological characteristic of the CFB-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the CFB gene in the subject.

54. The method of claim 53, wherein the determined physiological characteristic is one or more of: the CFB mRNA level, the CFB protein level in the subject, or CH50 activity, AH50, lactate dehydrogenase (LDH), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, and soluble C5b-9 complex.

55. The method of claim 54, wherein a reduction in one or more of the subject's CFB mRNA level, the CFB protein level in the subject, and/or a decrease in one or more of CH50 activity, AH50, lactate dehydrogenase (LDH), hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum indicates reduction of CFB gene expression in the subject.

56. A method of inhibiting expression of a CFB gene in a subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42 or a composition of any one of claims 43-47.

57. The method of claim 56, wherein the dsRNA agent is administered to the subject subcutaneously.

58. The method of claim 56, wherein the dsRNA agent is administered to the subject by IV administration.

59. The method of any one of claims 56-58, further comprising assessing inhibition of the CFB gene, following the administration of the dsRNA agent, wherein a means for the assessing comprises:

- 10 (i) determining one or more physiological characteristics of a CFB-associated disease or condition in the subject and
- (ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition and/or to a control physiological characteristic of the CFB-associated disease or condition,
- 15 wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the CFB gene in the subject.

60. The method of claim 60, wherein the determined physiological characteristic is one or more of: the CFB mRNA level, the CFB protein level in the subject, or CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum.

61. The method of claim 60, wherein a reduction in one or more of the subject's CFB mRNA level, the CFB protein level in the subject, and/or a decrease in one or more of CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum indicates reduction of CFB gene expression in the subject.

62. A method of treating a disease or condition associated with the presence of CFB protein, the method comprising administering to a subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42, or a composition of any one of claims 43-47, to inhibit CFB gene expression.

63. The method of claim 62, wherein the disease or condition is one or more of: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus erythematosus (SLE), Lupus Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and

- geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS), neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies- associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelitis optica (NMO), dense deposit disease, 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), cold agglutinin disease, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis.
64. The method of claim 63, further comprising administering an additional therapeutic regimen to the subject.
65. The method of claim 64, wherein the additional therapeutic regimen comprises: administering to the subject one or more CFB antisense polynucleotides of the invention, administering to the subject a non-CFB dsRNA therapeutic agent, and a behavioral modification in the subject.
66. The method of claim 65, wherein the non-CFB dsRNA therapeutic agent is one of more of: an inhibitor of C5, such as an anticomplement component C5 antibody, or antigen-binding fragment thereof (e.g., eculizumab, ravulizumab-cwvz, or pozelimab (REGN3918)) or a C5 peptide inhibitor (e.g., zilucoplan); C3 peptide inhibitor, such as compstatin.
67. The method of any one of claims 62-66, wherein the dsRNA agent is administered to the subject subcutaneously.
68. The method of any one of claims 62-66, wherein the dsRNA agent is administered to the subject by IV administration.
69. The method of any one of claims 62-69, further comprising determining an efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent in the subject.
70. The method of claim 69, wherein a means of determining an efficacy of the treatment in the subject comprises:

(i) determining one or more physiological characteristics of the CFB-associated disease or condition in the subject and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition

5 wherein the comparison indicates one or more of a presence, absence, and level of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

71. The method of claim 70, wherein the determined physiological characteristic is: the CFB mRNA level, the CFB protein level in the subject, or CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum .

72. The method of claim 70, wherein a reduction in one or more of the CFB mRNA level, the CFB protein level in the subject, and/or a decrease in one or more of CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum indicates the presence of efficacy of the administration of the double-stranded ribonucleic acid (dsRNA) agent to the subject.

73. A method of decreasing a level of CFB protein in a subject compared to a baseline pre-treatment level of CFB protein in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42, or a composition of any one of claims 43-47, to decrease the level of CFB gene expression.

74. The method of claim 73, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

75. A method of altering a physiological characteristic of a CFB-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition in the subject, the method comprising administering to the subject an effective amount of a double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-42, or a composition of any one of claims 43-47, to alter the physiological characteristic of the CFB-associated disease or condition in the subject.

76. The method of claim 75, wherein the dsRNA agent is administered to the subject subcutaneously or is administered to the subject by IV administration.

77. The method of any one of claims 75-76, wherein the physiological characteristic is one or more of: the CFB mRNA level, the CFB protein level in the subject, CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum.

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