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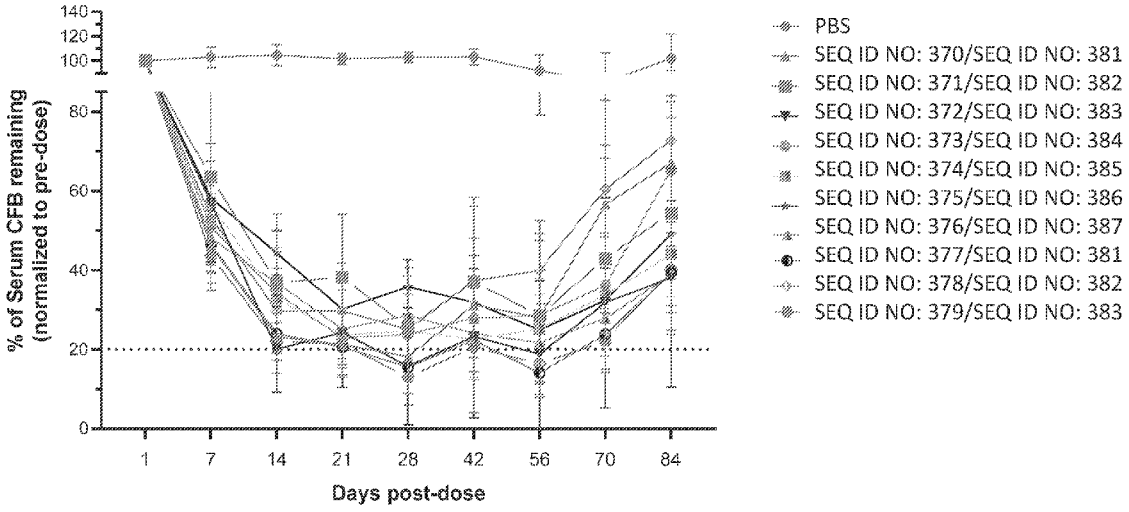
(54) Title: SMALL INTERFERING RNA TARGETING CFB AND USES THEREOF

FIG. 5B



(57) Abstract: This disclosure relates to isolated oligonucleotides comprising duplex regions targeting human CFB mRNA, and delivery systems, kits and compositions comprising the same, and methods of using the same for inhibiting or downregulating CFB gene expression.

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[Continued on next page]

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

SMALL INTERFERING RNA TARGETING CFB AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/433,735, filed December 19, 2022, the contents of which are incorporated herein by reference in their entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (SANB_018_001WO_SeqList_ST26.xml; Size: 454,399 bytes; and Date of Creation: December 15, 2023) are herein incorporated by reference in its entirety.

BACKGROUND

[0003] The complement system is a part of the innate immune system consisting of multiple soluble proteins that are present in the serum as inactive precursors. Upon activation, these complement components form an amplifying cascade that leads to the generation of bioactive effector compounds. This cascade plays a central role in maintaining cellular integrity and tissue homeostasis via the removal of damaged or dying cells, immune complexes, and cell debris. It also plays a role in immunomodulation, metabolism, inflammation, and host defense against pathogens. The complement system has three activation pathways, all of which revolve around the proteolytic cleavage of C3, a central component that serves as a convergence point for downstream effector function. Upon cleavage, the active subunit of complement factor B, Bb, combines with complement factor 3b component of C3 to form the alternative pathway C3 or C5 convertase. The central role of complement factor B (CFB) in the functioning of the alternative complement cascade makes it an ideal target for therapeutic modulation of complement.

[0004] Deficiencies or loss-of-function mutations of the ordinary complement components may lead to dysregulation of normal complement system function and possible overproduction of complement components. Excessive production and/or dysregulation is linked to an increasing number of ailments, for example, but not limited, to type 2 diabetes mellitus, cardiovascular, neurological, hematological, eye, kidney, and autoimmune diseases and/or disorders, and

infections. Accordingly, there is a need for therapies for subject having diseases, disorders and symptoms associated with elevated complement CFB expression levels. The present disclosure provides compositions targeting CFB and methods of reducing CFB expression for treatment of subjects having a complement-associated disease, disorder or symptom.

SUMMARY

[0005] The present disclosure provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein: the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0006] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0007] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0008] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0009] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at

least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0010] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0011] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0012] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0013] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0014] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0015] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions

selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0016] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0017] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is capable of inducing degradation of the CFB mRNA.

[0018] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, both the sense strand and the antisense strand are single stranded RNA molecules.

[0019] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the sense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang comprises at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the sense strand, the 3' overhang comprises two nucleotides.

[0020] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the antisense strand comprises a 3' overhang. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprises at least one nucleotide. In some embodiments, in the single stranded RNA molecule of the antisense strand, the 3' overhang comprises two nucleotides.

[0021] In some embodiments of the isolated oligonucleotide of the present disclosure, the 3' overhang comprises any one of thymidine-thymidine (dTdT), Adenine-Adenine (AA), Cysteine-Cysteine (CC), Guanine-Guanine (GG) or Uracil-Uracil (UU).

[0022] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises an RNA sequence of at least 20 nucleotides in length. In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises an RNA sequence of 20 nucleotides in length.

[0023] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises an RNA sequence of at least 22 nucleotides in length. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises an RNA sequence of 22 nucleotides in length.

[0024] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region is between 19 and 21 nucleotides in length. In some embodiments of the present disclosure, the double stranded region is 20 nucleotides in length.

[0025] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand and a sense strand, according to any one of the pairs of antisense strand and sense strand sequences in Table 1, as described in herein.

[0026] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35.

[0027] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69.

[0028] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strands.

[0029] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.1 nM.

[0030] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the

nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.02 nM.

[0031] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM.

[0032] The present disclosure also provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0033] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such

that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.1 nM.

[0034] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

[0035] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

[0036] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

[0037] The present disclosure also provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand or the antisense strand or both comprise one or more modified nucleotide(s). In some embodiments, the antisense strand comprises a mono methyl protected phosphate mimic (5'-MeEP). In some embodiments, in the sense strand or the antisense strand or both, a terminal or internal nucleotide is linked to a targeting ligand. In some embodiments, the targeting ligand comprises at least one GalNAc G1b moiety.

[0038] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the antisense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:

$3'(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5'

[0039] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:

$5'(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3'

[0040] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the antisense strand comprises any one of: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5' [MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' [MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' [MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID

NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' [mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'); or x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

[0041] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises any one of: i) a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3'); ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3'); iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3'); iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3'); v) a sense strand of nucleic acid sequence according to SEQ ID

NO: 385 (5'
[mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3'); vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5'
[mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3'); or vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5'
[mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

[0042] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the double stranded region comprises any one of: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5'
[MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5'
[mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5'
[MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5'
[mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5'
[MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5'
[mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3'); iv) an antisense strand of nucleic acid sequence according to SEQ

ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' [mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' [mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' [mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5'

[mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3'); or x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3').

[0043] The present disclosure also provides a vector encoding an isolated oligonucleotide disclosed herein.

[0044] The present disclosure also provides a delivery system comprising an isolated oligonucleotide or vector disclosed herein.

[0045] The present disclosure also provides a pharmaceutical composition comprising an isolated oligonucleotide, vector or delivery system disclosed herein, and a pharmaceutically acceptable carrier, diluent or excipient.

[0046] The present disclosure also provides a kit comprising an isolated oligonucleotide, vector, delivery system or a pharmaceutical composition disclosed herein.

[0047] The present disclosure also provides a method of inhibiting or downregulating the expression or level of CFB in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide, vector, delivery system or pharmaceutical composition disclosed herein.

[0048] The present disclosure also provides a method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide, vector, delivery system or pharmaceutical composition disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] **FIG. 1** is a graph showing the efficacy of siRNA compounds listed in **Table 2**, in silencing human CFB in cultured Huh-7 cells. The compounds were transfected into cells at 0.02 nM concentration. Data is presented as % of human CFB mRNA remaining relative to mock transfection when normalized to Gapdh mRNA levels (Mean, +/- SEM). Each bar represents a single compound tested.

[0050] **FIG. 2** is a graph showing the efficacy of siRNA compounds listed in **Table 2**, in silencing human CFB in cultured Huh-7 cells. The compounds were transfected into cells at 0.1 nM concentration. Data is presented as % of human CFB mRNA remaining relative to mock transfection when normalized to Gapdh mRNA levels (Mean, +/- SEM). Each bar represents a single compound tested.

[0051] **FIG. 3** is a graph showing the *in vivo* potency of a subset of compounds listed in **Table 2** in mouse HDI liver at 1 mg/kg at day 4 post-dosing. Data is presented as % of human CFB mRNA remaining relative to PBS when normalized to NeoR mRNA levels (Mean, +/- SEM).

[0052] **FIG. 4** is a graph showing the *in vivo* dose response of a subset of compounds listed in **Table 2** in mouse HDI liver at 0.25, 0.5, or 1 mg/kg at day 4 post-dosing. Data is presented as % of human CFB mRNA remaining relative to PBS when normalized to NeoR mRNA levels (Mean, +/- SEM).

[0053] **FIGS. 5A-5B** are graphs showing *in vivo* potency evaluations of compounds listed in **Table 3** in *Macaca fascicularis* after a 3 mg/kg single s.c. dosing. *Cyno* CFB mRNA remaining in liver (**FIG. 5A**) and serum CFB protein remaining (**FIG. 5B**) were measured over time. Data was normalized to pre-dose mRNA or protein levels of each animal.

DETAILED DESCRIPTION

[0054] The present disclosure provides isolated oligonucleotides (oligonucleotide(s)) that form a double stranded region, preferably small interfering RNAs (siRNAs), that can decrease complement CFB mRNA expression, in turn leading to a decrease in the degree of CFB protein expression in target cells. The oligonucleotides disclosed herein can have therapeutic application in regulating the expression of CFB, for treatment of diseases involving a complement component-associated disease such as, but not limited to Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-

Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation and neurodegenerative diseases.

[0055] In some aspects, the present invention provides compositions and methods of treating a subject having a disorder that would benefit from the reduction in complement CFB expression. In some aspects, the methods disclosed herein prevent at least one symptom in a subject having a disease or disorder that would benefit from reduction in complement CFB expression.

[0056] The present disclosure has identified specific regions within the CFB mRNA, that provide targets for binding double stranded oligonucleotides, e.g., siRNA, leading to reduction in level of expression of the CFB mRNA.

[0057] The complement factor B (CFB) mRNA sequence described herein, is an mRNA sequence encoded by a CFB gene according to GenBank Accession No. NM_001710.6:

GGGAAGGGAATGTGACCAGGTCTAGGTCTGGAGTTTCAGCTTGGACACTGAGCCAAGCAGACAA
GCAAAGCAAGCCAGGACACACCATCCTGCCCCAGGCCCAGCTTCTCTCCTGCCTTCCAACGCCA
TGGGGAGCAATCTCAGCCCCCAACTCTGCCTGATGCCCTTTATCTTGGGCCTCTTGTCTGGAGG
TGTGACCACCACTCCATGGTCTTTGGCCCGGCCCCAGGGATCCTGCTCTCTGGAGGGGGTAGAG
ATCAAAGGCGGCTCCTTCCGACTTCTCCAAGAGGGCCAGGCACTGGAGTACGTGTGTCCTTCTG
GCTTCTACCCGTACCCTGTGCAGACACGTACCTGCAGATCTACGGGGTCCTGGAGCACCCTGAA
GACTCAAGACCAAAAGACTGTCAGGAAGGCAGAGTGCAGAGCAATCCACTGTCCAAGACCACAC
GACTTCGAGAACGGGGAATACTGGCCCCGGTCTCCCTACTACAATGTGAGTGATGAGATCTCTT
TCCACTGCTATGACGGTTACACTCTCCGGGGCTCTGCCAATCGCACCTGCCAAGTGAATGGCCG
ATGGAGTGGGCAGACAGCGATCTGTGACAACGGAGCGGGGTACTGCTCCAACCCGGGCATCCCC
ATTGGCACAAGGAAGGTGGGCAGCCAGTACCGCCTTGAAGACAGCGTCACCTACCACTGCAGCC
GGGGGCTTACCCTGCGTGGCTCCCAGCGGCGAACGTGTCAGGAAGGTGGCTCTTGGAGCGGGAC
GGAGCCTTCCTGCCAAGACTCCTTCATGTACGACACCCCTCAAGAGGTGGCCGAAGCTTTCCTG
TCTTCCCTGACAGAGACCATAGAAGGAGTCGATGCTGAGGATGGGCACGGCCCAGGGGAACAAC
AGAAGCGGAAGATCGTCCTGGACCCTTCAGGCTCCATGAACATCTACCTGGTGCTAGATGGATC
AGACAGCATTGGGGCCAGCAACTTCACAGGAGCCAAAAAGTGTCTAGTCAACTTAATTGAGAAG
GTGGCAAGTTATGGTGTGAAGCCAAGATATGGTCTAGTGACATATGCCACATACCCCAAAATTT

GGGTCAAAGTGTCTGAAGCAGACAGCAGTAATGCAGACTGGGTCACGAAGCAGCTCAATGAAAT
CAATTATGAAGACCACAAGTTGAAGTCAGGGACTAACACCAAGAAGGCCCTCCAGGCAGTGTAC
AGCATGATGAGCTGGCCAGATGACGTCCCTCCTGAAGGCTGGAACCGCACCCGCCATGTCATCA
TCCTCATGACTGATGGATTGCACAACATGGGCGGGGACCCAATTACTGTCATTGATGAGATCCG
GGACTTGCTATACATTGGCAAGGATCGCAAAAACCCAAGGGAGGATTATCTGGATGTCTATGTG
TTTGGGGTCGGGCCTTTGGTGAACCAAGTGAACATCAATGCTTTGGCTTCCAAGAAAGACAATG
AGCAACATGTGTTCAAAGTCAAGGATATGGAAAACCTGGAAGATGTTTTCTACCAAATGATCGA
TGAAAGCCAGTCTCTGAGTCTCTGTGGCATGGTTTGGGAACACAGGAAGGGTACCGATTACCAC
AAGCAACCATGGCAGGCCAAGATCTCAGTCATTCGCCCTTCAAAGGGACACGAGAGCTGTATGG
GGGCTGTGGTGTCTGAGTACTTTGTGCTGACAGCAGCACATTGTTTCACTGTGGATGACAAGGA
ACACTCAATCAAGGTCAGCGTAGGAGGGGAGAAGCGGGACCTGGAGATAGAAGTAGTCCTATTT
CACCCCAACTACAACATTAATGGGAAAAAAGAAGCAGGAATTCCTGAATTTTATGACTATGACG
TTGCCCTGATCAAGCTCAAGAATAAGCTGAAATATGGCCAGACTATCAGGCCCATTTGTCTCCC
CTGCACCGAGGGAACAACTCGAGCTTTGAGGCTTCCTCCAACTACCACTTGCCAGCAACAAAAG
GAAGAGCTGCTCCCTGCACAGGATATCAAAGCTCTGTTTGTGTCTGAGGAGGAGAAAAAGCTGA
CTCGGAAGGAGGTCTACATCAAGAATGGGGATAAGAAAGGCAGCTGTGAGAGAGATGCTCAATA
TGCCCCAGGCTATGACAAAGTCAAGGACATCTCAGAGGTGGTCACCCCTCGGTTCCTTTGTACT
GGAGGAGTGAGTCCCTATGCTGACCCCAATACTTGCAGAGGTGATTCTGGCGGCCCCTTGATAG
TTCACAAGAGAAGTCGTTTCATTCAAGTTGGTGTAATCAGCTGGGGAGTAGTGGATGTCTGCAA
AAACCAGAAGCGGCAAAAGCAGGTACCTGCTCACGCCCGAGACTTTCACATCAACCTCTTTCAA
GTGCTGCCCTGGCTGAAGGAGAAACTCCAAGATGAGGATTTGGGTTTTCTATAAGGGGTTTCCT
GCTGGACAGGGGCGTGGGATTGAATTAAAACAGCTGCGACAACA (SEQ ID NO: 1).

[0058] The present disclosure provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0059] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0060] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0061] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0062] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0063] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0064] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0065] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at

least 99% identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0066] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0067] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0068] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0069] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0070] The CFB mRNA sequence according to SEQ ID NO: 1, as described herein, is any heterologous mRNA sequence with sufficient identity to a CFB according to Accession No. NM_001710.6, as described herein, that allows binding to the antisense strand of the oligonucleotides of the present disclosure.

[0071] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is capable of inducing degradation of the CFB mRNA.

[0072] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some

embodiments of the isolated oligonucleotide of the present disclosure, both the sense strand and the antisense strand are single stranded RNA molecules.

[0073] In some embodiments, the isolated oligonucleotide of the present disclosure is a small interfering RNA (siRNA). Accordingly, the disclosure provides siRNAs, wherein the siRNA comprises a sense region and antisense region complementary to the sense region that together form an RNA duplex, and wherein the sense region comprises a sequence at least 70% to 100% identical to a CFB mRNA sequence.

Definitions

[0074] "RNAi" or "RNA interference" refers to the process of sequence-specific post-transcriptional gene silencing, mediated by double-stranded RNA (dsRNA). Duplex RNA siRNA (small interfering RNA), miRNA (micro RNA), shRNA (short hairpin RNA), ddRNA (DNA-directed RNA), piRNA (Piwi-interacting RNA), or rasiRNA (repeat associated siRNA) and modified forms thereof are all capable of mediating RNA interference. These dsRNA molecules may be commercially available or may be designed and prepared based on known sequence information, etc. The antisense strand of these molecules can include RNA, DNA, PNA, or a combination thereof. These DNA/RNA chimera polynucleotide includes, but is not limited to, a double-strand polynucleotide composed of DNA and RNA that inhibits the expression of a target gene. These dsRNA molecules can also include one or more modified nucleotides, as described herein, which can be incorporated on either strand.

[0075] In the RNAi gene silencing or knockdown process, dsRNA comprising a first (antisense) strand that is complementary to a portion of a target gene and a second (sense) strand that is fully or partially complementary to the first antisense strand is introduced into an organism. After introduction into the organism, the target gene-specific dsRNA is processed into relatively small fragments (siRNAs) and can subsequently become distributed throughout the organism, decrease messenger RNA of target gene, leading to a phenotype that may come to closely resemble the phenotype arising from a complete or partial deletion of the target gene.

[0076] Certain dsRNAs in cells can undergo the action of Dicer enzyme, a ribonuclease III enzyme. Dicer can process the dsRNA into shorter pieces of dsRNA, i.e. siRNAs. RNAi also involves an endonuclease complex known as the RNA induced silencing complex (RISC). Following cleavage by Dicer, siRNAs enter the RISC complex and direct cleavage of a single stranded RNA target having a sequence complementary to the antisense strand of the siRNA

duplex. The other strand of the siRNA is the passenger strand. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex. siRNAs can thus down regulate or knock down gene expression by mediating RNA interference in a sequence-specific manner.

[0077] As used herein, "target gene" or "target sequence" refers to a gene or gene sequence whose corresponding RNA is targeted for degradation through the RNAi pathway using dsRNAs or siRNAs as described herein. To target a gene, for example using an siRNA, the siRNA comprises an antisense region complementary to, or substantially complementary to, at least a portion of the target gene or sequence, and sense strand complementary to the antisense strand. Once introduced into a cell, the siRNA directs the RISC complex to cleave an RNA comprising a target sequence, thereby degrading the RNA.

[0078] As used herein, "oligonucleotide", "nucleic acid," "nucleotide sequence," and "polynucleotide" are used interchangeably and encompass both RNA and DNA, including cDNA, genomic DNA, mRNA, synthetic (e.g., chemically synthesized) DNA or RNA and chimeras of RNA and DNA. The term polynucleotide, nucleotide sequence, or nucleic acid refers to a chain of nucleotides without regard to length of the chain. The nucleic acid can be double-stranded or single-stranded. Where single-stranded, the nucleic acid can be a sense strand or an antisense strand. The nucleic acid can be synthesized using oligonucleotide analogs or derivatives (e.g., inosine or phosphorothioate nucleotides). Such oligonucleotides can be used, for example, to prepare nucleic acids that have altered base-pairing abilities or increased resistance to nucleases. The present disclosure further provides a nucleic acid that is the complement (which can be either a full complement or a partial complement) of a nucleic acid, nucleotide sequence, or polynucleotide of this disclosure. When dsRNA is produced synthetically, less common bases, such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others can also be used for antisense, dsRNA, and ribozyme pairing. Other modifications, such as modification to the phosphodiester backbone, or the 2'-fluoro, the 2'-hydroxy or 2'O-methyl in the ribose sugar group of the RNA can also be made.

[0079] The term "isolated" can refer to a nucleic acid, nucleotide sequence or polypeptide that is substantially free of cellular material, viral material, and/or culture medium (when produced by recombinant DNA techniques), or chemical precursors or other chemicals (when chemically synthesized). Moreover, an "isolated fragment" is a fragment of a nucleic acid, nucleotide

sequence or polypeptide that is not naturally occurring as a fragment and would not be found in the natural state. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to provide the polypeptide or nucleic acid in a form in which it can be used for the intended purpose.

[0080] The term "region" or "fragment" is used interchangeably and as applied to an oligonucleotide.

[0081] The CFB mRNA sequence, as described herein, will be understood to mean a nucleotide sequence of reduced length relative to a reference nucleic acid or nucleotide sequence of the CFB mRNA sequence and comprising, consisting essentially of, and/or consisting of a nucleotide sequence of contiguous nucleotides identical or almost identical (e.g., 60%, 70%, 80%, 90%, 92%, 95%, 98% or 99% identical) to the reference nucleic acid or nucleotide sequence. Such a nucleic acid fragment according to the disclosure may be, where appropriate, included in a larger polynucleotide of which it is a constituent. In some embodiments, such fragments can comprise, consist essentially of, and/or consist of oligonucleotides having a length of at least about 8, 10, 12, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 150, 200, or more consecutive nucleotides of a nucleic acid or nucleotide sequence according to the disclosure.

[0082] As used herein, "complementary" polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. For example, the sequence "A-G-T" binds to the complementary sequence "T-C-A." It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

[0083] As used herein, the term "substantially complementary" is at least 90% (e.g., 91, 92, 93, 94, 95, 96, 97, 98 or 99%) complementary to the sense strand that is substantially identical to the nucleotide sequence within the defined regions in SEQ ID NO: 1. As used herein, the term "substantially complementary" means that two nucleic acid sequences are complementary at least at about 90%, 95% or 99% of their nucleotides.

[0084] In some embodiments, the two nucleic acid sequences can be complementary at least at 90%, 95%, 96%, 97%, 98%, 99% or more of their nucleotides. In some embodiments, the two

nucleic acid sequences can be between 90% to 95% complementary, between 70% to 100% complementary, between 95% and 96% complementary, between 90% and 100% complementary, between 96% to 97% complementary, between 60% to 80% complementary, between 97% and 98% complementary, between 70% and 90% complementary, between 98% and 99% complementary, between 80% and 100% complementary, or between 99% and 100% complementary.

[0085] The term "substantially complementary" can also mean that two nucleic acid sequences, sense strand and antisense strand have sufficient complementarity that allows binding between the sense strand and antisense strand to form a double stranded region comprising of between 19-25 nucleotides in length. The term "substantially complementary" can also mean that two nucleic acid sequences can hybridize under high stringency conditions, and such conditions are well known in the art.

[0086] As used herein, the term "substantially identical" or "sufficient identity" used interchangeably herein, is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% (e.g., between 70% to 805, 8-% to 90% or 90% to 95% or 95% to 99% or 99% to 100%) identical to the nucleotide sequence within the defined regions in SEQ ID NO: 1.

[0087] As used herein, the term "identity" means that sequences are compared with one another as follows. In order to determine the percentage identity of two nucleic acid sequences, the sequences can first be aligned with respect to one another in order subsequently to make a comparison of these sequences possible. For this e.g., gaps can be inserted into the sequence of the first nucleic acid sequence and the nucleotides can be compared with the corresponding position of the second nucleic acid sequence. If a position in the first nucleic acid sequence is occupied by the same nucleotide as is the case at a position in the second sequence, the two sequences are identical at this position. The percentage identity between two sequences is a function of the number of identical positions divided by the number of all the positions compared in the sequences investigated.

[0088] A "percent identity" or "% identity" as used interchangeably herein, for aligned segments of a test sequence and a reference sequence is the percent of identical components which are shared by the two aligned sequences divided by the total number of components in reference sequence segment, i.e., the entire reference sequence or a smaller defined part of the reference sequence.

[0089] The percentage identity of two sequences can be determined with the aid of a mathematical algorithm. A preferred, but not limiting, example of a mathematical algorithm which can be used for comparison of two sequences is the algorithm of Karlin et al. (1993), PNAS USA, 90:5873-5877. Such an algorithm is integrated in the NBLAST program, with which sequences which have a desired identity to the sequences of the present disclosure can be identified. In order to obtain a gapped alignment, as described here, the "Gapped BLAST" program can be used, as is described in Altschul et al. (1997), Nucleic Acids Res, 25:3389-3402. If BLAST and Gapped BLAST programs are used, the preset parameters of the particular program (e.g. NBLAST) can be used. The sequences can be aligned further using version 9 of GAP (global alignment program) of the "Genetic Computing Group" using the preset (BLOSUM62) matrix (values −4 to +11) with a gap open penalty of −12 (for the first zero of a gap) and a gap extension penalty of −4 (for each additional successive zero in the gap). After the alignment, the percentage identity is calculated by expressing the number of agreements as a percentage content of the nucleic acids in the sequence claimed. The methods described for determination of the percentage identity of two nucleic acid sequences can also be used correspondingly, if necessary, on the coded amino acid sequences.

[0090] Useful methods for determining sequence identity are also disclosed in Guide to Huge Computers (Martin J. Bishop, ed., Academic Press, San Diego (1994)), and Carillo, H., and Lipton, D., (Applied Math48:1073(1988)). More particularly, preferred computer programs for determining sequence identity include but are not limited to the Basic Local Alignment Search Tool (BLAST) programs which are publicly available from National Center Biotechnology Information (NCBI) at the National Library of Medicine, National Institute of Health, Bethesda, Md. 20894; see BLAST Manual, Altschul et al., NCBI, NLM, NIH; (Altschul et al., J. Mol. Biol. 215:403-410 (1990)); version 2.0 or higher of BLAST programs allows the introduction of gaps (deletions and insertions) into alignments; for peptide sequence BLASTX can be used to determine sequence identity; and, for polynucleotide sequence BLASTN can be used to determine sequence identity. Percent identity can be 70% identity or greater, e.g., at least 70% identity, at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 98% identity, at least 99% identity or 100% identity.

[0091] As used herein, "heterologous" refers to a nucleic acid sequence that either originates from another species or is from the same species or organism but is modified from either its

original form or the form primarily expressed in the cell. Thus, a nucleotide sequence derived from an organism or species different from that of the cell into which the nucleotide sequence is introduced, is heterologous with respect to that cell and the cell's descendants. In addition, a heterologous nucleotide sequence includes a nucleotide sequence derived from and inserted into the same natural, original cell type, but which is present in a non-natural state, e.g., a different copy number, and/or under the control of different regulatory sequences than that found in nature.

[0092] Double Stranded RNAs Targeting Human Complement Factor B (CFB)

[0093] The disclosure provides isolated oligonucleotides comprising a double stranded RNAs (dsRNAs) duplex region which target a CFB mRNA sequence for degradation. The double stranded RNA molecule of the disclosure may be in the form of any type of RNA interference molecule known in the art. In some embodiments, the double stranded RNA molecule is a small interfering RNA (siRNA). In other embodiments, the double stranded RNA molecule is a short hairpin RNA (shRNA) molecule. In other embodiments, the double stranded RNA molecule is a Dicer substrate that is processed in a cell to produce an siRNA. In other embodiments the double stranded RNA molecule is part of a microRNA precursor molecule.

[0094] In some embodiments, the dsRNA is a small interfering RNA (siRNA) which targets a CFB mRNA sequence for degradation. In some embodiments, the siRNA targeting CFB is packaged in a delivery system described herein (e.g., nanoparticle).

[0095] The isolated oligonucleotides of the present disclosure targeting CFB for degradation can comprise a sense strand at least 70% identical to any fragment of a CFB mRNA, for example the CFB mRNA of SEQ ID NO: 1. In some embodiments, the sense strand comprises or consists essentially of a sequence at least 70%, at least 80%, at least 90%, at least 95% or is 100% identical to any fragment of SEQ ID NO: 1. The siRNAs targeting CFB for degradation can comprise an antisense strand at least 70% identical to a sequence complementary to any fragment of a CFB mRNA, for example the CFB mRNA of SEQ ID NO: 1. In some embodiments, the antisense strand comprises or consists essentially of a sequence at least 70%, at least 80%, at least 90%, at least 95% or is 100% identical to a sequence complementary to any fragment of SEQ ID NO: 1. In some embodiments, the sense region and antisense regions are complementary, and base pair to form an RNA duplex structure. The fragment of the CFB mRNA that has percent identity to the sense region of the siRNA, and which is complementary

to the antisense region of the siRNA, can be protein coding sequence of the mRNA, an untranslated region (UTR) of the mRNA (5' UTR or 3' UTR), or both.

[0096] In some embodiments, the isolated oligonucleotide of the present disclosure comprises a sense region and antisense region complementary to the sense region that together form an RNA duplex, and the sense region comprises a sequence at least 70% identical to a CFB mRNA sequence. In some embodiments, the sense region is identical to a CFB mRNA sequence.

[0097] As used herein, the term "sense strand" or "sense region" refers to a nucleotide sequence of an siRNA molecule that is partially or fully complementary to at least a portion of a corresponding antisense strand or antisense region of the siRNA molecule. The sense strand of an isolated oligonucleotides of the present disclosure molecule can include a nucleic acid sequence having some percentage identity with a target nucleic acid sequence such as a CFB mRNA sequence. In some cases, the sense region may have 100% identity, i.e., complete identity or homology, to the target nucleic acid sequence. In other cases, there may be one or more mismatches between the sense region and the target nucleic acid sequence. For example, there may be 1, 2, 3, 4, 5, 6, or 7 mismatches between the sense region and the target nucleic acid sequence.

[0098] As used herein, the term "antisense strand" or "antisense region" refers to a nucleotide sequence of the isolated oligonucleotides of the present disclosure, that is partially or fully complementary to at least a portion of a target nucleic acid sequence. The antisense strand of an isolated oligonucleotides of the present disclosure molecule can include a nucleic acid sequence that is complementary to at least a portion of a corresponding sense strand of the isolated oligonucleotides.

[0099] In some embodiments, the sense region comprises a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region consists essentially of a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region comprises a sequence that is identical to a sequence of SEQ ID NO: 1 or a region of

SEQ ID NO: 1, as disclosed herein. In some embodiments, the sense region consists essentially of a sequence that is identical to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein.

[0100] In some embodiments, the sense region of the isolated oligonucleotides of the present disclosure targeting CFB has one or more mismatches between the sequence of the isolated oligonucleotides and the CFB sequence. For example, the sequence of the sense region may have 1, 2, 3, 4 or 5 mismatches between the sequence of the sense region of the isolated oligonucleotides and the CFB sequence. In some embodiments, the CFB sequence is a CFB 3' untranslated region sequence (3' UTR). Without wishing to be bound by theory, it is thought that siRNAs targeting the 3' UTR have elevated mismatch tolerance when compared to mismatches in the isolated oligonucleotides targeting coding regions of a gene. Further, the isolated oligonucleotides RNAs may be tolerant of mismatches outside the seed region. As used herein, the "seed region" of the isolated oligonucleotides refers to base pairs 2-8 of the antisense region of the isolated oligonucleotides, i.e., the strand of the isolated oligonucleotides that is complementary to and hybridizes to the target mRNA.

[0101] In some embodiments, the antisense region comprises a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% identical or 100% identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1, as disclosed herein. In some embodiments, the antisense region consists essentially of a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 97% identical, at least 99% or 100% identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1. In some embodiments, the antisense region comprises a sequence that is identical to a sequence complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1. In some embodiments, the sense region consists essentially of a sequence that is complementary to a sequence of SEQ ID NO: 1 or a region of SEQ ID NO: 1.

[0102] The antisense region of the CFB targeting isolated oligonucleotide of the present disclosure is complementary to the sense region. In some embodiments, the sense region and the antisense region are fully complementary (no mismatches). In some embodiments the antisense

region is partially complementary to the sense region, i.e., there are 1, 2, 3, 4 or 5 mismatches between the sense region and the antisense region.

[0103] In general, isolated oligonucleotide of the present disclosure comprise an RNA duplex that is about 16 to about 25 nucleotides in length. In some embodiments, the RNA duplex is between about 17 and about 24 nucleotides in length, between about 18 and about 23 nucleotides in length, or between about 19 and about 22 nucleotides in length. In some embodiments, the RNA duplex is 19 nucleotides in length. In some embodiments, the RNA duplex is 20 nucleotides in length.

[0104] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand is a single stranded RNA molecule. In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand is a single stranded RNA molecule. In some embodiments, both the sense strand and the antisense strand are single stranded RNA molecules. In some embodiments, the isolated oligonucleotide of the present disclosure is an siRNA targeting CFB that comprises two different single stranded RNAs, the first comprising the sense region and the second comprising the antisense region, which hybridize to form an RNA duplex.

[0105] In some embodiments, the isolated oligonucleotide of the present disclosure can have one or more overhangs from the duplex region. In some embodiments, the overhangs, which are non-base-paired, single strand regions, can be from one to eight nucleotides in length, or longer. In some embodiments, the overhang can be a 3' overhang, wherein the 3'-end of a strand has a single strand region of from one to eight nucleotides. In some embodiments, the overhang can be a 5' overhang, wherein the 5 '-end of a strand has a single strand region of from one to eight nucleotides. In some embodiments, the overhangs of the isolated oligonucleotide are the same length. In some embodiments, the overhangs of the isolated oligonucleotide are different lengths.

[0106] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the sense strand comprises a 3' overhang. In some embodiments, the 3' overhang of the single stranded RNA molecule of the sense strand comprises at least one nucleotide. In some embodiments, the 3' overhang of the single stranded RNA molecule of the sense strand comprises two nucleotides.

[0107] In some embodiments of the isolated oligonucleotide of the present disclosure, the single stranded RNA molecule of the antisense strand comprises a 3' overhang. In some

embodiments, the 3' overhang of the single stranded RNA molecule of the antisense strand comprises at least one nucleotide. In some embodiments, the 3' overhang of the single stranded RNA molecule of the antisense strand comprises two nucleotides.

[0108] In some embodiments of the isolated oligonucleotide of the present disclosure, both ends of isolated oligonucleotide have an overhang, for example, a 3' dinucleotide overhang on each end. In some embodiments, the overhangs at the 5'- and 3 '-ends are of different lengths. In some embodiments, the overhangs at the 5'- and 3 '-ends are of the same length.

[0109] In some embodiments of the isolated oligonucleotide of the present disclosure, the overhang can contain one or more deoxyribonucleotides, one or more ribonucleotides, or a combination of deoxyribonucleotides and ribonucleotides. In some embodiments, one, or both, of the overhang nucleotides of an siRNA may be 2'-deoxyribonucleotides.

[0110] In some embodiments of the isolated oligonucleotide of the present disclosure, the first single stranded RNA molecule comprises a first 3' overhang. In some embodiments, the second single stranded RNA molecule comprises a second 3' overhang. In some embodiments, the first and second 3' overhangs comprise a dinucleotide.

[0111] In some embodiments of the isolated oligonucleotide of the present disclosure, the 3' overhang comprises any one of thymidine-thymidine (dTdT), Adenine-Adenine (AA), Cysteine-Cysteine (CC), Guanine-Guanine (GG) or Uracil-Uracil (UU). In some embodiments, the isolated oligonucleotide of the present disclosure, the 3' overhang comprises a thymidine-thymidine (dTdT) or a Uracil-Uracil (UU) overhang. In some embodiments, the 3' overhang comprises a Uracil-Uracil (UU) overhang. Without wishing to be bound by theory, it is thought that 3' overhangs, such as dinucleotide overhangs, enhance siRNA mediated mRNA degradation by enhancing siRNA-RISC complex formation, and/or rate of cleavage of the target mRNA by the siRNA-RISC complex.

[0112] In some embodiments, the isolated oligonucleotide of the present disclosure can have one or more blunt ends, in which the duplex region ends with no overhang, and the strands are base paired to the end of the duplex region. In some embodiments, the isolated oligonucleotide of the present disclosure can have one or more blunt ends, or can have one or more overhangs, or can have a combination of a blunt end and an overhang end. For example, the 5' end of the siRNA can be blunt and the 3' end of the same isolated oligonucleotide comprise an overhang, or *vice versa*.

[0113] In some embodiments, both ends of the isolated oligonucleotide of the present disclosure are blunt ends.

[0114] In some embodiments of the isolated oligonucleotide of the present disclosure, the double stranded region comprises an antisense strand and a sense strand, according to any one of the pairs of antisense strand and sense strand sequences in Table 1, as described below.

[0115] The Complement System

[0116] The complement system is a critical component of the innate immune system and comprises a group of proteins that are normally present in an inactive state. These proteins are organized in three activation pathways: the classical, the lectin, and the alternative pathways.

[0117] Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertase and the C5-convertase. The first enzymatically-activated cascade, known as classical pathway, is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including Gram-negative bacteria.

[0118] As described in US 8,703,136, the classical pathway comprises several components, C1, C4, C2, C3 and C5 (listed by order in the pathway). Initiation of the classical pathway of the complement system occurs following binding and activation of the first complement component (C1) by both immune and non-immune activators. C1 comprises a calcium-dependent complex of components C1q, C1r and C1s, and is activated through binding of the C1q component. C1q contains six identical subunits and each subunit comprises three chains (the A, B and C chains). Each chain has a globular head region that is connected to a collagen-like tail. Binding and activation of C1q by antigen-antibody complexes occurs through the C1q head group region. Numerous non-antibody C1q activators, including proteins, lipids and nucleic acids, bind and activate C1q through a distinct site on the collagen-like stalk region. The C1qrs complex then catalyzes the activation of complement components C4 and C2, forming the C4b2a complex which functions as a C3 convertase.

[0119] The second enzymatically activated cascade, known as the alternative pathway, is a rapid, antibody-independent route for complement system activation and amplification. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and

activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials). The alternative pathway comprises several components, that include: C3, Complement Factor B (CFB), and Factor D (listed by order in the pathway). Activation of the alternative pathway occurs when C3b, a proteolytically cleaved and active form of C3, is bound to an activating surface agent such as a bacterium. CFB is then bound to C3b and cleaved by Factor D to yield the active enzyme, Bb. The resultant complement complex, C3bBb, is the alternative pathway C3 convertase. The enzyme C3b-Bb cleaves C3 to generate C3b, producing extensive deposition of C3b-Bb complexes on the activating surface.

[0120] Thus, both the classical and alternate complement pathways produce C3 convertases that split factor C3 into C3a and C3b. At this point, both C3 convertases further assemble into C5 convertases (C4b2a3b and C3b3bBb). These complexes subsequently cleave complement component C5 into two components: the C5a polypeptide (9 kDa) and the C5b polypeptide (170 kDa). The C5a polypeptide binds to a 7 transmembrane G-protein coupled receptor, which was originally associated with leukocytes and is now known to be expressed on a variety of tissues including hepatocytes and neurons. The C5a molecule is the primary chemotactic component of the human complement system and can trigger a variety of biological responses including leukocyte chemotaxis, smooth muscle contraction, activation of intracellular signal transduction pathways, neutrophil-endothelial adhesion, cytokine and lipid mediator release and oxidant formation.

[0121] The larger C5b fragment binds sequentially to later components of the complement cascade, C6, C7, C8 and C9 to form the C5b-9 membrane attack complex ("MAC"). The lipophylic C5b-9 MAC can directly lyse erythrocytes, and in greater quantities it is lytic for leukocytes and damaging to tissues such as muscle, epithelial and endothelial cells. In sublytic amounts, the C5b-9 MAC can stimulate upregulation of adhesion molecules, intracellular calcium increase and cytokine release. In addition, at sublytic concentrations the C5b-9 MAC can stimulate cells such as endothelial cells and platelets without causing cell lysis. The non-lytic effects of C5a and the C5b-9 MAC are comparable and interchangeable.

[0122] The lectin pathway is initiated when pattern-recognition molecules (MBL, CL-K1, and ficolins) bind to the so-called pathogen-associated molecular patterns (PAMPs) (D-mannose, N-acetyl-D-glucosamine, or acetyl groups), on the surface of pathogens or to apoptotic or necrotic cells (Beltrame et. al, 2015).

[0123] Although the complement system has an important role in the maintenance of health, it has the potential to cause or contribute to disease.

[0124] There are four diseases for which complement-targeted drugs are approved for routine clinical use by the US Food and Drug Administration (FDA) and the European Medicines Agency (Garred et. al., 2021). Eculizumab (Soliris), a mAb-blocking cleavage of C5, was shown to be very efficient in protecting from hemolysis in PNH in 2007 (Brodsky et al., 2008; Parker, 2009), and this was later followed by treatment of atypical hemolytic-uremic syndrome (aHUS) (Tschumi et al., 2011; Loirat et al., 2016). Recently it was also approved for the neurologic diseases generalized myasthenia gravis (Dhillon, 2018) and neuromyelitis optica spectrum disorders (Selmaj and Selmaj, 2019).

[0125] Eculizumab has been the only approved complement inhibitor for routine use until recently when ravulizumab (Ultomiris) and Zilucoplan were introduced. Ravulizumab is the second generation of eculizumab; in other words, some minor amino acid modifications were made in the eculizumab molecule, thereby increasing the half-life substantially so treatment intervals could be increased from every 2nd to every 8th week. It has the same binding site to C5 as eculizumab (i.e., blocking its cleavage and thereby preventing the release of C5a and formation of C5b-9) (Kulasekararaj et al., 2019; Lee et al., 2019; McKeage, 2019; Stern and Connell, 2019; Lee and Kulasekararaj, 2020).

[0126] Zilucoplan is an entirely different drug structurally from the antibody mentioned above but with the same principal function. It is a synthetic, macrocyclic peptide inhibitor for subcutaneous self-administration with principally the same function as eculizumab, blocking the cleavage of C5 (Beecher et al., 2019; Albazli et al., 2020; Howard et al., 2020). A phase 2 randomized, double blind, placebo-controlled, multicenter clinical trial demonstrated that Zilucoplan administration yielded rapid, meaningful, and sustained improvements over 12 weeks in a broad population of patients with moderate-to-severe acetylcholine-receptor-antibody–positive generalized myasthenia gravis (Howard et al., 2020). RA 101295, a close analog of Zilucoplan (RA101495), has been used in animal studies and has been shown to increase survival in baboon Escherichia coli sepsis (Keshari et al., 2017).

[0127] Accordingly, the isolated oligonucleotides disclosed in the present disclosure are useful in treating or preventing a disease or disorder associated with aberrant or increased expression or

activity of CFB or a disease or disorder where CFB plays a role. Exemplary isolated oligonucleotides of the present disclosure are described in **Table 1**.

[0128] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence selected from any one of the group of sense strand/passenger strand sequences listed in Table 1, Table 2 or Table 3. In some embodiments, the antisense strand comprises a sequence selected from any one of the group of antisense strand/guide strand sequences listed in Table 1, Table 2 or Table 3. In some embodiments, the sense and antisense regions comprise complementary sequences selected from the group listed in Table 1, Table 2 and Table 3.

[0129] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35.

[0130] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69.

[0131] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35; and the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69, wherein the antisense strand and the sense strand sequences have sufficient complementarity to allow formation of a double stranded region between the antisense and the sense strand.

[0132] Sequences of the Present Disclosure

[0133] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0134] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to

1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0135] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0136] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0137] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0138] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0139] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 503 to 523; and b) 2190 to 2210, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5'

UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

[0140] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0141] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0142] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0143] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1666 to 1686; e) 1821 to 1881; f) 2116 to 2136; g) 2232 to 2307; and h) 2394 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand

of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3'); xxvi) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

[0144] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein sense strand comprises a sequence that is substantially identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0145] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein sense strand comprises a sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0146] The present disclosure provides an isolated oligonucleotide comprising a sense and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

[0147] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from: a) 995 to 1019; b) 1606 to 1626; c) 1860 to 1880; and d) 2382 to 2402, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); or v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3').

[0148] ***At least 50% knockdown of CFB at 0.1 nM***

[0149] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.1 nM.

[0150] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5'

UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5'

CUGUGGUGUCUGAGUACUUA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

[0151] ***At least 50% knockdown of CFB at 0.02 nM***

[0152] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821

to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% (e.g., 50% to 55%, 55% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95% or 95% to 99%, 99% to 100%), at a dose of 0.02 nM.

[0153] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a sequence that is identical to a region between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a

sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

[0154] ***20-50% knockdown of CFB at 0.02 nM***

[0155] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from a) 493

to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% (e.g., 20% to 25%, 25% to 30%, 30% to 35%, 35% to 40%, 40% to 45% or 45% to 50%), at a dose of 0.02 nM.

[0156] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from a) 493 to 534; b) 991 to 1054; c) 1384 to 1500; d) 1606 to 1686; e) 1821 to 1881; f) 2116 to 2307; and g) 2382 to 2468, from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3'); vii) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3'); or xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5'

UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3').

[0157] The present disclosure provides an isolated oligonucleotide comprising a sense strand and an antisense strand, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

[0158] ***20-50% knockdown of CFB at 0.1 nM***

[0159] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.1 nM.

[0160] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.1 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' UGACACUUUUUGGCUCCUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 204 (5'

ACAGGAGCCAAAAAGUGUCA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UCUCUUGUGAACUAUCAAGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CCUUGAUAGUUCACAAGAGA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' UGUACAUGAAGGAGUCUUGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 197 (5' CCAAGACUCCUUCAUGUACA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 163 (5' UGUCAGCAUAGGGACUCACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' AGUGAGUCCCUAUGCUGACA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUUCAACUUGUGGUCUUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UGAAGACCACAAGUUGAAGA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UUUCUCAAUUAAGUUGACUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UAGUCAACUUAAUUGAGAAA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UCUCUCUCACAGCUGCCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' AAAGGCAGCUGUGAGAGAGA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCUUAUUCUUGAGCUUGAUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' GAUCAAGCUCAAGAAUAAGA 3'); xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5' UCUGACCUUGAUUGAGUGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' AACACUCAAUCAAGGUCAGA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAUUGCUCUGCACUCUGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' GCAGAGUGCAGAGCAAUCCA 3'); xiii) an antisense strand of

nucleic acid sequence according to SEQ ID NO: 134 (5' UAACAAUGUGCUGCUGUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' CUGACAGCAGCACAUUGUUA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UAUUGAGCAUCUCUCUCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UGUGAGAGAGAUGCUCAAUA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UCAUUCUUGAUGUAGACCUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' GAGGUCUACAUCAAGAAUGA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' UGAAACUCCAGACCUAGACCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' GGUCUAGGUCUGGAGUUUCA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCUUGAUGUAGACCUCCUUCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' GAAGGAGGUCUACAUCAAGA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 147 (5' UCAGAGCUUUGAUAUCCUGUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 257 (5' ACAGGAUAUCAAAGCUCUGA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' UCAUAACUUGCCACCUUCUCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' GAGAAGGUGGCAAGUUAUGA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 174 (5' UUUCUGGUUUUUGCAGACAUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 284 (5' AUGUCUGCAAAAACCAGAAA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 118 (5' UUUUCUUGGAAGCCAAAGCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 228 (5' UGCUUUGGCUUCCAAGAAAA 3'); xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UAAACAGAGCUUUGAUAUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' GGAUAUCAAAGCUCUGUUUA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' UGACUAGACACUUUUUGGCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' AGCCAAAAAGUGUCUAGUCA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 142 (5' UUUCUUGAGCUUGAUCAGGGCA

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' CCCUGAUCAAGCUCAAGAAA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UCAUAUUGAGCAUCUCUCUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' GAGAGAGAUGCUCAAUAUGA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUAUUGGGGUCAGCAUAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' CCUAUGCUGACCCCAAUACA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' UUGAAACUCCAGACCUAGACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' GUCUAGGUCUGGAGUUUCAA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' UAUCCAUCUAGCACCAGGUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UACCUGGUGCUAGAUGGAUA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGUGAACUAUCAAGGGGCCGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' CGGCCCCUUGAUAGUUCACA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 175 (5' UUUGGAGUUUCUCCUUCAGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 285 (5' GCUGAAGGAGAAACUCCAAA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' UAAACUCCAGACCUAGACCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' AGGUCUAGGUCUGGAGUUUA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 119 (5' UCUUUCUUGGAAGCCAAAGCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' GCUUUGGCUUCCAAGAAAGA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UCUUUCUUAUCCCCAUUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 264 (5' AAGAAUGGGGAUAAGAAAGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UCUAGACCUGGUCACAUUCCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' GGAAUGUGACCAGGUCUAGA 3'); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' UCUGUCUGAUCCAUCUAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UGCUAGAUGGAUCAGACAGA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 116 (5' UCAAAGCAUUGAUGUUCACUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' AGUGAACAUCAAUGCUUUGA 3'); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UGAGAGUGUAACCGUCAUAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' CUAUGACGGUUACACUCUCA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' UGUCGUACAUGAAGGAGUCUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' AGACUCCUUCAUGUACGACA 3'); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' UGAGUGUAACCGUCAUAGCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UGCUAUGACGGUUACACUCA 3'); xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3'); xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' UAUAACUUGCCACCUUCUCAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UGAGAAGGUGGCAAGUUAUA 3'); xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGAGCAUCUCUCUCACAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' CUGUGAGAGAGAUGCUCAAA 3'); xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' UCUCACAUUGUAGUAGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' CUCCCUACUACAAUGUGAGA 3'); xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' UGACUUCAACUUGUGGUCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 215 (5' AAGACCACAAGUUGAAGUCA 3'); xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UCAGGUUUUCCAUAUCCUUGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' CAAGGAUAUGGAAAACCUGA 3'); xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UAACUAUCAAGGGGCCGCCAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 276 (5'

UGGCGGCCCCUUGAUAGUUA 3'); xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCACAGAGACUCAGAGACUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' CAGUCUCUGAGUCUCUGUGA 3'); xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGAACACAUGUUGCUCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' GAGCAACAUGUGUUCAAAGA 3'); xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' UAUCAAUGACAGUAAUUGGGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' CCCAAUUACUGUCAUUGAUA 3'); L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' UCUUUUUGGCUCCUGUGAAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 203 (5' CUUCACAGGAGCCAAAAAGA 3'); or Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' UAACUCCAGACCUAGACCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' CAGGUCUAGGUCUGGAGUUA 3').

[0161] ***At least 50% knockdown of CFB at 0.1 nM***

[0162] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

[0163] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such

that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3'); xi) an antisense strand of

nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3'); xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UUUUGAACACAUGUUGCUCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UGAGCAACAUGUGUUCAAAA 3'); xxii) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 162 (5' UGAGAUGUCCUUGACUUUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' ACAAAGUCAAGGACAUCUCA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3'); xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAGACACAAACAGAGCUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 261 (5' AAAGCUCUGUUUGUGUCUGA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 143 (5' UAUUCUUGAGCUUGAUCAGGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' CCUGAUCAAGCUCAAGAAUA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAAAGUACUCAGACACCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UGUGGUGUCUGAGUACUUUA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3'); xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UGUUUUUGCAGACAUCCACUAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 283 (5' AGUGGAUGUCUGCAAAAACA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAGCAUCUCUCUCACAGCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 266 (5' AGCUGUGAGAGAGAUGCUCA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 141 (5' UCUUGAUCAGGGCAACGUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UGACGUUGCCCUGAUCAAGA

3’); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5’ UCUUGAUUGAGUGUUCCUUGUC 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5’ CAAGGAACACUCAAUCAAGA 3’); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5’ UGACUUCUCUUGUGAACUAUCA 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5’ AUAGUUCACAAGAGAAGUCA 3’); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5’ UAAUCCUCAUCUUGGAGUUUCU 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5’ AAACUCCAAGAUGAGGAUUA 3’); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5’ UAUAGACAUCCAGAUAAUCCUC 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5’ GGAUUAUCUGGAUGUCUAUA 3’); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5’ UCAUAGUCAUAAAAUUCAGGAA 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 249 (5’ CCUGAAUUUUAUGACUAUGA 3’); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5’ UCAUGUUGCUCAUUGUCUUUCU 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5’ AAAGACAAUGAGCAACAUGA 3’); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5’ UGAGACAAAUGGGCCUGAUAGU 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 255 (5’ UAUCAGGCCCAUUUGUCUCA 3’); xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5’ UCUCAUCAAUGACAGUAAUUGG 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5’ AAUUACUGUCAUUGAUGAGA 3’); xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5’ UGUCUUUCUUGGAAGCCAAAGC 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5’ UUUGGCUUCCAAGAAAGACA 3’); xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5’ UGAUCUGCAGGUACGUGUCUGC 3’), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5’ AGACACGUACCUGCAGAUCA 3’); xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5’ UCAUCAAUGACAGUAAUUGGGU 3’), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3'); xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3'); xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UGACUUUGAACACAUGUUGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 238 (5' GCAACAUGUGUUCAAAGUCA 3'); xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 161 (5' UCUUGACUUUGUCAUAGCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' AGGCUAUGACAAAGUCAAGA 3'); xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUCACAGAUCGCUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' AGACAGCGAUCUGUGACAAA 3'); xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UGAAUUCCUGCUUCUUUUUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' AAAAAAGAAGCAGGAAUUCA 3'); xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' UGAAAGAGAUCUCAUCACUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' GAGUGAUGAGAUCUCUUUCA 3'); L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3'); Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' UGUUGACUAGACACUUUUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' CAAAAAGUGUCUAGUCAACA 3'); Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 146 (5' UAAGUGGUAGUUGGAGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' CUUCCUCCAACUACCACUUA 3'); Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' UAUCACUCACAUUGUAGUAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 188 (5' CUACUACAAUGUGAGUGAUA 3'); Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' UUUCACACCAUAACUUGCCACC 3'), and a sense strand of nucleic acid sequence according

to SEQ ID NO: 213 (5' UGGCAAGUUAUGGUGUGAAA 3'); Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3'); Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3'); Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' UCAUGAAGGAGUCUUGGCAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' CUGCCAAGACUCCUUCAUGA 3'); Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3'); or Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3').

[0164] ***20-50% knockdown of CFB at 0.02 nM***

[0165] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

[0166] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such

that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM, wherein the double stranded region comprises: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3'); ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3'); iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3'); iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3'); v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3'); vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3'); vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3'); viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3'); ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3'); x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3'); xi) an antisense strand of nucleic acid sequence

according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3'); xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3'); xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3'); xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3'); xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3'); xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3'); xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3'); xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3'); xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3'); xxii) an antisense

strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3'); xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UCUUGAUUGAGUGUUCCUUGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' CAAGGAACACUCAAUCAAGA 3'); xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UAAUCCUCAUCUUGGAGUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5' AAACUCCAAGAUGAGGAUUA 3'); xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5' UAUAGACAUCCAGAUAAUCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' GGAUUAUCUGGAUGUCUAUA 3'); xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCAUGUUGCUCAUUGUCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' AAAGACAAUGAGCAACAUGA 3'); xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UCUCAUCAAUGACAGUAAUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' AAUUACUGUCAUUGAUGAGA 3'); xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGUCUUUCUUGGAAGCCAAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5' UUUGGCUUCCAAGAAAGACA 3'); xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UGAUCUGCAGGUACGUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' AGACACGUACCUGCAGAUCA 3'); xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCAUCAAUGACAGUAAUUGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3'); xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3'); xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3'); xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3'); xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3'); xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3'); xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3'); xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3'); xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3'); or xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3').

[0167] ***At least 50% knockdown of CFB at 0.02 nM***

[0168] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the

isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

[0169] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 5 to 38; b) 340 to 606; c) 776 to 828; d) 939 to 1227; e) 1305 to 1606; f) 1667 to 1746; g) 1815 to 2313; and h) 2378 to 2417, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM, wherein the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3').

[0170] ***In vivo Reduction of CFB expression***

[0171] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 995 to 1018; c) 1034 to 1054; d) 1384 to 1404; e) 1431 to 1500; f) 1606 to 1686; g) 1822 to 1849; h) 1860 to 1881; i) 2190 to 2210; j) 2239 to 2262; k) 2287 to 2307; l) 2382 to 2402; m) 2395 to 2415; and n) 2448 to 2468, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of CFB mRNA by at least 25% at a dose of 1mg/kg.

[0172] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 995 to 1018; c) 1034 to 1054; d) 1384 to 1404; e) 1431 to 1500; f) 1606 to 1686; g) 1822 to 1849; h) 1860 to 1881; i) 2190 to 2210; j) 2239 to 2262; k) 2287 to 2307; l) 2382 to 2402; m) 2395 to 2415; and n) 2448 to 2468, from the 5' end of a CFB mRNA sequence

according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 25% at a dose of 1 mg/kg, wherein the double stranded region comprises: i) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3'); ii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); iii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3'); iv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); v) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' ACUGCUAUGACGGUUACACA 3'); vi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3'); vii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3'); viii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3'); ix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3'); x) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA

3'); xi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3'); xii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); xiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3'); xiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3'); xv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3'); xvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3'); xvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); xviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); xix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3'); xx) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3'); xxi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence

according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); xxii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3'); xxiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3'); xxiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3'); xxv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3'); xxvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3'); xxvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3'); xxviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or xxix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

[0173] In some embodiments of the isolated oligonucleotide comprising a sense strand and an antisense strand, the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from: a) 493 to 534; b) 995 to 1018; c) 1034 to 1054; d) 1384 to 1404; e) 1431 to 1500; f) 1606 to 1686; g) 1822 to 1849; h) 1860 to 1881; i) 2190 to 2210; j) 2239 to 2262; k) 2287 to 2307; l) 2382 to 2402; m) 2395 to 2415; and n) 2448 to 2468, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense

strand such that the sense strand and the antisense strand together form a double stranded region, and the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 25% at a dose of 1 mg/kg, wherein the double stranded region comprises: i) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3'); ii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); iii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3'); iv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); v) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' ACUGCUAUGACGGUUACACA 3'); vi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3'); vii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3'); viii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3'); ix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3'); x) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3'); xi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU

3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); xii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3'); xiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3'); xiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3'); xv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); xvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); xvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3'); xviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3'); xix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3'); xx) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3'); xxi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3'); xxii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 171 (5'

UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3'); xxiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3'); xxiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or xxv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

[0174] In some embodiments, the isolated oligonucleotides of the present disclosure can comprise a linker, sometimes referred to as a loop. siRNAs comprising a linker or loop are sometimes referred to as short hairpin RNAs (shRNAs). In some embodiments, both the sense and the antisense regions of the siRNA are encoded by one single-stranded RNA. In these embodiments, and the antisense region and the sense region hybridize to form a duplex region. The sense and antisense regions are joined by a linker sequence, forming a "hairpin" or "stem-loop" structure. The siRNA can have complementary sense and antisense regions at opposing ends of a single stranded molecule, so that the molecule can form a duplex region with the complementary sequence portions, and the strands are linked at one end of the duplex region by a linker. The linker can be either a nucleotide or non-nucleotide linker or a combination thereof. The linker can interact with the first, and optionally, second strands through covalent bonds or non-covalent interactions.

[0175] Any suitable nucleotide linker sequence is envisaged as within the scope of the disclosure. An siRNA of this disclosure may include a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the nucleic acid to the antisense region of the nucleic acid. A nucleotide linker can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 nucleotides in length.

[0176] Examples of a non-nucleotide linker include an abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric agents, for example polyethylene glycols such as those having from 2 to 100 ethylene glycol units. Some

examples are described in Seela et al., Nucleic Acids Research, 1987, Vol. 15, pp. 3113-3129; Cload et al., J. Am. Chem. Soc, 1991, Vol. 113, pp. 6324-6326; Jaeschke et al., Tetrahedron Lett., 1993, Vol. 34, pp. 301; Arnold et al., WO 1989/002439; Usman et al., WO 1995/006731; Dudycz et al., WO 1995/011910, and Ferentz et al., J. Am. Chem. Soc, 1991, Vol. 113, pp. 4000-4002.

[0177] Examples of nucleotide linker sequences include, but are not limited to, AUG, CCC, UUCG, CCACC, AAGCAA, CCACACC and UUCAAGAGA.

[0178] In some embodiments, the isolated oligonucleotide of the present disclosure is an siRNA that can be a dsRNA of a length suitable as a Dicer substrate, which can be processed to produce a RISC active siRNA molecule. See, e.g., Rossi et al., US2005/0244858.

[0179] A Dicer substrate double stranded RNA (dsRNA) can be of a length sufficient that it is processed by Dicer to produce an active siRNA, and may further include one or more of the following properties: (i) the Dicer substrate dsRNA can be asymmetric, for example, having a 3' overhang on the antisense strand, (ii) the Dicer substrate dsRNA can have a modified 3' end on the sense strand to direct orientation of Dicer binding and processing of the dsRNA to an active siRNA, for example the incorporation of one or more DNA nucleotides, and (iii) the first and second strands of the Dicer substrate ds RNA can from 19-30 bp in length.

[0180] In some embodiments, the isolated oligonucleotide of the present disclosure comprises at least one modified nucleotide. In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise one or more modified nucleotide(s). In some embodiments, only the sense strand comprises one or more modified nucleotide(s). In some embodiments, only the antisense strand comprises one or more modified nucleotide(s). In some embodiments, both the sense strand and antisense strand comprise one or more modified nucleotide(s). In some embodiments, the isolated oligonucleotide is partially chemically modified. In some embodiments, the isolated oligonucleotide is fully chemically modified.

[0181] In some embodiments, the isolated oligonucleotide comprises at least two modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least three modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least four modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least five modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least six modified

nucleotides. In some embodiments, the isolated oligonucleotide comprises at least seven modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least eight modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least nine modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least ten modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least eleven modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least twelve modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least thirteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least fourteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least fifteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least sixteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least seventeen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least eighteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least nineteen modified nucleotides. In some embodiments, the isolated oligonucleotide comprises at least twenty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises more than twenty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between thirty and forty modified nucleotides. In some embodiments, the isolated oligonucleotide comprises between forty and fifty modified nucleotides.

[0182] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven modified

nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eleven modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fourteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen modified nucleotides. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty modified nucleotides.

[0183] In some embodiments, wherein the isolated oligonucleotide comprises more than one modified nucleotide, at least a first nucleotide comprises a first modification and at least a second nucleotide comprises a second modification. In some embodiments, the first modification and second modification are different. In some embodiments, the at least first nucleotide and the at least second nucleotide are located on different strands of the isolated oligonucleotide. In some embodiments, the at least first nucleotide and the at least second nucleotide are located on the same strand of the isolated oligonucleotide.

[0184] In some embodiments of the isolated oligonucleotide, wherein the isolated oligonucleotide comprises more than one modified nucleotide, at least a first modified nucleotide

comprises a first modification, and at least a second modified nucleotide comprises a second modification, and at least a third nucleotide comprises a third modification. In some embodiments, the isolated oligonucleotide comprises a first, a second, a third and a fourth modifications. In some embodiments, the isolated oligonucleotide comprises more than four modifications. In some embodiments, all modifications are on the sense strand. In some embodiments, all modifications are on the antisense strand. Any combination of locations of the modifications between the sense strand and antisense strand is envisaged within the isolated oligonucleotides of the present disclosure.

[0185] In some embodiments, the modified nucleotides are consecutively located on the sense strand or the antisense strand or both. In some embodiments, some but not all of the modified nucleotides are consecutively located on the sense strand or the antisense strand or both. In some embodiments, the modified nucleotides on the sense strand or the antisense strand or both are not consecutively located.

[0186] Envisaged within the present disclosure is an isolated oligonucleotide, wherein any nucleotide on the sense strand or antisense strand can be modified. In some embodiments, any nucleotide on the antisense strand can be modified. In some embodiments, any nucleotide on the antisense strand can be modified.

[0187] In some embodiments, the isolated oligonucleotide of the present disclosure comprises at least one modified nucleotide(s). In some embodiments, the one or more modified nucleotide(s) increases the stability or potency or both of the isolated oligonucleotide. In some embodiments, the one or more modified nucleotide(s) increases the stability of the RNA duplex, and siRNA.

[0188] Modifications that increase RNA stability include, but are not limited to, locked nucleic acids. As used herein, the term "locked nucleic acid" or "LNA" includes, but is not limited to, a modified RNA nucleotide in which the ribose moiety comprises a methylene bridge connecting the 2' oxygen and the 4' carbon. This methylene bridge locks the ribose in the 3'-endo confirmation, also known as the north confirmation, that is found in A-form RNA duplexes. The term inaccessible RNA can be used interchangeably with LNA. LNAs having a 2′-4′ cyclic linkage, as described in the International Patent Application WO 99/14226, WO 00/56746, WO 00/56748, and WO 00/66604, the contents of which are incorporated herein by reference.

[0189] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise at least one nucleotide having a modified phosphate backbone. In some embodiments, the sense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, the antisense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, wherein the isolated oligonucleotide of the present disclosure comprises a modified phosphate backbone, the modified phosphate backbone comprises a modified phosphodiester bond. In some embodiments, the modified phosphodiester bond is modified by replacing one or more oxygen atoms with a moiety, wherein the moiety is bonded to the phosphorus atom in the phosphodiester bond with a carbon, nitrogen, or sulfur atom in the moiety, or by forming a 2'-5' linkage. In some embodiments, the modified phosphodiester bond comprises phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate diester, mesyl phosphoramidate, or phosphonoacetate.

[0190] In some embodiments, the isolated oligonucleotide of the present disclosure comprises one or more non-natural base-containing nucleotide, a locked nucleotide, or an abasic nucleotide. In some embodiments, the one or more modified nucleotide comprises a phosphorothioate derivative or an acridinine substituted nucleotide. In some embodiments, the isolated oligonucleotides of the present disclosure comprise a phosphate mimic at the 5'-terminus of antisense strand, including but not limited to vinylphosphonate or other phosphate analogues. In some embodiments, the 5'-phosphate mimic is ethylphosphonate, vinylphosphonate or an analog thereof.

[0191] In some embodiments, the modified nucleotide comprises 5-fluorouracil , 5-bromouracil , 5-chlorouracil , 5-iodouracil , hypoxanthine , xanthine , 4-acetylcytosine , 5-(carboxyhydroxylmethyl) uracil , 5-carboxymethylaminomethyl-2-thiouridine , 5-carboxymethylaminomet-hyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methyl-aminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N -isopenten-yladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil , 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic

acid (v), 5-methyl-2-thiouracil , 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, or 2, 6-diaminopurine.

[0192] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise a terminal or internal nucleotide linked to one or more targeting ligands. In some embodiments, the terminal or internal nucleotide is linked to the one or more targeting ligands directly. In some embodiments, the terminal or internal nucleotide is linked to the one or more targeting ligands indirectly by a linker. In some embodiments, the one or more targeting ligands linked directly or indirectly to the terminal or internal nucleotide can further comprise a PK modulator. In some embodiments, the PK modulator is a competitive modulator, a positive allosteric modulator, a negative allosteric modulator or a neutral allosteric modulator. In some embodiments, the targeting ligand is selected from one or more of a carbohydrate, a peptide, a lipid, an antibody or a fragment thereof, an aptamer, an albumin, a fibrinogen, and a folate.

[0193] Modification of the Nucleotides

[0194] Provided herein is an isolated oligonucleotide, comprising: (a) a sense strand comprising X1 nucleotides, wherein at least one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, and X1 is an integer selected from 13-36, wherein the first modification and the second modification are different; and (b) an antisense strand comprising X2 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, and X2 is an integer selected from 18-31, wherein the third modification and the fourth modification are different.

[0195] In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure, is 18-21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 20-23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure, is 20 or 21 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22 or 23. In some embodiments, the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure equals the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure plus 2. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 21 and

the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 23. In some embodiments, the X1 nucleotides of the sense strand of the isolated oligonucleotide of the present disclosure is 20 and the X2 nucleotides of the antisense strand of the isolated oligonucleotide of the present disclosure is 22.

[0196] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide comprises: (a) a sense strand comprising 20 nucleotides, wherein at least one nucleotide is modified with a first modification, each of the remaining nucleotides is independently modified with a second modification, wherein the first modification and the second modification are the same or different; and (b) an antisense strand comprising 22 nucleotides, wherein at least one nucleotide is modified with a third modification, each of the remaining nucleotides is independently modified with a fourth modification, wherein the third modification and the fourth modification are the same or different.

[0197] In some embodiments, the first modification is modification of the sugar moiety of the at least one nucleotide at the 2'-position selected from 2'-F modification, 2'-CN modification, 2'-N3 modification, 2'-deoxy modification, and an equivalent thereof, and a combination thereof. In some embodiments, the first modification is 2'-F modification, 2'-CN modification, 2'-N3 modification, or 2'-deoxy modification, or a stereoisomer thereof. In some embodiments, the first modification is 2'-F modification, 2'-CN modification, or 2'-N3 modification, or a stereoisomer thereof. In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof.

[0198] In some embodiments, the second modification is modification of the sugar moiety of one or more of the remaining nucleotides at the 2'-position selected from 2'-C1-C6 alkyl, 2'-OR modification wherein R is C1-C6 alkyl optionally substituted with C1-C6 alkoxy, acetamide, phenyl, or heteroaryl comprising a 5- or 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, 2'-amino, and morpholino replacement, and an equivalent thereof, and a combination thereof. In some embodiments, the second modification is 2'-OR modification, or morpholino replacement, or a combination thereof. In some embodiments, the second modification is 2'-OR modification. In some embodiments, the second modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the second modification is 2'-O-methyl modification. In some embodiments, the second modification is morpholino replacement.

[0199] In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof, and the second modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the first modification is 2'-F modification or a stereoisomer thereof, and the second modification is 2'-O-methyl modification.

[0200] In some embodiments, the third modification is modification of the sugar moiety of the at least one nucleotide at the 2'-position selected from 2'-F modification, 2'-CN modification, 2'-N3 modification, 2'-deoxy modification, and an equivalent thereof, and a combination thereof. In some embodiments, the third modification is 2'-F modification, 2'-CN modification, 2'-N3 modification, or 2'-deoxy modification, or a stereoisomer thereof. In some embodiments, the third modification is 2'-F modification, 2'-CN modification, or 2'-N_3 modification, or a stereoisomer thereof. In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof.

[0201] In some embodiments, the fourth modification is modification of the sugar moiety of one or more of the remaining nucleotides at the 2'-position selected from 2'-C_1-C_6 alkyl, 2'-OR modification wherein R is C_1-C_6 alkyl optionally substituted with C_1-C_6 alkoxy, acetamide, phenyl, or heteroaryl comprising a 5- or 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, 2'-amino, and morpholino replacement, and an equivalent thereof, and a combination thereof. In some embodiments, the fourth modification is 2'-OR modification, or morpholino replacement, or a combination thereof. In some embodiments, the fourth modification is 2'-OR modification. In some embodiments, the fourth modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the fourth modification is 2'-O-methyl modification. In some embodiments, the fourth modification is morpholino replacement.

[0202] In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof, and the fourth modification is 2'-O-methyl modification or 2'-methoxyethoxy modification. In some embodiments, the third modification is 2'-F modification or a stereoisomer thereof, and the fourth modification is 2'-O-methyl modification.

[0203] Sense strand

[0204] In some embodiments of the isolated oligonucleotide of the present disclosure comprising a sense and an antisense strand, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three nucleotides are modified with the first modification. In some

embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least two of the at least three nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least three nucleotides modified with the first modification are consecutively located.

[0205] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, in the sense strand at least four nucleotides are modified with the first modification. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least four nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least four of the at least four nucleotides modified with the first modification are consecutively located.

[0206] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, in the sense strand at least five nucleotides are modified with the first modification. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least three of the at least five nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, at least four of the at least five nucleotides modified with the first modification are consecutively located.

[0207] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides modified with the first modification are located from position 10 to position 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0208] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, two of the at least three nucleotides modified with the first modification are located at positions selected from position 10, 11, 12, and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions selected from position 10, 11, 12, and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of

the present disclosure, one of the at least three nucleotides modified with the first modification is located at position 11 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0209] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions 11, 12 and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions 12, 13 and 14 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, three of the at least three nucleotides modified with the first modification are located at positions 10, 11 and 12 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0210] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 10 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 11 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 12 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of the at least four nucleotides modified with the first modification is located at position 14 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, one of

the at least four nucleotides modified with the first modification is located at position 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0211] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least four nucleotides modified with the first modification are located at positions 10, 11, 12 and 13 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0212] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least five nucleotides modified with the first modification are located at positions 10, 11, 12, 13 and 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0213] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises five nucleotides modified with the first modification, wherein the five nucleotides modified with the first modification are located at positions 10, 11, 12, 13 and 15 from the nucleotide complementary to the first nucleotide at the 5'-terminus of the antisense strand.

[0214] In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, not all of the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides modified with the first modification are consecutively located. In some embodiments, in the sense strand of the isolated oligonucleotide of the present disclosure, the at least three nucleotides, the at least four nucleotides, or the at least five nucleotides are modified with 2'-F modification.

[0215] In some embodiments, the sense strand of the isolated oligonucleotide of the present disclosure comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5' $(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3'.

[0216] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide,

F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3'.

[0217] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 37, 39, 49, 55, 56, 58 or 389.

[0218] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 58.

[0219] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 58, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 24.

[0220] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 56.

[0221] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 56, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 22.

[0222] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 37.

[0223] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 37, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3.

[0224] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 55.

[0225] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 55, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 21.

[0226] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 49.

[0227] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 49, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 15.

[0228] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 389.

[0229] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 389, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 6.

[0230] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', the sense strand comprises a nucleotide sequence according to SEQ ID NO: 39.

[0231] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 5' $(M)_g(F)_f(M)_e(F)_d(M)_c(F)_b(M)_a$ 3', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f and g is any one of 0-16, and wherein the sense strand is 5'$(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3', and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 49, the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 5.

[0232] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1829 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3').

[0233] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the

nucleotide positions 1825 to 1845, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3').

[0234] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 495 to 515, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3').

[0235] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1822 to 1842, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3').

[0236] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 1465 to 1485, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3').

[0237] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 514 to 534, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3').

[0238] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises a nucleotide sequence that is identical to a region between the nucleotide positions 503 to 523, from the 5' end of a CFB mRNA sequence according to SEQ ID

NO: 1, the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3').

[0239] Antisense strand

[0240] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most seven nucleotides are modified with the third modification.

[0241] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most four of the at most seven nucleotides modified with the third modification are located from position 2 to position 8 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at least one of the at most seven nucleotides are modified with the third modification is located at position 2 from the first nucleotide at the 5'-terminus of the antisense strand.

[0242] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at most two of the at most seven nucleotides modified with the third modification are consecutively located. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most two consecutively located of the at most seven nucleotides modified with the third modification are located at positions 2 and 3 from the first nucleotide at the 5'-terminus of the antisense strand.

[0243] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, at least one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two or three of the at most seven nucleotides modified with the third modification are located at positions selected from position 2, 3, 5, and 6 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, three of the at most seven nucleotides modified with the third modification are located at positions selected from position 2, 3, 5, and 6 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions

2 and 5 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions 2 and 3 from the first nucleotide at the 5'-terminus of the antisense strand.

[0244] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, three of the at most seven nucleotides modified with the third modification are located at positions 2, 3 and 5 from the first nucleotide at the 5'-terminus of the antisense strand.

[0245] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one or two of the at most seven nucleotides modified with the third modification are located at positions selected from position 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification are located at positions 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most seven nucleotides are modified with 2'-F modification. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, two of the at most seven nucleotides modified with the third modification is located at positions 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand.

[0246] In some embodiments of the isolated oligonucleotides of the present disclosure, wherein the antisense strand comprises at most seven nucleotides modified with the third modification, the at most seven nucleotides are modified with 2'-F modification. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 2 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 3 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the

isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 5 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 7 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 10 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 14 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, one of the at most seven nucleotides modified with the third modification is located at position 16 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the at most seven nucleotides modified with the third modification are located at positions 2, 3, 5, 7, 10, 14 and 16 from the first nucleotide at the 5'-terminus of the antisense strand.

[0247] In some embodiments, in the antisense strand of the isolated oligonucleotide of the present disclosure, the antisense strand comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5'.

[0248] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of:

3’$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5’, the antisense strand comprises a nucleotide sequence according to any one of SEQ ID NOs: 3, 5, 6, 15, 21, 22 or 24.

[0249] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2’-F modification (“F”), and nucleotides modified with 2’-O-methyl modification (“M”), according to the formula: 3’ $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5’, wherein M is 2’-O-methyl modified nucleotide, F is 2’-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3’$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5’, and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 24.

[0250] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2’-F modification (“F”), and nucleotides modified with 2’-O-methyl modification (“M”), according to the formula: 3’ $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5’, wherein M is 2’-O-methyl modified nucleotide, F is 2’-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3’$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5’, and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 24, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 58.

[0251] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2’-F modification (“F”), and nucleotides modified with 2’-O-methyl modification (“M”), according to the formula: 3’ $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5’, wherein M is 2’-O-methyl modified nucleotide, F is 2’-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3’$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5’, and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 22.

[0252] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2’-F modification (“F”), and nucleotides modified with 2’-O-methyl modification (“M”), according to the formula: 3’ $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5’, wherein M is

2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 22, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 56.

[0253] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3.

[0254] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 3, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 37.

[0255] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 21.

[0256] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 21, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 55.

[0257] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 15.

[0258] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 15, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 49.

[0259] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l,

m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 6.

[0260] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 6, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 389.

[0261] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 5.

[0262] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand of the isolated oligonucleotide comprises nucleotides modified with 2'-F modification ("F"), and nucleotides modified with 2'-O-methyl modification ("M"), according to the formula: 3' $(M)_a(F)_b(M)_c(F)_d(M)_e(F)_f(M)_g(F)_h(M)_i(F)_j(M)_k(F)_l(M)_m(F)_n(M)_o$ 5', wherein M is 2'-O-methyl modified nucleotide, F is 2'-F modified nucleotide, and a, b, c, d, e, f, g, h, i, j, k, l, m, n and o is any one of 0-16, wherein the antisense strand is any one of: 3'$(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5', and the antisense strand comprises a nucleotide sequence according to SEQ ID NO: 5, and the sense strand comprises a nucleotide sequence according to SEQ ID NO: 39.

[0263] Targeting Ligand

[0264] In some embodiments, in the sense strand or the antisense strand or both of the isolated oligonucleotide of the present disclosure, a terminal or internal nucleotide is linked to a targeting ligand. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 5' end of the sense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 3' end of the sense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 5' end of the antisense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides at the 3' end of the antisense strand of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand is attached to one or more nucleotides of the at least two single-stranded nucleotides at the 3'-terminus of the antisense strand of the isolated oligonucleotide of the present disclosure.

[0265] In some embodiments, the targeting ligand is selected from one or more of a carbohydrate, a peptide, a lipid, an antibody or a fragment thereof, an aptamer, an albumin, a fibrinogen, and a folate. In some embodiments, the targeting ligand binds to a surface protein on a cell expressing a target mRNA of the isolated oligonucleotide of the present disclosure. In some embodiments, the targeting ligand mediates entry of the isolated oligonucleotide of the present disclosure, into a cell expressing a target mRNA of the isolated oligonucleotide of the present disclosure.

[0266] In some embodiments, the targeting ligand is a therapeutic ligand. In some embodiments, the targeting ligand is a therapeutic antibody.

[0267] In some embodiments, the targeting ligand is attached to the isolated oligonucleotide of the present disclosure by a linker. In some embodiments, the linker is any one or a protein, a DNA, an RNA or a chemical compound. In some embodiments, the isolated oligonucleotide, the linker and the targeting ligand, of the present disclosure form a scaffold. As used herein, the term "scaffold" refers to a compound or complex that comprises a linker of the present disclosure, wherein the linker is covalently attached to either a ligand or an isolated oligonucleotide or both.

[0268] In some embodiments, the isolated oligonucleotide, the linker and the targeting ligand, of the present disclosure form a conjugate. As used herein, the term "conjugate" refers to a compound or complex that comprises an isolated oligonucleotide being covalently attached to a ligand via a linker of the present disclosure.

[0269] As used herein, the term "targeting ligand" or "ligand" refers to a moiety that, when being covalently attached to GalNAc an oligonucleotide), is capable of mediating its entry into, or facilitating or allowing its delivery to, a target site (e.g., a target cell or tissue). In some embodiments, the targeting ligand comprises a sugar ligand moiety (e.g., N-acetylgalactosamine (GalNAc)) which may direct uptake of an oligonucleotide into the liver.

[0270] In some embodiments, the targeting ligand binds to the asialoglycoprotein receptor (ASGPR). In some embodiments, the targeting ligand binds to (e.g., through ASGPR) the liver, such as the parenchymal cells of the liver.

[0271] Suitable targeting ligands include, but are not limited to, the ligands disclosed in Winkler (Ther. Deliv., 2013, 4(7): 791-809), PCT Patent Appl'n Pub. Nos. WO/2016/100401, WO/2012/089352, and WO/2009/082607, and U.S. Patent Appl'n Pub. Nos. 2009/0239814, 2012/0136042, 2013/0158824, and 2009/0247608, each of which is incorporated by reference.

[0272] In some embodiments, the targeting ligand comprises a carbohydrate moiety.

[0273] As used herein, "carbohydrate moiety" refers to a moiety which comprises one or more monosaccharide units each having at least six carbon atoms (which may be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. In some embodiments, the carbohydrate moiety comprises a monosaccharide, a disaccharide, a trisaccharide, or a tetrasaccharide. In some embodiments, the carbohydrate moiety comprises an oligosaccharide containing from about 4-9 monosaccharide units. In some embodiments, the carbohydrate moiety comprises a polysaccharide (e.g., a starch, a glycogen, a cellulose, or a polysaccharide gum).

[0274] In some embodiments, the carbohydrate moiety comprises a monosaccharide, a disaccharide, a trisaccharide, or a tetrasaccharide. In some embodiments, the carbohydrate moiety comprises an oligosaccharide (e.g., containing from about four to about nine monosaccharide units). In some embodiments, the carbohydrate moiety comprises a polysaccharide (e.g., a starch, a glycogen, a cellulose, or a polysaccharide gum).

[0275] In some embodiments, the ligand is capable of binding to a human asialoglycoprotein receptor (ASGPR), e.g., human asialoglycoprotein receptor 2 (ASGPR2).

[0276] In some embodiments, the carbohydrate moiety comprises a sugar (e.g., one, two, or three sugar). In some embodiments, the carbohydrate moiety comprises galactose or a derivative thereof (e.g., one, two, or three galactose or the derivative thereof). In some embodiments, the

carbohydrate moiety comprises N-acetylgalactosamine or a derivative thereof (e.g., one, two, or three N-acetylgalactosamine or the derivative thereof). In some embodiments, the carbohydrate moiety comprises N-acetyl-D-galactosylamine or a derivative thereof (e.g., one, two, or three N-acetyl-D-galactosylamine or the derivative thereof).

[0277] In some embodiments, the carbohydrate moiety comprises N-acetylgalactosamine (e.g., one, two, or three N-acetylgalactosamine). In some embodiments, the carbohydrate moiety comprises N-acetyl-D-galactosylamine (e.g., one, two, or three N-acetyl-D-galactosylamine).

[0278] In some embodiments, the carbohydrate moiety comprises mannose or a derivative thereof (e.g., mannose-6-phosphate). In some embodiments, the carbohydrate moiety further comprises a linking moiety that connects the one or more sugar (e.g., N-acetyl-D-galactosylamine) with a linker.

[0279] In some embodiments the linker comprises thioether (e.g., thiosuccinimide, or the hydrolysis analogue thereof), disulfide, triazole, phosphorothioate, phosphodiester, ester, amide, or any combination thereof. In some embodiments, the linker is a triantennary linking moiety. Suitable targeting ligands include, but are not limited to, the ligands disclosed in PCT Appl'n Pub. Nos. WO/2015/006740, WO/2016/100401, WO/2017/214112, WO/2018/039364, and WO/2018/045317, each of which is incorporated herein by reference.

[0280] In some embodiments, the targeting ligand comprises a lipid or a lipid moiety (e.g., one, two, or three lipid moiety). In some embodiments the lipid moiety comprises (e.g., one, two, of three of) C8-C24 fatty acid, cholesterol, vitamin, sterol, phospholipid, or any combination thereof.

[0281] In some embodiments, the targeting ligand comprises a peptide or a peptide moiety (e.g., one, two, or three peptide moiety). In some embodiments, the peptide moiety comprises (e.g., one, two, or three of) integrin, insulin, glucagon-like peptide, or any combination thereof. In some embodiments, the targeting ligand comprises an antibody or an antibody moiety (e.g., transferrin). In some embodiments, the targeting ligand comprises one, two, or three antibody moieties (e.g., transferrin).

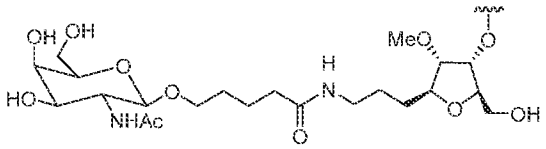
[0282] In some embodiments, the targeting ligand comprises an oligonucleotide (e.g., aptamer or CpG). In some embodiments, the targeting ligand comprises one, two, or three oligonucleotides (e.g., aptamer or CpG).

[0283] In some embodiments, the ligand comprises: one, two, or three sugar (e.g., N-acetyl-D-galactosylamine); one, two, or three lipid moieties; one, two, or three peptide moieties; one, two, or three antibody moieties; one, two, or three oligonucleotides; or any combination thereof.

[0284] In some embodiments, the linker is attached to the isolated oligonucleotide of the present disclosure, via a phosphate group, or an analog of a phosphate group, in the isolated oligonucleotide.

[0285] In some embodiments, the ligand comprises a sugar ligand moiety (e.g., N-acetylgalactosamine (GalNAc)) which may direct uptake of an oligonucleotide into the liver

[0286] In some embodiments, the ligand comprises GalNAc, or a derivative thereof. In some embodiments, the ligand comprises a GalNAc G1b structure shown below.



GalNAc G1b

[0287] In some embodiments, the ligand comprises three GalNAc moieties, or three derivatives thereof. In some embodiments, the ligand comprises three GalNAc G1b moieties. In some embodiments, wherein the ligand comprises three GalNAc G1b moieties, the GalNAc G1b moieties are consecutively located. In some embodiments, the consecutively located GalNAc G1b moieties are located on the 3' end of the sense strand. In some embodiments, wherein the ligand comprises three GalNAc G1b ("G1b") moieties that are consecutively located, the first G1b moiety is linked to the second G1b moiety and the second G1b is linked to the third G1b moiety. In some embodiments, the first GalNAc G1b moiety is linked to the sense strand of the isolated oligonucleotide of the present disclosure.

[0288] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the ligand comprises three GalNAc G1b ("G1b") moieties, wherein the first GalNAc G1b moiety is linked to the sense strand of the isolated oligonucleotide, the first GalNAc G1b moiety is also linked to the second GalNAc G1b moiety, and the second G1b is linked to the third G1b moiety. In some embodiments, wherein the ligand comprises three GalNAc G1b moieties, the three GalNAc G1b moieties are consecutively located on the 3' end of the sense strand.

[0289] In some embodiments of the isolated oligonucleotide of the present disclosure, the isolated oligonucleotide is linked to the ligand (e.g., GalNAc G1b, or three GalNAc G1b moieties). In some embodiments, the isolated oligonucleotide is linked to the ligand via an internal or terminal nucleotide of the isolated oligonucleotide. In some embodiments, the isolated oligonucleotide is linked to the ligand via a ligand linker. In some embodiments, the

[0290] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the isolated oligonucleotide comprises a sense and an antisense strand, and wherein the ligand comprises three GalNAc G1b moieties, and the three GalNAc G1b moieties are consecutively located on the 3' end of the sense strand, the ligand is linked to a terminal nucleotide on the sense strand of the isolated oligonucleotide. In some embodiments, the ligand is linked to a terminal nucleotide on the sense strand via a ligand linker. In some embodiments, the ligand linker is a monovalent linker. In some embodiments, the ligand linker is a bivalent linker. In some embodiments, the ligand linker is a trivalent linker.

[0291] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 495 to 534; b) 1465 to 1485; and c) 1822 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, a targeting ligand is attached to the 3' end of the sense strand. In some embodiments, the targeting ligand comprising three GalNAc G1b moieties.

[0292] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 495 to 534; b) 1465 to 1485; and c) 1822 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the targeting ligand comprises three GalNAc G1b moieties attached to the 3' end of the sense strand, the sense strand comprises a nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3'); SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3'); SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3'); SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3'); SEQ ID NO: 58 (5'

AAUUCCUGAAUUUUAUGACA 3'); or SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3').

[0293] The linkage at the 3' end of the isolated oligonucleotide of the present disclosure may be directly via 5', 3' or 2' hydroxyl groups, or indirectly, via a non-nucleotide linker or a nucleoside, utilizing either the 2' or 3' hydroxyl positions of the nucleoside. Linkages may also utilize a functionalized sugar or nucleobase of a 3' terminal nucleotide. In some embodiments, the ligand described herein can be attached to the isolated oligonucleotide of the present disclosure with various ligand linkers that can be cleavable or non-cleavable.

[0294] **Modification of the Phosphate Groups**

[0295] Modified Terminal Phosphate Groups

[0296] The present disclosure further provides oligonucleotides and conjugates containing modified phosphate groups (also referred to as phosphate mimics or phosphate derivatives) for nucleic acid delivery. The present disclosure also relates to uses of oligonucleotides and conjugates containing modified phosphate groups, e.g., in delivering nucleic acid and/or treating or preventing diseases.

[0297] In some embodiments, the present disclosure provides phosphate mimics of 5'-terminal nucleotides. Without wishing to be bound by theory, it is understood that, when being incorporated into oligonucleotides (e.g., at the 5'-terminus of the antisense strand), the phosphate mimics could improve the Ago2 binding/loading and enhance the metabolic stability of the oligonucleotides, thus enhancing the potency and duration of the isolated oligonucleotides (e.g., dsRNA or siRNA).

[0298] In some embodiments of the isolated oligonucleotides of the present disclosure, the oligonucleotides comprise 5'-terminal nucleotide modifications. In some embodiments, the 5'-terminal modifications provide the functional effect of a phosphate group, but are more stable in the environmental conditions that the oligonucleotide will be exposed to when administered to a subject. In some embodiments, the isolated oligonucleotide comprises phosphate mimics that are more resistant to phosphatases and other enzymes while minimizing negative impact on the oligonucleotide's function (e.g., minimizing any reduction in gene target knockdown when used as an RNAi inhibitor molecule).

[0299] In some embodiments, the 5'-terminal modification is a chemical modification. In some embodiments, the chemical modification enhances stability against nucleases or other enzymes that degrade or interfere with the structure or activity of the isolated oligonucleotide.

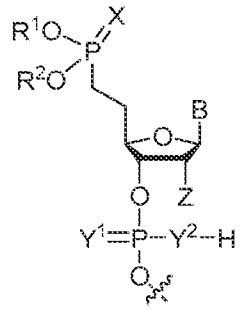
[0300] In some embodiments, the sense or antisense strand of the isolated oligonucleotides of the present disclosure comprise a 5'-terminal phosphate group. In some embodiments, the 5'-terminal phosphate group comprises an unmodified phosphate having the formula: -O-P(=O)(OH)OH. In some embodiments, the 5'-terminal phosphate group comprises a modified phosphate. In some embodiments, the 5'-terminal phosphate group comprises a modified phosphate having the formula $-CH_2-P(=X)(OR^1)OR^2$, wherein X is O or S, R^1 is H or C_1-C_6 alkyl, and R^2 is H or C_1-C_6 alkyl. In some embodiments, the modified phosphate is referred to as a "phosphate mimic".

[0301] The term, "halo" or "halogen", as used herein, refers to fluoro, chloro, bromo and iodo.

[0302] The term, "aryl", as used herein, includes groups with aromaticity, including "conjugated," or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[0303] The term, "alkyl" or "C_1-C_6 alkyl", as used herein, is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms. In some embodiments, the straight chain alkyl has one carbon atom. In some embodiments, the straight chain alkyl has two carbon atoms.

[0304] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



wherein:

B is H or a nucleobase moiety;

X is O or S;

R^1 is H or C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl;

Y^1 is O or S;

Y^2 is O or S;

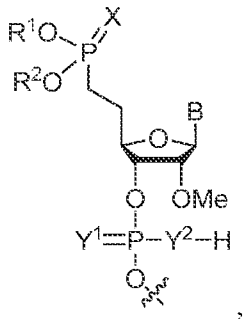
Z is H, halogen, or $-OR^Z$;

R^Z is H, C_1-C_6 alkyl, or -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), wherein the C_1-C_6 alkyl or -(C_1-C_6 alkyl)-(C_6-C_{10} aryl) is optionally substituted with one or more R^{Za};

each R^{Za} independently is halogen, C_1-C_6 alkyl, or -O-(C_1-C_6 alkyl), wherein the C_1-C_6 alkyl or -O-(C_1-C_6 alkyl) is optionally substituted with one or more halogen; and

indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[0305] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



wherein:

B is H or a nucleobase moiety;

X is O or S;

R^1 is H or C_1-C_6 alkyl;

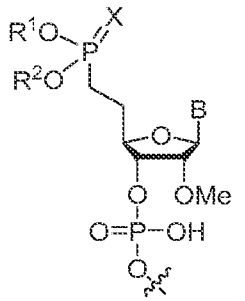
R^2 is H or C_1-C_6 alkyl;

Y^1 is O or S;

Y^2 is O or S; and

indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[0306] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides (e.g., siRNAs) as shown in the following formula:



,

wherein:

B is H or a nucleobase moiety;

X is O or S;

R^1 is H or C_1-C_6 alkyl;

R^2 is H or C_1-C_6 alkyl; and

 indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[0307] In some embodiments, X is O.

[0308] In some embodiments, X is S.

[0309] In some embodiments, R^1 is H.

[0310] In some embodiments, R^1 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0311] In some embodiments, R^1 is methyl.

[0312] In some embodiments, R^2 is H.

[0313] In some embodiments, R^2 is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0314] In some embodiments, R^2 is methyl.

[0315] In some embodiments, Y^1 is O.

[0316] In some embodiments, Y^1 is S.

[0317] In some embodiments, Y^2 is O.

[0318] In some embodiments, Y^2 is S.

[0319] In some embodiments, Z is H.

[0320] In some embodiments, Z is not H.

[0321] In some embodiments, Z is halogen (e.g., F, Cl, Br, or I).

[0322] In some embodiments, Z is F or Cl.

[0323] In some embodiments, Z is F

[0324] In some embodiments, Z is $-OR^Z$.

[0325] In some embodiments, Z is -OH.

[0326] In some embodiments, Z is not -OH.

[0327] In some embodiments, Z is -O-(C_1-C_6 alkyl) (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

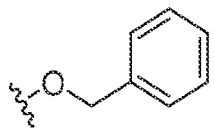
[0328] In some embodiments, Z is $-OCH_3$.

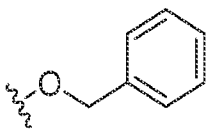
[0329] In some embodiments, Z is -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl) (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

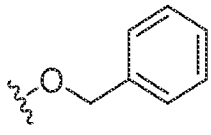
[0330] In some embodiments, Z is $-OCH_2CH_2OCH_3$.

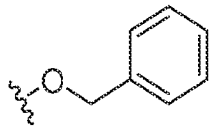
[0331] In some embodiments, Z is -O-(C_1-C_6 alkyl)-(C_6-C_{10} aryl) optionally substituted with one or more R^{Za}.

[0332] In some embodiments, Z is -O-(C_1-C_6 alkyl)-(C_6-C_{10} aryl).

[0333] In some embodiments, Z is  .

[0334] In some embodiments, Z is  optionally substituted with one or more R^{Za}.

[0335] In some embodiments, Z is  optionally substituted with one or more halogen.

[0336] In some embodiments, Z is  optionally substituted with one or more C_1-C_6 alkyl or -O-(C_1-C_6 alkyl), wherein the C_1-C_6 alkyl or -O-(C_1-C_6 alkyl) is optionally substituted with one or more halogen.

[0337] In some embodiments, R^Z is H.

[0338] In some embodiments, R^Z is not H.

[0339] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more R^{Za}.

[0340] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I) or -O-(C_1-C_6 alkyl) (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen.

[0341] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0342] In some embodiments, R^Z is methyl, ethyl, or propyl.

[0343] In some embodiments, R^Z is methyl.

[0344] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0345] In some embodiments, R^Z is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more -O-(C_1-C_6 alkyl) (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the -O-(C_1-C_6 alkyl) is optionally substituted with one or more halogen.

[0346] In some embodiments, R^Z is -(C_1-C_6 alkyl)-(C_6-C_{10} aryl) optionally substituted with one or more R^{Za}.

[0347] In some embodiments, R^Z is -(C_1-C_6 alkyl)-(C_6-C_{10} aryl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I), C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), or -O-(C_1-C_6 alkyl) (e.g., wherein the C_1-C_6 alkyl is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), wherein the C_1-C_6 alkyl or -O-(C_1-C_6 alkyl) is optionally substituted with one or more halogen.

[0348] In some embodiments, R^Z is -(C_1-C_6 alkyl)-(C_6-C_{10} aryl).

[0349] In some embodiments, at least one R^{Za} is halogen (e.g., F, Cl, Br, or I).

[0350] In some embodiments, at least one R^{Za} is F or Cl.

[0351] In some embodiments, at least one R^{Za} is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0352] In some embodiments, at least one R^{Za} is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

[0353] In some embodiments, at least one R^{Za} is C_1-C_6 alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0354] In some embodiments, at least one R^{Za} is -O-(C_1-C_6 alkyl) optionally substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0355] In some embodiments, at least one R^{Za} is -O-(C_1-C_6 alkyl).

[0356] In some embodiments, at least one R^{Za} is -O-(C_1-C_6 alkyl) substituted with one or more halogen (e.g., F, Cl, Br, or I).

[0357] In some embodiments, B is H.

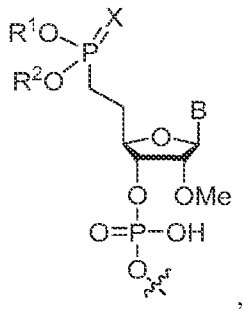
[0358] In some embodiments, B is a nucleobase moiety.

[0359] The term "nucleobase moiety", as used herein, refers to a nucleobase that is attached to the rest of the isolated oligonucleotides (e.g., dsRNA or siRNA) of the present disclosure, e.g., via an atom of the nucleobase or a functional group thereof.

[0360] In some embodiments, the nucleobase moiety is adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U).

[0361] In some embodiments, the nucleobase moiety is uracil (U).

[0362] In some embodiments, the phosphate mimic is linked to the 5'-terminus of the isolated oligonucleotides as shown in the following formula:



wherein:

B is a nucleobase moiety, wherein the nucleobase moiety is uracil (U), wherein the uracil is at position 1 from the 5'-terminus of the sense strand or at position 1 from the 5'-terminus of the antisense strand;

X is O;

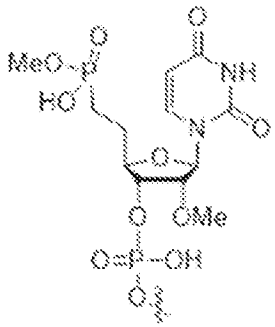
R^1 is C_1 alkyl;

R^2 is H; and

indicates an attachment to a nucleotide of the isolated oligonucleotide (e.g., siRNA).

[0363] In some embodiments of the isolated oligonucleotides of the present disclosure, the phosphate mimic is attached to the 5'-terminus of the antisense strand of the isolated oligonucleotide.

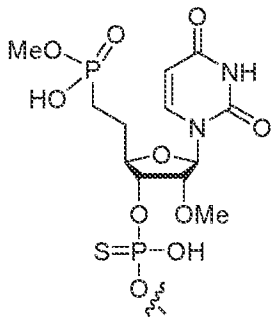
[0364] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-MeEPmU).



5'-MeEPmU,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide and "MeEP" is a mono methyl protected phosphate mimic.

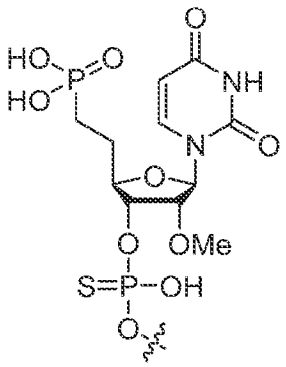
[0365] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-MeEPmUs).



5'-MeEPmUs,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide, "MeEP" is a mono methyl protected phosphate mimic, and "s" is a phosphorothioate internucleotide linkage.

[0366] In some embodiments, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand of the isolated oligonucleotide, having the following structure (5'-EPmUs).



5'-EPmUs,

wherein "mU" is a 2'-O-methyl modified uridine nucleotide, "EP" is a phosphate mimic, and "s" is a phosphorothioate internucleotide linkage.

[0367] The terms "5'-MeEP", "5' - MeEP", and "5' MeEP" are used interchangeably herein.

[0368] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 495 to 534; b) 1465 to 1485; and c) 1822 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, the antisense strand comprises a mono methyl protected phosphate mimic (MeEP). In some embodiments, the MeEP is linked to the 5' end of the antisense strand (5'-MeEP).

[0369] In some embodiments, wherein the MeEP is linked to the 5' end of the antisense strand, the phosphate mimic is attached to a 5'-terminal uridine of the antisense strand.

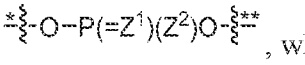
[0370] In some embodiments, the 5'-terminal uridine is a 2'-O-methyl modified nucleotide.

[0371] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 495 to 534; b) 1465 to 1485; and c) 1822 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the antisense strand comprises a 5'-MeEP linked to the 5' end of the antisense strand, the antisense strand comprises a nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'); SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'); SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'); SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'); SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'); SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'); or SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3').

[0372] In some embodiments of the isolated oligonucleotide of the present disclosure wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from: a) 495 to 534; b) 1465 to 1485; and c) 1822 to 1849, from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1, and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region, wherein the antisense strand comprises a 5'-MeEP linked to the 5' end of the antisense strand, the sense strand comprises a targeting ligand comprising three GalNAc G1b moieties attached to the 3' end of the sense strand.

[0373] Modified Backbone Phosphate/Phosphodiester Bond

[0374] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise at least one nucleotide having a modified phosphate backbone. In some embodiments, the sense strand of the isolated oligonucleotide comprises at least one nucleotide having a modified phosphate backbone. In some embodiments, the antisense strand of the isolated oligonucleotide comprises at least one nucleotide having a

modified phosphate backbone. In some embodiments, wherein the isolated oligonucleotide of the present disclosure comprises a modified phosphate backbone, the modified phosphate backbone comprises a modified phosphodiester bond. A phosphodiester bond comprises a linkage having the formula:  , wherein denotes attachment to a 3' carbon of a first nucleotide in the isolated oligonucleotide of the present disclosure, and denotes attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure. In some embodiments, the phosphodiester bond is unmodified, wherein Z^1 is O and Z^2 is OH or O^-. In some embodiments, the phosphodiester bond is modified, wherein Z^1 is O, S, NH, or N(C_1-C_6 alkyl) and Z^2 is OH, SH, NH_2, NH(C_1-C_6 alkyl), O^-, S^-, HN^-, or (C_1-C_6 alkyl)N^-, and wherein when Z^1 is O, Z^2 is not OH or O^-.

[0375] In some embodiments, Z_1 is O.

[0376] In some embodiments, Z_1 is S.

[0377] In some embodiments, Z_1 is NH.

[0378] In some embodiments, Z_1 is N(C_1-C_6 alkyl).

[0379] In some embodiments, Z_2 is OH.

[0380] In some embodiments, Z_2 is SH.

[0381] In some embodiments, Z_2 is NH_2.

[0382] In some embodiments, Z_2 is NH(C_1-C_6 alkyl).

[0383] In some embodiments, Z_2 is SH, NH_2, or NH(C_1-C_6 alkyl).

[0384] In some embodiments, Z_2 is O^-.

[0385] In some embodiments, Z_2 is S^-.

[0386] In some embodiments, Z_2 is HN^-.

[0387] In some embodiments, Z_2 is (C_1-C_6 alkyl)N^-.

[0388] In some embodiments, Z_2 is S^-, HN^-, or (C_1-C_6 alkyl)N^-.

[0389] In some embodiments, Z_1 is O and Z_2 is SH.

[0390] In some embodiments, Z_1 is O and Z_2 is NH_2.

[0391] In some embodiments, Z_1 is O and Z_2 is NH(C_1-C_6 alkyl).

[0392] In some embodiments, Z_1 is S and Z_2 is OH.

[0393] In some embodiments, Z_1 is S and Z_2 is SH.

[0394] In some embodiments, Z_1 is S and Z_2 is NH_2.

[0395] In some embodiments, Z_1 is S and Z_2 is $NH(C_1\text{-}C_6$ alkyl).

[0396] In some embodiments, Z_1 is NH and Z_2 is OH.

[0397] In some embodiments, Z_1 is NH and Z_2 is SH.

[0398] In some embodiments, Z_1 is NH and Z_2 is NH_2.

[0399] In some embodiments, Z_1 is NH and Z_2 is $NH(C_1\text{-}C_6$ alkyl).

[0400] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is OH.

[0401] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is SH.

[0402] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is NH_2.

[0403] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is $NH(C_1\text{-}C_6$ alkyl).

[0404] In some embodiments, Z_1 is O and Z_2 is S^-.

[0405] In some embodiments, Z_1 is O and Z_2 is HN^-.

[0406] In some embodiments, Z_1 is O and Z_2 is $(C_1\text{-}C_6$ alkyl)N^-.

[0407] In some embodiments, Z_1 is S and Z_2 is O^-.

[0408] In some embodiments, Z_1 is S and Z_2 is S^-.

[0409] In some embodiments, Z_1 is S and Z_2 is HN^-.

[0410] In some embodiments, Z_1 is S and Z_2 is $(C_1\text{-}C_6$ alkyl)N^-.

[0411] In some embodiments, Z_1 is NH and Z_2 is O^-.

[0412] In some embodiments, Z_1 is NH and Z_2 is S^-.

[0413] In some embodiments, Z_1 is NH and Z_2 is HN^-.

[0414] In some embodiments, Z_1 is NH and Z_2 is $(C_1\text{-}C_6$ alkyl)N^-.

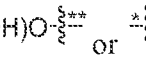
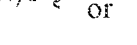
[0415] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is O^-.

[0416] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is S^-.

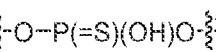
[0417] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is HN^-.

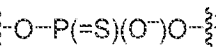
[0418] In some embodiments, Z_1 is $N(C_1\text{-}C_6$ alkyl) and Z_2 is $(C_1\text{-}C_6$ alkyl)N^-.

[0419] In some embodiments, the modified phosphodiester bond comprises a phosphorothioate internucleotide linkage.

[0420] In some embodiments, the modified phosphodiester bond comprises  or  , wherein denotes attachment to a 3' carbon of a first nucleotide in the isolated oligonucleotide of the present disclosure; and denotes

attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure.

[0421] In some embodiments, the modified phosphodiester bond comprises  , wherein denotes attachment to a 3' carbon of a first nucleotide in the isolated oligonucleotide of the present disclosure; and denotes attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure.

[0422] In some embodiments, the modified phosphodiester bond comprises  , wherein denotes attachment to a 3' carbon of a first nucleotide in the isolated oligonucleotide of the present disclosure; and denotes attachment to a 5' carbon of a second nucleotide in the isolated oligonucleotide of the present disclosure.

[0423] In some embodiments, the isolated oligonucleotide of the present disclosure comprises at least one modified phosphodiester bond(s). In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand or the antisense strand or both comprise one or more modified phosphodiester bonds. In some embodiments, only the sense strand comprises one or more modified phosphodiester bonds. In some embodiments, only the antisense strand comprises one or more modified phosphodiester bonds. In some embodiments, both the sense strand and antisense strand comprise one or more modified phosphodiester bonds.

[0424] In some embodiments, the isolated oligonucleotide comprises at least two modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least three modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least four modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least five modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least six modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least seven modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least eight modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least nine modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least ten modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least eleven modified phosphodiester bonds. In some embodiments, the isolated

oligonucleotide comprises at least twelve modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least thirteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least fourteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least fifteen modified phosphodiester bonds. some embodiments, the isolated oligonucleotide comprises at least sixteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least seventeen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least eighteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least nineteen modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises at least twenty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises more than twenty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between thirty and forty modified phosphodiester bonds. In some embodiments, the isolated oligonucleotide comprises between forty and fifty modified phosphodiester bonds.

[0425] In some embodiments, the isolated oligonucleotide comprises at least two phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least three phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least four phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least five phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least six phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least seven phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eight phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least nine phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least ten phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eleven phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least twelve phosphorothioate internucleotide linkages. In some embodiments, the isolated

oligonucleotide comprises at least thirteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least fourteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least fifteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least sixteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least seventeen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least eighteen phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises at least nineteen phosphorothioate internucleotide linkages. some embodiments, the isolated oligonucleotide comprises at least twenty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises more than twenty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between twenty and thirty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between thirty and forty phosphorothioate internucleotide linkages. In some embodiments, the isolated oligonucleotide comprises between forty and fifty phosphorothioate internucleotide linkages.

[0426] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one modified phosphodiester bond(s). In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine modified

phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eleven modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fourteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen modified phosphodiester bonds. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty modified phosphodiester bonds.

[0427] In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least one phosphorothioate internucleotide linkage(s). In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least two phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least three phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least four phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least five phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least six phosphorothioate internucleotide linkages. some

embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seven phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eight phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nine phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least ten phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eleven phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twelve phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least thirteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fourteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least fifteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least sixteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least seventeen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least eighteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least nineteen phosphorothioate internucleotide linkages. In some embodiments, the sense strand and/or the antisense strand of the isolated oligonucleotide each comprise at least twenty phosphorothioate internucleotide linkages.

[0428] In some embodiments, the modified phosphodiester bonds are consecutively located on the sense strand or the antisense strand or both. In some embodiments, some but not all of the modified phosphodiester bonds are consecutively located on the sense strand or the antisense strand or both. In some embodiments, the modified phosphodiester bonds on the sense strand or the antisense strand or both are not consecutively located.

[0429] Envisaged within the present disclosure is an isolated oligonucleotide, wherein any phosphodiester bond on the sense strand or antisense strand can be modified. In some embodiments, any phosphodiester bond on the antisense strand can be modified. In some embodiments, any phosphodiester bond on the antisense strand can be modified.

[0430] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds. In some embodiments, the between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises less than five modified phosphodiester bonds. In some embodiments, the antisense strand comprises one, two, three, or four modified phosphodiester bonds. In some embodiments, wherein the antisense strand comprises one, two, three, or four modified phosphodiester bonds, the one, two, three, or four modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the antisense strand comprises four modified phosphodiester bonds. In some embodiments, wherein the antisense strand comprises four modified phosphodiester bonds. the modified phosphodiester bonds comprise phosphorothioate.

[0431] In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 1 and position 2 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 2 and position 3 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 20 and position 21 from the first nucleotide at the 5'-terminus of the antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide bonds, the phosphorothioate internucleotide linkages connect the nucleotides at position 21 and position 22 from the first nucleotide at the 5'-terminus of the

antisense strand. In some embodiments, wherein the antisense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, wherein the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 and 2, position 2 and 3, position 20 and 21, and position 21 and 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[0432] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[0433] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand comprises at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[0434] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises four phosphorothioate internucleotide linkages. In some embodiments, wherein the antisense strand comprises four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand.

[0435] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds. In some embodiments, the between one and twenty, between one and fifteen, between one and ten, between one and five, or less than five modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the sense strand comprises less than five modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises less than five modified phosphodiester bonds, the sense strand comprises one, two, three, or four modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises one, two,

three, or four modified phosphodiester bonds, the one, two, three, or four modified phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, the sense strand comprises four modified phosphodiester bonds. In some embodiments, wherein the sense strand comprises four modified phosphodiester bonds, the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages.

[0436] In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, the phosphodiester bonds comprise phosphorothioate internucleotide linkages. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 1 and position 2 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 2 and position 3 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 18 and position 19 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages connect the nucleotides at position 19 and position 20 from the first nucleotide at the 5'-terminus of the sense strand. In some embodiments, wherein the sense strand comprises at least one, at least two, at least three, or at least four modified phosphodiester bonds, wherein the modified phosphodiester bonds comprise phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 and 2, position 2 and 3, position 18 and 19, and position 19 and 20 from the first nucleotide at the 5'-terminus of the sense strand.

[0437] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises at least one, at least two, at least three, or at least four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are

located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[0438] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises at least four phosphorothioate internucleotide linkages, the at least four phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[0439] In some embodiments of the isolated oligonucleotide of the present disclosure, the sense strand comprises four phosphorothioate internucleotide linkages. In some embodiments, wherein the sense strand comprises four phosphorothioate internucleotide linkages, the phosphorothioate internucleotide linkages are located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[0440] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the antisense strand and the sense strand comprise four phosphorothioate internucleotide linkages, the antisense strand comprises phosphorothioate internucleotide linkages located between nucleotides at position 1 to 3 and nucleotides at position 20 to 22 from the first nucleotide at the 5'-terminus of the antisense strand, and the sense strand comprises phosphorothioate internucleotide linkages located between nucleotides at position 1 to 3 and nucleotides at position 18 to 20 from the first nucleotide at the 5'-terminus of the sense strand.

[0441] In some embodiments of the isolated oligonucleotide of the present disclosure, the antisense strand comprises any one of: i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5' [MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' [MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' [MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' [mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'); or

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

[0442] In some embodiments of the isolated oligonucleotide of the present disclosure, wherein the sense strand comprises any one of:

i) a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3');

iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3');

iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3');

v) a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' [mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3');

vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' [mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3'); or

vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' [mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

[0443] In some embodiments of the isolated oligonucleotide of the present disclosure is selected from:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5' [MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' [MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' [MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' [mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' [mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' [mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' [mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3'); or

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3'), wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic, and "G1b" is a GalNAc G1b moiety.

[0444] *Nucleic Acids and Vectors*

[0445] The present disclosure also provides a vector encoding at least one isolated oligonucleotide disclosed herein. In some embodiments, the vector is any one of a plasmid, a cosmid or a viral vector. In some embodiments, the vector is an adenoviral vector. In some embodiments, the vector is a lentiviral vector. In some embodiments, the plasmid is an expression plasmid. In some embodiments, the vector encodes one isolated oligonucleotide disclosed herein. In some embodiments, the vector encodes more than one isolated oligonucleotide disclosed herein. In some embodiments, the vector encodes, two, three, four, or five isolated oligonucleotides disclosed herein. In some embodiments, the vector encodes more than five isolated oligonucleotides disclosed herein.

[0446] The disclosure provides nucleic acids comprising the sequences encoding the isolated oligonucleotides (e.g., dsRNAs or siRNAs) targeting CFB described herein.

[0447] In some embodiments, the nucleic acids are ribonucleic acids (RNAs). In some embodiments, the nucleic acids are deoxyribonucleic acids (DNAs). The DNAs may be a vector or a plasmid, e.g., an expression vector.

[0448] A "vector" is any nucleic acid molecule for the cloning of and/or transfer of a nucleic acid into a cell. A vector may be a replicon to which another nucleotide sequence may be attached to allow for replication of the attached nucleotide sequence. A "replicon" can be any genetic element (e.g., plasmid, phage, cosmid, chromosome, viral genome) that functions as an autonomous unit of nucleic acid replication in vivo, i.e., capable of replication under its own control. The term "vector" includes both viral and nonviral (e.g., plasmid) nucleic acid molecules for introducing a nucleic acid into a cell *in vitro*, *ex vivo*, and/or *in vivo*. A large number of vectors known in the art may be used to manipulate nucleic acids, incorporate response elements and promoters into genes, etc. For example, the insertion of the nucleic acid fragments corresponding to response elements and promoters into a suitable vector can be accomplished by ligating the appropriate nucleic acid fragments into a chosen vector that has complementary cohesive termini. Alternatively, the ends of the nucleic acid molecules may be enzymatically modified or any site may be produced by ligating nucleotide sequences (linkers) to the nucleic acid termini Such vectors may be engineered to contain sequences encoding selectable markers that provide for the selection of cells that contain the vector and/or have incorporated the nucleic acid of the vector into the cellular genome. Such markers allow identification and/or selection of host cells that incorporate and express the proteins encoded by the marker. A "recombinant" vector refers to a viral or non-viral vector that comprises one or more heterologous nucleotide sequences (i.e., transgenes), e.g., two, three, four, five or more heterologous nucleotide sequences.

[0449] By the term "express" or "expression" of a polynucleotide coding sequence, it is meant that the sequence is transcribed, and optionally, translated. Typically, according to the present disclosure, expression of a coding sequence of the disclosure will result in production of the polypeptide of the disclosure. The entire expressed polypeptide or fragment can also function in intact cells without purification.

[0450] In some embodiments, the vector is an expression vector for manufacturing siRNAs of the disclosure. Exemplary expression vectors may comprise a sequence encoding the sense and/or antisense strand of the isolated oligonucleotide of the present disclosure, under the control of a suitable promoter for transcription. Interfering RNAs may be expressed from a variety of eukaryotic promoters known to those of ordinary skill in the art, including pol III promoters, such as the U6 or H1 promoters, or pol II promoters, such as the cytomegalovirus promoter. Those of skill in the art will recognize that these promoters can also be adapted to allow inducible expression of the interfering RNA.

[0451] The isolated oligonucleotide of the present disclosure (e.g., dsRNAs and siRNAs) can be expressed endogenously from plasmid or viral expression vectors, or from minimal expression cassettes, for example, PCR generated fragments comprising one or more promoters and an appropriate template or templates for transcribing the siRNA. Examples of commercially available plasmid-based expression vectors for shRNA include members of the pSilencer series (Ambion) and pCpG-siRNA (InvivoGen). Examples of kits for production of PCR-generated shRNA expression cassettes include Silencer Express (Ambion) and siXpress (Mirus)

[0452] Viral vectors for the *in vivo* expression of the isolated oligonucleotides (e.g., siRNAs and dsRNAs) in eukaryotic cells are also contemplated as within the scope of the instant disclosure. Viral vectors may be derived from a variety of viruses including adenovirus, adeno-associated virus, lentivirus (e.g., HIV, FIV, and EIAV), and herpes virus. Examples of commercially available viral vectors for shRNA expression include pSilencer adeno (Ambion) and pLenti6/BLOCK-iT™-DEST (Invitrogen). Selection of viral vectors, methods for expressing the siRNA from the vector and methods of delivering the viral vector, for example incorporated within a nanoparticle, are within the ordinary skill of one in the art.

[0453] It will be apparent to those skilled in the art that any suitable vector, optionally incorporated into a nanoparticle, can be used to deliver the isolated oligonucleotides of the present dislclosre (e.g., dsRNAs or siRNAs) described herein to a cell or subject. The vector can be delivered to cells in vivo. In other embodiments, the vector can be delivered to cells ex vivo, and then cells containing the vector are delivered to the subject. The choice of delivery vector can be made based on a number of factors known in the art, including age and species of the target host, in vitro versus in vivo delivery, level and persistence of expression desired, intended

purpose (e.g., for therapy or screening), the target cell or organ, route of delivery, size of the isolated polynucleotide, safety concerns, and the like.

[0454] *Delivery Systems*

[0455] The present disclosure also provides a delivery system comprising at least one isolated oligonucleotide disclosed herein or vector of the present disclosure encoding at least one isolated oligonucleotide disclosed herein. In some embodiments, the delivery system is any one of a liposome, a nanoparticle, a polymer based delivery system or a ligand-conjugate delivery system. In some embodiments, the ligand-conjugate delivery system comprises one or more of an antibody, a peptide, a sugar moiety or a combination thereof.

[0456] In some embodiments, the delivery system of the present disclosure comprises nanoparticles comprising the isolated oligonucleotides of the present disclosure (e.g., siRNA or dsRNAs) targeting a CFB mRNA for degradation. In some embodiments, the nanoparticle comprises a polymer-based nanoparticle, a lipid-polymer based nanoparticle, a metal based nanoparticle, a carbon nanotube based nanoparticle, a nanocrystal or a polymeric micelle. In some embodiments, the polymer-based nanoparticle comprises a multiblock copolymer, a diblock copolymer, a polymeric micelle or a hyperbranched macromolecule. In some embodiments, the polymer-based nanoparticle comprises a multiblock copolymer a diblock copolymer. In some embodiments, the polymer-based nanoparticle is pH responsive. In some embodiments, the polymer-based nanoparticle further comprises a buffering component.

[0457] In some embodiments, the delivery system comprises a liposome. Liposomes are spherical vesicles having at least one lipid bilayer, and in some embodiments, an aqueous core. In some embodiments, the lipid bilayer of the liposome may comprise phospholipids. An exemplary but non-limiting example of a phospholipid is phosphatidylcholine, but the lipid bilayer may comprise additional lipids, such as phosphatidylethanolamine. Liposomes may be multilamellar, i.e. consisting of several lamellar phase lipid bilayers, or unilamellar liposomes with a single lipid bilayer. Liposomes can be made in a particular size range that makes them viable targets for phagocytosis. Liposomes can range in size from 20 nm to 100 nm, 100 nm to 400 nm, 1 μM and larger, or 200 nm to 3 μM. Examples of lipidoids and lipid-based formulations are provided in U.S. Published Application 20090023673. In other embodiments, the one or more lipids are one or more cationic lipids. One skilled in the art will recognize which liposomes are appropriate for siRNA encapsulation.

[0458] In some embodiments, the liposome or the nanoparticle of the present disclosure comprises a micelle. A micelle is an aggregate of surfactant molecules. An exemplary micelle comprises an aggregate of amphiphilic macromolecules, polymers or copolymers in aqueous solution, wherein the hydrophilic head portions contact the surrounding solvent, while the hydrophobic tail regions are sequestered in the center of the micelle.

[0459] In some embodiments, the nanoparticle comprises a nanocrystal. Exemplary nanocrystals are crystalline particles with at least one dimension of less than 1000 nanometers, preferably of less than 100 nanometers.

[0460] In some embodiments, the nanoparticle comprises a polymer-based nanoparticle. In some embodiments, the polymer comprises a multiblock copolymer, a diblock copolymer, a polymeric micelle or a hyperbranched macromolecule. In some embodiments, the particle comprises one or more cationic polymers. In some embodiments, the cationic polymer is chitosan, protamine, polylysine, polyhistidine, polyarginine or poly(ethylene)imine. In other embodiments, the one or more polymers contain the buffering component, degradable component, hydrophilic component, cleavable bond component or some combination thereof.

[0461] In some embodiments, the nanoparticles or some portion thereof are degradable. In other embodiments, the lipids and/or polymers of the nanoparticles are degradable.

[0462] In some embodiments, any of these delivery systems of the present disclosure can comprise a buffering component. In other embodiments, any of the of the present disclosure can comprise a buffering component and a degradable component. In still other embodiments, any of the of the present disclosure can comprise a buffering component and a hydrophilic component. In yet other embodiments, any of the of the present disclosure can comprise a buffering component and a cleavable bond component. In yet other embodiments, any of the of the present disclosure can comprise a buffering component, a degradable component and a hydrophilic component. In still other embodiments, any of the of the present disclosure can comprise a buffering component, a degradable component and a cleavable bond component. In further embodiments, any of the of the present disclosure can comprise a buffering component, a hydrophilic component and a cleavable bond component. In yet another embodiment, any of the of the present disclosure can comprise a buffering component, a degradable component, a hydrophilic component and a cleavable bond component. In some embodiments, the particle is

composed of one or more polymers that contain any of the aforementioned combinations of components.

[0463] In some embodiments of the isolated oligonucleotides of the present disclosure, the delivery system comprises a ligand-conjugate delivery system. In some embodiments, the ligand-conjugate delivery system comprises one or more of an antibody, a peptide, a sugar moiety, lipid or a combination thereof

[0464] In further embodiments, the isolated oligonucleotide of the present disclosure targeting a CFB mRNA (e.g., siRNA or dsRNA) is conjugated to, complexed to, or encapsulated by the one or more lipids or polymers of the delivery system. In further embodiments, the isolated oligonucleotide of the present disclosure targeting a CFB mRNA (e.g., siRNA or dsRNA) can be encapsulated in the hollow core of a nanoparticle. Alternatively, or in addition, the isolated oligonucleotide of the present disclosure targeting a CFB mRNA (e.g., siRNA or dsRNA) can be incorporated into the lipid or polymer-based shell of the delivery system, for example via intercalation. Alternatively, or in addition, the isolated oligonucleotide of the present disclosure targeting a CFB mRNA (e.g., siRNA or dsRNA) can be attached to the surface of the delivery system. In some embodiments, the isolated oligonucleotide of the present disclosure targeting a CFB mRNA (e.g., siRNA or dsRNA) is conjugated to one or more lipids or polymers of the delivery system, e.g. via covalent attachment.

[0465] In some embodiments, the ligand conjugate delivery system further comprises a targeting agent. In some embodiments, the targeting agent comprises a peptide ligand, a nucleotide ligand, a polysaccharide ligand, a fatty acid ligand, a lipid ligand, a small molecule ligand, an antibody, an antibody fragment, an antibody mimetic or an antibody mimetic fragment.

[0466] In some embodiments, the isolated oligonucleotide disclosed herein may further comprise a ligand that facilitates delivery or uptake of the isolated oligonucleotide to a particular tissue or cell, such as a liver cell. In certain embodiments, the ligand targets delivery of the RNAi construct to hepatocytes. In these and other embodiments, the ligand may comprise galactose, galactosamine or N-acetyl-galactosamine (GalNAc). In certain embodiments, the ligand comprises a multivalent galactose or multivalent GalNAc moiety, such as a trivalent or tetravalent galactose or GalNAc moiety. The ligand can be covalently attached to the 5 'or 3' end of the sense strand of the RNAi construct, optionally via a linker.

[0467] In some embodiments, the targeting agent comprises a binding partner for a cell surface protein that is upregulated or overexpressed or normally expressed in a target cell encoding CFB mRNA and expressing CFB protein. In some embodiments, the binding partner can be a transmembrane peptidoglycan expressed on the surface of many types of such cells. Targeting of cell surface protein by the delivery system of the present disclosure thus provides superior delivery and specificity of the compositions of the disclosure to target cells. In some embodiments, the target cell can be any one of an intestinal cell, an arterial cell, a cell of the cardiovascular system, a hepatocyte, a pancreatic cell or a combination thereof.

[0468] In some embodiments, the delivery system of the present disclosure comprises a polymer based delivery system. In some embodiments, polymer based delivery system comprises a blending polymer. In some embodiments, the blending polymer is a copolymer comprising a degradable component and hydrophilic component. In some embodiments, the degradable component of the blending polymer is a polyester, poly(ortho ester), poly(ethylene imine), poly(caprolactone), polyanhydride, poly(acrylic acid), polyglycolide or poly(urethane). In some embodiments, the degradable component of the blending polymer is poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the hydrophilic component of the blending polymer is a polyalkylene glycol or a polyalkylene oxide. In some embodiments, the polyalkylene glycol is polyethylene glycol (PEG). In other embodiments, the polyalkylene oxide is polyethylene oxide (PEO).

[0469] In some embodiments, the delivery system of the present disclosure is a polymer-based nanoparticle. Polymer based nanoparticles comprise one or more polymers. In some embodiments, the one or more polymers comprise a polyester, poly(ortho ester), poly(ethylene imine), poly(caprolactone), polyanhydride, poly(acrylic acid), polyglycolide or poly(urethane). In still other embodiments, the one or more polymers comprise poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the one or more polymers comprise poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the one or more polymers comprise poly(lactic acid) (PLA). In some embodiments, the one or more polymers comprise polyalkylene glycol or a polyalkylene oxide. In some embodiments, the polyalkylene glycol is polyethylene glycol (PEG) or the polyalkylene oxide is polyethylene oxide (PEO).

[0470] In some embodiments, the polymer-based nanoparticle comprises poly(lactic-co-glycolic acid) PLGA polymers. In some embodiments, the PLGA nanoparticle further comprises a targeting agent, as described herein.

[0471] In some embodiments, the delivery system of the present disclosure is a nanoparticle of average characteristic dimension of less than about 500 nm, 400 nm, 300 nm, 250 nm, 200 nm, 180 nm, 150 nm, 120 nm, 100 nm, 90 nm, 80 nm, 70 nm, 60 nm, 50 nm, 40 nm, 30 nm or 20 nm. In other embodiments, the nanoparticle has an average characteristic dimension of 10 nm, 20 nm, 30 nm, 40 nm, 50 nm, 60 nm, 70 nm, 80 nm, 90 nm, 100 nm, 120 nm, 150 nm, 180 nm, 200 nm, 250 nm or 300 nm. In further embodiments, the nanoparticle has an average characteristic dimension of 10-500 nm, 10-400 nm, 10-300 nm, 10-250 nm, 10-200 nm, 10-150 nm, 10-100 nm, 10-75 nm, 10-50 nm, 50-500 nm, 50-400 nm, 50-300 nm, 50-200 nm, 50-150 nm, 50-100 nm, 50-75 nm, 100-500 nm, 100-400 nm, 100-300 nm, 100-250 nm, 100-200 nm, 100-150 nm, 150-500 nm, 150-400 nm, 150-300 nm, 150-250 nm, 150-200 nm, 200-500 nm, 200-400 nm, 200-300 nm, 200-250 nm, 200-500 nm, 200-400 nm or 200-300 nm.

[0472] *Therapeutic Agents*

[0473] In some embodiments, the delivery system of the present disclosure is administered with one or more additional therapeutic agents. In some embodiments, the additional therapeutic agents can be a steroid, an anti-inflammatory agent, an antibody, a fusion protein, a small molecule, or combination thereof. In some embodiments, the additional therapeutic agent is incorporated into a delivery system of the present disclosure comprising at least one isolated oligonucleotide targeting CFB disclosed herein. In some embodiments, the additional therapeutic agent is conjugated to, complexed to, or encapsulated by the one or more lipids or polymers of the delivery system. Additional therapeutic agents can be encapsulated in the hollow core of delivery system. Alternatively, additionally, additional therapeutic agents can be incorporated into the lipid or polymer-based shell of the delivery system, for example via intercalation. Alternatively, additionally, additional therapeutic agents can be attached to the surface of the delivery system. In some embodiments, the additional therapeutic agents are conjugated to one or more lipids or polymers of the delivery system, e.g. via covalent attachment.

[0474] In some embodiments, the additional therapeutic agent and the delivery system comprising at least one isolated oligonucleotide targeting CFB disclosed herein are formulated in the same composition. For example, the delivery system comprising at least one isolated

oligonucleotide of the present disclosure targeting CFB and the additional therapeutic agent can be formulated in the same pharmaceutical composition.

[0475] In some embodiments, the additional therapeutic agent and the delivery system comprising at least one isolated oligonucleotide targeting CFB disclosed herein are formulated as separate compositions, e.g., for separate administration to a subject.

[0476] *Pharmaceutical Compositions*

[0477] The present disclosure also provides a pharmaceutical composition comprising at least one oligonucleotide disclosed herein, a vector of the present disclosure encoding at least one isolated oligonucleotide disclosed herein, or a delivery system of the present disclosure, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0478] The pharmaceutical compositions of the disclosure can optionally comprise therapeutic agents, pharmaceutical agents, carriers, adjuvants, dispersing agents, diluents, and the like. In some embodiments, the pharmaceutical composition comprises a therapeutic agent, such as a chemotherapeutic agent. In some embodiments, the therapeutic agent is formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB of the present disclosure.

[0479] In some embodiments, an additional therapeutic agent is not formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB of the present disclosure, but both the delivery system and the therapeutic agent are formulated in the same pharmaceutical composition. In some embodiments, an additional therapeutic agent is not formulated in the delivery system comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB of the present disclosure, and the delivery system and the therapeutic agent are formulated in separate pharmaceutical compositions.

[0480] Pharmaceutical compositions of the present disclosure can contain any of the reagents discussed above, and one or more of a pharmaceutically acceptable carrier, a diluent or an excipient.

[0481] A pharmaceutical composition of the present disclosure is in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active

ingredient (e.g., a formulation of the disclosed agent) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active agent is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0482] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0483] "Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0484] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), intraperitoneal (into the body cavity) and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, intraperitoneal or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or

dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit/dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use.

[0485] The pharmaceutical compositions containing the nanoparticles described herein may be manufactured in a manner that is generally known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active agents into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0486] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required nanoparticle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable

to include isotonic agents, for example, sugars, polyalcohols such as manitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0487] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active age can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the agents in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or agents of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0488] For administration by inhalation, the agents are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0489] The pharmaceutical compositions of the present disclosure can be prepared with pharmaceutically acceptable carriers that will protect the one or more isolated oligonucleotides (e.g., dsRNAs or siRNAs) targeting CFB mRNA of the present disclosure against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art, and the materials can be obtained commercially. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0490] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active agent and the particular therapeutic effect to be achieved.

[0491] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0492] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids.

[0493] Techniques for formulation and administration of the disclosed compositions of the disclosure can be found in Remington: the Science and Practice of Pharmacy, 19th edition, Mack Publishing Co., Easton, PA (1995).

[0494] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0495] *Methods of Making Isolated Oligonucleotides*

[0496] Provided herein are methods of making the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting CFB of the present disclosure and delivery systems comprising same.

[0497] The one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting CFB of the present disclosure, may be generated exogenously by chemical synthesis, by *in vitro*

transcription, or by cleavage of longer double-stranded RNA with Dicer or another appropriate nuclease with similar activity. Chemically synthesized siRNAs, produced from protected ribonucleoside phosphoramidites using a conventional DNA/RNA synthesizer, may be obtained from commercial suppliers. The siRNAs can be purified by extraction with a solvent or resin, precipitation, electrophoresis, chromatography, or a combination thereof, for example. Alternatively, siRNAs may be used with little if any purification to avoid losses due to sample processing.

[0498] In some embodiments, the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting CFB of the present disclosure can be produced using an expression vector into which a nucleic acid encoding the double stranded RNA has been cloned, for example under control of a suitable promoter.

[0499] In some embodiments, the one or more oligonucleotides of (e.g., dsRNAs or siRNAs) targeting CFB of the present disclosure can be incorporated in a delivery system of the present disclosure (e.g., a nanoparticle).

[0500] Delivery systems comprising dsRNAs or siRNAs of the disclosure can be prepared by any suitable means known in the art. For example, polymeric nanoparticles can be prepared using various methods including, but not limited to, solvent evaporation, spontaneous emulsification, solvent diffusion, desolation, dialysis, ionic gelation, nanoprecipitation, salting out, spray drying and supercritical fluid methods. The dispersion of preformed polymers and the polymerization of monomers are two additional strategies for preparation of polymeric nanoparticles. However, the choice of an appropriate method depends upon various factors, which will be known to the person of ordinary skill in the art.

[0501] Sterile injectable solutions comprising a delivery system of the disclosure can be prepared by incorporating the one or more isolated oligonucleotides (e.g. dsRNA and siRNA) targeting CFB disclosed herein, in the delivery systems (e.g. nanoparticle) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated herein, as required, followed by filtered sterilization. Alternatively, or in addition, sterilization can be achieved through other means such as radiation or gas. Generally, dispersions are prepared by incorporating the delivery particles into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and

freeze drying that yields a powder of delivery system comprising the one or more isolated oligonucleotides (e.g. dsRNA and siRNA) targeting CFB disclosed herein, plus any additional desired ingredient from a previously sterile filtered solution thereof.

[0502] *Methods of Use*

[0503] The present disclosure also provides a method of inhibiting or downregulating the expression or level of complement CFB in a subject in need thereof, wherein the method comprises administering to the subject an effective amount at least one isolated oligonucleotide disclosed herein, at least one vector disclosed herein, at least one delivery system disclosed herein, or at least one pharmaceutical composition disclosed herein.

[0504] The present disclosure also provides a method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of complement CFB or a disease or disorder where complement CFB plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide disclosed herein, at least one vector disclosed herein, at least one delivery system disclosed herein, or at least one pharmaceutical composition disclosed herein.

[0505] The present disclosure also provides at least one isolated oligonucleotide disclosed herein, a vector of the of the present disclosure encoding at least one isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure, for use in treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role, in a subject in need thereof.

[0506] The present disclosure also provides use of at least one isolated oligonucleotide disclosed herein, a vector of the of the present disclosure encoding at least one isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure, in the manufacture of a medicament for treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role in a subject in need thereof.

[0507] Provided herein are methods of inhibiting or downregulating CFB expression or activity in a cell, comprising contacting the cell with the one or more oligonucleotides (e.g., dsRNA or siRNA) targeting CFB as described herein. The one or more oligonucleotides (e.g., dsRNA or siRNA) targeting CFB as described herein can reduce or inhibit CFB activity through

the RNAi pathway. The cell can be *in vitro*, *in vivo* or *ex vivo*. For example, the cell can be from a cell line, or *in vivo* in a subject in need thereof.

[0508] In some embodiments, the one or more oligonucleotides (e.g., dsRNA or siRNA) targeting CFB as described herein are capable of inducing RNAi-mediated degradation of an CFB mRNA in a cell of a subject.

[0509] As used herein, the terms "contacting," "introducing" and "administering" are used interchangeably and refer to a process by which dsRNA or siRNA of the present disclosure or a nucleic acid molecule encoding a dsRNA or siRNA of this disclosure is delivered to a cell in order to inhibit or alter or modify expression of a target gene. The dsRNA may be administered in a number of ways including, but not limited to, direct introduction into a cell (i.e., intracellularly) and/or extracellular introduction into a cavity, interstitial space, or into the circulation of the organism.

[0510] "Introducing" in the context of a cell or organism means presenting the nucleic acid molecule to the organism and/or cell in such a manner that the nucleic acid molecule gains access to the interior of a cell. Where more than one nucleic acid molecule is to be introduced these nucleic acid molecules can be assembled as part of a single polynucleotide or nucleic acid construct, or as separate polynucleotide or nucleic acid constructs, and can be located on the same or different nucleic acid constructs. Accordingly, these polynucleotides can be introduced into cells in a single transformation event or in separate transformation events. Thus, the term "transformation" as used herein refers to the introduction of a heterologous nucleic acid into a cell. Transformation of a cell may be stable or transient.

[0511] The term "inhibit" or "reduce" or grammatical variations thereof, as used herein, refer to a decrease or diminishment in the specified level or activity of at least about 5%, about 10%, about 15%, about 25%, about 35%, about 40%, about 50%, about 60%, about 75%, about 80%, about 90%, about 95% or more. In some embodiments, the inhibition or reduction results in little or essentially no detectible activity (at most, an insignificant amount, *e.g.*, less than about 10% or even 5%).

[0512] In contrast, the term "increase" or grammatical variations thereof as used herein refers to an increase or elevation in the specified level or activity of at least about 5%, about 10%, about 15%, about 25%, about 35%, about 40%, about 50%, about 60%, about 75%, about 80%, about 90%, about 95% or more. Increases in activity can be described in terms of fold change.

For example, activity can be increased 1.2X, 1.5X, 2X, 3X, 5X, 6X, 7X, 8X, 9X, 10X or more compared to a baseline level of activity.

[0513] As used herein, the term "IC50" or "IC_{50} value" refers to the concentration of an agent where cell viability is reduced by half. The IC_{50} is thus a measure of the effectiveness of an agent in inhibiting a biological process. In an exemplary model, cell lines are cultured using standard techniques, treated with any of the one or more oligonucleotides (e.g., dsRNA or siRNA) targeting CFB as described herein, and the IC_{50} value of the oligonucleotides (e.g., dsRNA or siRNA) targeting CFB is calculated after 24, 48 and/or 72 hours to determine its effectiveness in downregulating or inhibiting the level of CFB mRNA or protein to 50%, as compared to the level of CFB mRNA or protein in an untreated cell or in the same cell before initiation of treatment with the isolated oligonucleotide.

[0514] Methods of monitoring of CFB mRNA and/or protein expression can be used to characterize gene silencing, and to determine the effectiveness of the compositions described herein. Expression of CFB may be evaluated by any technique known in the art. Examples thereof include immunoprecipitations methods, utilizing CFB antibodies in assays such as ELISAs, western blotting, or immunohistochemistry to visualize CFB protein expression in cells, or flow cytometry. Additional methods include various hybridization methods utilizing a nucleic acid that specifically hybridizes with a nucleic acid encoding CFB or a unique fragment thereof, or a transcription product (e.g., mRNA) or splicing product of said nucleic acid, northern blotting methods, Southern blotting methods, and various PCR-based methods such as RT-PCR, qPCR or digital droplet PCR. CFB mRNA expression may additionally be assessed using high throughput sequencing techniques.

[0515] Methods of assaying the effect of individual isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB include transfecting representative cell lines with isolated oligonucleotides and measuring viability. For example, cells from representative cell lines can be transfected using methods known in the art, such as the RNAiMAX Lipofectamine kit (Invitrogen) and cultured using any suitable technique known in the art. Optionally additional therapeutic agents as described herein can be added at variable concentrations to cell culture media following transfection. Following a suitable incubation period, such as 24-96 hours, cell viability can be measured using methods such as Cell Titer Glo 2.0 (Promega) to determine cell

viability, and/or CFB mRNA and protein levels can be assessed using the methods described herein.

[0516] In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the at least one isolated oligonucleotide, the vector, the delivery system, or the pharmaceutical composition is administered parenterally. In some embodiments, the parenteral administration is intravenous, subcutaneous, intraperitoneal, or intramuscular.

[0517] In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the subject is a human. In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the subject experiences symptoms of or suffers from Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation and neurodegenerative diseases.

[0518] In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the method comprises administering the at least one isolated oligonucleotide, the vector, the delivery system, or the pharmaceutical composition, in combination with at least a second therapeutic agent. In some embodiments, the second therapeutic agent is an antibody, a small molecule drug, a peptide, a nucleotide molecule, or a combination thereof. In some embodiments, the second therapeutic agent is an isolated oligonucleotide of the present disclosure.

[0519] The present disclosure also provides a method of inhibiting or downregulating the expression or level of CFB in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of a first and at least a second oligonucleotides disclosed herein, wherein the first and at least second oligonucleotides comprise different sequences. In some embodiments, the first and at least second oligonucleotides are administered simultaneously. In some embodiments, the first and at least second oligonucleotides are administered sequentially.

[0520] In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the subject is a human. In some embodiments of the methods of inhibiting or downregulating CFB expression or activity in a cell of the present disclosure, the subject experiences symptoms of or suffers from Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation and neurodegenerative diseases, or a related disorder or symptom associated with an overreactive inflammatory response.

[0521] In some embodiments of the method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role of the present disclosure, the subject is a human. In some embodiments of the method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role of the present disclosure, the disease or disorder is or is associated with Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation, a neurodegenerative diseases, or a related disorder or symptom associated with an overreactive inflammatory response.

[0522] In some embodiments of the use for treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role of the present disclosure, the subject is a human. In some embodiments of the use for treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role of the present disclosure, the disease or disorder is or is associated with Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-

Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation, neurodegenerative diseases, or a related disorder or symptom associated with an overreactive inflammatory response.

[0523] In some embodiments of the use in the manufacture of a medicament for treatment or prevention of a disease or disorder associated with aberrant or increased expression or activity of CFB of the present disclosure, the subject is a human. In some embodiments, the subject is not a human. In some embodiments, the disease or disorder is or is associated with Paroxysmal Nocturnal Hemoglobinuria (PNH), rheumatoid arthritis, ischemia-reperfusion injuries, Multiple Sclerosis (MS), Guillain-Barre syndrome, Systemic lupus erythmatosis, C3 Glomerulonephritis, atypical Hemolytic Uremic Syndrome (aHUS), Myasthenia Gravis (MG), Neuromyelistis Optic nerve and Spinal Cord (NMOSD), Dense Deposit Disease (DDD), Age-related Macular Degeneration (AMD), IgA nephropathy, Multifocal Motor Neuropathy (MMN), organ transplantation, neurodegenerative diseases, or a related disorder or symptom associated with an overreactive inflammatory response.

[0524] *Routes of administration*

[0525] Nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure can be administered to a subject by many of the well-known methods currently used for therapeutic treatment. For example, for treatment of mammalian diseases associated with expression or activity of CFB, a compositions comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB of the present disclosure may be injected directly into cells, injected into the blood stream or body cavities, taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0526] The compositions comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure can be administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperintoneally,

subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the parenteral administration comprises intramuscular, intraperitoneal, subcutaneous or intravenous administration. One skilled in the art will recognize the advantages of certain routes of administration.

[0527] Compositions of the disclosure may be administered parenterally. Systemic administration of compositions comprising nanoparticles of the disclosure can also be by intravenous, transmucosal, subcutaneous, intraperitoneal, intramuscular or transdermal means. For intravenous parenteral administration, compositions comprising nanoparticles may be administered by injection or by infusion. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[0528] *Dosages*

[0529] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing or treatment of the condition or symptom associated with expression or activity of CFB. Dosages may vary depending on the age and size of the subject and the type and severity of the disease or disorder associated with CFB expression.

[0530] The term "effective amount" or "therapeutically effective amount", as used interchangeably herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, inhibit, downregulate or control the expression of CFB or symptoms associated with aberrant or abnormal expression of CFB in a subject, or to exhibit a detectable therapeutic or inhibitory effect in a subject. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0531] For any of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure, the therapeutically effective amount can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. In some embodiments, a standard xenograft or patient derived xenograft mouse model can be used to determine the effectiveness of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., the maximum tolerated dose and no observable adverse effect dose. Pharmaceutical compositions that exhibit large therapeutic windows are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0532] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0533] The dosage of nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure, required depends on the choice of the route of administration; the nature of the formulation; the nature of the patient's illness; the subject's size, weight, surface area, age, and sex; other drugs being administered; and the judgment of the attending physician. Wide variations in the needed dosage are to be expected in view of the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection (e.g., 2-, 3-, 4-, 6-, 8-, 10-; 20-, 50-, 100-, 150-, or more fold). Variations in these dosage levels can be adjusted using standard empirical routines for optimization as is well understood in the art. Administrations can be single or multiple. Encapsulation of the inhibitor in

a suitable delivery vehicle (e.g., capsules or implantable devices) may increase the efficiency of delivery, particularly for oral delivery.

[0534] A therapeutically effective dose of the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting CFB mRNA of the present disclosure, can optionally be combined with approved amounts of therapeutic agents, and described herein.

[0535] *Kits and Articles of Manufacture*

[0536] The present disclosure also provides kits comprising at least one isolated oligonucleotide disclosed herein, a vector of the present disclosure encoding an isolated oligonucleotide disclosed herein, a delivery system of the present disclosure, or a pharmaceutical composition of the present disclosure. In some embodiments, the vector encodes one isolated oligonucleotide disclosed herein. In some embodiments, the vector encodes more than one isolated oligonucleotide disclosed herein.

[0537] The kits are for use in the treatment of diseases related to abnormal or aberrant expression of human CFB. The kits are for use in downregulating or inhibiting expression of complement CFB partially or completely. In some embodiments, the kit is for use in the treatment of disease or downregulating or inhibiting expression of CFB in a mammal. In some embodiments, the mammal is a human, a mouse, a rat, a rabbit, a pig, a bovine, a canine, a feline, an ungulate, an ape, a monkey or an equine species. In some embodiments, the mammal is a human

[0538] In some embodiments of the kits of the disclosure, the kit comprises nanoparticles. Nanoparticles comprising the one or more isolated oligonucleotides (e.g., dsRNA or siRNA) targeting complement CFB mRNA of the present disclosure, can be lyophilized before being packaged in the kit, or can be provided in solution with a pharmaceutically acceptable carrier, diluent of excipient.

[0539] In some embodiments of the kits of the disclosure, the kit comprises a therapeutically effective amount of a composition comprising the delivery system of the present disclosure comprising one or more of the isolated oligonucleotides of the present disclosure targeting complement CFB (dsRNA or siRNA), and instructions for use of the same. In some embodiments, the kit further comprises at least one additional therapeutic agents, as described herein.

[0540] Articles of manufacture of the present disclosure include, but are not limited to, instructions for use of the kit in treating diseases related to abnormal or aberrant expression of complement CFB or diseases related to expression of complement CFB.

[0541] In some embodiments, the kits further comprise instructions for administering the isolated oligonucleotides, the vector, the delivery systems and the pharmaceutical compositions of the disclosure.

[0542] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0543] SEQUENCES OF THE DISCLOSURE

[0544] Table 1. Exemplary Sequences of the Present Application

SEQ ID NO:	Antisense strand (guide)			SEQ ID NO:	Sense strand (passenger)		
	sequence	start pos.	end pos.		sequence	start pos.	end pos.
2	UAAAGAGAUCUCAUCACUCACA	493	513	36	UGAGUGAUGAGAUCUCUUUA	495	513
3	UGGAAAGAGAUCUCAUCACUCA	495	515	37	AGUGAUGAGAUCUCUUUCCA	497	515
4	UCAGUGGAAAGAGAUCUCAUCA	499	519	38	AUGAGAUCUCUUUCCACUGA	501	519
5	UAUAGCAGUGGAAAGAGAUCUC	503	523	39	GAUCUCUUUCCACUGCUAUA	505	523
6	UGUGUAACCGUCAUAGCAGUGG	514	534	40	AUCUCUUUCCACUGCUAUGA	516	534
7	UUUGACUAGACACUUUUUGGCU	991	1011	41	CCAAAAAGUGUCUAGUCAAA	993	1011
8	UUAAGUUGACUAGACACUUUUU	995	1015	42	AAAGUGUCUAGUCAACUUAA	997	1015
9	UAAUUAAGUUGACUAGACACUU	998	1018	43	GUGUCUAGUCAACUUAAUUA	1000	1018
10	UCAAUUAAGUUGACUAGACACU	999	1019	44	UGUCUAGUCAACUUAAUUGA	1001	1019
11	UAUAUCUUGGCUUCACACCAUA	1034	1054	45	UGGUGUGAAGCCAAGAUAUA	1036	1054
12	UUAGACAUCCAGAUAAUCCUCC	1384	1404	46	AGGAUUAUCUGGAUGUCUAA	1386	1404
13	UAAGCAUUGAUGUUCACUUGGU	1431	1451	47	CAAGUGAACAUCAAUGCUUA	1433	1451
14	UAAAGCAUUGAUGUUCACUUGG	1432	1452	48	AAGUGAACAUCAAUGCUUUA	1434	1452
15	UAACACAUGUUGCUCAUUGUCU	1465	1485	49	ACAAUGAGCAACAUGUGUUA	1467	1485
16	UUUGACUUUGAACACAUGUUGC	1474	1494	50	AACAUGUGUUCAAAGUCAAA	1476	1494
17	UAUAUCCUUGACUUUGAACACA	1480	1500	51	UGUUCAAAGUCAAGGAUAUA	1482	1500
18	UGAGAUCUUGGCCUGCCAUGGU	1606	1626	52	CAUGGCAGGCCAAGAUCUCA	1608	1626
19	UAAGUACUCAGACACCACAGCC	1666	1686	53	CUGUGGUGUCUGAGUACUUA	1668	1686
20	UAUUCAGGAAUUCCUGCUUCUU	1821	1841	54	GAAGCAGGAAUUCCUGAAUA	1823	1841
21	UAAUUCAGGAAUUCCUGCUUCU	1822	1842	55	AAGCAGGAAUUCCUGAAUUA	1824	1842

22	UUAAAAUUCAGGAAUUCCUGCU	1825	1845	56	CAGGAAUUCCUGAAUUUUAA	1827	1845
23	UAUAAAAUUCAGGAAUUCCUGC	1826	1846	57	AGGAAUUCCUGAAUUUUAUA	1828	1846
24	UGUCAUAAAAUUCAGGAAUUCC	1829	1849	58	AAUUCCUGAAUUUUAUGACA	1831	1849
25	UUAUUCUUGAGCUUGAUCAGGG	1860	1880	59	CUGAUCAAGCUCAAGAAUAA	1862	1880
26	UUUAUUCUUGAGCUUGAUCAGG	1861	1881	60	UGAUCAAGCUCAAGAAUAAA	1863	1881
27	UUUGACUUUGUCAUAGCCUGGG	2116	2136	61	CAGGCUAUGACAAAGUCAAA	2118	2136
28	UAAGUAUUGGGGUCAGCAUAGG	2190	2210	62	UAUGCUGACCCCAAUACUUA	2192	2210
29	UUUCUCUUGUGAACUAUCAAGG	2232	2252	63	UUGAUAGUUCACAAGAGAAA	2234	2252
30	UAAACGACUUCUCUUGUGAACU	2239	2259	64	UUCACAAGAGAAGUCGUUUA	2241	2259
31	UUUUUUGCAGACAUCCACUACU	2287	2307	65	UAGUGGAUGUCUGCAAAAAA	2289	2307
32	UCAUCUUGGAGUUUCUCCUUCA	2382	2402	66	AAGGAGAAACUCCAAGAUGA	2384	2402
33	UAACCCAAAUCCUCAUCUUGGA	2394	2414	67	CAAGAUGAGGAUUUGGGUUA	2396	2414
34	UAAACCCAAAUCCUCAUCUUGG	2395	2415	68	AAGAUGAGGAUUUGGGUUUA	2397	2415
35	UCAGCUGUUUUAAUUCAAUCCC	2448	2468	69	GAUUGAAUUAAAACAGCUGA	2450	2468

[0545] Table 2. Exemplary Sequences of the Present Application and Their Potency

								% of gene remaining at 0.02 nM		% of gene remaining at 0.1 nM	
Guide Strand 3' end	Start	End	Guide strand sequence (5'-3')	SEQ ID	Passenger strand sequence (5'-3')	SEQ ID		Mean	SEM	Mean	SEM
514	493	513	UAAAGAGAUCU CAUCACUCACA	2	UGAGUGAUGAG AUCUCUUUA	36	*	43.43	4.73	24.37	3.42
516	495	515	UGGAAAGAGAU CUCAUCACUCA	3	AGUGAUGAGAU CUCUUUCCA	37	*^	40.97	2.39	28.17	0.34
520	499	519	UCAGUGGAAAG AGAUCUCAUCA	4	AUGAGAUCUCU UUCCACUGA	38	*	44.83	2.22	23.37	1.51
524	503	523	UAUAGCAGUGG AAAGAGAUCUC	5	GAUCUCUUUCC ACUGCUAUA	39	*^	50.03	1.14	30.43	1.36
535	514	534	UGUGUAACCGU CAUAGCAGUGG	6	ACUGCUAUGAC GGUUACACA	389	*^	39.33	1.84	23.90	1.31
1012	991	1011	UUUGACUAGAC ACUUUUUGGCU	7	CCAAAAAGUGU CUAGUCAAA	41		52.13	2.17	34.10	0.40
1016	995	1015	UUAAGUUGACU AGACACUUUUU	8	AAAGUGUCUAG UCAACUUAA	42	*	51.37	4.56	33.03	1.42
1019	998	1018	UAAUUAAGUUG ACUAGACACUU	9	GUGUCUAGUCA ACUUAAUUA	43	*^	40.30	2.32	26.87	0.64
1020	999	1019	UCAAUUAAGUU GACUAGACACU	10	UGUCUAGUCAA CUUAAUUGA	44		55.20	0.46	33.03	1.07
1055	1034	1054	UAUAUCUUGGC UUCACACCAUA	11	UGGUGUGAAGC CAAGAUAUA	45	*	56.97	4.32	29.03	3.70
1405	1384	1404	UUAGACAUCCA GAUAAUCCUCC	12	AGGAUUAUCUG GAUGUCUAA	46	*	43.30	1.97	33.90	7.10
1452	1431	1451	UAAGCAUUGAU GUUCACUUGGU	13	CAAGUGAACAU CAAUGCUUA	47	*^	44.70	1.02	26.90	0.95
1453	1432	1452	UAAAGCAUUGA UGUUCACUUGG	14	AAGUGAACAUC AAUGCUUUA	48	*	46.33	0.64	25.60	2.80
1486	1465	1485	UAACACAUGUU GCUCAUUGUCU	15	ACAAUGAGCAA CAUGUGUUA	49	*^	54.57	1.47	19.50	0.40

1495	1474	1494	UUUGACUUUGA ACACAUGUUGC	16	AACAUGUGUUC AAAGUCAAA	50	*	50.83	3.94	19.47	1.71
1501	1480	1500	UAUAUCCUUGA CUUUGAACACA	17	UGUUCAAAGUC AAGGAUAUA	51	*^	63.20	3.68	20.03	1.87
1627	1606	1626	UGAGAUCUUGG CCUGCCAUGGU	18	CAUGGCAGGCC AAGAUCUCA	52	*	57.23	3.58	23.57	1.53
1687	1666	1686	UAAGUACUCAG ACACCACAGCC	19	CUGUGGUGUCU GAGUACUUA	53	*^	59.27	1.15	25.77	1.68
1842	1821	1841	UAUUCAGGAAU UCCUGCUUCUU	20	GAAGCAGGAAU UCCUGAAUA	54		64.80	5.31	26.83	3.54
1843	1822	1842	UAAUUCAGGAA UUCCUGCUUCU	21	AAGCAGGAAUU CCUGAAUUA	55	*^	55.90	3.38	23.27	1.64
1846	1825	1845	UUAAAAUUCAG GAAUUCCUGCU	22	CAGGAAUUCCU GAAUUUUAA	56	*^	40.50	2.80	19.67	0.63
1847	1826	1846	UAUAAAAUUCA GGAAUUCCUGC	23	AGGAAUUCCUG AAUUUUAUA	57	*	41.40	1.37	19.63	0.19
1850	1829	1849	UGUCAUAAAAU UCAGGAAUUCC	24	AAUUCCUGAAU UUUAUGACA	58	*^	42.47	2.41	20.90	1.27
1881	1860	1880	UUAUUCUUGAG CUUGAUCAGGG	25	CUGAUCAAGCU CAAGAAUAA	59	*^	55.80	1.15	25.87	2.51
1882	1861	1881	UUUAUUCUUGA GCUUGAUCAGG	26	UGAUCAAGCUC AAGAAUAAA	60	*^	53.17	0.72	23.67	0.84
2137	2116	2136	UUUGACUUUGU CAUAGCCUGGG	27	CAGGCUAUGAC AAAGUCAAA	61		60.13	1.28	28.33	1.73
2211	2190	2210	UAAGUAUUGGG GUCAGCAUAGG	28	UAUGCUGACCC CAAUACUUA	62	*^	45.90	0.66	22.03	0.55
2253	2232	2252	UUUCUCUUGUG AACUAUCAAGG	29	UUGAUAGUUCA CAAGAGAAA	63		65.70	6.05	27.37	1.87
2260	2239	2259	UAAACGACUUC UCUUGUGAACU	30	UUCACAAGAGA AGUCGUUUA	64	*^	35.63	1.77	17.40	0.25
2308	2287	2307	UUUUUUGCAGA CAUCCACUACU	31	UAGUGGAUGUC UGCAAAAAA	65	*^	55.07	1.11	26.80	1.00
2403	2382	2402	UCAUCUUGGAG UUUCUCCUUCA	32	AAGGAGAAACU CCAAGAUGA	66	*^	55.00	6.03	22.67	1.08
2415	2394	2414	UAACCCAAAUC CUCAUCUUGGA	33	CAAGAUGAGGA UUUGGGUUA	67		62.33	4.60	30.17	2.59
2416	2395	2415	UAAACCCAAAU CCUCAUCUUGG	34	AAGAUGAGGAU UUGGGUUUA	68	*^	43.23	2.84	23.47	1.18
2469	2448	2468	UCAGCUGUUUU AAUUCAAUCCC	35	GAUUGAAUUAA AACAGCUGA	69	*	46.93	1.82	26.27	0.58
26	5	25	UCUAGACCUGG UCACAUUCCCU	70	GGAAUGUGACC AGGUCUAGA	180		100.03	3.94	67.63	7.63
36	15	35	UAACUCCAGAC CUAGACCUGGU	71	CAGGUCUAGGU CUGGAGUUA	181		108.53	4.32	78.45	3.15
37	16	36	UAAACUCCAGA CCUAGACCUGG	72	AGGUCUAGGUC UGGAGUUUA	182		98.97	2.02	64.50	4.10
38	17	37	UGAAACUCCAG ACCUAGACCUG	73	GGUCUAGGUCU GGAGUUUCA	183		93.00	2.25	57.85	4.35
39	18	38	UUGAAACUCCA GACCUAGACCU	74	GUCUAGGUCUG GAGUUUCAA	184		104.73	3.46	62.15	2.75
361	340	360	UGAUCUGCAGG UACGUGUCUGC	75	AGACACGUACC UGCAGAUCA	185		77.90	2.10	42.35	0.35
432	411	431	UGGAUUGCUCU GCACUCUGCCU	76	GCAGAGUGCAG AGCAAUCCA	186		85.77	3.30	56.10	2.58
499	478	498	UCUCACAUUGU AGUAGGGAGAC	77	CUCCCUACUAC AAUGUGAGA	187		97.10	6.87	73.23	1.84
503	482	502	UAUCACUCACA UUGUAGUAGGG	78	CUACUACAAUG UGAGUGAUA	188		82.03	4.17	47.53	0.52
504	483	503	UCAUCACUCAC AUUGUAGUAGG	79	UACUACAAUGU GAGUGAUGA	189		67.43	4.90	36.47	0.65

515	494	514	UGAAAGAGAUC UCAUCACUCAC	80	GAGUGAUGAGA UCUCUUUCA	190		81.27	1.79	44.30	2.51
518	497	517	UGUGGAAAGAG AUCUCAUCACU	81	UGAUGAGAUCU CUUUCCACA	191		72.37	5.56	35.30	2.81
525	504	524	UCAUAGCAGUG GAAAGAGAUCU	82	AUCUCUUUCCA CUGCUAUGA	192		65.07	4.10	35.40	0.84
537	516	536	UGAGUGUAACC GUCAUAGCAGU	83	UGCUAUGACGG UUACACUCA	193		103.20	2.51	70.37	1.43
539	518	538	UGAGAGUGUAA CCGUCAUAGCA	84	CUAUGACGGUU ACACUCUCA	194		109.37	5.79	70.03	2.07
607	586	606	UUUGUCACAGA UCGCUGUCUGC	85	AGACAGCGAUC UGUGACAAA	195		96.17	3.42	44.00	1.21
797	776	796	UCAUGAAGGAG UCUUGGCAGGA	86	CUGCCAAGACU CCUUCAUGA	196		85.97	6.60	49.30	2.57
800	779	799	UGUACAUGAAG GAGUCUUGGCA	87	CCAAGACUCCU UCAUGUACA	197		88.77	1.81	52.10	1.55
801	780	800	UCGUACAUGAA GGAGUCUUGGC	88	CAAGACUCCUU CAUGUACGA	198		66.07	1.73	34.07	0.58
803	782	802	UGUCGUACAUG AAGGAGUCUUG	89	AGACUCCUUCA UGUACGACA	199		93.53	0.84	70.07	1.95
829	808	828	UAAAGCUUCGG CCACCUCUUGA	90	AAGAGGUGGCC GAAGCUUUA	200		78.67	29.34	31.83	1.53
960	939	959	UAUCCAUCUAG CACCAGGUAGA	91	UACCUGGUGCU AGAUGGAUA	201		91.50	1.18	63.07	3.87
967	946	966	UCUGUCUGAUC CAUCUAGCACC	92	UGCUAGAUGGA UCAGACAGA	202		98.17	1.33	68.70	3.66
1001	980	1000	UCUUUUUGGCU CCUGUGAAGUU	93	CUUCACAGGAG CCAAAAAGA	203		109.17	2.98	78.10	3.41
1005	984	1004	UGACACUUUUU GGCUCCUGUGA	94	ACAGGAGCCAA AAAGUGUCA	204		86.37	2.29	50.30	3.93
1010	989	1009	UGACUAGACAC UUUUUGGCUCC	95	AGCCAAAAAGU GUCUAGUCA	205		92.17	2.23	59.93	1.49
1013	992	1012	UGUUGACUAGA CACUUUUUGGC	96	CAAAAAGUGUC UAGUCAACA	206		82.50	3.56	47.10	0.87
1017	996	1016	UUUAAGUUGAC UAGACACUUUU	97	AAGUGUCUAGU CAACUUAAA	207		53.50	0.20	35.40	0.78
1022	1001	1021	UCUCAAUUAAG UUGACUAGACA	98	UCUAGUCAACU UAAUUGAGA	208		73.60	3.65	49.90	4.61
1024	1003	1023	UUUCUCAAUUA AGUUGACUAGA	99	UAGUCAACUUA AUUGAGAAA	209		88.37	2.39	54.10	4.71
1037	1016	1036	UAUAACUUGCC ACCUUCUCAAU	100	UGAGAAGGUGG CAAGUUAUA	210		89.93	3.15	71.40	1.91
1038	1017	1037	UCAUAACUUGC CACCUUCUCAA	101	GAGAAGGUGGC AAGUUAUGA	211		89.57	6.29	58.70	4.31
1041	1020	1040	UCACCAUAACU UGCCACCUUCU	102	AAGGUGGCAAG UUAUGGUGA	212		78.73	4.21	48.87	1.43
1045	1024	1044	UUUCACACCAU AACUUGCCACC	103	UGGCAAGUUAU GGUGUGAAA	213		85.37	3.25	48.60	2.84
1178	1157	1177	UCUUCAACUUG UGGUCUUCAUA	104	UGAAGACCACA AGUUGAAGA	214		86.87	2.84	53.00	2.23
1180	1159	1179	UGACUUCAACU UGUGGUCUUCA	105	AAGACCACAAG UUGAAGUCA	215		86.97	4.64	73.60	8.92
1228	1207	1227	UCUCAUCAUGC UGUACACUGCC	106	CAGUGUACAGC AUGAUGAGA	216		73.07	3.92	49.53	1.16
1326	1305	1325	UUAAUUGGGUC CCCGCCCAUGU	107	AUGGGCGGGGA CCCAAUUAA	217		74.17	2.55	70.60	1.90
1333	1312	1332	UAUGACAGUAA UUGGGUCCCCG	108	GGGACCCAAUU ACUGUCAUA	218		75.57	0.93	43.20	3.30
1334	1313	1333	UAAUGACAGUA AUUGGGUCCCC	109	GGACCCAAUUA CUGUCAUUA	219		78.07	1.61	49.10	1.50

1335	1314	1334	UCAAUGACAGU AAUUGGGUCCC	110	GACCCAAUUAC UGUCAUUGA	220		67.87	3.27	39.03	1.98
1337	1316	1336	UAUCAAUGACA GUAAUUGGGUC	111	CCCAAUUACUG UCAUUGAUA	221		96.20	2.17	77.10	2.16
1338	1317	1337	UCAUCAAUGAC AGUAAUUGGGU	112	CCAAUUACUGU CAUUGAUGA	222		60.00	2.71	43.00	6.99
1340	1319	1339	UCUCAUCAAUG ACAGUAAUUGG	113	AAUUACUGUCA UUGAUGAGA	223		73.97	1.59	42.07	1.77
1406	1385	1405	UAUAGACAUCC AGAUAAUCCUC	114	GGAUUAUCUGG AUGUCUAUA	224		69.53	2.30	41.03	0.12
1407	1386	1406	UCAUAGACAUC CAGAUAAUCCU	115	GAUUAUCUGGA UGUCUAUGA	225		76.00	1.30	44.83	4.68
1454	1433	1453	UCAAAGCAUUG AUGUUCACUUG	116	AGUGAACAUCA AUGCUUUGA	226		92.70	4.40	69.80	2.41
1458	1437	1457	UAAGCCAAAGC AUUGAUGUUCA	117	AACAUCAAUGC UUUGGCUUA	227		64.30	4.36	37.23	1.52
1466	1445	1465	UUUUCUUGGAA GCCAAAGCAUU	118	UGCUUUGGCUU CCAAGAAAA	228		85.47	1.85	59.80	0.95
1467	1446	1466	UCUUUCUUGGA AGCCAAAGCAU	119	GCUUUGGCUUC CAAGAAAGA	229		88.23	4.54	65.93	2.16
1469	1448	1468	UGUCUUUCUUG GAAGCCAAAGC	120	UUUGGCUUCCA AGAAAGACA	230		71.17	1.75	42.10	1.44
1475	1454	1474	UCUCAUUGUCU UUCUUGGAAGC	121	UUCCAAGAAAG ACAAUGAGA	231		73.60	2.15	53.47	3.22
1478	1457	1477	UUUGCUCAUUG UCUUUCUUGGA	122	CAAGAAAGACA AUGAGCAAA	232		69.57	4.68	38.90	2.16
1479	1458	1478	UGUUGCUCAUU GUCUUUCUUGG	123	AAGAAAGACAA UGAGCAACA	233		61.23	2.82	36.33	3.02
1481	1460	1480	UAUGUUGCUCA UUGUCUUUCUU	124	GAAAGACAAUG AGCAACAUA	234		62.70	1.70	50.73	6.51
1482	1461	1481	UCAUGUUGCUC AUUGUCUUUCU	125	AAAGACAAUGA GCAACAUGA	235		78.77	6.54	41.27	1.64
1490	1469	1489	UUUUGAACACA UGUUGCUCAUU	126	UGAGCAACAUG UGUUCAAAA	236		92.00	0.71	36.37	3.64
1491	1470	1490	UCUUUGAACAC AUGUUGCUCAU	127	GAGCAACAUGU GUUCAAAGA	237		111.67	1.64	75.03	4.55
1493	1472	1492	UGACUUUGAAC ACAUGUUGCUC	128	GCAACAUGUGU UCAAAGUCA	238		100.37	1.19	43.60	3.69
1506	1485	1505	UUUUCCAUAUC CUUGACUUUGA	129	AAAGUCAAGGA UAUGGAAAA	239		71.53	3.49	26.70	1.76
1511	1490	1510	UCAGGUUUUCC AUAUCCUUGAC	130	CAAGGAUAUGG AAAACCUGA	240		98.37	2.03	73.90	2.69
1563	1542	1562	UCACAGAGACU CAGAGACUGGC	131	CAGUCUCUGAG UCUCUGUGA	241		99.33	4.91	74.73	5.32
1607	1586	1606	UUUGCUUGUGG UAAUCGGUACC	132	UACCGAUUACC ACAAGCAAA	242		76.37	3.24	35.80	1.56
1688	1667	1687	UAAAGUACUCA GACACCACAGC	133	UGUGGUGUCUG AGUACUUUA	243		81.20	2.55	38.33	4.78
1710	1689	1709	UAACAAUGUGC UGCUGUCAGCA	134	CUGACAGCAGC ACAUUGUUA	244		92.07	6.25	56.87	11.06
1742	1721	1741	UCUUGAUUGAG UGUUCCUUGUC	135	CAAGGAACACU CAAUCAAGA	245		78.00	2.25	40.33	4.77
1747	1726	1746	UCUGACCUUGA UUGAGUGUUCC	136	AACACUCAAUC AAGGUCAGA	246		96.17	5.47	55.57	6.20
1836	1815	1835	UGAAUUCCUGC UUCUUUUUUCC	137	AAAAAAGAAGC AGGAAUUCA	247		84.13	1.22	44.07	5.74
1848	1827	1847	UCAUAAAAUUC AGGAAUUCCUG	138	GGAAUUCCUGA AUUUUAUGA	248		68.40	2.10	29.40	2.10
1854	1833	1853	UCAUAGUCAUA AAAUUCAGGAA	139	CCUGAAUUUUA UGACUAUGA	249		86.67	3.20	41.07	0.79

1856	1835	1855	UGUCAUAGUCA UAAAAUUCAGG	140	UGAAUUUUAUG ACUAUGACA	250		70.17	4.04	30.03	3.42
1871	1850	1870	UCUUGAUCAGG GCAACGUCAUA	141	UGACGUUGCCC UGAUCAAGA	251		90.70	2.77	39.70	4.51
1879	1858	1878	UUUCUUGAGCU UGAUCAGGGCA	142	CCCUGAUCAAG CUCAAGAAA	252		99.63	2.39	60.50	4.31
1880	1859	1879	UAUUCUUGAGC UUGAUCAGGGC	143	CCUGAUCAAGC UCAAGAAUA	253		82.77	2.34	36.93	1.48
1883	1862	1882	UCUUAUUCUUG AGCUUGAUCAG	144	GAUCAAGCUCA AGAAUAAGA	254		88.63	4.09	55.10	3.84
1919	1898	1918	UGAGACAAAUG GGCCUGAUAGU	145	UAUCAGGCCCA UUUGUCUCA	255		83.83	2.23	41.43	1.23
1971	1950	1970	UAAGUGGUAGU UGGAGGAAGCC	146	CUUCCUCCAAC UACCACUUA	256		85.97	0.99	47.40	3.92
2021	2000	2020	UCAGAGCUUUG AUAUCCUGUGC	147	ACAGGAUAUCA AAGCUCUGA	257		91.37	3.18	58.10	2.70
2023	2002	2022	UAACAGAGCUU UGAUAUCCUGU	148	AGGAUAUCAAA GCUCUGUUA	258		66.20	1.68	30.37	2.63
2024	2003	2023	UAAACAGAGCU UUGAUAUCCUG	149	GGAUAUCAAAG CUCUGUUUA	259		92.77	1.10	59.83	3.00
2025	2004	2024	UCAAACAGAGC UUUGAUAUCCU	150	GAUAUCAAAGC UCUGUUUGA	260		74.77	2.16	31.10	3.00
2031	2010	2030	UCAGACACAAA CAGAGCUUUGA	151	AAAGCUCUGUU UGUGUCUGA	261		89.27	7.05	36.90	3.43
2072	2051	2071	UCUUGAUGUAG ACCUCCUUCCG	152	GAAGGAGGUCU ACAUCAAGA	262		93.67	2.58	57.90	4.35
2076	2055	2075	UCAUUCUUGAU GUAGACCUCCU	153	GAGGUCUACAU CAAGAAUGA	263		92.13	0.26	57.50	5.41
2088	2067	2087	UCUUUCUUAUC CCCAUUCUUGA	154	AAGAAUGGGGA UAAGAAAGA	264		149.93	24.82	67.17	3.57
2103	2082	2102	UCUCUCUCACA GCUGCCUUUCU	155	AAAGGCAGCUG UGAGAGAGA	265		94.53	4.90	54.93	0.84
2109	2088	2108	UGAGCAUCUCU CUCACAGCUGC	156	AGCUGUGAGAG AGAUGCUCA	266		82.23	2.93	39.60	2.90
2111	2090	2110	UUUGAGCAUCU CUCUCACAGCU	157	CUGUGAGAGAG AUGCUCAAA	267		107.80	3.18	72.93	0.78
2112	2091	2111	UAUUGAGCAUC UCUCUCACAGC	158	UGUGAGAGAGA UGCUCAAUA	268		96.43	3.88	56.97	2.84
2114	2093	2113	UAUAUUGAGCA UCUCUCUCACA	159	UGAGAGAGAUG CUCAAUAUA	269		75.13	0.37	35.33	0.41
2115	2094	2114	UCAUAUUGAGC AUCUCUCUCAC	160	GAGAGAGAUGC UCAAUAUGA	270		108.77	2.29	61.07	1.71
2138	2117	2137	UCUUGACUUUG UCAUAGCCUGG	161	AGGCUAUGACA AAGUCAAGA	271		83.90	1.97	43.90	1.96
2146	2125	2145	UGAGAUGUCCU UGACUUUGUCA	162	ACAAAGUCAAG GACAUCUCA	272		82.03	5.27	36.37	1.85
2201	2180	2200	UGUCAGCAUAG GGACUCACUCC	163	AGUGAGUCCCU AUGCUGACA	273		89.60	3.33	52.43	4.78
2209	2188	2208	UGUAUUGGGGU CAGCAUAGGGA	164	CCUAUGCUGAC CCCAAUACA	274		107.57	6.53	61.70	3.85
2222	2201	2221	UAUCACCUCUG CAAGUAUUGGG	165	CAAUACUUGCA GAGGUGAUA	275		74.30	8.75	25.57	3.38
2243	2222	2242	UAACUAUCAAG GGGCCGCCAGA	166	UGGCGGCCCCU UGAUAGUUA	276		91.70	0.99	74.00	3.85
2246	2225	2245	UGUGAACUAUC AAGGGGCCGCC	167	CGGCCCCUUGA UAGUUCACA	277		91.93	3.69	63.67	5.62
2248	2227	2247	UUUGUGAACUA UCAAGGGGCCG	168	GCCCCUUGAUA GUUCACAAA	278		75.07	1.39	34.10	0.42
2251	2230	2250	UCUCUUGUGAA CUAUCAAGGGG	169	CCUUGAUAGUU CACAAGAGA	279		92.43	2.42	51.23	4.15

2256	2235	2255	UGACUUCUCUU GUGAACUAUCA	170	AUAGUUCACAA GAGAAGUCA	280		81.60	4.46	40.70	5.31
2263	2242	2262	UAUGAAACGAC UUCUCUUGUGA	171	ACAAGAGAAGU CGUUUCAUA	281	*	25.67	1.21	15.67	1.05
2307	2286	2306	UUUUUGCAGAC AUCCACUACUC	172	GUAGUGGAUGU CUGCAAAAA	282		73.33	2.54	33.47	1.39
2309	2288	2308	UGUUUUUGCAG ACAUCCACUAC	173	AGUGGAUGUCU GCAAAAACA	283		90.23	1.30	39.10	1.81
2314	2293	2313	UUUCUGGUUUU UGCAGACAUCC	174	AUGUCUGCAAA AACCAGAAA	284		105.50	1.12	58.97	0.86
2399	2378	2398	UUUGGAGUUUC UCCUUCAGCCA	175	GCUGAAGGAGA AACUCCAAA	285		93.83	0.44	63.83	0.75
2402	2381	2401	UAUCUUGGAGU UUCUCCUUCAG	176	GAAGGAGAAAC UCCAAGAUA	286		75.43	3.16	28.63	1.52
2405	2384	2404	UCUCAUCUUGG AGUUUCUCCUU	177	GGAGAAACUCC AAGAUGAGA	287		73.90	4.95	29.13	1.56
2409	2388	2408	UAAUCCUCAUC UUGGAGUUUCU	178	AAACUCCAAGA UGAGGAUUA	288		75.87	1.47	40.83	0.98
2418	2397	2417	UGAAAACCCAA AUCCUCAUCUU	179	GAUGAGGAUUU GGGUUUUCA	289		69.60	2.10	31.33	0.87
40	19	39	UCUGAAACUCC AGACCUAGACC	290	UCUAGGUCUGG AGUUUCAGA	330		101.87	1.80	80.17	6.81
53	32	52	UCUCAGUGUCC AAGCUGAAACU	291	UUUCAGCUUGG ACACUGAGA	331		112.07	3.92	143.13	36.85
260	239	259	UGAUCUCUACC CCCUCCAGAGA	292	UCUGGAGGGGG UAGAGAUCA	332		116.10	9.49	119.00	16.30
287	266	286	UUUGGAGAAGU CGGAAGGAGCC	293	CUCCUUCCGAC UUCUCCAAA	333		144.60	43.86	109.80	20.04
290	269	289	UCUCUUGGAGA AGUCGGAAGGA	294	CUUCCGACUUC UCCAAGAGA	334		107.80	4.53	80.40	4.60
341	320	340	UCACAGGGUAC GGGUAGAAGCC	295	CUUCUACCCGU ACCCUGUGA	335		113.43	13.79	112.25	3.05
569	548	568	UCACUUGGCAG GUGCGAUUGGC	296	CAAUCGCACCU GCCAAGUGA	336		125.73	1.47	117.47	3.80
571	550	570	UUUCACUUGGC AGGUGCGAUUG	297	AUCGCACCUGC CAAGUGAAA	337		130.47	4.37	130.53	5.79
763	742	762	UCUCCAAGAGC CACCUUCCUGA	298	AGGAAGGUGGC UCUUGGAGA	338		106.90	6.02	89.33	0.82
790	769	789	UGAGUCUUGGC AGGAAGGCUCC	299	AGCCUUCCUGC CAAGACUCA	339		104.97	8.54	110.57	0.99
805	784	804	UGUGUCGUACA UGAAGGAGUCU	300	ACUCCUUCAUG UACGACACA	340		106.17	1.59	95.70	2.21
839	818	838	UGGAAGACAGG AAAGCUUCGGC	301	CGAAGCUUUCC UGUCUUCCA	341		101.45	10.35	102.47	7.63
844	823	843	UGUCAGGGAAG ACAGGAAAGCU	302	CUUUCCUGUCU UCCCUGACA	342		159.80	39.70	82.20	2.85
867	846	866	UCAUCGACUCC UUCUAUGGUCU	303	ACCAUAGAAGG AGUCGAUGA	343		108.70	9.41	93.63	3.23
938	917	937	UGUUCAUGGAG CCUGAAGGGUC	304	CCCUUCAGGCU CCAUGAACA	344		161.93	45.43	106.77	4.94
939	918	938	UUGUUCAUGGA GCCUGAAGGGU	305	CCUUCAGGCUC CAUGAACAA	345		127.33	7.65	100.87	4.07
940	919	939	UAUGUUCAUGG AGCCUGAAGGG	306	CUUCAGGCUCC AUGAACAUA	346		103.23	10.15	83.83	1.24
947	926	946	UCAGGUAGAUG UUCAUGGAGCC	307	CUCCAUGAACA UCUACCUGA	347		115.17	7.69	92.57	5.27
950	929	949	UCACCAGGUAG AUGUUCAUGGA	308	CAUGAACAUCU ACCUGGUGA	348		104.07	2.74	83.27	1.64
956	935	955	UAUCUAGCACC AGGUAGAUGUU	309	CAUCUACCUGG UGCUAGAUA	349		106.43	0.54	107.10	10.08

957	936	956	UCAUCUAGCAC CAGGUAGAUGU	310	AUCUACCUGGU GCUAGAUGA	350		100.70	5.93	105.60	11.23
1192	1171	1191	UGUGUUAGUCC CUGACUUCAAC	311	UGAAGUCAGGG ACUAACACA	351		91.97	2.11	80.83	2.71
1289	1268	1288	UCAUGAGGAUG AUGACAUGGCG	312	CCAUGUCAUCA UCCUCAUGA	352		98.53	2.86	91.97	2.07
1291	1270	1290	UGUCAUGAGGA UGAUGACAUGG	313	AUGUCAUCAUC CUCAUGACA	353		91.70	5.82	82.33	1.39
1327	1306	1326	UGUAAUUGGGU CCCCGCCCAUG	314	UGGGCGGGGAC CCAAUUACA	354		120.30	1.84	102.47	4.76
1329	1308	1328	UCAGUAAUUGG GUCCCCGCCCA	315	GGCGGGGACCC AAUUACUGA	355		126.17	10.02	113.37	12.38
1331	1310	1330	UGACAGUAAUU GGGUCCCCGCC	316	CGGGGACCCAA UUACUGUCA	356		118.13	1.67	103.50	4.35
1332	1311	1331	UUGACAGUAAU UGGGUCCCCGC	317	GGGGACCCAAU UACUGUCAA	357		108.43	2.72	96.57	3.34
1505	1484	1504	UUUCCAUAUCC UUGACUUUGAA	318	CAAAGUCAAGG AUAUGGAAA	358		107.93	3.46	93.23	0.95
1508	1487	1507	UGUUUUCCAUA UCCUUGACUUU	319	AGUCAAGGAUA UGGAAAACA	359		102.67	2.46	88.57	3.01
1951	1930	1950	UCUCAAAGCUC GAGUUGUUCCC	320	GAACAACUCGA GCUUUGAGA	360		99.80	2.96	94.70	4.51
2033	2012	2032	UCUCAGACACA AACAGAGCUUU	321	AGCUCUGUUUG UGUCUGAGA	361		100.67	2.18	87.47	4.79
2069	2048	2068	UGAUGUAGACC UCCUUCCGAGU	322	UCGGAAGGAGG UCUACAUCA	362		101.30	3.64	92.60	7.44
2087	2066	2086	UUUUCUUAUCC CCAUUCUUGAU	323	CAAGAAUGGGG AUAAGAAAA	363		103.07	1.24	83.03	4.30
2141	2120	2140	UGUCCUUGACU UUGUCAUAGCC	324	CUAUGACAAAG UCAAGGACA	364		102.63	4.02	82.33	5.04
2245	2224	2244	UUGAACUAUCA AGGGGCCGCCA	325	GCGGCCCCUUG AUAGUUCAA	365		103.47	8.19	83.60	9.88
2249	2228	2248	UCUUGUGAACU AUCAAGGGGCC	326	CCCCUUGAUAG UUCACAAGA	366		97.70	2.51	93.40	4.48
2324	2303	2323	UCUUUUGCCGC UUCUGGUUUUU	327	AAACCAGAAGC GGCAAAAGA	367		122.60	1.11	97.73	4.12
2336	2315	2335	UAGCAGGUACC UGCUUUUGCCG	328	GCAAAAGCAGG UACCUGCUA	368		100.27	2.46	89.90	1.43
2400	2379	2399	UCUUGGAGUUU CUCCUUCAGCC	329	CUGAAGGAGAA ACUCCAAGA	369		106.20	1.87	92.43	2.38

* Exemplary results of *in vivo* CFB dose response in HDI mouse liver are shown in FIG. 3

^ Exemplary results of *in vivo* CFB dose response in HDI mouse liver are shown in FIG. 4

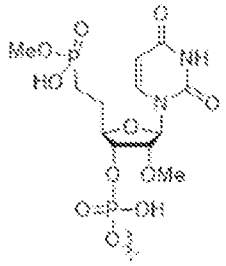
[0546] Table 3. Exemplary Modified Sequences of the Disclosure

	Sequence	SEQ ID NO:
G (5'-3')	[MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC]	SEQ ID NO: 370
P (5'-3')	[mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b]	SEQ ID NO: 381
G (5'-3')	[MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU]	SEQ ID NO: 371

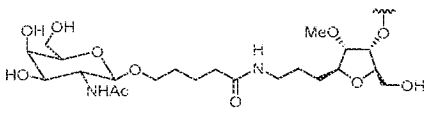
P (5'-3')	[mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b]	SEQ ID NO: 382
G (5'-3')	[MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA]	SEQ ID NO: 372
P (5'-3')	[mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b]	SEQ ID NO: 383
G (5'-3')	[MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU]	SEQ ID NO: 373
P (5'-3')	[mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b]	SEQ ID NO: 384
G (5'-3')	[MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU]	SEQ ID NO: 374
P (5'-3')	[mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b]	SEQ ID NO: 385
G (5'-3')	[MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG]	SEQ ID NO: 375
P (5'-3')	[mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b]	SEQ ID NO: 386
G (5'-3')	[MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC]	SEQ ID NO: 376
P (5'-3')	[mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b]	SEQ ID NO: 387
G (5'-3')	[mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC]	SEQ ID NO: 377
P (5'-3')	[mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b]	SEQ ID NO: 381
G (5'-3')	[mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU]	SEQ ID NO: 378
P (5'-3')	[mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b]	SEQ ID NO: 382
G (5'-3')	[mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA]	SEQ ID NO: 379
P (5'-3')	[mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b]	SEQ ID NO: 383

G: guide strand, P: passenger strand

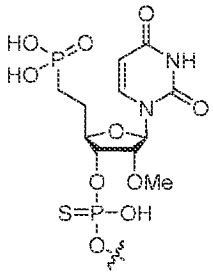
"m" indicates 2'-O-methyl modification, "f" indicates a 2'-F modification, "EPmU" is a phosphate mimic linked to a 5'-terminal uracil (shown below); "MeEPmU" is a mono methyl protected phosphate mimic linked to a 5'-terminal uracil (shown below), "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNAc G1b moiety (shown below).



(5'-MeEPmU)



(GalNAc G1b)



(5'-EPmUs)

[0547] EXAMPLES

[0548] EXAMPLE 1: Design and efficacy of siRNA compounds against human complement factor B (CFB) mRNA

[0549] *Compound Design*

[0550] A set of 184 siRNAs compounds against human CFB transcript (Accession No: NM_001710.6) were designed (see **Table 2**).

[0551] *Oligonucleotide Synthesis*

[0552] Oligonucleotides were prepared by solid-phase synthesis according to standard protocols. Briefly, oligonucleotide synthesis was conducted on a solid support to incorporate each nucleoside phosphoramidites from 3'-end to 5'-end to prepare oligo single strands. ETT or BTT was used as an activator for the coupling reaction. Iodine in water/pyridine/THF was used to oxidize phosphite-triester (P(III)) to afford phosphate backbones and DDTT was used for the preparation of phosphorothioate linkages. Aqueous ammonium was used to cleave oligos from solid support and to remove protecting groups globally. The oligonucleotide crude was then concentrated by Genevac and purified by AEX-HPLC. The pure fractions were combined and concentrated, and their purity was analyzed by LC-MS. The oligonucleotides were then dialyzed against water using MidiTrap G-25 column, concentrated, and their OD amounts were measured.

[0553] To prepare siRNA duplexes, the sense and antisense strands were annealed at 95 °C for 10 min, based on equal molar amounts, and cooled down to room temperature. The duplex purity was determined by AEX-HPLC, and the solutions were lyophilized to afford the desired siRNA duplex powder.

[0554] *In vitro Screening*

[0555] The compounds were diluted into the desired concentration with PBS. The diluted compounds were then transfected into the cultured Huh-7 cells with Lipofectamine RNAiMAX (Invitrogen-13778-150) reagents on Day 0. Each compound was tested at concentrations of 0.02 nM and 0.1 nM. At 24 hours post transfection on Day 1, mRNA was extracted from the transfected cells using RNeasy 96 kit (Qiagen-74182).

[0556] The percentage of human CFB mRNA remaining in cells relative to mock transfection when normalized to Gapdh mRNA levels, was determined for each compound at a concentration of either 0.02 nM and 0.1 nM. The results identified several compounds that were able to reduce the level of human CFB mRNA in transfected cells by 20% to 50% or more than 50% at the defined concentrations as described in **Table 2** and **FIG. 1** and **FIG. 2**). Also, several compounds from shown in bold in **Table 2** were able to reduce the level of human CFB mRNA in transfected cells by between 20% to 50% or at least 50% at 0.02 nM and 0.1 nM (see **Table 2**, and **FIG. 1** and **FIG. 2**). In summary, the present disclosure identifies numerous siRNA compounds that reduce the level of CFB mRNA in target cells when administered at a dosage of 0.02 nM or 0.1 nM, or at both concentrations.

[0557] *In vivo HDI screening*

[0558] A subset of compounds with GalNAc conjugations from **Table 2** were formulated in 1X PBS dosed on day 1 through subcutaneous dosing to BALB/c female animals (6~8 weeks old). Animals then received 10μg of pcDNA3.1-hsCFB plasmids on day 4. Liver biopsies were taken on day 5 for mRNA remaining analysis through RT-qPCR.

[0559] For dose response study, 6-8 weeks old female BALB/c mice were dosed subcutaneously at 0.25 mg/kg (grey triangles), 0.5 mg/kg (grey squares) or 1 mg/kg (black circles) (**FIG. 4**). The control animals were dosed with PBS. Animals were sacrificed 4 days post-dose and liver samples were collected for RNA extraction and human CFB mRNA expression analysis by RT-qPCR. The results of the experiments are shown in **FIG. 3** and **FIG. 4**. The tested compounds were able to reduce the level of human CFB mRNA.

[0560] *In vivo potency and duration evaluation in Macaca fascicularis*

[0561] To determine CFB knockdown in non-human primates, a nonterminal study was conducted in cynomolgus macaques. A subset of the compounds with GalNAc conjugations (**Table 3**) were tested. A liver biopsy was taken from *cyno* monkeys in the study to determine the baseline mRNA expression level one week before dosing (Day -7). Animals were dosed with a single dose of 3mg/kg subcutaneously a week after a biopsy (Day 1). A biopsy of the liver was taken at 15, 29, 57, 85 and 113 days post dosing. Serum samples were collected 7, 14, 21, 28, 42, 56, 70 and 84 days post dosing. Liver samples were used for mRNA remaining analysis by RT-qPCR and blood samples were used for serum CFB protein analysis by ELISA.

[0562] *RT-qPCR*

[0563] Liver mRNA samples were prepared with RNeasy Plus mini kit (Qiagen, 74104). mRNAs were reverse transcribed into cDNAs using High-Capacity cDNA Reverse transcription kits with RNase Inhibitors (Thermo, 4374967). TaqMan multiplex qPCR assays (Thermo, 4444557) were performed to determine the relative CFB mRNA levels over time.

[0564] *ELISA*

[0565] CFB Human ELISA kit (Abcam, ab137973) was validated for cross reactivity to Cynomolgus monkey. Serum samples were diluted 1:3,000 and ELISA were performed. CFB protein level (μg/ml) was calculated based on standard curve and normalized to pre-dose. The results of the experiment are shown in **FIGS. 5A** and **5B**. As shown in **FIG. 5A** by Day 15, all compounds had reduced liver CFB mRNA by at least 80% relative to pre-dosing levels (Day -7). The maximum reduction in CFB mRNA for all compounds was seen at Day 15 post-dosing, as shown in **FIG. 5A**. As shown in **FIG. 5B** by Days, 14, 21, 28, 42 and 56 all compounds had reduced serum CFB protein by at least 60% relative to pre-dosing levels (Day -7). The maximum reduction in serum CFB protein for all compounds was seen at Day 28 post-dosing, as shown in **FIG. 5B**.

[0566] Additional embodiments of the disclosure include the following:

Embodiment 1. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

Embodiment 2. The isolated oligonucleotide of embodiment 1, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 3. The isolated oligonucleotide of embodiment 1, wherein the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 4. The isolated oligonucleotide of any one of embodiments 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 5. The isolated oligonucleotide of embodiment 4, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 6. The isolated oligonucleotide of embodiment 4, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 7. The isolated oligonucleotide of any one of embodiments 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 8. The isolated oligonucleotide of embodiment 7, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 9. The isolated oligonucleotide of embodiment 7, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 10. The isolated oligonucleotide of any one of embodiments 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 11. The isolated oligonucleotide of embodiment 10, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 12. The isolated oligonucleotide of embodiment 10, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

Embodiment 13. The isolated oligonucleotide of any one of embodiments 1-12, wherein the isolated oligonucleotide is capable of inducing degradation of the CFB mRNA.

Embodiment 14. The isolated oligonucleotide of any one of embodiments 1-13, wherein either the sense strand or antisense strand is a single stranded RNA molecule.

Embodiment 15. The isolated oligonucleotide of any one of embodiments 1-13, wherein both the sense strand and the antisense strand are single stranded RNA molecules.

Embodiment 16. The isolated oligonucleotide of any one of embodiments 1-15, wherein the antisense strand comprises a 3' overhang.

Embodiment 17. The isolated oligonucleotide of embodiment 16, wherein the 3' overhang comprises at least one nucleotide.

Embodiment 18. The isolated oligonucleotide of any one of embodiments 1-17, wherein the sense strand comprises an RNA sequence of at least 20 nucleotides in length.

Embodiment 19. The isolated oligonucleotide of any one of embodiments 1-18, wherein the antisense strand comprises an RNA sequence of at least 22 nucleotides in length.

Embodiment 20. The isolated oligonucleotide of any one of embodiments 1-19, wherein the double stranded region is between 19 and 21 nucleotides in length.

Embodiment 21. The isolated oligonucleotide of any one of embodiments 1-20, wherein the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35.

Embodiment 22. The isolated oligonucleotide of any one of embodiments 1-21, wherein the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69.

Embodiment 23. The isolated oligonucleotide of embodiment 6, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

Embodiment 24. The isolated oligonucleotide of embodiment 9, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

Embodiment 25. The isolated oligonucleotide of embodiment 12, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); or

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3').

Embodiment 26. The isolated oligonucleotide of any one of embodiments 1-25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

Embodiment 27. The isolated oligonucleotide of embodiment 26, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

Embodiment 28. The isolated oligonucleotide of any one of embodiments 1-25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

Embodiment 29. The isolated oligonucleotide of embodiment 28, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

Embodiment 30. The isolated oligonucleotide of embodiment 25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

Embodiment 31. The isolated oligonucleotide of embodiment 30, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3'); or

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3').

Embodiment 32. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 5 to 38;

b) 340 to 606;

c) 776 to 828;

d) 939 to 1227;

e) 1305 to 1606;

f) 1667 to 1746;

g) 1815 to 2313; and

h) 2378 to 2417,

from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

Embodiment 33. The isolated oligonucleotide of embodiment 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.1 nM.

Embodiment 34. The isolated oligonucleotide of embodiment 33, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' UGACACUUUUUGGCUCCUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 204 (5' ACAGGAGCCAAAAAGUGUCA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UCUCUUGUGAACUAUCAAGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CCUUGAUAGUUCACAAGAGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' UGUACAUGAAGGAGUCUUGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 197 (5' CCAAGACUCCUUCAUGUACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 163 (5' UGUCAGCAUAGGGACUCACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' AGUGAGUCCCUAUGCUGACA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUUCAACUUGUGGUCUUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UGAAGACCACAAGUUGAAGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UUUCUCAAUUAAGUUGACUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UAGUCAACUUAAUUGAGAAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UCUCUCUCACAGCUGCCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' AAAGGCAGCUGUGAGAGAGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCUUAUUCUUGAGCUUGAUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' GAUCAAGCUCAAGAAUAAGA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5' UCUGACCUUGAUUGAGUGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' AACACUCAAUCAAGGUCAGA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAUUGCUCUGCACUCUGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' GCAGAGUGCAGAGCAAUCCA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UAACAAUGUGCUGCUGUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' CUGACAGCAGCACAUUGUUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UAUUGAGCAUCUCUCUCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UGUGAGAGAGAUGCUCAAUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UCAUUCUUGAUGUAGACCUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' GAGGUCUACAUCAAGAAUGA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' UGAAACUCCAGACCUAGACCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' GGUCUAGGUCUGGAGUUUCA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCUUGAUGUAGACCUCCUUCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' GAAGGAGGUCUACAUCAAGA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 147 (5' UCAGAGCUUUGAUAUCCUGUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 257 (5' ACAGGAUAUCAAAGCUCUGA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' UCAUAACUUGCCACCUUCUCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' GAGAAGGUGGCAAGUUAUGA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 174 (5' UUUCUGGUUUUUGCAGACAUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 284 (5' AUGUCUGCAAAAACCAGAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 118 (5' UUUUCUUGGAAGCCAAAGCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 228 (5' UGCUUUGGCUUCCAAGAAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UAAACAGAGCUUUGAUAUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' GGAUAUCAAAGCUCUGUUUA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' UGACUAGACACUUUUUGGCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' AGCCAAAAAGUGUCUAGUCA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 142 (5' UUUCUUGAGCUUGAUCAGGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' CCCUGAUCAAGCUCAAGAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UCAUAUUGAGCAUCUCUCUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' GAGAGAGAUGCUCAAUAUGA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUAUUGGGGUCAGCAUAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' CCUAUGCUGACCCCAAUACA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' UUGAAACUCCAGACCUAGACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' GUCUAGGUCUGGAGUUUCAA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' UAUCCAUCUAGCACCAGGUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UACCUGGUGCUAGAUGGAUA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGUGAACUAUCAAGGGGCCGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' CGGCCCCUUGAUAGUUCACA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 175 (5' UUUGGAGUUUCUCCUUCAGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 285 (5' GCUGAAGGAGAAACUCCAAA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' UAAACUCCAGACCUAGACCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' AGGUCUAGGUCUGGAGUUUA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 119 (5' UCUUUCUUGGAAGCCAAAGCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' GCUUUGGCUUCCAAGAAAGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UCUUUCUUAUCCCCAUUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 264 (5' AAGAAUGGGGAUAAGAAAGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UCUAGACCUGGUCACAUUCCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' GGAAUGUGACCAGGUCUAGA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' UCUGUCUGAUCCAUCUAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UGCUAGAUGGAUCAGACAGA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 116 (5' UCAAAGCAUUGAUGUUCACUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' AGUGAACAUCAAUGCUUUGA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UGAGAGUGUAACCGUCAUAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' CUAUGACGGUUACACUCUCA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' UGUCGUACAUGAAGGAGUCUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' AGACUCCUUCAUGUACGACA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' UGAGUGUAACCGUCAUAGCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UGCUAUGACGGUUACACUCA 3');

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3');

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' UAUAACUUGCCACCUUCUCAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UGAGAAGGUGGCAAGUUAUA 3');

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGAGCAUCUCUCUCACAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' CUGUGAGAGAGAUGCUCAAA 3');

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' UCUCACAUUGUAGUAGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' CUCCCUACUACAAUGUGAGA 3');

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' UGACUUCAACUUGUGGUCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 215 (5' AAGACCACAAGUUGAAGUCA 3');

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UCAGGUUUUCCAUAUCCUUGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' CAAGGAUAUGGAAAACCUGA 3');

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UAACUAUCAAGGGGCCGCCAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 276 (5' UGGCGGCCCCUUGAUAGUUA 3');

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCACAGAGACUCAGAGACUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' CAGUCUCUGAGUCUCUGUGA 3');

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGAACACAUGUUGCUCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' GAGCAACAUGUGUUCAAAGA 3');

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' UAUCAAUGACAGUAAUUGGGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' CCCAAUUACUGUCAUUGAUA 3');

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' UCUUUUUGGCUCCUGUGAAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 203 (5' CUUCACAGGAGCCAAAAAGA 3'); or

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' UAACUCCAGACCUAGACCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' CAGGUCUAGGUCUGGAGUUA 3').

Embodiment 35. The isolated nucleotide of embodiment 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

Embodiment 36. The isolated oligonucleotide of embodiment 35, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UUUUGAACACAUGUUGCUCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UGAGCAACAUGUGUUCAAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 162 (5' UGAGAUGUCCUUGACUUUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' ACAAAGUCAAGGACAUCUCA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAGACACAAACAGAGCUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 261 (5' AAAGCUCUGUUUGUGUCUGA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 143 (5' UAUUCUUGAGCUUGAUCAGGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' CCUGAUCAAGCUCAAGAAUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAAAGUACUCAGACACCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UGUGGUGUCUGAGUACUUUA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UGUUUUUGCAGACAUCCACUAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 283 (5' AGUGGAUGUCUGCAAAAACA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAGCAUCUCUCUCACAGCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 266 (5' AGCUGUGAGAGAGAUGCUCA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 141 (5' UCUUGAUCAGGGCAACGUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UGACGUUGCCCUGAUCAAGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UCUUGAUUGAGUGUUCCUUGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' CAAGGAACACUCAAUCAAGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGACUUCUCUUGUGAACUAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' AUAGUUCACAAGAGAAGUCA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UAAUCCUCAUCUUGGAGUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5' AAACUCCAAGAUGAGGAUUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5' UAUAGACAUCCAGAUAAUCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' GGAUUAUCUGGAUGUCUAUA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5' UCAUAGUCAUAAAAUUCAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 249 (5' CCUGAAUUUUAUGACUAUGA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCAUGUUGCUCAUUGUCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' AAAGACAAUGAGCAACAUGA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGAGACAAAUGGGCCUGAUAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 255 (5' UAUCAGGCCCAUUUGUCUCA 3');

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UCUCAUCAAUGACAGUAAUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' AAUUACUGUCAUUGAUGAGA 3');

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGUCUUUCUUGGAAGCCAAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5' UUUGGCUUCCAAGAAAGACA 3');

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UGAUCUGCAGGUACGUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' AGACACGUACCUGCAGAUCA 3');

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCAUCAAUGACAGUAAUUGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3');

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3');

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UGACUUUGAACACAUGUUGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 238 (5' GCAACAUGUGUUCAAAGUCA 3');

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 161 (5' UCUUGACUUUGUCAUAGCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' AGGCUAUGACAAAGUCAAGA 3');

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUCACAGAUCGCUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' AGACAGCGAUCUGUGACAAA 3');

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UGAAUUCCUGCUUCUUUUUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' AAAAAAGAAGCAGGAAUUCA 3');

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' UGAAAGAGAUCUCAUCACUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' GAGUGAUGAGAUCUCUUUCA 3');

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3');

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' UGUUGACUAGACACUUUUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' CAAAAAGUGUCUAGUCAACA 3');

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 146 (5' UAAGUGGUAGUUGGAGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' CUUCCUCCAACUACCACUUA 3');

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' UAUCACUCACAUUGUAGUAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 188 (5' CUACUACAAUGUGAGUGAUA 3');

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' UUUCACACCAUAACUUGCCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 213 (5' UGGCAAGUUAUGGUGUGAAA 3');

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3');

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3');

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' UCAUGAAGGAGUCUUGGCAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' CUGCCAAGACUCCUUCAUGA 3');

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3'); or

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3').

Embodiment 37. The isolated oligonucleotide of embodiment 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

Embodiment 38. The isolated oligonucleotide of embodiment 37, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UCUUGAUUGAGUGUUCCUUGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' CAAGGAACACUCAAUCAAGA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UAAUCCUCAUCUUGGAGUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5' AAACUCCAAGAUGAGGAUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5' UAUAGACAUCCAGAUAAUCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' GGAUUAUCUGGAUGUCUAUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCAUGUUGCUCAUUGUCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' AAAGACAAUGAGCAACAUGA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UCUCAUCAAUGACAGUAAUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' AAUUACUGUCAUUGAUGAGA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGUCUUUCUUGGAAGCCAAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5' UUUGGCUUCCAAGAAAGACA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UGAUCUGCAGGUACGUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' AGACACGUACCUGCAGAUCA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCAUCAAUGACAGUAAUUGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3'); or

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3').

Embodiment 39. The isolated oligonucleotide of embodiment 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

Embodiment 40. The isolated oligonucleotide of embodiment 39, wherein the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3').

Embodiment 41. The isolated oligonucleotide of any one of embodiments 1ssssss-40, wherein the sense strand or the antisense strand or both comprise one or more modified nucleotide(s).

Embodiment 42. A vector encoding the isolated oligonucleotide of any one of embodiments 1-41.

Embodiment 43. A delivery system comprising the isolated oligonucleotide of any one of embodiments 1-41 or the vector of embodiment 42.

Embodiment 44. A pharmaceutical composition comprising at least one isolated oligonucleotide of any one of embodiments 1-41, the vector of embodiment 42, or the delivery system of embodiment 43, and a pharmaceutically acceptable carrier, diluent or excipient.

Embodiment 45. A kit comprising at least one isolated oligonucleotide of any one of embodiments 1-41, the vector of embodiment 42, the delivery system of embodiment 43, or the pharmaceutical composition of embodiment 44.

Embodiment 46. A method of inhibiting or downregulating the expression or level of CFB in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide of any one of embodiments 1-41, the vector of embodiment 42, the delivery system of embodiment 43, or the pharmaceutical composition of embodiment 44.

Embodiment 47. A method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide of any one of embodiments 1-41, the vector of embodiment 42, the delivery system of embodiment 43, or the pharmaceutical composition of embodiment 44.

Embodiment 48. The isolated oligonucleotide of embodiment 1, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 25% at a dose of 1mg/kg.

Embodiment 49. The isolated oligonucleotide of embodiment 48, wherein the double stranded region comprises: i) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3');

v) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' ACUGCUAUGACGGUUACACA 3');

vi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

vii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

viii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

ix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

x) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

xi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

xvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

xix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xx) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xxi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3');

xxii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

xxiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3');

xxiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xxv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3');

xxvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3');

xxviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or

xxix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

Embodiment 50. The isolated oligonucleotide of embodiment 48, wherein the double stranded region comprises: i) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3');

v) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 391 (5' ACUGCUAUGACGGUUACACA 3');

vi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

viii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

ix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

x) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');
xiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');
xv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');
xvi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');
xvii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');
xviii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');
xix) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');
xx) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3');
xxi) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');
xxii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3');

xxiii) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxiv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or

xxv) an anti-sense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

CLAIMS

What is claimed is:

1. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

2. The isolated oligonucleotide of claim 1, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

3. The isolated oligonucleotide of claim 1, wherein the sense strand comprises a nucleotide sequence that is identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1606 to 1686;

e) 1821 to 1881;

f) 2116 to 2307; and

g) 2382 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

4. The isolated oligonucleotide of any one of claims 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

5. The isolated oligonucleotide of claim 4, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

6. The isolated oligonucleotide of claim 4, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 503 to 523; and

b) 2190 to 2210,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

7. The isolated oligonucleotide of any one of claims 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

8. The isolated oligonucleotide of claim 7, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

9. The isolated oligonucleotide of claim 7, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 493 to 534;

b) 991 to 1054;

c) 1384 to 1500;

d) 1666 to 1686;

e) 1821 to 1881;

f) 2116 to 2136;

g) 2232 to 2307; and

h) 2394 to 2468,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

10. The isolated oligonucleotide of any one of claims 1-3, wherein the sense strand comprises a nucleotide sequence that is substantially identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

11. The isolated oligonucleotide of claim 10, wherein the sense strand comprises a nucleotide sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

12. The isolated oligonucleotide of claim 10, wherein the sense strand comprises a nucleotide sequence that is identical to a region between any one of the nucleotide positions selected from:

a) 995 to 1019;

b) 1606 to 1626;

c) 1860 to 1880; and

d) 2382 to 2402,

from the 5' end of a human CFB mRNA sequence according to SEQ ID NO: 1.

13. The isolated oligonucleotide of any one of claims 1-12, wherein the isolated oligonucleotide is capable of inducing degradation of the CFB mRNA.

14. The isolated oligonucleotide of any one of claims 1-13, wherein either the sense strand or antisense strand is a single stranded RNA molecule.

15. The isolated oligonucleotide of any one of claims 1-13, wherein both the sense strand and the antisense strand are single stranded RNA molecules.

16. The isolated oligonucleotide of any one of claims 1-15, wherein the antisense strand comprises a 3' overhang.

17. The isolated oligonucleotide of claim 16, wherein the 3' overhang comprises at least one nucleotide.

18. The isolated oligonucleotide of any one of claims 1-17, wherein the sense strand comprises an RNA sequence of at least 20 nucleotides in length.

19. The isolated oligonucleotide of any one of claims 1-18, wherein the antisense strand comprises an RNA sequence of at least 22 nucleotides in length.

20. The isolated oligonucleotide of any one of claims 1-19, wherein the double stranded region is between 19 and 21 nucleotides in length.

21. The isolated oligonucleotide of any one of claims 1-20, wherein the antisense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 2-35.

22. The isolated oligonucleotide of any one of claims 1-21, wherein the sense strand comprises a nucleotide sequence according to any one of: SEQ ID NOs: 36-69.

23. The isolated oligonucleotide of claim 6, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

24. The isolated oligonucleotide of claim 9, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3'); or

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3').

25. The isolated oligonucleotide of claim 12, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3'); or

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3').

26. The isolated oligonucleotide of any one of claims 1-25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

27. The isolated oligonucleotide of claim 26, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

28. The isolated oligonucleotide of any one of claims 1-25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

29. The isolated oligonucleotide of claim 28, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 2 (5' UAAAGAGAUCUCAUCACUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 36 (5' UGAGUGAUGAGAUCUCUUUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 3 (5' UGGAAAGAGAUCUCAUCACUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 37 (5' AGUGAUGAGAUCUCUUUCCA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 4 (5' UCAGUGGAAAGAGAUCUCAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 38 (5' AUGAGAUCUCUUUCCACUGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 6 (5' UGUGUAACCGUCAUAGCAGUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 389 (5' ACUGCUAUGACGGUUACACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 9 (5' UAAUUAAGUUGACUAGACACUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 43 (5' GUGUCUAGUCAACUUAAUUA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 12 (5' UUAGACAUCCAGAUAAUCCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 46 (5' AGGAUUAUCUGGAUGUCUAA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 13 (5' UAAGCAUUGAUGUUCACUUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 47 (5' CAAGUGAACAUCAAUGCUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 14 (5' UAAAGCAUUGAUGUUCACUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 48 (5' AAGUGAACAUCAAUGCUUUA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 22 (5' UUAAAAUUCAGGAAUUCCUGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 56 (5' CAGGAAUUCCUGAAUUUUAA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 23 (5' UAUAAAAUUCAGGAAUUCCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 57 (5' AGGAAUUCCUGAAUUUUAUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 24 (5' UGUCAUAAAAUUCAGGAAUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 58 (5' AAUUCCUGAAUUUUAUGACA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 30 (5' UAAACGACUUCUCUUGUGAACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 64 (5' UUCACAAGAGAAGUCGUUUA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 34 (5' UAAACCCAAAUCCUCAUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 68 (5' AAGAUGAGGAUUUGGGUUUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 35 (5' UCAGCUGUUUUAAUUCAAUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 69 (5' GAUUGAAUUAAAACAGCUGA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 5 (5' UAUAGCAGUGGAAAGAGAUCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 39 (5' GAUCUCUUUCCACUGCUAUA 3'); or

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 28 (5' UAAGUAUUGGGGUCAGCAUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 62 (5' UAUGCUGACCCCAAUACUUA 3').

30. The isolated oligonucleotide of claim 25, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

31. The isolated oligonucleotide of claim 30, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 8 (5' UUAAGUUGACUAGACACUUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 42 (5' AAAGUGUCUAGUCAACUUAA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 10 (5' UCAAUUAAGUUGACUAGACACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 44 (5' UGUCUAGUCAACUUAAUUGA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 18 (5' UGAGAUCUUGGCCUGCCAUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 52 (5' CAUGGCAGGCCAAGAUCUCA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 25 (5' UUAUUCUUGAGCUUGAUCAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 59 (5' CUGAUCAAGCUCAAGAAUAA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 32 (5' UCAUCUUGGAGUUUCUCCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 66 (5' AAGGAGAAACUCCAAGAUGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 31 (5' UUUUUUGCAGACAUCCACUACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 65 (5' UAGUGGAUGUCUGCAAAAAA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 33 (5' UAACCCAAAUCCUCAUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 67 (5' CAAGAUGAGGAUUUGGGUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 26 (5' UUUAUUCUUGAGCUUGAUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 60 (5' UGAUCAAGCUCAAGAAUAAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 27 (5' UUUGACUUUGUCAUAGCCUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 61 (5' CAGGCUAUGACAAAGUCAAA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 29 (5' UUUCUCUUGUGAACUAUCAAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 63 (5' UUGAUAGUUCACAAGAGAAA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 15 (5' UAACACAUGUUGCUCAUUGUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 49 (5' ACAAUGAGCAACAUGUGUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 16 (5' UUUGACUUUGAACACAUGUUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 50 (5' AACAUGUGUUCAAAGUCAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 17 (5' UAUAUCCUUGACUUUGAACACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 51 (5' UGUUCAAAGUCAAGGAUAUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 19 (5' UAAGUACUCAGACACCACAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 53 (5' CUGUGGUGUCUGAGUACUUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 20 (5' UAUUCAGGAAUUCCUGCUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 54 (5' GAAGCAGGAAUUCCUGAAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 21 (5' UAAUUCAGGAAUUCCUGCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 55 (5' AAGCAGGAAUUCCUGAAUUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 7 (5' UUUGACUAGACACUUUUUGGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 41 (5' CCAAAAAGUGUCUAGUCAAA 3'); or

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 11 (5' UAUAUCUUGGCUUCACACCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 45 (5' UGGUGUGAAGCCAAGAUAUA 3').

32. An isolated oligonucleotide comprising a sense strand and an antisense strand, wherein:

the sense strand comprises a nucleotide sequence that is substantially identical to a region comprising 19-25 nucleotides between any one of the nucleotide positions selected from:

a) 5 to 38;

b) 340 to 606;

c) 776 to 828;

d) 939 to 1227;

e) 1305 to 1606;

f) 1667 to 1746;

g) 1815 to 2313; and

h) 2378 to 2417,

from the 5' end of a CFB mRNA sequence according to SEQ ID NO: 1,

and the antisense strand is substantially complementary to the sense strand such that the sense strand and the antisense strand together form a double stranded region.

33. The isolated oligonucleotide of claim 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.1 nM.

34. The isolated oligonucleotide of claim 33, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 94 (5' UGACACUUUUUGGCUCCUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 204 (5' ACAGGAGCCAAAAAGUGUCA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 169 (5' UCUCUUGUGAACUAUCAAGGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 279 (5' CCUUGAUAGUUCACAAGAGA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 87 (5' UGUACAUGAAGGAGUCUUGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 197 (5' CCAAGACUCCUUCAUGUACA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 163 (5' UGUCAGCAUAGGGACUCACUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 273 (5' AGUGAGUCCCUAUGCUGACA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 104 (5' UCUUCAACUUGUGGUCUUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 214 (5' UGAAGACCACAAGUUGAAGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 99 (5' UUUCUCAAUUAAGUUGACUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 209 (5' UAGUCAACUUAAUUGAGAAA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 155 (5' UCUCUCUCACAGCUGCCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 265 (5' AAAGGCAGCUGUGAGAGAGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 144 (5' UCUUAUUCUUGAGCUUGAUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 254 (5' GAUCAAGCUCAAGAAUAAGA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 136 (5' UCUGACCUUGAUUGAGUGUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 246 (5' AACACUCAAUCAAGGUCAGA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 76 (5' UGGAUUGCUCUGCACUCUGCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 186 (5' GCAGAGUGCAGAGCAAUCCA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 134 (5' UAACAAUGUGCUGCUGUCAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 244 (5' CUGACAGCAGCACAUUGUUA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 158 (5' UAUUGAGCAUCUCUCUCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 268 (5' UGUGAGAGAGAUGCUCAAUA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 153 (5' UCAUUCUUGAUGUAGACCUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 263 (5' GAGGUCUACAUCAAGAAUGA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 73 (5' UGAAACUCCAGACCUAGACCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 183 (5' GGUCUAGGUCUGGAGUUUCA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 152 (5' UCUUGAUGUAGACCUCCUUCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 262 (5' GAAGGAGGUCUACAUCAAGA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 147 (5' UCAGAGCUUUGAUAUCCUGUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 257 (5' ACAGGAUAUCAAAGCUCUGA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 101 (5' UCAUAACUUGCCACCUUCUCAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 211 (5' GAGAAGGUGGCAAGUUAUGA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 174 (5' UUUCUGGUUUUUGCAGACAUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 284 (5' AUGUCUGCAAAAACCAGAAA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 118 (5' UUUUCUUGGAAGCCAAAGCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 228 (5' UGCUUUGGCUUCCAAGAAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 149 (5' UAAACAGAGCUUUGAUAUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 259 (5' GGAUAUCAAAGCUCUGUUUA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 95 (5' UGACUAGACACUUUUUGGCUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 205 (5' AGCCAAAAAGUGUCUAGUCA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 142 (5' UUUCUUGAGCUUGAUCAGGGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 252 (5' CCCUGAUCAAGCUCAAGAAA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 160 (5' UCAUAUUGAGCAUCUCUCUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 270 (5' GAGAGAGAUGCUCAAUAUGA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 164 (5' UGUAUUGGGGUCAGCAUAGGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 274 (5' CCUAUGCUGACCCCAAUACA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 74 (5' UUGAAACUCCAGACCUAGACCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 184 (5' GUCUAGGUCUGGAGUUUCAA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 91 (5' UAUCCAUCUAGCACCAGGUAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 201 (5' UACCUGGUGCUAGAUGGAUA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 167 (5' UGUGAACUAUCAAGGGGCCGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 277 (5' CGGCCCCUUGAUAGUUCACA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 175 (5' UUUGGAGUUUCUCCUUCAGCCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 285 (5' GCUGAAGGAGAAACUCCAAA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 72 (5' UAAACUCCAGACCUAGACCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 182 (5' AGGUCUAGGUCUGGAGUUUA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 119 (5' UCUUUCUUGGAAGCCAAAGCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 229 (5' GCUUUGGCUUCCAAGAAAGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 154 (5' UCUUUCUUAUCCCCAUUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 264 (5' AAGAAUGGGGAUAAGAAAGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 70 (5' UCUAGACCUGGUCACAUUCCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 180 (5' GGAAUGUGACCAGGUCUAGA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 92 (5' UCUGUCUGAUCCAUCUAGCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 202 (5' UGCUAGAUGGAUCAGACAGA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 116 (5' UCAAAGCAUUGAUGUUCACUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 226 (5' AGUGAACAUCAAUGCUUUGA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 84 (5' UGAGAGUGUAACCGUCAUAGCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 194 (5' CUAUGACGGUUACACUCUCA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 89 (5' UGUCGUACAUGAAGGAGUCUUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 199 (5' AGACUCCUUCAUGUACGACA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 83 (5' UGAGUGUAACCGUCAUAGCAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 193 (5' UGCUAUGACGGUUACACUCA 3');

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3');

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 100 (5' UAUAACUUGCCACCUUCUCAAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 210 (5' UGAGAAGGUGGCAAGUUAUA 3');

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 157 (5' UUUGAGCAUCUCUCUCACAGCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 267 (5' CUGUGAGAGAGAUGCUCAAA 3');

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 77 (5' UCUCACAUUGUAGUAGGGAGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 187 (5' CUCCCUACUACAAUGUGAGA 3');

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 105 (5' UGACUUCAACUUGUGGUCUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 215 (5' AAGACCACAAGUUGAAGUCA 3');

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 130 (5' UCAGGUUUUCCAUAUCCUUGAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 240 (5' CAAGGAUAUGGAAAACCUGA 3');

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 166 (5' UAACUAUCAAGGGGCCGCCAGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 276 (5' UGGCGGCCCCUUGAUAGUUA 3');

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 131 (5' UCACAGAGACUCAGAGACUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 241 (5' CAGUCUCUGAGUCUCUGUGA 3');

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 127 (5' UCUUUGAACACAUGUUGCUCAU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 237 (5' GAGCAACAUGUGUUCAAAGA 3');

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 111 (5' UAUCAAUGACAGUAAUUGGGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 221 (5' CCCAAUUACUGUCAUUGAUA 3');

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 93 (5' UCUUUUUGGCUCCUGUGAAGUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 203 (5' CUUCACAGGAGCCAAAAAGA 3'); or

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 71 (5' UAACUCCAGACCUAGACCUGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 181 (5' CAGGUCUAGGUCUGGAGUUA 3').

35. The isolated nucleotide of claim 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.1 nM.

36. The isolated oligonucleotide of claim 35, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3');

xviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 126 (5' UUUUGAACACAUGUUGCUCAUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 236 (5' UGAGCAACAUGUGUUCAAAA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 162 (5' UGAGAUGUCCUUGACUUUGUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 272 (5' ACAAAGUCAAGGACAUCUCA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3');

xxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 151 (5' UCAGACACAAACAGAGCUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 261 (5' AAAGCUCUGUUUGUGUCUGA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 143 (5' UAUUCUUGAGCUUGAUCAGGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 253 (5' CCUGAUCAAGCUCAAGAAUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 133 (5' UAAAGUACUCAGACACCACAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 243 (5' UGUGGUGUCUGAGUACUUUA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3');

xxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 173 (5' UGUUUUUGCAGACAUCCACUAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 283 (5' AGUGGAUGUCUGCAAAAACA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 156 (5' UGAGCAUCUCUCUCACAGCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 266 (5' AGCUGUGAGAGAGAUGCUCA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 141 (5' UCUUGAUCAGGGCAACGUCAUA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 251 (5' UGACGUUGCCCUGAUCAAGA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UCUUGAUUGAGUGUUCCUUGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' CAAGGAACACUCAAUCAAGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 170 (5' UGACUUCUCUUGUGAACUAUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 280 (5' AUAGUUCACAAGAGAAGUCA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UAAUCCUCAUCUUGGAGUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5' AAACUCCAAGAUGAGGAUUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5' UAUAGACAUCCAGAUAAUCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' GGAUUAUCUGGAUGUCUAUA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 139 (5' UCAUAGUCAUAAAAUUCAGGAA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 249 (5' CCUGAAUUUUAUGACUAUGA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCAUGUUGCUCAUUGUCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' AAAGACAAUGAGCAACAUGA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 145 (5' UGAGACAAAUGGGCCUGAUAGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 255 (5' UAUCAGGCCCAUUUGUCUCA 3');

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UCUCAUCAAUGACAGUAAUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' AAUUACUGUCAUUGAUGAGA 3');

xLi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGUCUUUCUUGGAAGCCAAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5' UUUGGCUUCCAAGAAAGACA 3');

xLii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UGAUCUGCAGGUACGUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' AGACACGUACCUGCAGAUCA 3');

xLiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCAUCAAUGACAGUAAUUGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3');

xLiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3');

xLv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 128 (5' UGACUUUGAACACAUGUUGCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 238 (5' GCAACAUGUGUUCAAAGUCA 3');

xLvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 161 (5' UCUUGACUUUGUCAUAGCCUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 271 (5' AGGCUAUGACAAAGUCAAGA 3');

xLvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 85 (5' UUUGUCACAGAUCGCUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 195 (5' AGACAGCGAUCUGUGACAAA 3');

xLviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 137 (5' UGAAUUCCUGCUUCUUUUUUCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 247 (5' AAAAAAGAAGCAGGAAUUCA 3');

xLix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 80 (5' UGAAAGAGAUCUCAUCACUCAC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 190 (5' GAGUGAUGAGAUCUCUUUCA 3');

L) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3');

Li) an antisense strand of nucleic acid sequence according to SEQ ID NO: 96 (5' UGUUGACUAGACACUUUUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 206 (5' CAAAAAGUGUCUAGUCAACA 3');

Lii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 146 (5' UAAGUGGUAGUUGGAGGAAGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 256 (5' CUUCCUCCAACUACCACUUA 3');

Liii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 78 (5' UAUCACUCACAUUGUAGUAGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 188 (5' CUACUACAAUGUGAGUGAUA 3');

Liv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 103 (5' UUUCACACCAUAACUUGCCACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 213 (5' UGGCAAGUUAUGGUGUGAAA 3');

Lv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3');

Lvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3');

Lvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 86 (5' UCAUGAAGGAGUCUUGGCAGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 196 (5' CUGCCAAGACUCCUUCAUGA 3');

Lviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3'); or

Lix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3').

37. The isolated oligonucleotide of claim 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by 20% to 50% at a dose of 0.02 nM.

38. The isolated oligonucleotide of claim 37, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 165 (5' UAUCACCUCUGCAAGUAUUGGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 275 (5' CAAUACUUGCAGAGGUGAUA 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 129 (5' UUUUCCAUAUCCUUGACUUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 239 (5' AAAGUCAAGGAUAUGGAAAA 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 176 (5' UAUCUUGGAGUUUCUCCUUCAG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 286 (5' GAAGGAGAAACUCCAAGAUA 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 177 (5' UCUCAUCUUGGAGUUUCUCCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 287 (5' GGAGAAACUCCAAGAUGAGA 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 138 (5' UCAUAAAAUUCAGGAAUUCCUG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 248 (5' GGAAUUCCUGAAUUUUAUGA 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 140 (5' UGUCAUAGUCAUAAAAUUCAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 250 (5' UGAAUUUUAUGACUAUGACA 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 148 (5' UAACAGAGCUUUGAUAUCCUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 258 (5' AGGAUAUCAAAGCUCUGUUA 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 150 (5' UCAAACAGAGCUUUGAUAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 260 (5' GAUAUCAAAGCUCUGUUUGA 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 179 (5' UGAAAACCCAAAUCCUCAUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 289 (5' GAUGAGGAUUUGGGUUUUCA 3');

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 90 (5' UAAAGCUUCGGCCACCUCUUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 200 (5' AAGAGGUGGCCGAAGCUUUA 3');

xi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 172 (5' UUUUUGCAGACAUCCACUACUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 282 (5' GUAGUGGAUGUCUGCAAAAA 3');

xii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 88 (5' UCGUACAUGAAGGAGUCUUGGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 198 (5' CAAGACUCCUUCAUGUACGA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 168 (5' UUUGUGAACUAUCAAGGGGCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 278 (5' GCCCCUUGAUAGUUCACAAA 3');

xiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 81 (5' UGUGGAAAGAGAUCUCAUCACU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 191 (5' UGAUGAGAUCUCUUUCCACA 3');

xv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 159 (5' UAUAUUGAGCAUCUCUCUCACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 269 (5' UGAGAGAGAUGCUCAAUAUA 3');

xvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 82 (5' UCAUAGCAGUGGAAAGAGAUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 192 (5' AUCUCUUUCCACUGCUAUGA 3');

xvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 97 (5' UUUAAGUUGACUAGACACUUUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 207 (5' AAGUGUCUAGUCAACUUAAA 3');

xiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 132 (5' UUUGCUUGUGGUAAUCGGUACC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 242 (5' UACCGAUUACCACAAGCAAA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 123 (5' UGUUGCUCAUUGUCUUUCUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 233 (5' AAGAAAGACAAUGAGCAACA 3');

xx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 79 (5' UCAUCACUCACAUUGUAGUAGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 189 (5' UACUACAAUGUGAGUGAUGA 3');

xxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 117 (5' UAAGCCAAAGCAUUGAUGUUCA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 227 (5' AACAUCAAUGCUUUGGCUUA 3');

xxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 122 (5' UUUGCUCAUUGUCUUUCUUGGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 232 (5' CAAGAAAGACAAUGAGCAAA 3');

xxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 110 (5' UCAAUGACAGUAAUUGGGUCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 220 (5' GACCCAAUUACUGUCAUUGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 135 (5' UCUUGAUUGAGUGUUCCUUGUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 245 (5' CAAGGAACACUCAAUCAAGA 3');

xxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 178 (5' UAAUCCUCAUCUUGGAGUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 288 (5' AAACUCCAAGAUGAGGAUUA 3');

xxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 114 (5' UAUAGACAUCCAGAUAAUCCUC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 224 (5' GGAUUAUCUGGAUGUCUAUA 3');

xxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 125 (5' UCAUGUUGCUCAUUGUCUUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 235 (5' AAAGACAAUGAGCAACAUGA 3');

xxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 113 (5' UCUCAUCAAUGACAGUAAUUGG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 223 (5' AAUUACUGUCAUUGAUGAGA 3');

xix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 120 (5' UGUCUUUCUUGGAAGCCAAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 230 (5' UUUGGCUUCCAAGAAAGACA 3');

xxx) an antisense strand of nucleic acid sequence according to SEQ ID NO: 75 (5' UGAUCUGCAGGUACGUGUCUGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 185 (5' AGACACGUACCUGCAGAUCA 3');

xxxi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 112 (5' UCAUCAAUGACAGUAAUUGGGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 222 (5' CCAAUUACUGUCAUUGAUGA 3');

xxxii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 108 (5' UAUGACAGUAAUUGGGUCCCCG 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 218 (5' GGGACCCAAUUACUGUCAUA 3');

xxxiii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 115 (5' UCAUAGACAUCCAGAUAAUCCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 225 (5' GAUUAUCUGGAUGUCUAUGA 3');

xxxiv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 102 (5' UCACCAUAACUUGCCACCUUCU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 212 (5' AAGGUGGCAAGUUAUGGUGA 3');

xxxv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 109 (5' UAAUGACAGUAAUUGGGUCCCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 219 (5' GGACCCAAUUACUGUCAUUA 3');

xxxvi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 106 (5' UCUCAUCAUGCUGUACACUGCC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 216 (5' CAGUGUACAGCAUGAUGAGA 3');

xxxvii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 98 (5' UCUCAAUUAAGUUGACUAGACA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 208 (5' UCUAGUCAACUUAAUUGAGA 3');

xxxviii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 124 (5' UAUGUUGCUCAUUGUCUUUCUU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 234 (5' GAAAGACAAUGAGCAACAUA 3');

xxxix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 121 (5' UCUCAUUGUCUUUCUUGGAAGC 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 231 (5' UUCCAAGAAAGACAAUGAGA 3'); or

xL) an antisense strand of nucleic acid sequence according to SEQ ID NO: 107 (5' UUAAUUGGGUCCCCGCCCAUGU 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 217 (5' AUGGGCGGGGACCCAAUUAA 3').

39. The isolated oligonucleotide of claim 32, wherein the isolated oligonucleotide attenuates expression of the CFB mRNA by at least 50% at a dose of 0.02 nM.

40. The isolated oligonucleotide of claim 39, wherein the double stranded region comprises an antisense strand of nucleic acid sequence according to SEQ ID NO: 171 (5' UAUGAAACGACUUCUCUUGUGA 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 281 (5' ACAAGAGAAGUCGUUUCAUA 3').

41. The isolated oligonucleotide of any one of claims 1-40, wherein the sense strand or the antisense strand or both comprise one or more modified nucleotide(s).

42. The isolated oligonucleotide of claim 41, wherein the antisense strand comprises a mono methyl protected phosphate mimic (5'-MeEP).

43. The isolated oligonucleotide of any one of claims 1-42, wherein in the sense strand or the antisense strand or both, a terminal or internal nucleotide is linked to a targeting ligand.

44. The isolated oligonucleotide of claim 43, wherein the targeting ligand comprises at least one GalNAc G1b moiety.

45. The isolated oligonucleotide of any one of claims 1-44, wherein the antisense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:

$3'(M)_0(F)_0(M)_6(F)_1(M)_1(F)_1(M)_3(F)_1(M)_2(F)_1(M)_1(F)_1(M)_1(F)_2(M)_1$ 5'.

46. The isolated oligonucleotide of any one of claims 1-45, wherein the sense strand comprises nucleotides modified with 2'-F modification, and nucleotides modified with 2'-O-methyl modification, according to the formula:

$5'(M)_0(F)_0(M)_5(F)_1(M)_1(F)_4(M)_9$ 3'.

47. The isolated oligonucleotide of any one of claims 1-46, wherein the antisense strand comprises any one of:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5' [MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' [MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' [MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' [mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'); or

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'),

wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, "MeEP" is a mono methyl protected phosphate mimic.

48. The isolated oligonucleotide of any one of claims 1-47, wherein the sense strand comprises any one of:

i) a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ii) a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3');

iii) a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3');

iv) a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3');

v) a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' [mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3');

vi) a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' [mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3'); or

vii) a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' [mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3'),

wherein "m" is a 2'-O-methyl modified nucleotide, "f" is a 2'-F modified nucleotide, "s" is a phosphorothioate internucleotide linkage, and "G1b" is a GalNac G1b moiety.

49. The isolated oligonucleotide of claim 47, wherein the double stranded region comprises:

i) an antisense strand of nucleic acid sequence according to SEQ ID NO: 370 (5' [MeEPmUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 371 (5' [MeEPmUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3');

iii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 372 (5' [MeEPmUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3');

iv) an antisense strand of nucleic acid sequence according to SEQ ID NO: 373 (5' [MeEPmUs][fAs][fA][mU][fU][mC][fA][mG][mG][fA][mA][mU][mU][fC][mC][fU][mG][mC][mU][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 384 (5' [mAs][mAs][mG][mC][mA][fG][mG][fA][fA][fU][fU][mC][mC][mU][mG][mA][mA][mUs][mUs][mA][G1b][G1b][G1b] 3');

v) an antisense strand of nucleic acid sequence according to SEQ ID NO: 374 (5' [MeEPmUs][fAs][fA][mC][fA][mC][fA][mU][mG][fU][mU][mG][mC][fU][mC][fA][mU][mU][mG][mUs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 385 (5' [mAs][mCs][mA][mA][mU][fG][mA][fG][fC][fA][fA][mC][mA][mU][mG][mU][mG][mUs][mUs][mA][G1b][G1b][G1b] 3');

vi) an antisense strand of nucleic acid sequence according to SEQ ID NO: 375 (5' [MeEPmUs][fGs][fU][mG][fU][mA][fA][mC][mC][fG][mU][mC][mA][fU][mA][fG][mC][mA][mG][mUs][mGs][mG] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 386 (5' [mAs][mCs][mU][mG][mC][fU][mA][fU][fG][fA][fC][mG][mG][mU][mU][mA][mC][mAs][mCs][mA][G1b][G1b][G1b] 3');

vii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 376 (5' [MeEPmUs][fAs][fU][mA][fG][mC][fA][mG][mU][fG][mG][mA][mA][fA][mG][fA][mG][mA][mU][mCs][mUs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 387 (5' [mGs][mAs][mU][mC][mU][fC][mU][fU][fU][fC][fC][mA][mC][mU][mG][mC][mU][mAs][mUs][mA][G1b][G1b][G1b] 3');

viii) an antisense strand of nucleic acid sequence according to SEQ ID NO: 377 (5' [mUs][fGs][fU][mC][fA][mU][fA][mA][mA][fA][mU][mU][mC][fA][mG][fG][mA][mA][mU][mUs][mCs][mC] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 381 (5' [mAs][mAs][mU][mU][mC][fC][mU][fG][fA][fA][fU][mU][mU][mU][mA][mU][mG][mAs][mCs][mA][G1b][G1b][G1b] 3');

ix) an antisense strand of nucleic acid sequence according to SEQ ID NO: 378 (5' [mUs][fUs][fA][mA][fA][mA][fU][mU][mC][fA][mG][mG][mA][fA][mU][fU][mC][mC][mU][mGs][mCs][mU] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 382 (5' [mCs][mAs][mG][mG][mA][fA][mU][fU][fC][fC][fU][mG][mA][mA][mU][mU][mU][mUs][mAs][mA][G1b][G1b][G1b] 3'); or

x) an antisense strand of nucleic acid sequence according to SEQ ID NO: 379 (5' [mUs][fGs][fG][mA][fA][mA][fG][mA][mG][fA][mU][mC][mU][fC][mA][fU][mC][mA][mC][mUs][mCs][mA] 3'), and a sense strand of nucleic acid sequence according to SEQ ID NO: 383 (5' [mAs][mGs][mU][mG][mA][fU][mG][fA][fG][fA][fU][mC][mU][mC][mU][mU][mU][mCs][mCs][mA][G1b][G1b][G1b] 3').

50. A vector encoding the isolated oligonucleotide of any one of claims 1-49.

51. A delivery system comprising the isolated oligonucleotide of any one of claims 1-49 or the vector of claim 50.

52. A pharmaceutical composition comprising at least one isolated oligonucleotide of any one of claims 1-49, the vector of claim 50, or the delivery system of claim 51, and a pharmaceutically acceptable carrier, diluent or excipient.

53. A kit comprising at least one isolated oligonucleotide of any one of claims 1-49, the vector of claim 50, the delivery system of claim 51, or the pharmaceutical composition of claim 52.

54. A method of inhibiting or downregulating the expression or level of CFB in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide of any one of claims 1-49, the vector of claim 50, the delivery system of claim 51, or the pharmaceutical composition of claim 52.

55. A method of treating or preventing a disease or disorder associated with aberrant or increased expression or activity of CFB or a disease or disorder where CFB plays a role in a subject in need thereof, wherein the method comprises administering to the subject an effective amount of at least one isolated oligonucleotide of any one of claims 1-49, the vector of claim 50, the delivery system of claim 51, or the pharmaceutical composition of claim 52.

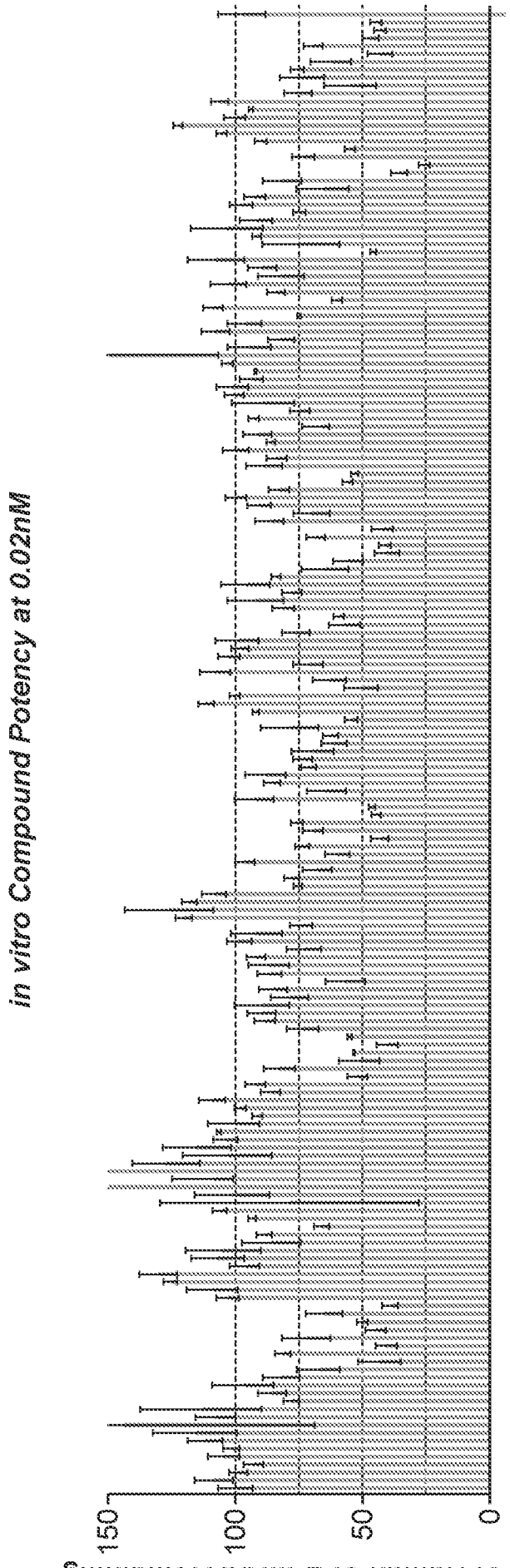

in vitro Compound Potency at 0.02nM
% of Human CFB mRNA remaining
150
100
50
0

FIG. 1

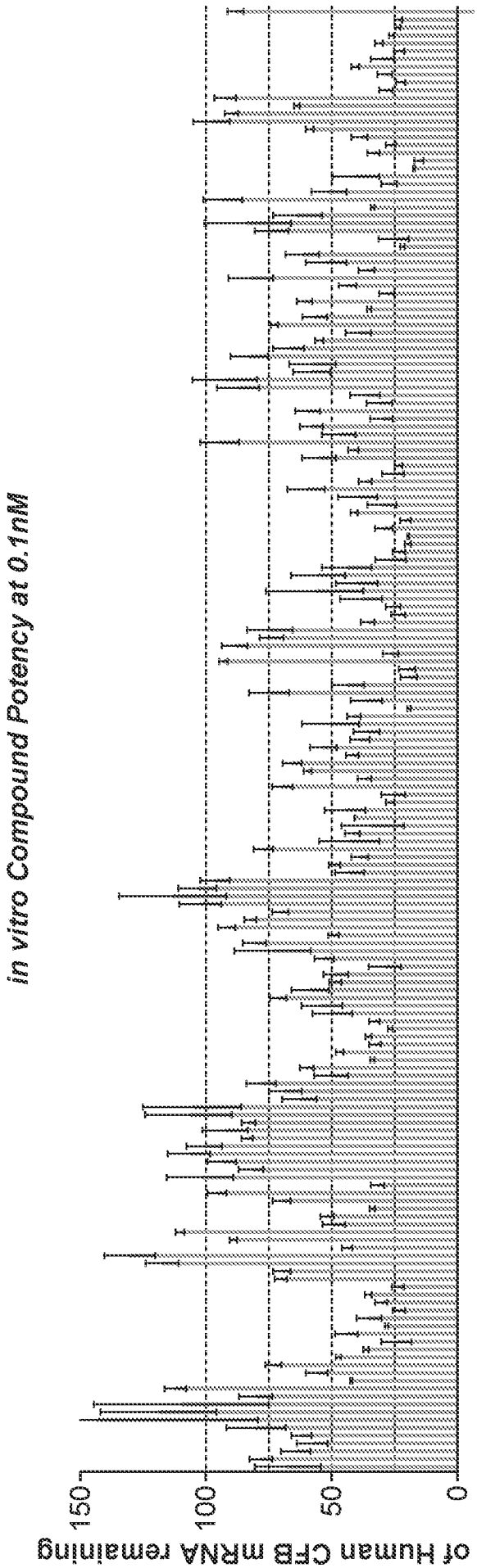
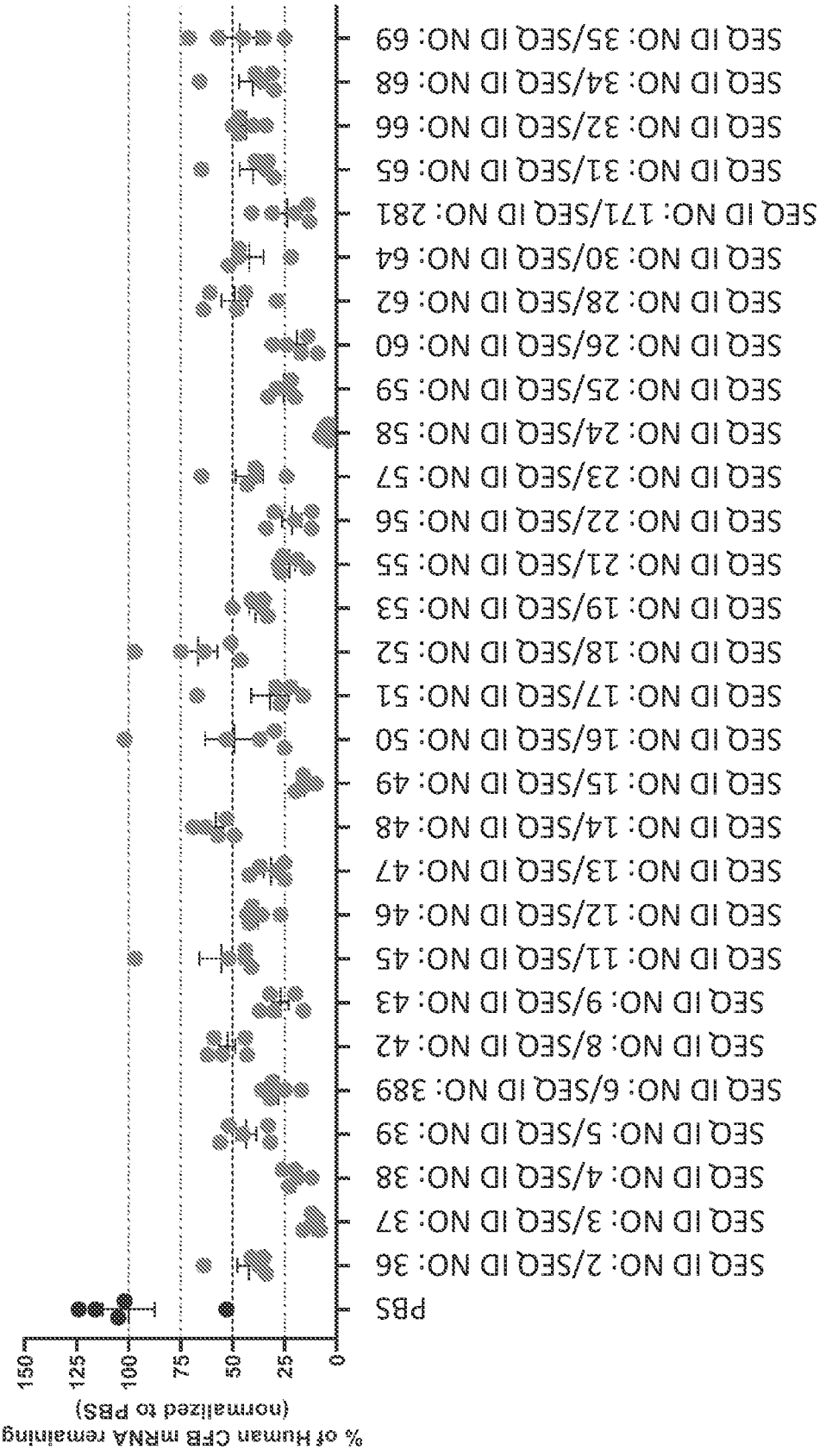

in vitro Compound Potency at 0.1nM
% of Human CFB mRNA remaining
150
100
50
0

FIG. 2

FIG. 3


% of Human CFB mRNA remaining
(normalized to PBS)
150
125
100
75
50
25
0
PBS
SEQ ID NO: 2/SEQ ID NO: 36
SEQ ID NO: 3/SEQ ID NO: 37
SEQ ID NO: 4/SEQ ID NO: 38
SEQ ID NO: 5/SEQ ID NO: 39
SEQ ID NO: 6/SEQ ID NO: 389
SEQ ID NO: 8/SEQ ID NO: 42
SEQ ID NO: 9/SEQ ID NO: 43
SEQ ID NO: 11/SEQ ID NO: 45
SEQ ID NO: 12/SEQ ID NO: 46
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SEQ ID NO: 15/SEQ ID NO: 49
SEQ ID NO: 16/SEQ ID NO: 50
SEQ ID NO: 17/SEQ ID NO: 51
SEQ ID NO: 18/SEQ ID NO: 52
SEQ ID NO: 19/SEQ ID NO: 53
SEQ ID NO: 21/SEQ ID NO: 55
SEQ ID NO: 22/SEQ ID NO: 56
SEQ ID NO: 23/SEQ ID NO: 57
SEQ ID NO: 24/SEQ ID NO: 58
SEQ ID NO: 25/SEQ ID NO: 59
SEQ ID NO: 26/SEQ ID NO: 60
SEQ ID NO: 28/SEQ ID NO: 62
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SEQ ID NO: 171/SEQ ID NO: 281
SEQ ID NO: 31/SEQ ID NO: 65
SEQ ID NO: 32/SEQ ID NO: 66
SEQ ID NO: 34/SEQ ID NO: 68
SEQ ID NO: 35/SEQ ID NO: 69

FIG. 4

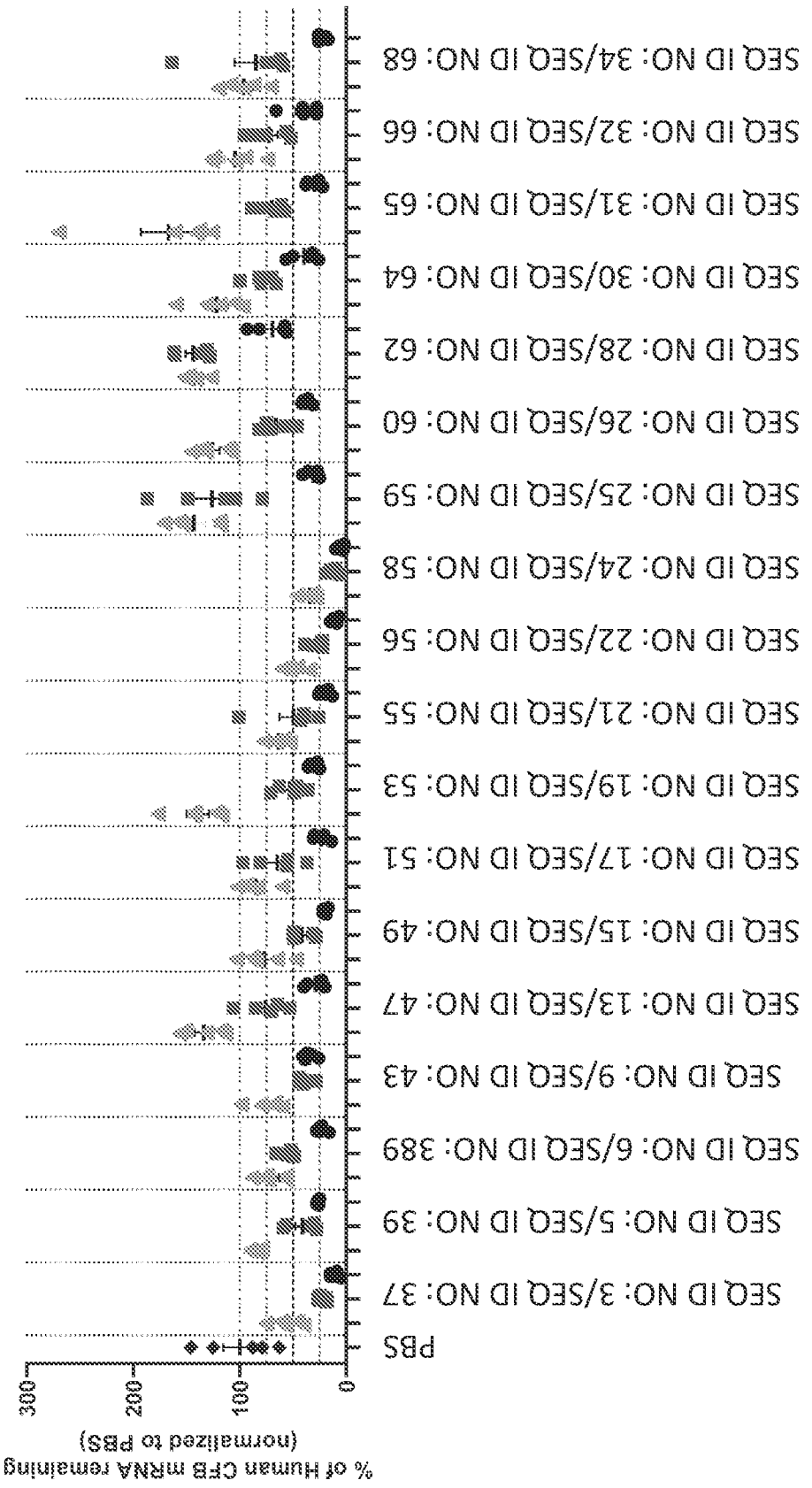
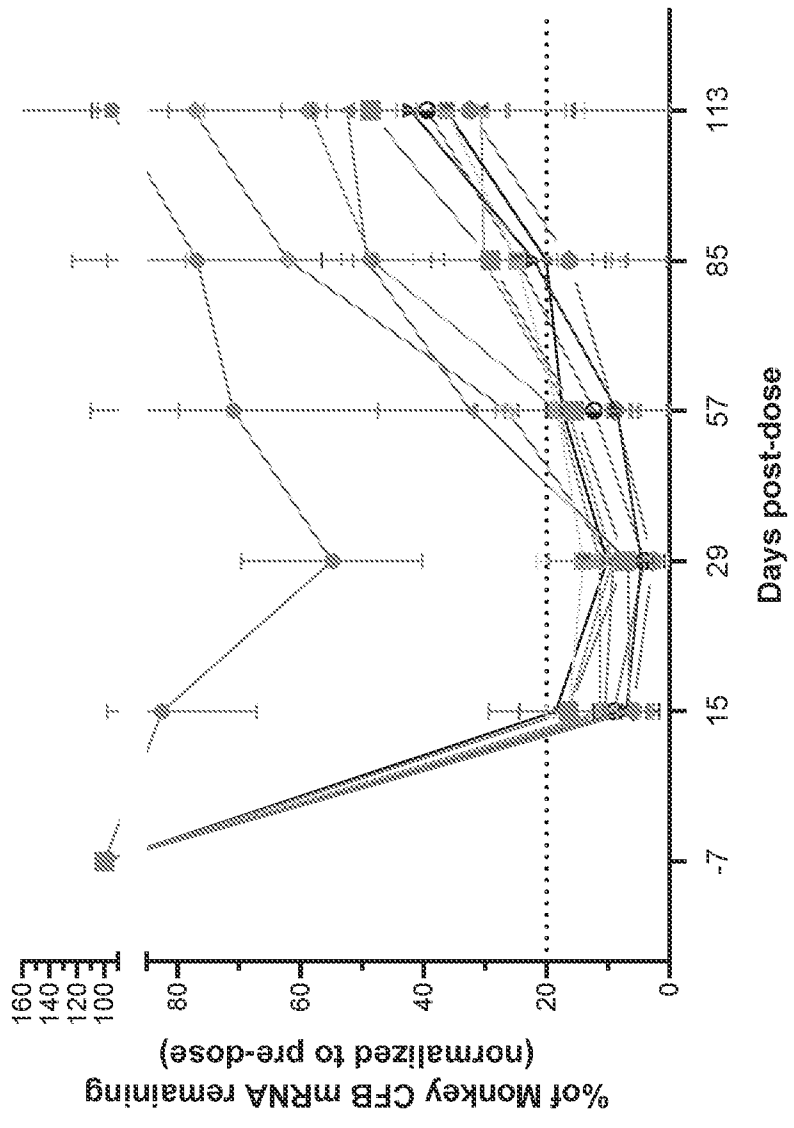

% of Human CFB mRNA remaining
(normalized to PBS)
300
200
100
0
PBS
SEQ ID NO: 3/SEQ ID NO: 37
SEQ ID NO: 5/SEQ ID NO: 39
SEQ ID NO: 6/SEQ ID NO: 389
SEQ ID NO: 9/SEQ ID NO: 43
SEQ ID NO: 13/SEQ ID NO: 47
SEQ ID NO: 15/SEQ ID NO: 49
SEQ ID NO: 17/SEQ ID NO: 51
SEQ ID NO: 19/SEQ ID NO: 53
SEQ ID NO: 21/SEQ ID NO: 55
SEQ ID NO: 22/SEQ ID NO: 56
SEQ ID NO: 24/SEQ ID NO: 58
SEQ ID NO: 25/SEQ ID NO: 59
SEQ ID NO: 26/SEQ ID NO: 60
SEQ ID NO: 28/SEQ ID NO: 62
SEQ ID NO: 30/SEQ ID NO: 64
SEQ ID NO: 31/SEQ ID NO: 65
SEQ ID NO: 32/SEQ ID NO: 66
SEQ ID NO: 34/SEQ ID NO: 68

FIG. 5A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SEQ ID NO: 370/SEQ ID NO: 381
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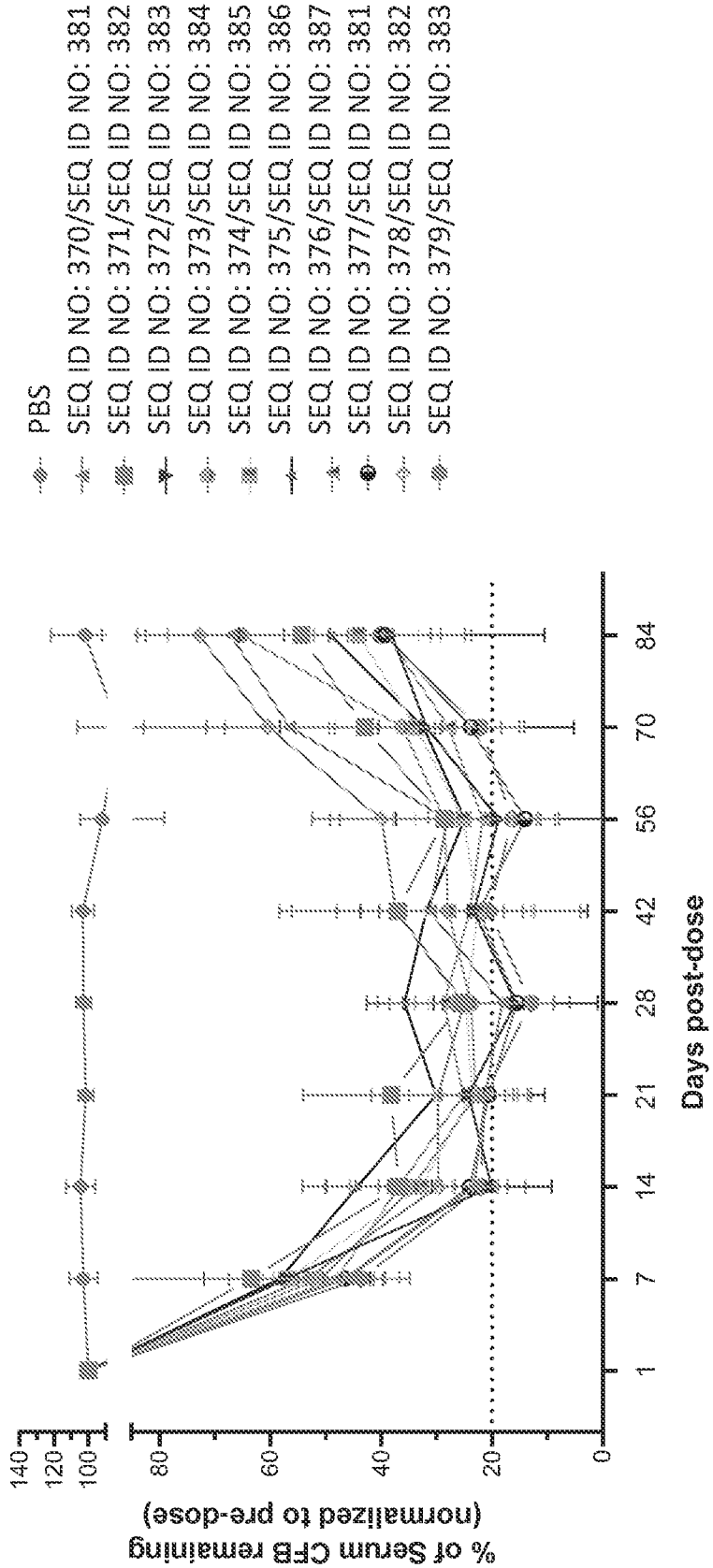
SEQ ID NO: 376/SEQ ID NO: 387
SEQ ID NO: 377/SEQ ID NO: 381
SEQ ID NO: 378/SEQ ID NO: 382
SEQ ID NO: 379/SEQ ID NO: 383
%of Monkey CFB mRNA remaining
(normalized to pre-dose)
160
140
120
100
80
60
40
20
0
-7
15
29
57
85
113
Days post-dose

FIG. 5B


PBS
SEQ ID NO: 370/SEQ ID NO: 381
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SEQ ID NO: 376/SEQ ID NO: 387
SEQ ID NO: 377/SEQ ID NO: 381
SEQ ID NO: 378/SEQ ID NO: 382
SEQ ID NO: 379/SEQ ID NO: 383
% of Serum CFB remaining
(normalized to pre-dose)
140
120
100
80
60
40
20
0
1
7
14
21
28
42
56
70
84
Days post-dose