Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: l and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other.

2. The dsRNA agent of claim 1, wherein the dsRNA agent includes a sense strand and an antisense strand, wherein the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 483-513, 486-516, 491-521, 483-521,513-543, 987-1017, 989-1019, 1317-1347, 2237-2267, 2439-2469 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2, wherein the sense strand and the antisense strand can be partially, substantially, or fully complementary to each other;

preferably, the sense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from any one of the nucleotide sequences of nucleotides 488-508, 491-511, 496-516, 488-516, 518-538, 992-1012, 994-1014, 1322-1342, 2242-2262, 2444-2464 of SEQ ID NO: 1, and the antisense strand comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from the corresponding nucleotide sequence of SEQ ID NO:2.

3. The dsRNA agent of claim 1, wherein said antisense strand comprises a region of complementarity to a CFB RNA transcript RNA transcript which comprises at least 15 contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from any one of the antisense sequences listed in any one of Tables 1-3; or

said antisense strand comprises a region of complementarity to a CFB RNA transcript which comprises at least 15 contiguous nucleotides from any one of the antisense sequences listed in any one of Tables 1-3.

4. The dsRNA agent of claim 1, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent comprises a sense strand and an antisense strand, nucleotide positions 2 to 18 in the antisense strand comprising a region of complementarity to a CFB RNA transcript, wherein the region of complementarity comprises at least 15, 16, 17, 18, 19, 20 or 21 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3, and optionally comprising a targeting ligand;
preferably, the region of complementarity to a CFB RNA transcript comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by no more than 3 nucleotides from one of the antisense sequences listed in one of Tables 1-3.

5. The dsRNA agent of any one of claims 1-4, wherein the antisense strand of dsRNA is substantially or fully complementary to any one of a target region of SEQ ID NO: 1, and preferably the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-3;
preferably, the sense strand sequence is at least substantially complementary to or fully complementary to the antisense strand sequence in the dsRNA agent, preferably, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-3;
preferably, the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-3.

6. The dsRNA of any one of claims 1-5, wherein the dsRNA agent comprises at least one modified nucleotide;
preferably, all or substantially all of the nucleotides of the sense strand and/or the antisense strand are modified nucleotides;
preferably, the one or more modified nucleotides are independently selected from the group consisting of: a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, a 2'-deoxy nucleotide, a 2'3'-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2'-F-Arabino nucleotide,

a 2’-methoyxyethyl nucleotide, an abasic nucleotide, an ribitol, inverted nucleotide, an inverted abasic nucleotide, an isomannide nucleotide, an inverted 2’-Ome nucleotide, an inverted 2’-deoxy nucleotide, a 2’-amino-modified nucleotide, a 2’-alkyl-modified nucleotide, a mopholino nucleotide, a 3’-OMe nucleotide, a nucleotide comprising a 5’-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2’-amino-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

7. The dsRNA agent of claim 1-6, wherein the double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of CFB, wherein the dsRNA agent including a sense strand and an antisense strand, wherein the sense strand is complementary to the antisense strand, wherein the antisense strand comprises a region complementary to part of a CFB RNA transcript, wherein each strand is about 15 to about 30 nucleotides in length, wherein the sense strand comprises sequence may be represented by formula (I):

$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$ (I)

wherein:

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

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

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

(II)

wherein:

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

each N_L independently represents a modified or unmodified nucleotide but not a 2'-fluoro-modified nucleotide, and n is an integer of 0 to 7; or

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

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

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

(III)

wherein:

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

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

8. The dsRNA agent of any one of claims 1-7, comprises an E-vinylphosphonate nucleotide at the 5′ end of the guide strand;

preferably, the dsRNA agent comprises at least one phosphorothioate internucleoside linkage; or

the sense strand comprises at least one phosphorothioate internucleoside linkage; or

the antisense strand comprises at least one phosphorothioate internucleoside linkage; or

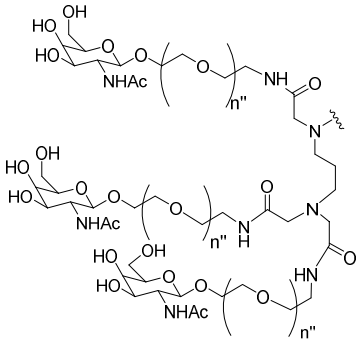
the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages; or

the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages.

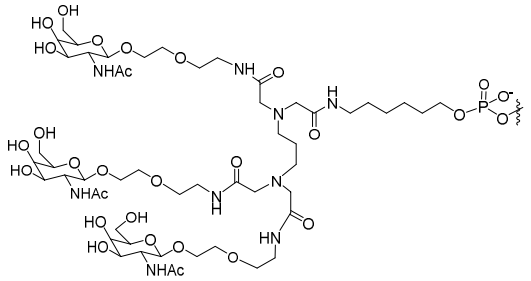
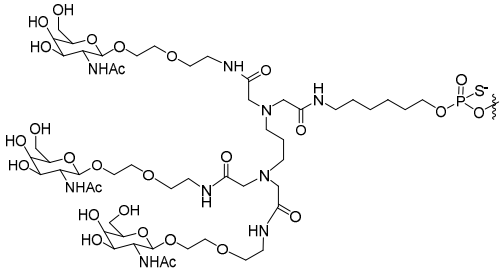
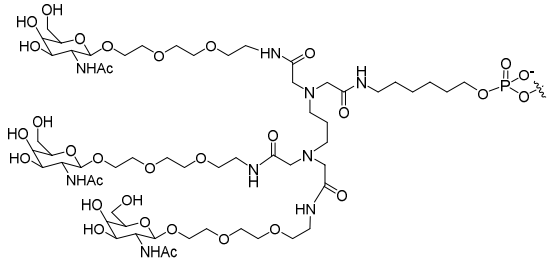
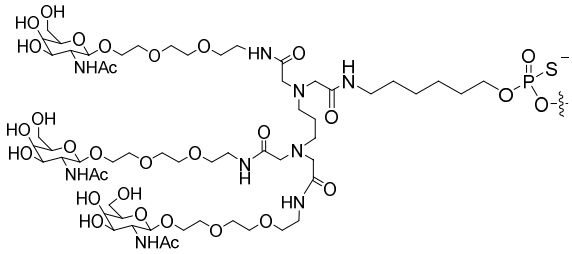
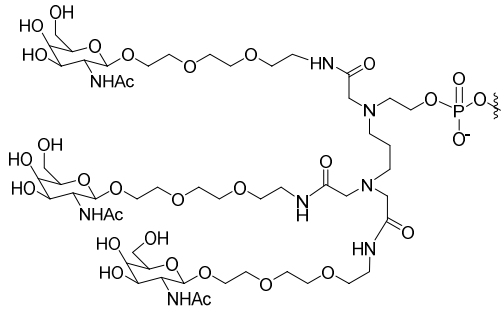
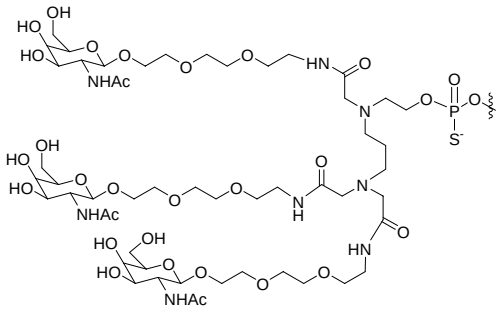
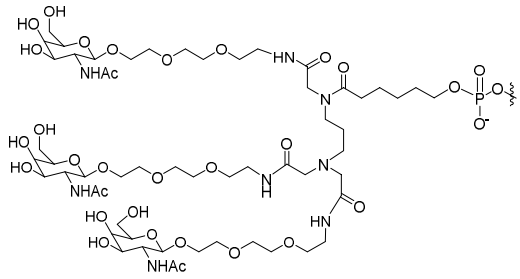
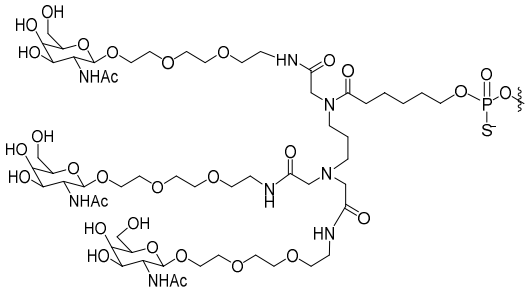
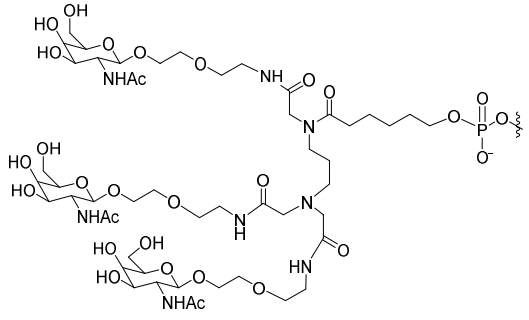
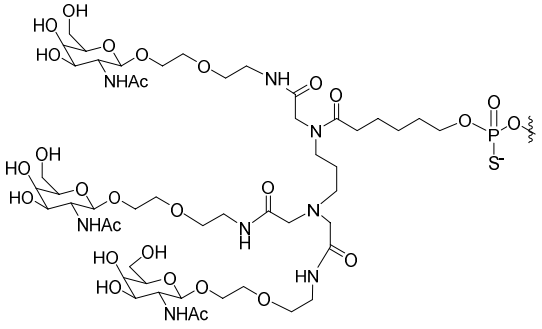
9. The dsRNA agent of any one of claims 1-8, wherein the modified sense strand is a modified sense strand sequence set forth in one of Tables 2-3; or
the modified antisense strand is a modified antisense strand sequence set forth in one of Tables 2-3;
preferably. the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity is between 16 and 23 nucleotides in length;
preferably, the region of complementarity is 19-21 nucleotides in length.

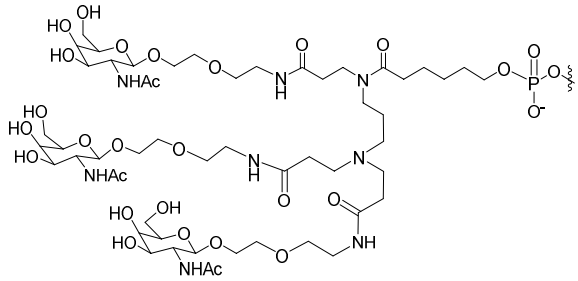
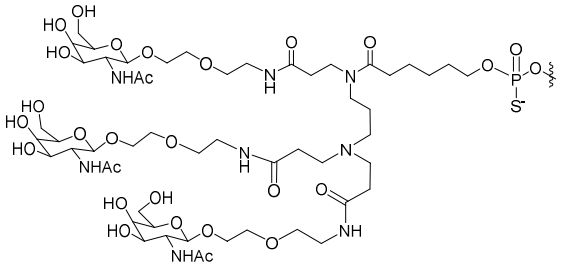
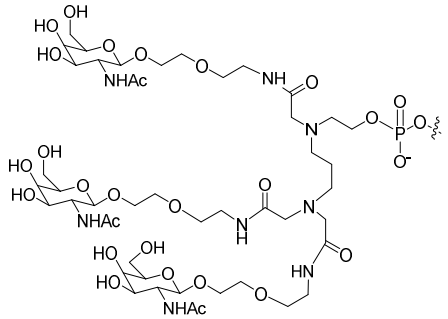
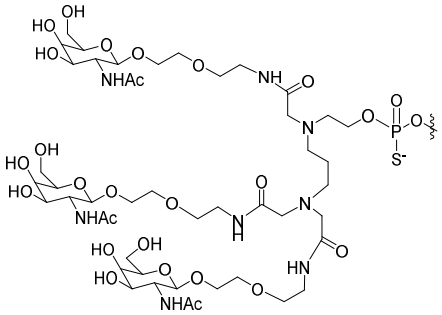
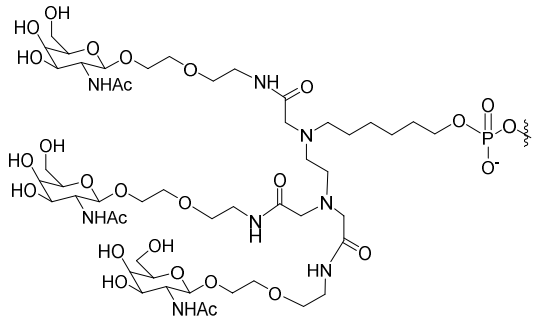
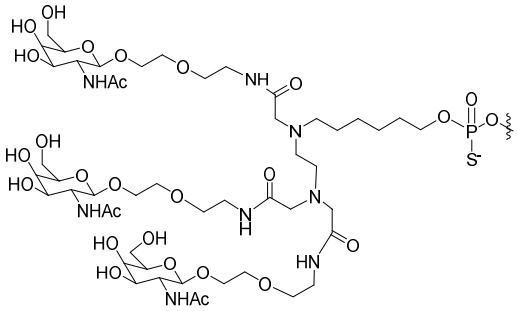
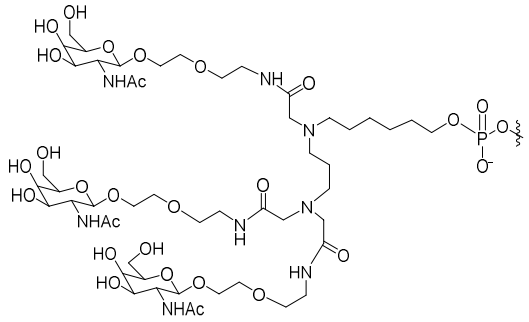
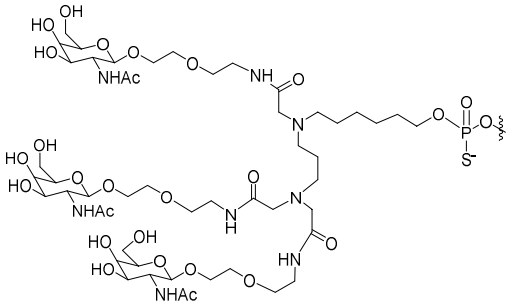
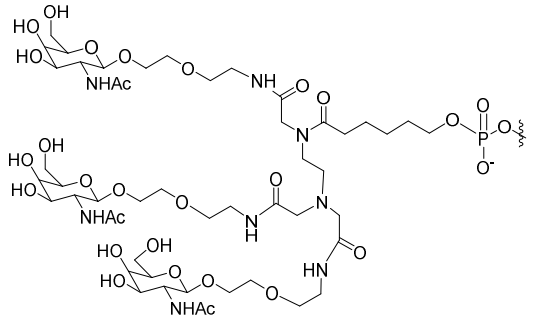
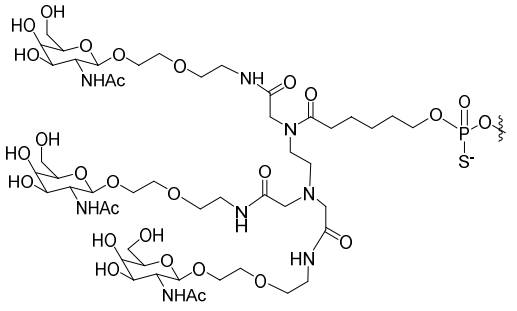
10. The dsRNA agent of any one of claims 1-9, wherein each strand is no more than 30 nucleotides in length; or
each strand is no more than 25 nucleotides in length; or
each strand is no more than 23 nucleotides in length.

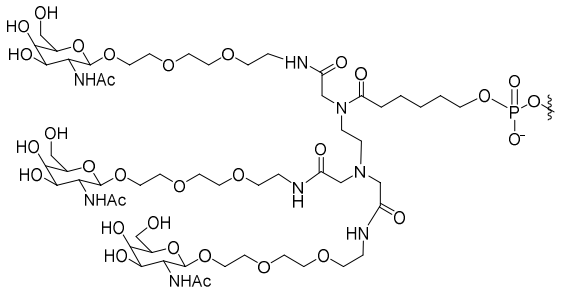
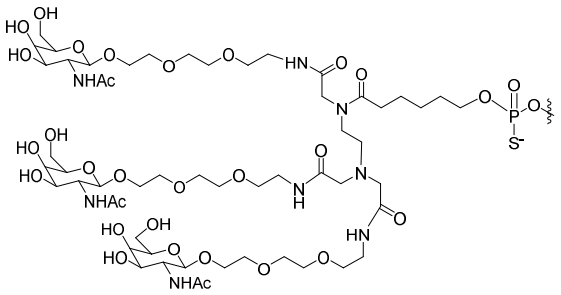
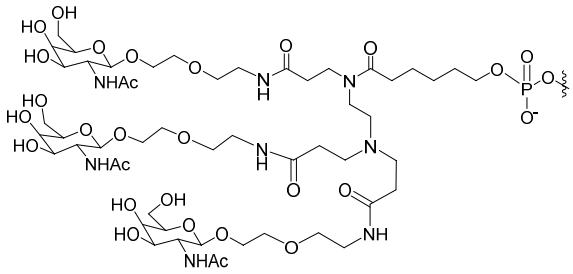
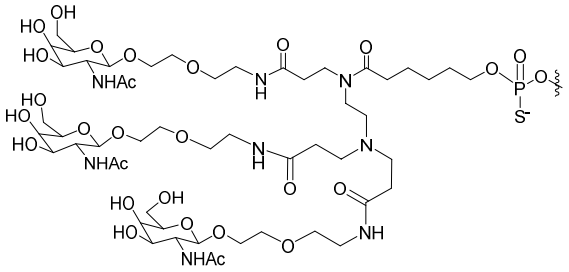
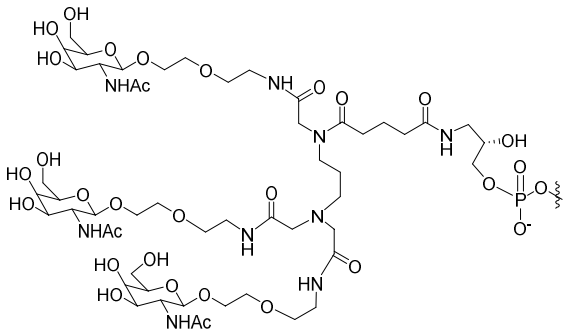
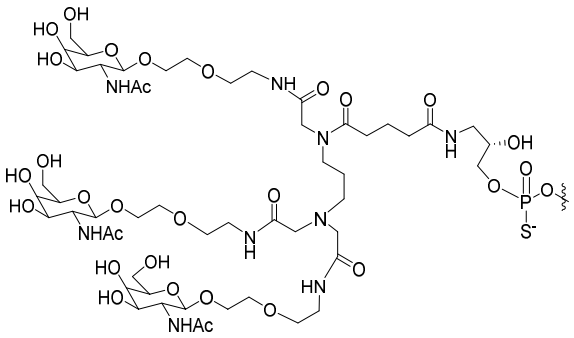
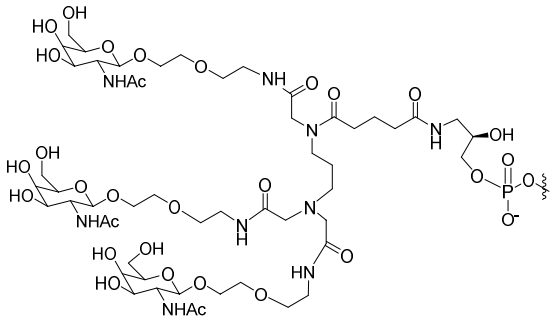
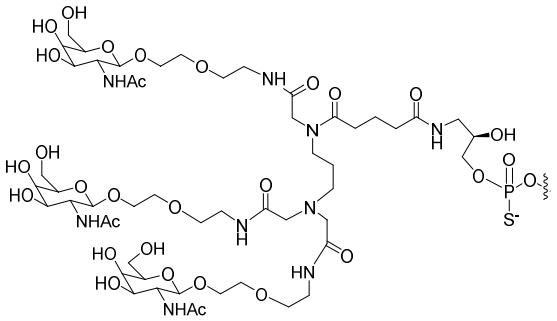
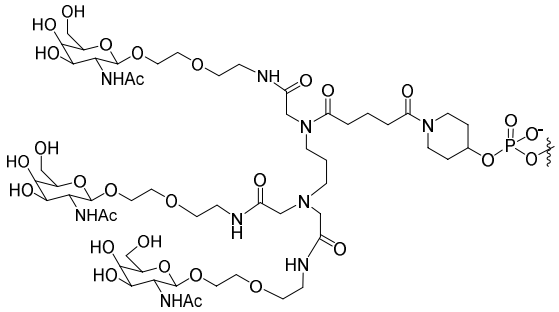
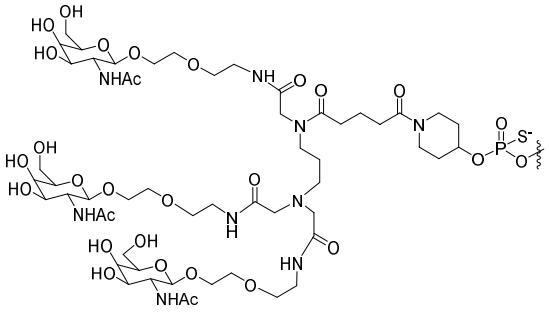
11. The dsRNA agent of any one of claims 1-10, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups;
preferably, the one or more targeting groups or linking groups are conjugated to the sense strand;
preferably, the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc);
preferably, the targeting group has a structure:

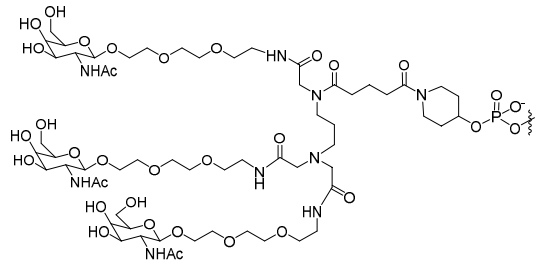
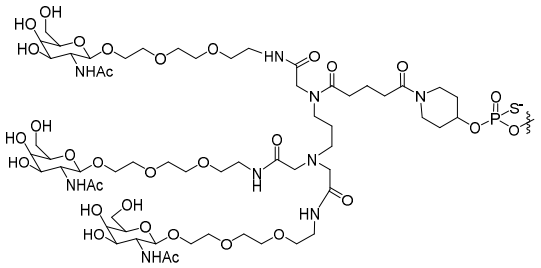


n" are independently selected from 1 or 2;
preferably, the targeting group has a structure:

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

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

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

 GLO-16	 GLS-16*

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12. The dsRNA agent of any one of claims 1-11, wherein the dsRNA agent comprises a targeting group that is conjugated to the 5’-terminal end of the sense strand; or
the dsRNA agent comprises a targeting group that is conjugated to the 3'-terminal end of the sense strand; or
the antisense strand comprises one inverted abasic residue at 3’-terminal end; or
the sense strand comprises one or two inverted abasic residues or imann residues at 3’ or/and 5’ terminal end;
preferably, the dsRNA agent has two blunt ends; or
at least one strand comprises a 3’ overhang of at least 1 nucleotide; or
at least one strand comprises a 3’ overhang of at least 2 nucleotides.

13. The dsRNA agent of any one of claims 1-12 wherein the CFB RNA transcript is SEQ ID NO: 1.

14. A composition comprising a dsRNA agent of any one of claims 1-13;
preferably, the composition further comprises a pharmaceutically acceptable carrier;
preferably, the composition further comprises one or more additional therapeutic agents;
preferably, the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial;
preferably, the composition is formulated for subcutaneous administration or is formulated for intravenous (IV) administration.

15. A cell comprising a dsRNA agent of any one of claims 1-13, optionally, the cell is a mammalian cell, optionally a human cell.

16. Use of the double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for inhibiting the expression of a CFB gene in a cell.

17. Use of the double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for inhibiting expression of a CFB gene in a subject;
preferably, the dsRNA agent is formulated to be administered subcutaneously; or
the dsRNA agent is formulated to be administered by IV administration.

18. Use of the double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for treating a disease or condition associated with the presence of CFB protein in a subject;
preferably, the disease or condition is one or more of: autoimmune diseases, complement system dysfunction including aberrant upregulation of complement components such as CFB, C3 glomerulopathy (C3G), systemic lupus erythematosus (SLE), Lupus Nephritis, Ig-mediated kidney pathologies such as IgA nephropathy and primary membranous nephropathy, nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration(AMD)including dry AMD and geographic atrophy, typical or infectious hemolytic uremic syndrome (tHUS), atypical hemolytic uremic syndrome(aHUS), asthma, psoriasis, thrombotic microangiopathy, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria(PNH), rheumatic disease, rheumatoid arthritis, multiple sclerosis (MS), neuromyelitis optica (NMO), immune complex-mediated glomerulonephritis (IC-mediated GN), post-infectious glomerulonephritis (PIGN), antineutrophil cytoplasmic autoantibodies- associated vasculitis (ANCA-AV), antiphospholipid antibody syndrome (APS), dysbiotic periodontal disease, malarial anaemia, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, myasthenia gravis (MG), neuromyelistis optica (NMO), dense deposit disease, Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic

shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), cold agglutinin disease, humoral and vascular transplant rejection, graft dysfunction, myocardial infarction, sensitization towards a transplant, hyperlipidemia, and sepsis.

19. The use of claim 18, further comprising an additional therapeutic regimen;
preferably, the additional therapeutic regimen comprises one or more CFB antisense polynucleotides of the invention, a non-CFB dsRNA therapeutic agent, and a behavioral modification in the subject;
preferably, the non-CFB dsRNA therapeutic agent is one of more of: an inhibitor of C5, such as an anticomplement component C5 antibody, or antigen-binding fragment thereof (e.g., eculizumab, ravulizumab-cwvz, or pozelimab (REGN3918)) or a C5 peptide inhibitor (e.g., zilucoplan); C3 peptide inhibitor, such as compstatin;
preferably, the dsRNA agent is formulated to be administered subcutaneously;
preferably, the dsRNA agent is formulated to be administered by IV administration.

20. Use of the double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for decreasing a level of CFB protein in a subject compared to a baseline pre-treatment level of CFB protein in the subject;
preferably, the dsRNA agent is formulated to be administered subcutaneously or is formulated to be administered to by IV administration.

21. Use of the double-stranded ribonucleic acid (dsRNA) agent of any one of claims 1-13 or the composition of claim 14 in the manufacture of a medicament for altering a physiological characteristic of a CFB-associated disease or condition in a subject compared to a baseline pre-treatment physiological characteristic of the CFB-associated disease or condition in the subject;
preferably, the dsRNA agent is formulated to be administered subcutaneously or is formulated to be administered by IV administration;
preferably, the physiological characteristic is one or more of: the CFB mRNA level, the CFB protein level in the subject, CH50 activity, AH50, lactate dehydrogenase (LDH) , hemoglobin levels; the level of any one or more of C3, C9, C5, C5a, C5b, soluble C5b-9 complex and lipid level in blood or serum.