

We claim:

1. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding CFB, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20.
2. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-665, 1133-1185, 1133-1173, 1133-1167, 1143-1173, 1540-1563, 1976-2002, 2386-2438, 2386-2418, 2386-2413, and 2389-1418 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.
3. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-655, 643-665, 928-950, 1133-1155, 1140-1162, 1141-1163, 1143-1165, 1145-1167, 1148-1170, 1150-1172, 1151-1173, 1185-1207, 1306-1328, 1534-1556, 1540-1562, 1541-1563, 1976-1998, 1979-2001, 1980-2002, 2078-2100, 2386-2408, 2388-2410, 2389-2411, 2391-2413, 2393-2415, 2395-2417, 2396-2418, 2438-2460, and 2602-2624 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.
4. The dsRNA agent of any one of claims 1-3, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-560018, AD-559375, AD-559160, AD-559374, AD-559060, AD-559721, AD-559026, AD-558225, AD-557069, AD-558068, AD-557422, AD-558063, AD-558066, AD-556701, AD-558657, AD-559020, AD-559023, AD-558860, AD-560019, AD-560016, AD-559008, AD-559717, AD-557072, AD-558097, AD-557774, AD-557070, AD-558065, AD-557853, AD-557079.

5. A double stranded ribonucleic acid (dsRNA) for inhibiting expression of complement factor B (CFB) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides
5 153-175; 202-224; 219-241; 254-276; 304-326; 321-343; 347-369; 402-424; 418-440; 447-469; 491-513; 528-550; 549-571; 566-588; 591-613; 792-814; 819-841; 967-989; 1042-1064; 1234-1256; 1250-1272; 1269-1291; 1335-1357; 1354-1376; 1372-1394; 1422-1444; 1496-1518; 1670-1692; 1716-1738; 1757-1779; 1774-1796; 1793-1815; 1844-1866; 1871-1893; 1909-1931; 1924-1947; 1947-1969; 2161-2183; 2310-2332; 2330-2352; 2355-2377; 2494-2516; and 2527-2549 of SEQ ID
10 NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8, where a substitution of a T with a U in either SEQ ID NO: 1 or SEQ ID NO: 8 does not count as a difference.
6. The dsRNA agent of claim 1 or 5, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by nor more than three nucleotides from any one of the antisense
15 strand nucleotide sequences of a duplex selected from the group consisting of AD-560132.1; AD-560099.1; AD-559998.1; AD-559993.1; AD-559973.1; AD-559882.1; AD-559706.1; AD-559704.1; AD-559688.1; AD-559668.1; AD-559641.1; AD-559609.1; AD-559590.1; AD-559573.1; AD-559532.1; AD-559486.1; AD-559330.1; AD-559274.1; AD-559226.1; AD-559208.1; AD-559189.1; AD-559124.1; AD-559105.1; AD-559089.1; AD-558935.1; AD-558879.1; AD-558777.1; AD-
20 558750.1; AD-558637.1; AD-558612.1; AD-558595.1; AD-558574.1; AD-558555.1; AD-558511.1; AD-558482.1; AD-558466.1; AD-558450.1; AD-558424.1; AD-558407.1; AD-558393.1; AD-558378.1; AD-558361.1; AD-558312.1.
7. The dsRNA agent of any one of claims 1-6, wherein the dsRNA agent comprises at least one modified nucleotide.
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8. The dsRNA agent of any one of claims 1-7, wherein substantially all of the nucleotides of the sense strand; substantially all of the nucleotides of the antisense strand comprise a modification; or substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand comprise a modification.
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9. The dsRNA agent of any one of claims 1-8, wherein all of the nucleotides of the sense strand comprise a modification; all of the nucleotides of the antisense strand comprise a modification; or all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.
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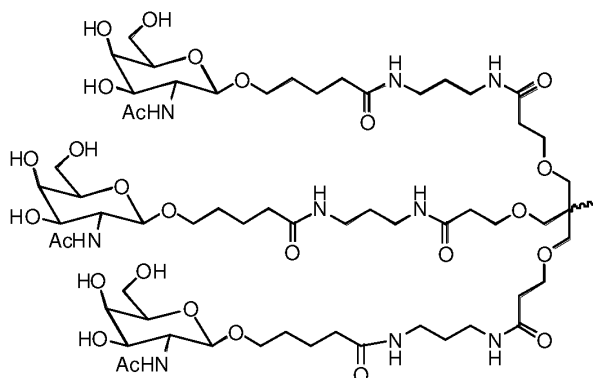
10. The dsRNA agent of any one of claims 7-9, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxythymidine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-
 5 modified nucleotide, 2'-C-alkyl-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a
 10 nucleotide comprising a methylphosphonate group, a nucleotide comprising a 2'-phosphate, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a thermally destabilizing nucleotide, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.
- 15 11. The dsRNA agent of any one of claims 7-9, wherein the modifications on the nucleotides are selected from the group consisting of LNA, HNA, CeNA, 2'-methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-C-allyl, 2'-fluoro, 2'-deoxy, 2'-hydroxyl, and a glycol modified nucleotide (GNA); and combinations thereof.
- 20 12. The dsRNA of any one of claims 7-9, wherein at least one of the modified nucleotides is selected from the group consisting of a deoxy-nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a glycol modified nucleotide (GNA), a nucleotide comprising a 2'-phosphate, a vinyl-phosphonate nucleotide, and 2'-O hexadecyl nucleotide modifications; and combinations thereof.
- 25 13. The dsRNA of any one of claims 7-9, wherein at least one of the modifications on the nucleotides is a thermally destabilizing nucleotide modification.
14. The dsRNA of claim 13, wherein the thermally destabilizing nucleotide modification is
 30 selected from the group consisting of an abasic modification; a mismatch with the opposing nucleotide in the duplex; and destabilizing sugar modification, a 2'-deoxy modification, an acyclic nucleotide, an unlocked nucleic acids (UNA), and a glycol modified nucleic acid (GNA).
15. The dsRNA agent of any one of claims 1-14, wherein the double stranded region is 19-30
 35 nucleotide pairs in length.

16. The dsRNA agent of claim 15, wherein the double stranded region is 19-25 nucleotide pairs in length.
17. The dsRNA agent of claim 15, wherein the double stranded region is 19-23 nucleotide pairs in length.
18. The dsRNA agent of claim 15, wherein the double stranded region is 23-27 nucleotide pairs in length.
19. The dsRNA agent of claim 15, wherein the double stranded region is 21-23 nucleotide pairs in length.
20. The dsRNA agent of any one of claims 1-19, wherein each strand is independently no more than 30 nucleotides in length.
21. The dsRNA agent of any one of claims 1-20, wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length.
22. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is at least 17 nucleotides in length.
23. The dsRNA agent of any one of claims 1-22, wherein the region of complementarity is 19-23 nucleotides in length.
24. The dsRNA agent of any one of claims 1-21, wherein the region of complementarity is 19-21 nucleotides in length.
25. The dsRNA agent of any one of claims 1-24, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.
26. The dsRNA agent of any one of claims 1-24, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.
27. The dsRNA agent of any one of claims 1-26, further comprising a ligand.
28. The dsRNA agent of claim 27, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.

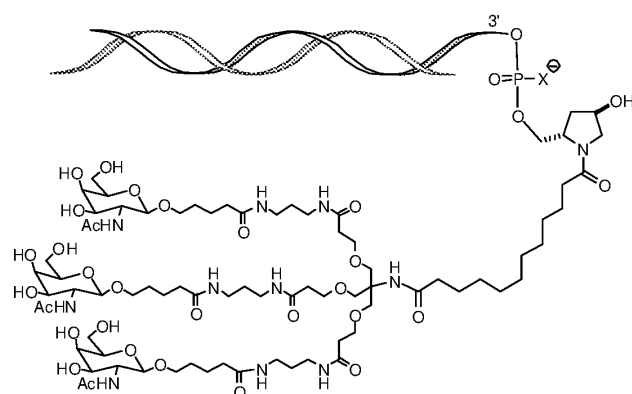
29. The dsRNA agent of claim 27 or 28, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

30. The dsRNA agent of any one of claims 27-29, wherein the ligand is one or more GalNAc derivatives attached through a monovalent, bivalent, or trivalent branched linker.

31. The dsRNA agent of claim 29 or 30, wherein the ligand is



32. The dsRNA agent of claim 31, wherein the dsRNA agent is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

33. The dsRNA agent of claim 32, wherein the X is O.

34. The dsRNA agent of any one of claims 1-33, wherein the dsRNA agent further comprises at least one phosphorothioate or methylphosphonate internucleotide linkage.

35. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 3'-terminus of one strand.

36. The dsRNA agent of claim 35, wherein the strand is the antisense strand.
37. The dsRNA agent of claim 35, wherein the strand is the sense strand.
- 5 38. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the 5'-terminus of one strand.
39. The dsRNA agent of claim 38, wherein the strand is the antisense strand.
- 10 40. The dsRNA agent of claim 38, wherein the strand is the sense strand.
41. The dsRNA agent of claim 34, wherein the phosphorothioate or methylphosphonate internucleotide linkage is at the both the 5'- and 3'-terminus of one strand.
- 15 42. The dsRNA agent of claim 41, wherein the strand is the antisense strand.
43. The dsRNA agent of any one of claims 1-42, wherein the base pair at the 1 position of the 5'-end of the antisense strand of the duplex is an AU base pair.
- 20 44. A cell containing the dsRNA agent of any one of claims 1-43.
45. A pharmaceutical composition for inhibiting expression of a gene encoding complement factor B (CFB) comprising the dsRNA agent of any one of claims 1-43.
- 25 46. The pharmaceutical composition of claim 45, wherein dsRNA agent is in an unbuffered solution.
47. The pharmaceutical composition of claim 46, wherein the unbuffered solution is saline or water.
- 30 48. The pharmaceutical composition of claim 42, wherein said dsRNA agent is in a buffer solution.
49. The pharmaceutical composition of claim 48, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.
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50. The pharmaceutical composition of claim 49, wherein the buffer solution is phosphate buffered saline (PBS).

51. A method of inhibiting expression of a complement factor B (CFB) gene in a cell, the
5 method comprising contacting the cell with the dsRNA agent of any one of claims 1-43, or the
pharmaceutical composition of any one of claims 45-50, thereby inhibiting expression of the CFB
gene in the cell.

52. The method of claim 51, wherein the cell is within a subject.

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53. The method of claim 52, wherein the subject is a human.

54. The method of claim 53, wherein the subject has a complement factor B- (CFB)-associated
disorder.

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55. The method of any one of claims 51-54, wherein contacting the cell with the dsRNA agent
inhibits the expression of complement factor B by at least 50%, 60%, 70%, 80%, 90%, or 95%.

56. The method of any one of claims 51-55, wherein inhibiting expression of complement factor
20 B decreases complement factor B protein level in serum of the subject by at least 50%, 60%, 70%,
80%, 90%, or 95%.

57. A method of treating a subject having a disorder that would benefit from reduction in
complement factor B expression, comprising administering to the subject a therapeutically effective
25 amount of the dsRNA agent of any one of claims 1-43, or the pharmaceutical composition of any one
of claims 45-50, thereby treating the subject having the disorder that would benefit from reduction in
complement factor B expression.

58. A method of preventing at least one symptom in a subject having a disorder that would
30 benefit from reduction in complement factor B expression, comprising administering to the subject a
prophylactically effective amount of the dsRNA agent of any one of claims 1-43, or the
pharmaceutical composition of any one of claims 45-50, thereby preventing at least one symptom in
the subject having the disorder that would benefit from reduction in complement factor B expression.

59. The method of claim 57 or 58, wherein the disorder is a complement factor B-associated
disorder.

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60. The method of claim 59, wherein the complement factor B-associated disease is selected from the group consisting of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), asthma, rheumatoid arthritis (RA); antiphospholipid antibody syndrome; lupus nephritis; ischemia-reperfusion injury; typical or infectious hemolytic uremic syndrome
 5 (tHUS); dense deposit disease (DDD); neuromyelitis optica (NMO); multifocal motor neuropathy (MMN); multiple sclerosis (MS); macular degeneration (e.g., age-related macular degeneration (AMD)); hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); spontaneous fetal loss; Pauci-immune vasculitis; epidermolysis bullosa; recurrent fetal loss; pre-eclampsia, traumatic brain injury, myasthenia gravis, cold agglutinin
 10 disease, dermatomyositis bullous pemphigoid, Shiga toxin E. coli-related hemolytic uremic syndrome, C3 neuropathy, anti-neutrophil cytoplasmic antibody-associated vasculitis (e.g., granulomatosis with polyangiitis (previously known as Wegener granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis), humoral and vascular transplant rejection, graft dysfunction, myocardial infarction (e.g., tissue damage and ischemia in myocardial infarction), an
 15 allogenic transplant, sepsis (e.g., poor outcome in sepsis), Coronary artery disease, dermatomyositis, Graves' disease, atherosclerosis, Alzheimer's disease, systemic inflammatory response sepsis, septic shock, spinal cord injury, glomerulonephritis, Hashimoto's thyroiditis, type I diabetes, psoriasis, pemphigus, autoimmune hemolytic anemia (AIHA), ITP, Goodpasture syndrome, Degos disease, antiphospholipid syndrome (APS), catastrophic APS (CAPS), a cardiovascular disorder, myocarditis,
 20 a cerebrovascular disorder, a peripheral (e.g., musculoskeletal) vascular disorder, a renovascular disorder, a mesenteric/enteric vascular disorder, vasculitis, Henoch-Schönlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis, immune complex vasculitis, Takayasu's disease, dilated cardiomyopathy, diabetic angiopathy, Kawasaki's disease (arteritis), venous gas embolus (VGE), and restenosis following stent placement,
 25 rotational atherectomy, and percutaneous transluminal coronary angioplasty (PTCA).

61. The method of claim 59, wherein the complement factor B-associated disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous
 30 nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis.

62. The method of claim 59, wherein the complement factor B-associated disease is selected from the group consisting of C3 glomerulopathy, systemic lupus erythematosus (SLE), e.g., Lupus Nephritis, IgA nephropathy, diabetic nephropathy, and polycystic kidney disease.

63. The method of any one of claims 57-62, wherein the subject is human.

64. The method of any one of claims 57-63, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to 50 mg/kg or at a dose of about 5 mg or 1000 mg.
65. The method of any one of claims 57-64, wherein the dsRNA agent is administered to the subject subcutaneously.
66. The method of any one of claims 57-65, further comprising administering to the subject an agent for the treatment of a CFB-associated disease.
67. The method of any one of claims 57-65, further comprising administering to the subject an iRNA agent targeting complement component C5 or an iRNA agent targeting complement component C3.
68. The method of any one of claims 57-67, further comprising determining the level of complement factor B in a sample(s) from the subject.
69. The method of claim 68, wherein the level of complement factor B in the subject sample(s) is a complement factor B protein level in a blood or serum sample(s).
70. A kit comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.
71. A vial comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.
72. A syringe comprising the dsRNA agent of any one of claims 1-43 or the pharmaceutical composition of any one of claims 45-50.