CLAIMS

1. Use of a double-stranded RNAi molecule in the manufacture of a medicament for preventing at least one symptom in a human subject having a disorder that would benefit from reduction in *SERPINC1* expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequence 5' – UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3' end.

2. Use of a double-stranded RNAi molecule in the manufacture of a medicament for treating a human subject having a disorder that would benefit from reduction in *SERPINC1* expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequence 5' – UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3' end.

3. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the frequency of bleeding episodes in a human subject having a disorder that would benefit from reduction in *SERPINC1* expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequence 5' – UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3' end.

4. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual bleeding rate (ABR) in a human subject having a disorder that would benefit from reduction in *SERPINC1* expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequence 5' – UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3' end.

5. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual spontaneous bleeding rate (AsBR) in a human subject having a disorder that

would benefit from reduction in *SERPINC1* expression, wherein the medicament is to be administered to the subject at a fixed dose of 40 mg to 90 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand, the antisense strand comprising a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the sequence 5' – UUGAAGUAAAUGGUGUUAACCAG – 3' (SEQ ID NO: 15), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, and wherein the sense strand is conjugated to a ligand attached at the 3' end.

6. The use of any one of claims 1-5, wherein the medicament is to be administered to the subject once a month, once every six weeks, once every two months, or quarterly.

7. The use of any one of claims 1-6, wherein the medicament is to be administered to the subject at a fixed dose of 50 mg of the RNAi molecule.

8. The use of any one of claims 1-6, wherein the medicament is to be administered to the subject at a fixed dose of 80 mg of the RNAi molecule.

9. The use of any one of claims 1-8, wherein the medicament is to be administered subcutaneously.

10. The use of any one of claims 1-9, wherein the use of the medicament lowers *SERPINC1* activity in the subject by 70% to 95%.

11. The use of any one of claims 1-10, wherein the use of the medicament increases peak thrombin levels in the subject to within the range of peak thrombin levels in a subject that does not have a disorder that would benefit from reduction in *SERPINC1* expression.

12. The use of any one of claims 1-11, wherein the use of the medicament is sufficient to achieve peak thrombin generation levels in the subject to about the same level achieved by administration to the subject of Factor VIII.

13. The use of any one of claims 1-12, wherein the use of the medicament is sufficient to achieve a peak thrombin generation level in the subject that is greater than about 40% of the peak thrombin generation level achieved in the subject following administration of Factor VIII.

14. The use of any one of claims 1-13, wherein the use of the medicament decreases the annual bleed rate (ABR) of the subject by 80 to 95% as compared to the median historical on-demand ABR of subjects having a disorder that would benefit from reduction in *SERPINC1* expression that are not administered the RNAi molecule.

15. The use of any one of claims 1-14, wherein the disorder is a bleeding disorder.

16. The use of claim 15, wherein the bleeding disorder is an acquired bleeding disorder or an inherited bleeding disorder.

17. The use of claim 15, wherein the bleeding disorder is a hemophilia.

18. The use of claim 17, wherein the hemophilia is hemophilia A or hemophilia B; the hemophilia is hemophilia A and the subject is an inhibitor subject; or the hemophilia is hemophilia B and the subject is an inhibitor subject.

19. The use of any one of claims 1-18, wherein the medicament is to be administered subcutaneously.

20. The use of any one of claims 1-19, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

21. The use of any one of claims 1-20, wherein the modified nucleotides are independently selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

22. The use of any one of claims 1-21, wherein the region of complementarity is at least 17 nucleotides in length.

23. The use of any one of claims 1-22, wherein the region of complementarity is between 19 and 21 nucleotides in length.

24. The use of claim 23, wherein the region of complementarity is 19 nucleotides in length.

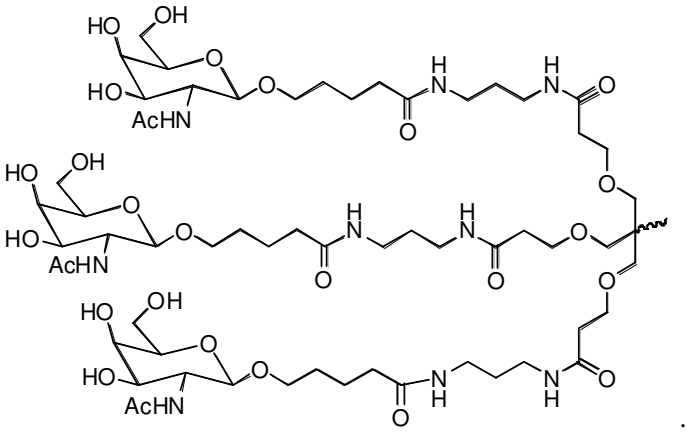
25. The use of any one of claims 1-24, wherein each strand is no more than 30 nucleotides in length.

26. The use of any one of claims 1-25, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

27. The use of any one of claims 1-26, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

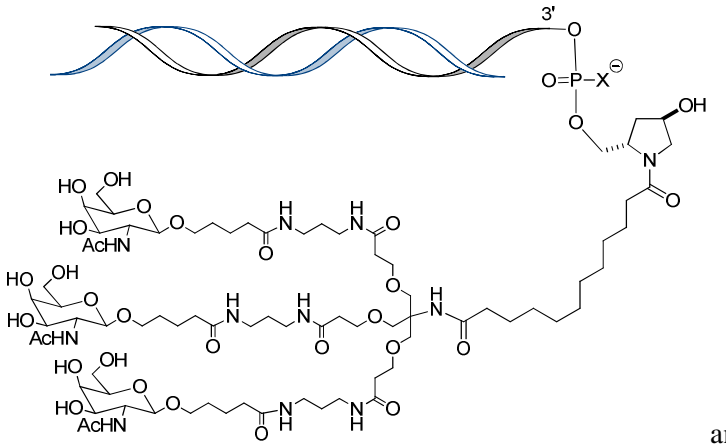
28. The use of any one of claims 1-27, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.

29. The use of any one of claims 1-28, wherein the ligand is



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30. The use of claim 29, wherein the RNAi molecule is conjugated to the ligand as shown in the following schematic



and, wherein X is O or S.

31. The use of claim 30, wherein the X is O.

32. The use of any one of claims 1-31, wherein the region of complementarity consists of the sequence 5’ – UUGAAGUAAAUGGUGUUAACCAG – 3’ (SEQ ID NO: 15).

33. The use of any one of claims 1-32, wherein the RNAi molecule comprises a sense strand comprising the sequence 5’ – GGUUAACACCAUUUACUUCAA – 3’ (SEQ ID NO: 16), and an antisense strand comprising the sequence 5’ – UUGAAGUAAAUGGUGUUAACCAG – 3’ (SEQ ID NO: 15).

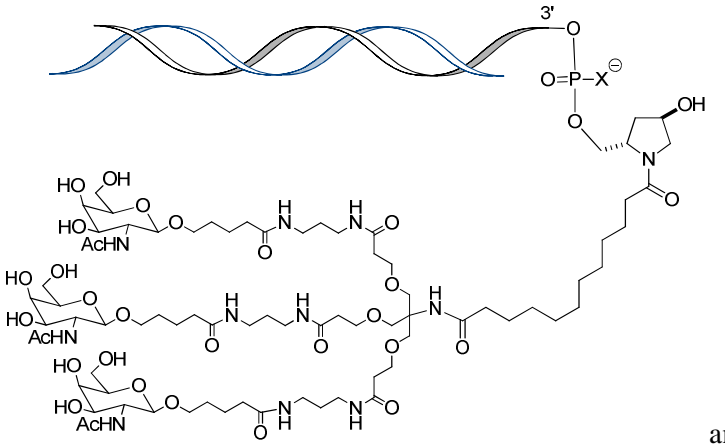
34. The use of claim 33, wherein the sequence of the sense strand comprises 5’ – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the sequence of the antisense strand comprises 5’ – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

wherein a, c, g, and u are 2’-O-methyl (2’-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2’-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage.

35. The use of any one of claims 1-34, wherein the sequence of the sense strand comprises 5’ – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3’ (SEQ ID NO:13) and the sequence of the antisense strand comprises 5’ – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3’ (SEQ ID NO:14),

wherein a, c, g, and u are 2’-O-methyl (2’-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2’-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein the sense strand is conjugated to the ligand as shown in the following schematic



and, wherein X is O.

36. The use of any one of claims 1-35, wherein the medicament is a pharmaceutical composition.

37. The use of claim 36, wherein the pharmaceutical composition comprises an unbuffered solution.

38. The use of claim 37, wherein the unbuffered solution is saline or water.

39. The use of claim 36, wherein the pharmaceutical composition comprises a buffered solution.

40. The use of claim 39, wherein the buffered solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

41. The use of claim 40, wherein the buffered solution is a phosphate buffered saline (PBS).

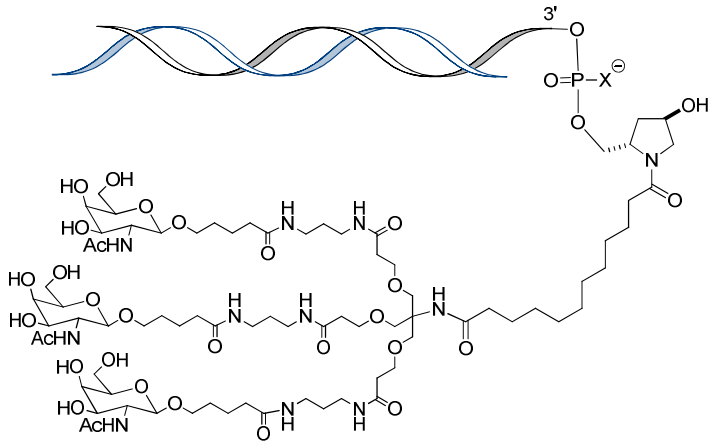
42. Use of a double-stranded RNAi molecule in the manufacture of a medicament for preventing at least one symptom in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 80 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

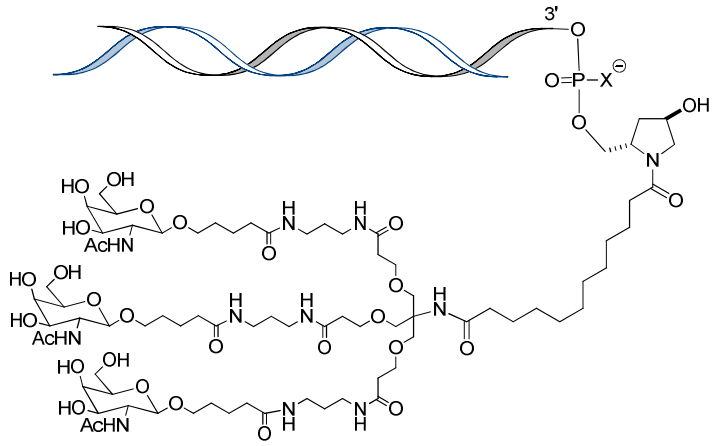
43. Use of a double-stranded RNAi molecule in the manufacture of a medicament for treating a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 80 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

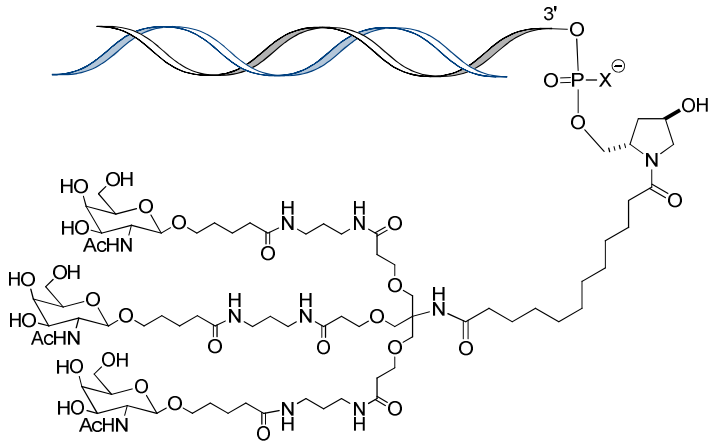
44. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the frequency of bleeding episodes in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 80 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

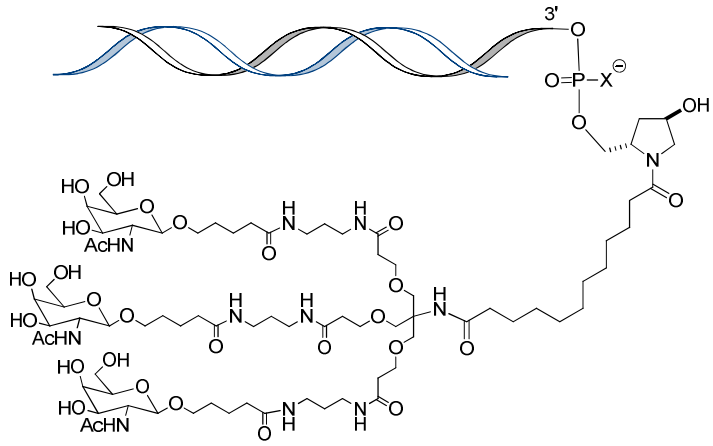
45. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual bleeding rate (ABR) in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 80 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

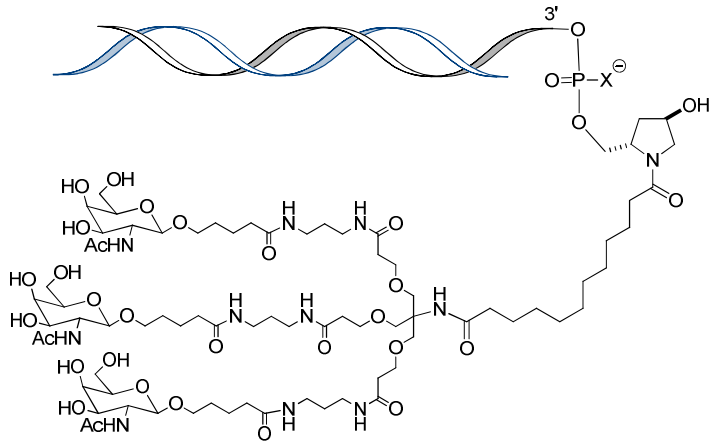
46. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual spontaneous bleeding rate (AsBR) in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 80 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

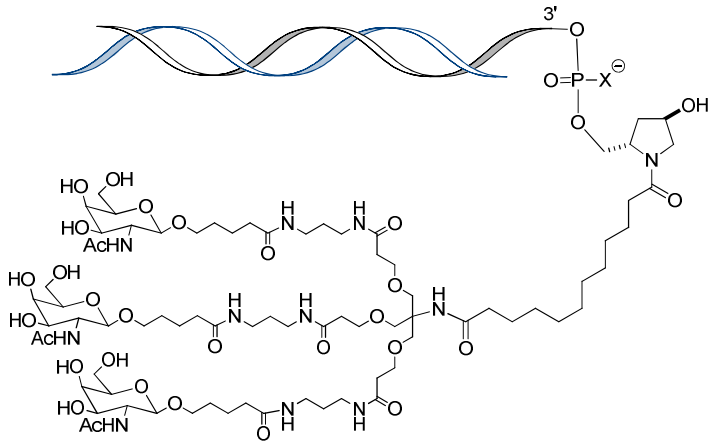
47. Use of a double-stranded RNAi molecule in the manufacture of a medicament for preventing at least one symptom in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 50 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

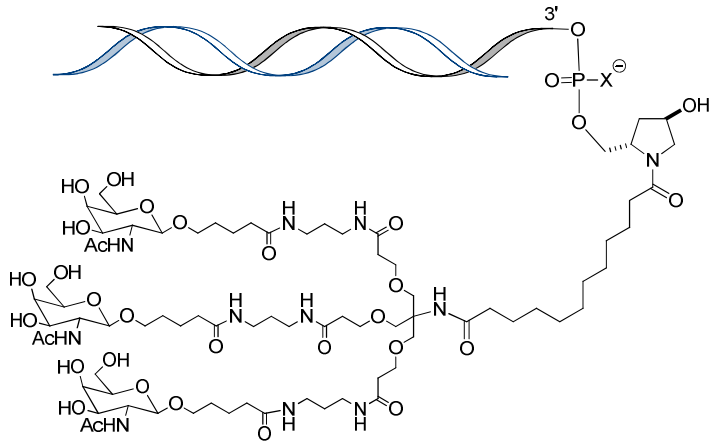
48. Use of a double-stranded RNAi molecule in the manufacture of a medicament for treating a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 50 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5' – GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

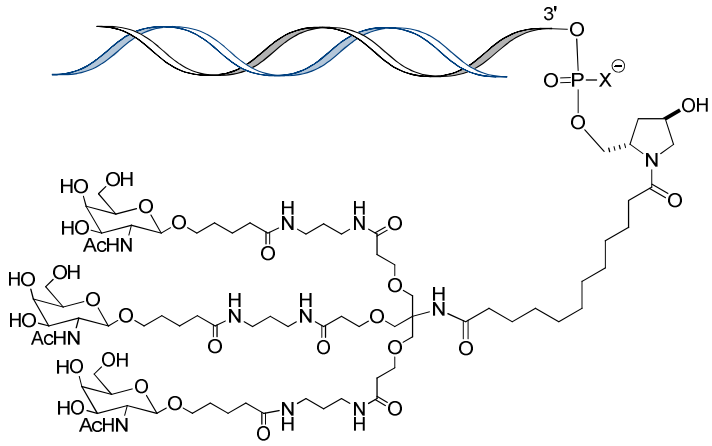
49. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the frequency of bleeding episodes in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 50 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

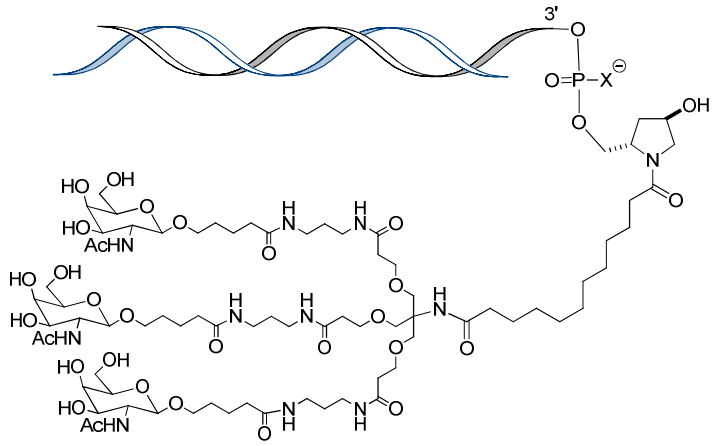
50. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual bleeding rate (ABR) in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 50 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

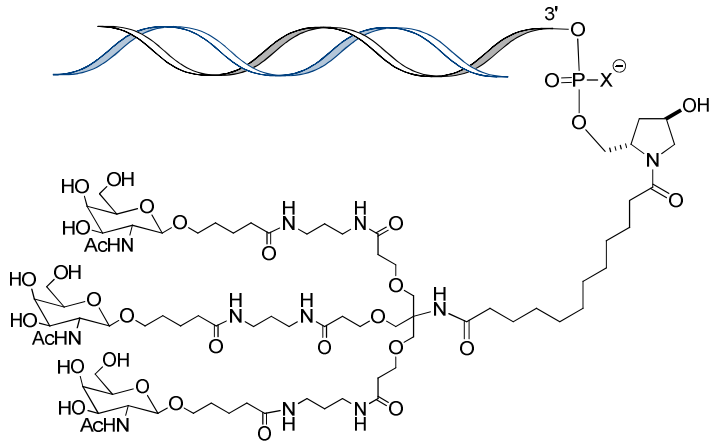
51. Use of a double-stranded RNAi molecule in the manufacture of a medicament for reducing the annual spontaneous bleeding rate (AsBR) in a human subject having a hemophilia, wherein the medicament is to be subcutaneously administered to the subject once a month at a fixed dose of 50 mg of the RNAi molecule,

wherein the RNAi molecule comprises a sense strand and an antisense strand forming a double-stranded region, and

wherein the sense strand has the sequence 5'-GfsgsUfuAfaCfaCfCfAfuUfuAfcUfuCfaAf – 3' (SEQ ID NO:13) and the antisense strand has the sequence 5' – usUfsgAfaGfuAfaAfuggUfgUfuAfaCfcsasg – 3' (SEQ ID NO:14),

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, C, G, and U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, C, G, and U, respectively; and s is a phosphorothioate linkage; and

wherein a ligand is conjugated to the 3' end of the sense strand as shown in the schematic:



and, wherein X is O.

52. The use of any one of claims 4, 45, or 50, wherein the use of the medicament reduces ABR of the subject to one or less.

53. The use of any one of claims 5, 46, or 51 wherein the use of the medicament reduces AsBR of the subject to zero.

54. The use of any one of claims 42-53, wherein the medicament is a pharmaceutical composition.

55. The use of claim 54, wherein the pharmaceutical composition comprises a buffered solution.

56. The use of claim 55, wherein the buffered solution is phosphate buffered saline (PBS).

57. The use of any one of claims 42-56, wherein the subject is a hemophilia A patient with inhibitors or a hemophilia B patient with inhibitors.

58. The use of any one of claims 42-56, wherein the subject is a hemophilia A patient without inhibitors or a hemophilia B patient without inhibitors.