CLAIMS

What is claimed is:

1) An aptamer that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs.: 4, 1, 2, 3, 5, 6, 7, 8, 9 and 10.

2) The aptamer of claim 1, wherein the TFPI is human TFPI.

3) The aptamer of claim 1 or 2, wherein the aptamer has a dissociation constant for human TFPI of 100 nM or less.

4) The aptamer of any one of claims 1 to 3, wherein the aptamer comprises at least one chemical modification.

5) The aptamer of claim 4, wherein the modification is selected from the group consisting of: a chemical substitution at a sugar position, a chemical substitution at an internucleotide linkage, and a chemical substitution at a base position.

6) The aptamer of claim 4, wherein the modification is selected from the group consisting of: incorporation of a modified nucleotide; a 3' cap; a 5' cap; conjugation to a high molecular weight, non-immunogenic compound; conjugation to a lipophilic compound; incorporation of a CpG motif; and incorporation of a phosphorothioate or phosphorodithioate into the phosphate backbone.

7) The aptamer of claim 6, wherein the high molecular weight, non-immunogenic, compound is polyethylene glycol.

8) The aptamer of claim 6 or 7, wherein the 3' cap is an inverted deoxythymidine cap.

9) The aptamer of any one of claims 1 to 8 or a salt thereof comprising the nucleic acid sequence set forth below:
mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA (SEQ ID NO: 1) (ARC26835), wherein "dN" is a deoxynucleotide and "mN" is a 2'-OMe containing nucleotide.

10) The aptamer of any one of claims 1 to 8 or a salt thereof comprising the nucleic acid sequence set forth below:
mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2) (ARC17480), wherein "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-OMe containing nucleotide.

11) The aptamer of any one of claims 1 to 8 or a salt thereof comprising the nucleic acid sequence set forth below:
NH_2-mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 3) (ARC19498), wherein "NH_2" is from a 5'-hexylamine linker phosphoramidite, "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-OMe containing nucleotide.

12) The aptamer of any one of claims 1 to 8 or a salt thereof comprising the nucleic acid sequence set forth below:
PEG40K-NH-mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 4) (ARC19499), wherein "NH" is from a 5'-hexylamine linker phosphoramidite, "PEG" is a polyethylene glycol, "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-OMe containing nucleotide.

13) A pharmaceutical composition comprising a therapeutically effective amount of the aptamer of any one of claims 1 to 12 or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

14) Use of the aptamer of any one of claims 1 to 12 or the composition of claim 13 in the manufacture of a medicament, for treating, preventing, delaying the progression of or ameliorating a bleeding disorder mediated by TFPI in a subject.

15) The use of claim 14, wherein the subject is a mammal.

16) The use of claim 15, wherein the mammal is a human.

17) The use of any one of claims 14 to 16, wherein the bleeding disorder is selected from the group consisting of: prophylaxis and/or on-demand therapy for coagulation factor deficiencies, congenital or acquired, mild/moderate/severe, including Hemophilia A (Factor VIII-deficiency), Hemophilia B (Factor IX deficiency) and Hemophilia C (Factor XI deficiency); Hemophilia A or B with inhibitors; other factor deficiencies (V, VII, X, XIII, prothrombin, fibrinogen); deficiency of α2-plasmin inhibitor; deficiency of plasminogen activator inhibitor 1; multiple factor deficiency; functional factor abnormalities (*e.g.*, dysprothrombinemia); joint hemorrhage (hemarthrosis) including but not limited to ankle, elbow and knee; spontaneous bleeding in other locations (muscle, gastrointestinal, mouth, *etc.*); hemorrhagic stroke; intracranial hemorrhage; lacerations and other hemorrhage associate with trauma; acute traumatic coagulopathy; coagulopathy associated with cancer (*e.g.*, acute promyelocytic leukemia); von Willebrand's Disease; disseminated intravascular coagulation; liver disease; menorrhagia and thrombocytopenia.

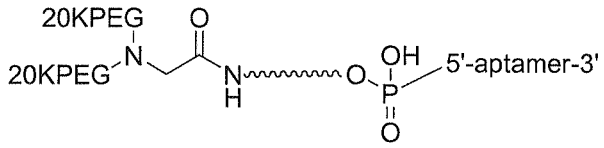
18) The use of any one of claims 14 to 17, wherein the composition is to be administered prior to, during and/or after a medical procedure.

19) The use of any one of claims 14 to 18, wherein the composition is to be administered in combination with another drug.

20) The use of any one of claims 14 to 19, wherein the composition is to be administered in combination with another therapy.

21) A kit comprising the aptamer of any one of claims 1 to 12.

22) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:

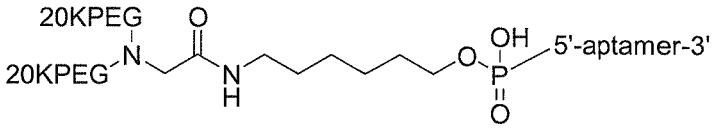


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wherein HN ~~~~ PO_3H is from a 5'-amine linker phosphoramidite, and wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide, and wherein 20KPEG is a mPEG moiety having a molecular weight of 20 kDa.

23) The aptamer of claim 22, wherein the linker is selected from the group consisting of: 2-18 consecutive CH_2 groups, 2-12 consecutive CH_2 groups, 4-8 consecutive CH_2 groups and 6 consecutive CH_2 groups.

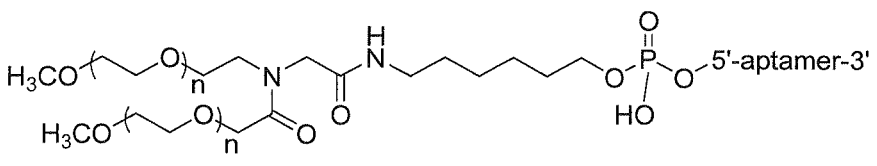
24) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:



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wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide, and wherein 20KPEG is a mPEG moiety having a molecular weight of 20 kDa.

25) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:



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wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "n" is approximately 450, "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide.

26) A method of producing an aptamer that binds to tissue factor pathway inhibitor (TFPI), the method comprising the step of chemically synthesizing a nucleic acid having a nucleic acid sequence according to a nucleic acid sequence of any one of claims 1 to 12 or 22 to 25.

27) The method of claim 26 wherein the method further comprises formulating a pharmaceutical composition by mixing the synthesized nucleic acid sequence, or a salt thereof, with a pharmaceutically acceptable carrier or diluent.

28) The method of claim 27 wherein the method further comprises formulating a pharmaceutical composition by mixing the synthesized nucleic acid sequence or a salt thereof, with a pharmaceutically acceptable carrier or diluent.

29) An aptamer that binds to human tissue factor pathway inhibitor (TFPI) and comprises a stem and loop motif having the nucleotide sequence of SEQ ID NO: 4, wherein:
a) any one or more of nucleotides 1, 2, 3, 4, 6, 8, 11, 12, 13, 17, 20, 21, 22, 24, 28, 30 and 32 may be modified from a 2'-OMe substitution to a 2'-deoxy substitution;
b) any one or more of nucleotides 5, 7, 15, 19, 23, 27, 29 and 31 may be modified from a 2'-OMe uracil to either a 2'-deoxy uracil or a 2'-deoxy thymine;
c) nucleotide 18 may be modified from a 2'-OMe uracil to a 2'-deoxy uracil; and/or
d) any one or more of nucleotides 14, 16 and 25 may be modified from a 2'-deoxy cytosine to either a 2'-OMe cytosine or a 2'-fluoro cytosine.

30) An aptamer that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises a primary nucleic acid sequence selected from the group consisting of SEQ ID NOs.: 4, 1, 2, 3, 5, 6, 7, 8, 9 and 10.

What is claimed is:

1) An aptamer that binds to tissue factor pathway inhibitor (TFPI) wherein the aptamer competes, either directly or indirectly, for binding to TFPI with a reference antibody selected from the group consisting of: AD4903.

2) An aptamer that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs.: 4, 1, 2, 3, 5, 6, 7, 8, 9 and 10.

3) The aptamer of claim 1, wherein the TFPI is human TFPI.

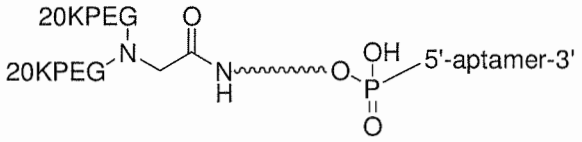
4) The aptamer of claim 2 or 3, wherein the aptamer has a dissociation constant for human TFPI of 100 nM or less.

5) The aptamer of claim 2, 3 or 4, wherein the aptamer comprises at least one chemical modification.

6) The aptamer of claim 5, wherein the modification is selected from the group consisting of: a chemical substitution at a sugar position, a chemical substitution at an internucleotide linkage, and a chemical substitution at a base position.

7) The aptamer of claim 5, wherein the modification is selected from the group consisting of: incorporation of a modified nucleotide; a 3' cap; a 5' cap; conjugation to a high molecular weight, non-immunogenic compound; conjugation to a lipophilic compound; incorporation of a CpG motif; and incorporation of a phosphorothioate or phosphorodithioate into the phosphate backbone.

8) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:

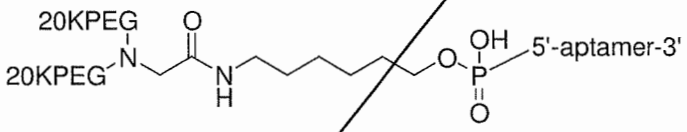


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wherein HN PO$_3$H is from a 5'-amine linker phosphoramidite, and wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide, and wherein 20KPEG is a mPEG moiety having a molecular weight of 20 kDa.

9) The aptamer of claim 8, wherein the linker is selected from the group consisting of: 2-18 consecutive CH_2 groups, 2-12 consecutive CH_2 groups, 4-8 consecutive CH_2 groups and 6 consecutive CH_2 groups.

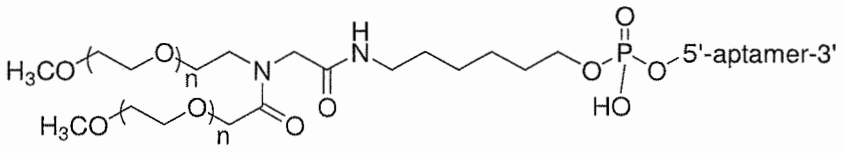
10) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:



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wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide, and wherein 20KPEG is a mPEG moiety having a molecular weight of 20 kDa.

11) An aptamer or a salt thereof that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises the following structure:



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wherein the aptamer comprises the nucleic acid sequence of mG-mG-mA-mA-mU-mA-mU-mA-dC-mU-mU-mG-mG-dC-mU-dC-mG-mU-mU-mA-mG-mG-mU-mG-dC-mG-mU-mA-mU-mA-mU-mA-3T (SEQ ID NO: 2), wherein "n" is approximately 450, "3T" is an inverted deoxythymidine, "dN" is a deoxynucleotide and "mN" is a 2'-O Methyl containing nucleotide.

12) An aptamer that binds to human tissue factor pathway inhibitor (TFPI) wherein the aptamer competes for binding to TFPI with a reference aptamer selected from the group consisting of: SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 10.

13) An aptamer that binds to human tissue factor pathway inhibitor (TFPI) and comprises a stem and loop motif having the nucleotide sequence of SEQ ID NO: 4, wherein:
a) any one or more of nucleotides 1, 2, 3, 4, 6, 8, 11, 12, 13, 17, 20, 21, 22, 24, 28, 30 and 32 may be modified from a 2'-OMe substitution to a 2'-deoxy substitution;
b) any one or more of nucleotides 5, 7, 15, 19, 23, 27, 29 and 31 may be modified from a 2'-OMe uracil to either a 2'-deoxy uracil or a 2'-deoxy thymine;
c) nucleotide 18 may be modified from a 2'-OMe uracil to a 2'-deoxy uracil; and/or
d) any one or more of nucleotides 14, 16 and 25 may be modified from a 2'-deoxy cytosine to either a 2'-OMe cytosine or a 2'-fluoro cytosine.

14) An aptamer that binds to tissue factor pathway inhibitor (TFPI), wherein the aptamer comprises a primary nucleic acid sequence selected from the group consisting of SEQ ID NOs.: 4, 1, 2, 3, 5, 6, 7, 8, 9 and 10.