inhibitors of the cofactor activity of Protein S for both APC and TFPI (dual inhibitor of cofactor activity), and wherein the antibody is human, humanized, or chimeric. In some preferred examples, the antibodies provided herein specifically bind Protein S.

[0005a] In one aspect, the present disclosure refers to an antibody that binds Protein S, wherein the antibody comprises:

a heavy chain comprising a heavy chain variable region comprising a CDR-H1, a CDR-H2, and a CDR-H3; and

a light chain comprising a light chain variable region comprising a CDR-L1, a CDR-L2, and a CDR-L3,

wherein

(a) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 12, the CDR-L3 comprises the amino acid sequence of SEQ ID NO:21, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 33, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 45, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 57;

(b) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 15, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 24, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 36, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 48, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 60; or

(c) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 16, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 31, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 43, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 55, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 67.

[0006] In another example, provided herein are antibodies that bind Protein S, wherein the antibodies are capable of promoting coagulation and/or modulating a component in the coagulation cascade.

[0007] In another example, provided herein are exemplary Protein S antibodies comprising any one or more of the amino acid sequences of the complementarity determining region (CDR) sequences provided in Tables 1A, 1B, 1C, 2A, 2B, and 2C. In another example, the exemplary Protein S antibodies comprise any one of the CDR-L1 amino acid sequences of Table 1A; any one of the CDR-L2 amino acid sequences of Table 1B; any one of the CDR-L3 amino acid sequences of Table 1C; any one of the CDR-H1 amino acid sequences of Table 2A; any one of the CDR-H2 amino acid sequences of Table 2B; any one of the CDR-H3 amino acid sequences of Table 2B. In another example, provided herein are exemplary Protein S antibodies comprising the combinations of variable light chains and variable heavy chains presented in Table 4C. In another example, provided herein are the sequences of different antibodies as presented in Table 6. In another example, provided herein are nucleic acids encoding for any of the Protein S antibodies provided herein.

[0008] In another example, provided herein are pharmaceutical compositions comprising any one of the Protein S antibodies provided herein, and optionally a pharmaceutically acceptable excipient.

[0008a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody disclosed herein, and a pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a nucleic acid encoding for the antibody disclosed herein. In one example, the present disclosure refers to a vector comprising the nucleic acid disclosed herein.

[0009] Provided herein are methods of using the exemplary Protein S antibodies described herein. Accordingly, in one example, provided herein is an *in vitro* method of promoting the coagulation of blood, comprising contacting any one of the Protein S antibodies provided herein with a blood sample.

[0009a] In one aspect, the present disclosure refers to an *in vitro* method of promoting the coagulation of blood, comprising contacting the antibody disclosed herein with a blood sample.

[0010] In another example, provided herein is a method of promoting the coagulation of blood in a subject in need thereof, comprising administering to the subject any of the exemplary Protein S antibodies provided herein, or pharmaceutical compositions provided herein. In examples, the route of administration is subcutaneous.

[0010a] In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating von Willebrand disease (vWD) in a human subject in need thereof.

[0011] In another example, provided herein is a method of promoting the generation of thrombin in a subject in need thereof, comprising administering to the subject any of the Protein S antibodies provided herein, or pharmaceutical compositions provided herein.

[0011a] In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a coagulation factor deficiencyin a human subject in need thereof.

[0012] In another example, provided herein is a method of treating a condition in a subject in need thereof, comprising administering to the subject any of the Protein S antibodies provided herein, or pharmaceutical compositions provided herein, wherein the condition is selected from the group consisting of: bleeding disorders, platelet disorders, trauma, bleeding resulting from a surgery or a medical procedure, and combinations thereof.

[0012a] In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating bleeding disorder, a platelet disorder, trauma, or bleeding resulting from a surgery or a medical procedure in a human subject in need thereof, wherein the condition is selected from the group consisting of: bleeding disorders, platelet disorders, trauma, and bleeding resulting from a surgery or a medical procedure.

[0013] In another example, provided herein is the use of any one of the Protein S antibodies or pharmaceutical compositions provided herein, for the treatment of a condition in a subject in need thereof. The condition may be selected from the group consisting of: bleeding disorders, platelet disorders, trauma, bleeding resulting from a surgery or a medical procedure, and combinations thereof.

[0014] In another example, any one of the Protein S antibodies or pharmaceutical compositions provided herein, may be used for the manufacture of a medicament for the treatment of a condition in a subject in need thereof. The condition may be selected from the group consisting of: bleeding disorders, platelet disorders, trauma, bleeding resulting from a surgery or a medical procedure, and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIG. 1** depicts a schematic diagram of Protein S showing the modular domains of Protein S.

[0016] **FIGS. 2A-2B** depict the results of screening assays performed to assess APC and TFPI cofactor activity, respectively, using control Protein S antibodies. In this and subsequent figures, ProS = Protein S; mAb = monoclonal antibody; pAb = polyclonal antibody; PRP = platelet rich plasma.

[0017] **FIGS. 3-4** depict peak thrombin levels generated by Protein S monoclonal antibodies, identified from hybridoma libraries, in the APC cofactor and TFPI cofactor screening assays, respectively.

CLAIMS

1. An antibody that binds Protein S, wherein the antibody comprises:

a heavy chain comprising a heavy chain variable region comprising a CDR-H1, a CDR-H2, and a CDR-H3; and

a light chain comprising a light chain variable region comprising a CDR-L1, a CDR-L2, and a CDR-L3,

wherein

(a) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 12, the CDR-L3 comprises the amino acid sequence of SEQ ID NO:21, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 33, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 45, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 57;

(b) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 15, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 24, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 36, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 48, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 60; or

(c) the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 16, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 31, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 43, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 55, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 67.

2. The antibody of claim 1, wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 12, the CDR-L3 comprises the amino acid sequence of SEQ ID NO:21, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 33, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 45, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 57.

3. The antibody of claim 2, wherein the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 69 and the heavy chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 70.

4. The antibody of claim 1, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 69 and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 70.

5. The antibody of claim 1, wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 1, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 15, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 24, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 36, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 48, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 60.

6. The antibody of claim 5, wherein the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 75 and wherein the heavy chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 76.

7. The antibody of claim 1, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 75 and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 76.

8. The antibody of claim 1, wherein the CDR-L1 comprises the amino acid sequence of SEQ ID NO: 10, the CDR-L2 comprises the amino acid sequence of SEQ ID NO: 16, the CDR-L3 comprises the amino acid sequence of SEQ ID NO: 31, the CDR-H1 comprises the amino acid sequence of SEQ ID NO: 43, the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 55, and the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 67.

9. The antibody of claim 8, wherein the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 89 and wherein the heavy chain variable region comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 90.

10. The antibody of claim 1, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 89 and the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 90.

11. The antibody of any one of claims 1 to 10, wherein the antibody is human, humanized, or chimeric.

12. The antibody of any one of claims 1 to 11, wherein the antibody is a full-length antibody.

13. The antibody of any one of claims 1 to 12, wherein the antibody comprises a heavy chain constant region, wherein the heavy chain constant region is a human Fc domain.

14. The antibody of claim 13, wherein the human Fc domain is IgG1, IgG2, IgG3, or IgG4.

15. The antibody of claim 13, wherein the human Fc domain is a human IgG4 domain.

16. The antibody of claim 15, wherein the human IgG4 Fc domain comprises at least one amino acid substitution relative to the IgG4 sequence of SEQ ID NO: 218 at a position selected from the group consisting of: 215, 221, 222, 228, 234, 235, 236, 239, 240, 241, 243, 244, 245, 247, 250, 252, 254, 256, 262, 263, 264, 265, 266, 267, 268, 269, 270, 292, 296, 297, 298, 299, 300, 305, 313, 324, 325, 326, 327, 328, 329, 330, 332, 333, 334, 345, 396, 428, 430, 433, 434, and 440, wherein the position numbers of the amino acid residues are of the EU numbering scheme.

17. The antibody of claim 16, wherein the at least one amino acid substitution increases serum half-life of the antibody.

18. The antibody of claim 17, wherein the at least one amino acid substitution comprises T250Q/M428L, M252Y/S254T/T256E, M428L/N434S, S267E/L328F, N325S/L328F, or H433K/N434F.

19. The antibody of claim 17, wherein the at least one amino acid substitution comprises M428L/N434S.

20. The antibody of claim 16, wherein the at least one amino acid substitution reduces effector function.

21. The antibody of claim 20, wherein the at least one amino acid substitution comprises L235E or F234A/L235A.

22. The antibody of claim 20, wherein the at least one amino acid substitution comprises L235E.

23. The antibody of claim 16, wherein the at least one amino acid substitution reduces Fab-arm exchange.

24. The antibody of claim 23, wherein the at least one amino acid substitution comprises S228P.

25. The antibody of claim 18, wherein the at least one amino acid substitution further comprises S228P.

26. The antibody of claim 18, wherein the at least one amino acid substitution further comprises L235E or F234A/L235A.

27. The antibody of claim 25, wherein the at least one amino acid substitution further comprises L235E or F234A/L235A.

28. The antibody of any one of claims 1 to 27, wherein the antibody comprises a light chain constant region.

29. The antibody of claim 28, wherein the light chain constant region comprises the amino acid sequence of SEQ ID NO: 214.

30. The antibody of claim 28, wherein the light chain constant region comprises the amino acid sequence of SEQ ID NO: 215.

31. The antibody of any one of claims 1 to 10, wherein the antibody is a bispecific antibody, a single chain antibody (scFv), an Fab fragment, an F(ab)2 fragment, an F(ab')2 fragment, a dsFv diabody fragment, an Fc fragment, or an Fd fragment.

32. The antibody of any one of claims 1 to 31, wherein the antibody is conjugated.

33. The antibody of claim 32, wherein the antibody is conjugated to a label.

34. A pharmaceutical composition comprising the antibody of any one of claims 1 to 33, and a pharmaceutically acceptable excipient.

35. A nucleic acid encoding for the antibody of any one of claims 1 to 31.

36. An *in vitro* method of promoting the coagulation of blood, comprising contacting the antibody of any one of claims 1 to 33 with a blood sample.

37. Use of the pharmaceutical composition of claim 34, in the manufacture of a medicament for treating von Willebrand disease (vWD) in a human subject in need thereof.

38. The use of claim 37, wherein the vWD is a subtype selected from the group consisting of vWD Type 1, vWD Type 2A, vWD Type 2B, vWD Type 2N, vWD Type 2M, vWD Type 3, and acquired vWD.

39. Use of the pharmaceutical composition of claim 34, in the manufacture of a medicament for treating a coagulation factor deficiency in a human subject in need thereof.

40. Use of the pharmaceutical composition of claim 34, in the manufacture of a medicament for treating a bleeding disorder, a platelet disorder, trauma, or bleeding resulting from a surgery or a medical procedure in a human subject in need thereof.

41. The use of claim 40, wherein the human subject has a bleeding disorder selected from the group consisting of a menorrhagia, Factor I deficiency, Factor II deficiency, Factor V deficiency, Factor VII deficiency, Factor X deficiency, Factor XI deficiency, Factor VIII

deficiency (hemophilia A), Factor IX deficiency (hemophilia B), trauma, and hereditary hemorrhagic telangiectasia.

42. The use of claim 40 , wherein the human subject has a platelet disorder selected from the group consisting of: Bernard-Soulier syndrome, Glanzmann’s thrombasthenia, and platelet storage pool deficiency, including Gray platelet syndrome, Quebec platelet disorder, and MYH9-related thrombocytopenia (MYH9RD).