CLAIMS:

1. A method for preventing or reducing bleeding in a subject undergoing anticoagulant therapy with a factor Xa inhibitor, comprising administering to the subject an effective amount of a factor Xa protein derivative that binds to the factor Xa inhibitor and does not assemble into a prothrombinase complex.

2. A method for selectively binding and inhibiting an exogenously administered factor Xa inhibitor in a subject, comprising administering to the subject an effective amount of a Xa protein derivative that binds to the factor Xa inhibitor and does not assemble into a prothrombinase complex.

3. The method of claim 1 or claim 2, wherein the factor Xa protein derivative binds to the factor Xa inhibitor either directly or indirectly.

4. The method of claim 3, wherein the derivative has either reduced or no procoagulant activity.

5. The method of any preceding claim, wherein the derivative is a Gla-deficient factor Xa protein derivative or a des-Gla factor Xa protein.

6. The method of any preceding claim, wherein the derivative has a modified active site.

7. The method of any preceding claim, wherein the derivative comprises at least amino acid residues 46 to 448 of SEQ ID NO. 3 or an equivalent thereof.

8. The method of any preceding claim, wherein the derivative comprises at least amino acid residues 46 to 139 and 195 to 448 of SEQ ID NO. 3 or an equivalent thereof.

9. The method of any preceding claim, wherein the derivative lacks a light chain of fXa and contains a serine protease catalytic domain present in the heavy chain.

10. The method of any preceding claim wherein the derivative is a polypeptide comprising the amino acid sequence of SEQ ID NO. 5.

11. The method of any preceding claim, wherein the derivative includes a catalytic domain optionally chemically or recombinantly modified to lack proteolytic activity but maintain structural characteristics necessary for binding, said domain derived from either:

a. mammalian proteases selected from the group consisting of plasma kallikrein, thrombin, and trypsin; or

b. bacterial protease subtilisin.

12. The method of any preceding claim, wherein the derivative comprises an amino acid sequence of SEQ ID NO. 7 with a modified light chain or an equivalent thereof.

13. The method of any preceding claim, wherein the derivative comprises a modified light chain to reduce phospholipid membrane binding.

14. The method of any preceding claim, wherein the modified light chain comprises at least one amino acid substitution, addition, or deletion in the Gla-domain as compared to the Gla-domain of a wild type human factor Xa protein.

15. The method of any preceding claim, wherein the derivative is selected from the group consisting of an uncarboxylated, undercarboxylated, and decarboxylated factor Xa protein.

16. The method of any preceding claim, wherein the derivative comprises the heavy chain of SEQ ID NO. 7 that is modified or an equivalent thereof.

17. The method of any preceding claim, wherein the derivative is modified by at least one amino acid substitution of an amino acid selected from the group consisting of Glu216, Glu218, Arg332, Arg347, Lys351, and Ser379.

18. The method of any preceding claim, wherein Ser379 is modified to dehydro-alanine or alanine.

19. The method of any preceding claim, wherein the derivative is des-Gla anhydro-fXa having an amino acid sequence of SEQ ID NO. 10 or an equivalent thereof.

20. The method of any preceding claim, wherein the derivative is des-Gla fXa-S379A having an amino acid sequence of SEQ ID NO. 11 or an equivalent thereof.

21. The method of any preceding claim, wherein the derivative has reduced interaction with ATIII, cofactors fV/fVa and/or fVIII/fVIIIa and comprises an amino acid sequence of SEQ ID NO. 7 or an equivalent thereof.

22. The method of any preceding claim, wherein the derivative comprises the amino acid sequence of SEQ ID NO. 12 or 13 or 15 or a polypeptide having at least 80% homology to SEQ ID NO. 12 or 13 or 15.

23. The method of any preceding claim, wherein the derivative has at least one amino acid substitution at amino acid position Arg306, Glu310, Arg347, Lys351, Lys414, or Arg424.

24. The method of any preceding claim, wherein the derivative has a modification in the EGF domain, said modification is selected from the group consisting of deletion of the EGF1 domain, deletion of the EGF2 domain, and deletion of both the EGF1 and EGF2 domains.

25. The method of any preceding claim, wherein the derivative is conjugated to a moiety capable of extending circulating half life of the derivative.

26. The method of claim 25, wherein the moiety is selected from the group consisting of polyethylene glycol, an acyl group, a liposome, an encapsulating agent, a carrier protein, an artificial phospholipid membrane, a nanoparticle, Fc peptide fragment, a chimeric protein comprising a Fc carrier domain and fXa derivative and combinations thereof.

27. The method of of any preceding claim, wherein the method further comprises administering an effective amount of an agent that extends circulating half-life of the derivative.

28. The method of claim 27, wherein the agent is an anti-fXa antibody that specifically recognizes and binds the exosite of fXa or an alpha-2-macroglobulin bound fXa derivative.

29. The method of any preceding claim wherein the factor Xa inhibitor is selected from the group consisting of fondaparinux, idraparinux, biotinylated idraparinux, enoxaparin, fragmin, NAP-5, rNAPc2, tissue factor pathway inhibitor, DX-9065a, YM-60828, YM-150, apixaban, rivaroxaban, PD-348292, otamixaban, DU-176b, LY517717, GSK913893, razaxaban, low molecular weight heparin, betrixaban or a pharmaceutically acceptable salt thereof, and combinations thereof.

30. The method of claim 29 wherein the factor Xa inhibitor is selected from betrixaban, rivaraoxaban, apixaban, low molecular weight heparin, and combinations thereof.

31. The method of any preceding claim, wherein the subject is experiencing a clinical major bleeding event selected from the group consisting of hemorrhage, bleeding into vital organs, bleeding requiring re-operation or a new therapeutic procedure, and a bleeding index of equal to or more than 2.0 with an associated overt bleeding.

32. The method of any preceding claim, wherein the subject is experiencing a bleeding event selected from the group consisting of persistent or recurrent epistaxis, rectal or urinary tract bleeding without the need for a therapeutic procedure, substantial injection site-hematomas, spontaneous hematomas at non-injection site, hematomas occurring with trivial trauma, substantial blood loss, and bleeding requiring unplanned transfusion.

33. The method of any preceding claim, wherein the derivative is administered prior to a surgery.

34. A pharmaceutical composition comprising a factor Xa derivative protein that binds to a factor Xa inhibitor and does not assemble into a prothrombinase complex and a pharmaceutically acceptable carrier.

35. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 12 or a polypeptide having at least 80% homology to SEQ ID NO. 12.

36. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 12.

37. An isolated two chain polypeptide comprising the amino acid sequence of SEQ ID NO. 13 or a polypeptide having at least 80% homology to SEQ ID NO. 13.

38. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 15 or a polypeptide having at least 80% homology to SEQ ID NO. 15.

39. A peptide conjugate comprising a carrier covalently or non-covalently linked to a polypeptide as in one of claims 35-38.

40. The peptide conjugate of claim 39 wherein the carrier is a liposome, a micelle, a pharmaceutically acceptable polymer, or a pharmaceutically acceptable carrier.

41. A pharmaceutical composition comprising a carrier and a polypeptide as in one of claims 35-38.

42. A polynucleotide encoding for a polypeptide as in one of claims 35-38.

43. An antibody that binds a polypeptide as in one of claims 35-38.

44. The antibody of claim 43 wherein the antibody is a polyclonal antibody, a monoclonal antibody, a chimeric antibody or a humanized antibody.

45. A biologically active fragment of the antibody of claim 43.

46. The antibody of claim 43 wherein the antibody is detectably labeled.

47. A composition comprising the antibody of claim 43 and a carrier.

48. A composition comprising the antibody fragment of claim 45.

49. An antibody-peptide complex comprising the antibody of claim 46 and a polypeptide that specifically binds to the antibody.

50. The complex of claim 49 wherein the polypeptide is the polypeptide against which the antibody is raised.

51. The complex of claim 49 wherein the antibody is a polyclonal antibody, a monoclonal antibody, a chimeric antibody or a humanized antibody.

52. A method for preparing a polypeptide as in one of claims 35-38 comprising expressing a polynucleotide encoding the polypeptide as in one of claims 35-38 in a prokaryotic or eukaryotic host cell.

53. The method of claim 52 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO. 12 and the polynucleotide comprises the nucleotide sequence of SEQ ID NO. 16.

54. The method of claim 52 wherein the host cell is a Chinese hamster ovary cell.

55. The method as in one of claims 52-54 further comprising isolating the polypeptide.

56. An isolated prokaryotic or eukaryotic host cell comprising a polynucleotide encoding polypeptide as in one of claims 35-38.

57. A composition comprising a carrier and a prokaryotic or eukaryotic host cell of claim 56.

58. A method of preventing or reducing bleeding in a subject undergoing anticoagulant therapy with a factor Xa inhibitor comprising administering to the subject an effective amount of a composition of claim 41.

59. A method of selectively binding and inhibiting an exogenously administered factor Xa inhibitor in a subject undergoing anticoagulant therapy with a factor Xa inhibitor comprising administering to the subject an effective amount of a composition of claim 41.

60. The method of claim 58 or 59 wherein the factor Xa inhibitor is selected from the group consisting of fondaparinux, idraparinux, biotinylated idraparinux, enoxaparin, fragmin, NAP-5, rNAPc2, tissue factor pathway inhibitor, DX-9065a, YM-60828, YM-150, apixaban, rivaroxaban, PD-348292, otamixaban, DU-176b, LY517717,

GSK913893, razaxaban, low molecular weight heparin, betrixaban or a pharmaceutically acceptable salt thereof, and combinations thereof.

61. The method of claim 60 wherein the factor Xa inhibitor is selected from betrixaban, rivaraoxaban, apixaban, low molecular weight heparin, and combinations thereof.

62. The method of claim 60, wherein the derivative is administered prior to a surgery.

CLAIMS:

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 10, 11, 12 or 13 or an amino acid sequence having at least 80% sequence identity to SEQ ID NO. 10, 11, 12 or 13, wherein the polypeptide has (a) reduced procoagulant activity compared to wild-type factor Xa, (b) is capable of binding to a factor Xa inhibitor, and (c) does not assemble into a prothrombinase complex.

2. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 10, 11, 12 or 13 or an amino acid sequence having at least 95% sequence identity to SEQ ID NO. 10, 11, 12 or 13, wherein the polypeptide (a) has reduced procoagulant activity compared to wild-type factor Xa, (b) is capable of binding to a factor Xa inhibitor and (c) does not assemble into a prothrombinase complex.

3. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO. 10, 11, 12 or 13.

4. An isolated two-chain polypeptide comprising the amino acid sequence of SEQ ID NO. 13.

5. An isolated two-chain polypeptide comprising a first chain comprising the amino acid sequence of SEQ ID NO. 14 or a first amino acid sequencing having at least 95% sequence identity to SEQ ID NO. 14 and a second chain comprising the amino acid sequence of SEQ ID NO. 15 or a second amino acid sequence having at least 95% sequence identity to SEQ ID NO. 15,

wherein the polypeptide further comprises a disulfide bond between a first Cysteine residue at position 98 (Cys98) of the first chain and a second Cysteine residue at position 108 (Cys108) of the second chain, and

wherein the polypeptide (a) does not have Serine at position 185 of the second chain, (b) is capable of binding to a factor Xa inhibitor and (c) does not assemble into a prothrombinase complex,

wherein numbering of the amino acid residues of the first chain and second chain are relative to SEQ ID NO. 14 or 15, respectively.

6. The isolated two-chain polypeptide of claim 5, comprising an amino acid residue that is modified to be different from natural amino acids.

7. An isolated two-chain polypeptide comprising a first chain of the amino acid sequence of SEQ ID NO. 14, a second chain of the amino acid sequence of SEQ ID NO. 15, and a disulfide bond between a first Cysteine residue at position 98 (Cys98) of SEQ ID NO. 14 and a second Cysteine residue at position 108 (Cys108) of SEQ ID NO. 15, wherein the polypeptide comprises an amino acid residue that is modified to be different from natural amino acids.

8. A peptide conjugate comprising a carrier covalently or non-covalently linked to a polypeptide of any one of claims 1-7.

9. The peptide conjugate of claim 8, wherein the carrier is a liposome, a micelle, a pharmaceutically acceptable polymer, or a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising a carrier and a polypeptide of any one of claims 1-7.

11. A polynucleotide encoding for a polypeptide of any one of claims 1-7.

12. An *in vitro* method for preparing a polypeptide of any one of claims 1-7 comprising expressing a polynucleotide encoding the polypeptide in a prokaryotic or eukaryotic host cell.

13. The method of claim 12, wherein the host cell is a Chinese hamster ovary cell.

14. The method of claim 12, further comprising isolating the polypeptide.

15. An isolated prokaryotic or eukaryotic host cell comprising a polynucleotide encoding the polypeptide of any one of claims 1-7.

16. A composition comprising a carrier and a prokaryotic or eukaryotic host cell of claim 15.

17. Use of a composition of claim 10 in the manufacture of a medicament for reducing bleeding in a subject undergoing anticoagulant therapy with a factor Xa inhibitor.

18. Use of a composition of claim 10 in the manufacture of a medicament for selectively binding and inhibiting an exogenously administered factor Xa inhibitor in a subject undergoing anticoagulant therapy with a factor Xa inhibitor.

19. The use of claim 17 or 18, wherein the factor Xa inhibitor is selected from the group consisting of fondaparinux, idraparinux, biotinylated idraparinux, enoxaparin, fragmin, NAP-5, rNAPc2, tissue factor pathway inhibitor, DX-9065a, YM-60828, YM-150, apixaban, rivaroxaban, PD-348292, otamixaban, DU-176b, LY517717, GSK913893, razaxaban, low molecular weight heparin, betrixaban or a pharmaceutically acceptable salt thereof, and combinations thereof.

20. The use of claim 19, wherein the factor Xa inhibitor is selected from betrixaban, rivaroxaban, apixaban, low molecular weight heparin, or combinations thereof.