CLAIMS:

1. A modified factor VII (FVII) polypeptide, comprising an amino acid modification in a FVII polypeptide or a catalytically active fragment thereof that contains the modification, wherein:

the modification is at a position corresponding to position D196, K197 or K199 in a FVII polypeptide having a sequence of amino acids set forth in SEQ ID NO:3 or in corresponding residues at an aligned locus in a FVII polypeptide;

corresponding residues are identified by alignment with SEQ ID NO:3; and

the modification corresponds to replacement(s) selected from among D196L, D196I, K197E, K197D, K197L, K197M, K197I, K197V, K197Y, K197F, K197W, K199D and K199E in SEQ ID NO:3, whereby the modified FVII polypeptide or active fragment thereof exhibits increased coagulant activity compared with the unmodified FVII polypeptide that does not contain the amino acid replacement(s); and

the increased coagulant activity results from one or both of: 1) increased resistance of the modified FVII to tissue factor pathway inhibitor (TFPI); and 2) increased catalytic activity compared with the unmodified FVII polypeptide.

2. The modified FVII polypeptide of claim 1, wherein the unmodified FVII polypeptide comprises a sequence of amino acids set forth in any of SEQ ID Nos:1-3.

3. The modified FVII polypeptide of claim 1, wherein the sequence of amino acid residues of unmodified FVII polypeptide consists of a sequence of amino acids set forth in any of SEQ ID Nos:1-3.

4. The modified FVII polypeptide of any of claims 1-3, wherein the modification in a FVII polypeptide is selected from among D196L, D196I, K197E, K197D, K197L, K197M, K197I, K197V, K197Y, K197F, K197W and K199E.

5. The modified FVII polypeptide of claim 1, wherein the modification in a FVII polypeptide corresponds to replacement selected from among K197E, K197D, K197L, K197M, K197I, K197V, K197Y, K197F, K197W and K199E.

6. The modified FVII polypeptide of claim 1, wherein the modification in a FVII polypeptide corresponds to K197Y.

7. The modified FVII polypeptide of any of claims 1-3, comprising a further amino acid modification that is a replacement or insertion at a position corresponding to a position selected from among D196, K197, K199, G237, T239, R290 and K341.

8. The modified FVII polypeptide of claim 7, wherein the further amino acid modification is selected from among a replacement corresponding to D196K, D196R, D196A, D196Y, D196F, D196W, D196L, D196I, K197Y, K197A, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199A, K199D, K199E, G237W, G237T, G237I, G237V, T239A, R290A, R290E, R290D, R290N, R290Q, R290K, K341E, K341R, K341N, K341M, K341D and K341Q.

9. The modified FVII polypeptide of claim 7, wherein the further modification is an amino acid insertion selected from among insertions corresponding to G237T238insA, G237T238insS, G237T238insV, G237T238insAS, G237T238insSA, D196K197insK, D196K197insR, D196K197insY, D196K197insW, D196K197insA, D196K197insM, K197I198insE, K197I198insY, K197I198insA and K197I198insS.

10. The modified FVII polypeptide of any of claims 7-9, comprising modifications selected from among D196R/K197E/K199E, D196K/K197E/K199E, D196R/K197E/K199E/R290E, D196R/K197M/K199E, D196R/K197M/ K199E/R290E, K197E/K341Q, K197L/K341Q, K197E/G237V/K341Q, K197E/K199E, K197E/G237V, K199E/K341Q and K197E/K199E/K341Q.

11. The modified factor VII (FVII) polypeptide of claim 1, comprising two or more modifications in the FVII polypeptide or active fragment thereof, wherein:

the two or more amino acid modifications are selected from among amino acid modifications corresponding to D196K, D196R, D196A, D196Y, D196F, D196M, D196W, D196L, D196I, K197Y, K197A, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199A, K199D, K199E, G237W, G237T, G237I, G237V, T239A, R290A, R290E, R290D, R290N, R290Q, R290K, K341E, K341R, K341N, K341M, K341D, K341Q, G237T238insA, G237T238insS, G237T238insV, G237T238insAS, G237T238insSA, D196K197insK, D196K197insR, D196K197insY, D196K197insW, D196K197insA, D196K197insM, K197I198insE, K197I198insY, K197I198insA and K197I198insS in a FVII polypeptide having a sequence of amino acids set forth in SEQ ID NO:3 or in corresponding residues at an aligned locus in a FVII polypeptide; and

at least one modification is selected from among D196L, D196I, K197E, K197D, K197L, K197M, K197I, K197V, K197Y, K197F, K197W, K199D and K199E, and the second modification is different from the first modification.

12. The modified FVII polypeptide of claim 11, wherein the FVII polypeptide contains 2, 3, 4, 5, 6 or 7 modifications in the FVII polypeptide having a sequence of amino acids set forth in any of SEQ ID NOs: 1-3.

13. The modified FVII polypeptide of any one of claims 1-12, comprising modifications selected from among D196R/ K197E/ K199E, D196K/ K197E/ K199E, D196R/ K197E/ K199E/R290E, D196R/ K197M/ K199E, D196R/ K197M/ K199E/R290E, K197E/K341Q, K197L/K341Q, K197E/G237V/K341Q, K197E/K199E, K197E/G237V, K199E/K341Q and K197E/K199E/K341Q.

14. The modified FVII polypeptide of any of claims 1-13 that exhibits increased resistance to tissue factor pathway inhibitor (TFPI) compared with the unmodified FVII polypeptide.

15. The modified FVII polypeptide of any of claims 1-13, wherein the sequence of amino acid residues of the unmodified FVII polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:3.

16. The modified FVII polypeptide of any of claims 1-13, comprising a sequence of amino acids set forth in any of SEQ ID NOS: 21, 23-26, 28, 29, 128-133, 229, 230, 232-235, 243, 244, 248 and 250.

17. The modified FVII polypeptide of any of claims 1-13, consisting of a sequence of amino acids set forth in any of SEQ ID NOS: 21, 23-26, 28, 29, 128-133, 229, 230, 232-235, 243, 244, 248 and 250.

18. The modified FVII polypeptide of any of claims 1-17, wherein the unmodified FVII polypeptide is a human polypeptide.

19. The modified FVII polypeptide of any of claims 1, 5, 11 and 12, wherein the unmodified FVII polypeptide is a non-human polypeptide.

20. The modified FVII polypeptide of any of claims 1-19 that is a FVIIa polypeptide.

21. The modified FVII polypeptide of any of claims 1-20, further comprising a chemical modification or a post-translational modification.

22. The modified FVII polypeptide of any of claims 1-21 that is glycosylated, carboxylated, hydroxylated, sulfated, phosphorylated, albuminated or conjugated to a polyethylene glycol (PEG) moiety.

23. The modified FVII polypeptide of any of claims 1-22 that is a two-chain polypeptide.

24. The modified FVII polypeptide of any of claims 1-22, that is a two-chain activated Factor VII (FVIIa) polypeptide that is cleaved between the residues corresponding to arginine at position 152 and the isoleucine at position 153 of SEQ ID NO:3.

25. The modified FVII polypeptide of any of claims 1-23 that is activated.

26. The modified FVII polypeptide of claim 25, wherein activation resulted from proteolytic cleavage by autoactivation, cleavage by Factor IX (FIXa), cleavage by Factor X (FXa), cleavage by Factor XII (FXIIa) or cleavage by thrombin.

27. The modified FVII polypeptide of any of claims 1-22 that is a single-chain polypeptide.

28. The modified FVII polypeptide of any of claims 1-27, comprising a modification selected from among Gla Swap FIX, Gla Swap FX, Gla Swap Prot C, Gla Swap Prot S, Gla Swap Thrombin.

29. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FVII polypeptide of any of claims 1-28.

30. A vector, comprising the nucleic acid molecule of claim 29.

31. The vector of claim 30 that is a prokaryotic vector, viral vector or a eukaryotic vector.

32. The vector of claim 31 that is a mammalian vector.

33. The vector of claim 31 that is a viral vector selected from among an adenovirus, an adeno-associated-virus, a retrovirus, a herpes virus, a lentivirus, a poxvirus and a cytomegalovirus.

34. A cell, comprising a vector of any of claims 30-33.

35. The cell of claim 34 that is a eukaryotic cell.

36. The cell of claim 35 that is a mammalian cell.

37. The cell of claim 36 that is selected from among baby hamster kidney cells (BHK-21) or 293 cells and CHO cells.

38. The cell of claim 34 that is a yeast cell.

39. The cell of claim 38 that is a *Pichia sp.* cell.

40. The cell of claim 38 that is a *Pichia pastoris* cell.

41. A modified FVII polypeptide that is produced by the cell of any of claims 34-40.

42. A pharmaceutical composition, comprising a therapeutically effective concentration or amount of a modified FVII polypeptide of any of claims 1-28 and 41, in a pharmaceutically acceptable vehicle.

43. The pharmaceutical composition of claim 42 that is formulated for local, systemic, or topical administration.

44. The pharmaceutical composition of claim 42 or claim 43 that is formulated for oral, nasal, pulmonary buccal, transdermal, subcutaneous, intraduodenal, enteral, parenteral, intravenous, or intramuscular administration.

45. The pharmaceutical composition of any of claims 42-44 that is formulated for controlled- release.

46. The pharmaceutical composition of any of claims 42-45 that is formulated for single-dosage administration.

47. The modified FVII polypeptide of any of claims 1-28 and 41 for use in treating a disease or condition selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, factor VII deficiency, bleeding disorders, surgical bleeding, and bleeding resulting from trauma.

48. Use of a modified FVII polypeptide of any of claims 1-28 and 41 in the preparation of a medicament for treatment of a disease or condition selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, factor VII deficiency, bleeding disorders, surgical bleeding, and bleeding resulting from trauma.

49. The modified FVII polypeptide or use of claim 48, wherein the disease or condition is hemophilia A or hemophilia B or hemophilia C.

50. The modified FVII polypeptide or use of claim 48, wherein the disease or condition is hemophilia that is congenital or acquired.

51. The modified FVII polypeptide or use of claim 48, wherein the disease or condition is due to a bleeding complication due to surgery or trauma.

52. The modified FVII polypeptide or use of claim 51, wherein the bleeding is manifested as acute haemarthroses, chronic haemophilic arthropathy, haematomas, haematuria, central nervous system bleedings, gastrointestinal bleedings, or cerebral haemorrhage.

53. The modified FVII polypeptide or use of claim 51, wherein the surgery is heart surgery, angioplasty, lung surgery, abdominal surgery, spinal surgery, brain surgery, vascular surgery, dental surgery, or organ transplant surgery.

54. The modified FVII polypeptide or use of claim 53, wherein the transplant surgery is selected from among transplantation of bone marrow, heart, lung, pancreas, and liver.

55. The modified FVII polypeptide or use of any of claims 47-54, wherein the subject has autoantibodies to factor VIII or factor IX.

56. The modified FVII polypeptide or use of any of claims 47-54 in combination with one or more additional coagulation factors.

57. The modified FVII polypeptide or use of claim 56, wherein the one or more additional coagulation factors are selected from among plasma purified or recombinant coagulation factors, procoagulants, such as vitamin K, vitamin K derivative and protein C inhibitors, plasma, platelets, red blood cells and corticosteroids.

58. A kit, comprising the pharmaceutical composition of any one of claims 42-46, a device for administration of the composition and, optionally, instructions for administration.

59. A method of producing a modified FVII polypeptide, comprising culturing the cell of any of claims 34-40 under conditions whereby the modified FVII polypeptide is expressed.

60. The method of claim 59, further comprising isolating the modified FVII polypeptide.

CLAIMS:

1. A modified factor VII (FVII) polypeptide, comprising an amino acid modification in a FVII polypeptide or a catalytically active fragment thereof that contains the modification, wherein

the modification is at a position corresponding to position D196, K197 or K199 in a FVII polypeptide having a sequence of amino acids set forth in SEQ ID NO:3 or in corresponding residues in a FVII polypeptide; and

the modification is replacement by a hydrophobic or acidic amino acid, wherein

the hydrophobic or acidic amino acid is selected from among Val (V), Leu (L), Ile (I), Phe (F), Trp (W), Met (M), Tyr (Y), Cys (C), Asp (D) and Glu (E), whereby the modification results in decreased interaction with an inhibitory protein compared to a FVII polypeptide that does not include the further modification to thereby increase the coagulant activity of the modified FVII polypeptide.

2. A modified FVII polypeptide of claim 1, wherein the modification in a FVII polypeptide is selected from among D196F, D196W, D196L, D196I, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199D and K199E.

3. A modified FVII polypeptide of claim 1, wherein the modification in a FVII polypeptide is D196Y or K197Y.

4. A modified FVII polypeptide of claim 1 or claim 2, comprising a further amino acid replacement or insertion at a position corresponding to a position selected from among D196, K197, K199, G237, T239, R290 and K341, wherein the first modification and further modification are at different amino acids.

5. A modified FVII polypeptide of claim 4, wherein the further amino acid modification is selected from among D196K, D196R, D196A, D196Y, D196F, D196W, D196L, D196I, K197Y, K197A, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199A, K199D, K199E, G237W, G237T, G237I, G237V, T239A, R290A, R290E, R290D, R290N, R290Q, R290K, K341E, K341R, K341N, K341M, K341D and K341Q.

6. A modified FVII polypeptide of claim 4, wherein the further modification is an amino acid insertion selected from among G237T238insA, G237T238insS, G237T238insV, G237T238insAS, G237T238insSA, D196K197insK, D196K197insR, D196K197insY, D196K197insW, D196K197insA, D196K197insM, K197I198insE, K197I198insY, K197I198insA and K197I198insS.

7. A modified FVII polypeptide of any of claims 4-6, comprising modifications selected from among D196R/K197E/K199E, D196K/K197E/K199E, D196R/K197E/K199E/R290E, D196R/K197M/K199E, D196R/K197M/ K199E/R290E, D196K/K197L, D196F/ K197L, D196L/ K197L, D196M/K197L, D196W/K197L,

D196F/K197E, D196W/K197E, K196V/K197E, K197E/K341Q, K197L/K341Q, K197E/G237V/K341Q, K197E/K199E, K197E/G237V, K199E/K341Q and K197E/K199E/K341Q.

8. A modified factor VII (FVII) polypeptide, comprising a modification in a FVII polypeptide, allelic or species variant thereof or active fragments thereof, selected from among amino acid modifications corresponding to D196R, D196Y, D196F, D196W, D196L, D196I, K197Y, K197E, K197D, K197L, K197M, K197M, K197I, K197V, K197F, K197W, K199D, K199E, G237W, G237I, G237V, R290M, R290V, K341M, K341D, G237T238insA, G237T238insS, G237T238insV, G237T238insAS, G237T238insSA, D196K197insK, D196K197insR, D196K197insY, D196K197insW, D196K197insA, D196K197insM, K197I198insE, K197I198insY, K197I198insA or K197I198insS in a FVII polypeptide having a sequence of amino acids set forth in SEQ ID NO:3 or in corresponding residues in a FVII polypeptide.

9. A modified FVII polypeptide of claim 8, comprising a further modification that is a amino acid replacement or insertion at a position corresponding at a position corresponding to a position selected from among D196, K197, K199, G237, T239, R290 and K341, wherein the further modification is in a different position from the first modification.

10. A modified FVII polypeptide of claim 9, wherein the further amino acid modification is selected from among D196K, D196R, D196A, D196Y, D196F, D196M, D196W, D196L, D196I, K197Y, K197A, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199A, K199D, K199E, G237W, G237T, G237I, G237V, T239A, R290A, R290E, R290D, R290N, R290Q, R290K, K341E, K341R, K341N, K341M, K341D, and K341Q.

11. A modified FVII polypeptide of claim 9, comprising modifications selected from among D196R/R290E, D196R/R290D, D196R/K197E/K199E, D196K/K197E/K199E, D196R/K197E/K199E/R290E, D196R/K197M/K199E, D196R/K197M/K199E/R290E, D196K/K197L, D196F/K197L, D196L/K197L, D196M/K197L, D196W/K197L, D196F/K197E, D196W/K197E, K197L/K341Q, G237V/K341Q, K197E/G237V/K341Q, K197E/K199E, K197E/G237V, K199E/K341Q, K197E/K199E/K341Q and K196V/K197E.

12. A modified factor VII (FVII) polypeptide, comprising two or more modifications in a FVII polypeptide, allelic and species variant thereof or active fragments thereof, wherein:

the two or more amino acid modifications are selected from among amino acid modifications corresponding to D196K, D196R, D196A, D196Y, D196F, D196M, D196W, D196L, D196I, K197Y, K197A, K197E, K197D, K197L, K197M, K197I, K197V, K197F, K197W, K199A, K199D, K199E, G237W, G237T, G237I, G237V, T239A, R290A, R290E, R290D, R290N, R290Q, R290K, K341E, K341R, K341N, K341M, K341D, K341Q, G237T238insA, G237T238insS, G237T238insV, G237T238insAS, G237T238insSA, D196K197insK, D196K197insR, D196K197insY, D196K197insW, D196K197insA, D196K197insM, K197I198insE, K197I198insY, K197I198insA or K197I198insS in a FVII

polypeptide having a sequence of amino acids set forth in SEQ ID NO:3 or in corresponding residues in a FVII polypeptide.

13. A modified FVII polypeptide of claim 12, wherein the FVII polypeptide contains 2, 3, 4, 5, 6 or 7 modifications.

14. A modified FVII polypeptide of claim 12 or claim 13, comprising modifications selected from among D196R/R290E, D196K/R290E, D196R/R290D, D196R/ K197E/ K199E, D196K/ K197E/ K199E, D196R/ K197E/ K199E/R290E, D196R/ K197M/ K199E, D196R/ K197M/ K199E/R290E, D196K/K197L, D196F/ K197L, D196L/ K197L, D196M/K197L, D196W/ K197L, D196F/K197E, D196W/K197E, D196V/K197E, K197E/K341Q, K197L/K341Q, G237V/K341Q, K197E/G237V/K341Q, K197E/K199E, K197E/G237V, K199E/K341Q, K197E/K199E/K341Q and K197E/G237V/M298Q.

15. A modified FVII polypeptide of any of claims 1-14 that exhibits increased resistance to tissue factor pathway inhibitor (TFPI) compared with the unmodified FVII polypeptide.

16. A modified FVII polypeptide of any of claims 1-14, wherein the unmodified FVII polypeptide has a sequence of amino acids set forth in SEQ ID NO:3.

17. A modified FVII polypeptide of any of claims 1-14 having a sequence of amino acids set forth in any of SEQ ID NOS: 18-43, 125-146, 206-235, 241-246 and 248-250.

18. A modified FVII polypeptide of any of claims 1-14, wherein the unmodified FVII polypeptide is an allelic or species variant of the polypeptide set forth in SEQ ID NO:3.

19. The modified factor VII (FVII) polypeptide, comprising:

a heterologous gamma-carboxyglutamate (Gla) domain from a vitamin K-dependent protein, or a sufficient contiguous portion thereof to effect phospholipid binding, wherein:

the modified FVII polypeptide has procoagulant activity; and

the sufficient portion is 30 or more contiguous amino acids from the heterologous Gla domain, whereby phospholipid binding of the FVII polypeptide is altered compared to the FVII polypeptide with its native Gla domain.

20. A modified FVII polypeptide of any of claims 1-19 that is a human polypeptide.

21. A modified FVII polypeptide of any of claims 1-19 that is a non-human polypeptide.

22. A modified FVII polypeptide of any of claims 1-21 that is a mature polypeptide.

23. A modified FVII polypeptide of any of claims 1-21 that is a mature polypeptide.

24. A modified FVII polypeptide of any of claims 1-23, further comprising a chemical modification or a post-translational modification.

25. A modified FVII polypeptide of any of claims 1-24 that is glycosylated, carboxylated, hydroxylated, sulfated, phosphorylated, albuminated or conjugated to a polyethylene glycol (PEG) moiety.

26. A modified FVII polypeptide of any of claims 1-25 that is a single-chain polypeptide.

27. A modified FVII polypeptide of any of claims 1-25 that is a two-chain polypeptide.

28. A modified FVII polypeptide of any of claims 1-27 that is activated.

29. A modified FVII polypeptide of claim 28, wherein activation resulted from proteolytic cleavage by autoactivation, cleavage by Factor IX (FIXa), cleavage by Factor X (FXa), cleavage by Factor XII (FXIIa) or cleavage by thrombin.

30. A modified FVII polypeptide of any of claims 1-29 that retains one or more activities of the unmodified FVII polypeptide.

31. The modified FVII polypeptide of any of claims 1-30, comprising a modification selected from among Gla Swap FIX, Gla Swap FX, Gla Swap Prot C, Gla Swap Prot S, Gla Swap Thrombin.

32. A modified FVII polypeptide of claim 30 or 31, wherein the one or more activities are selected from among tissue factor (TF) binding, factor X (FX) activation, Factor IX (FIX) activation, phospholipid binding, and coagulation activity.

33. A modified polypeptide of any of claims 1-32, wherein the coagulation activity is increased.

34. A nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FVII polypeptide of any of claims 1-33.

35. A vector, comprising the nucleic acid molecule of claim 34.

36. A vector of claim 35 that is a prokaryotic vector, viral vector or a eukaryotic vector.

37. A vector of claim 36 that is a mammalian vector.

38. A vector of claim 36 that is s viral vector selected from among an adenovirus, an adeno-associated-virus, a retrovirus, a herpes virus, a lentivirus, a poxvirus and a cytomegalovirus.

39. A cell, comprising a vector of any of claims 35-38.

40. The cell of claim 39 that is a eukaryotic cell.

41. The cell of claim 40 that is a mammalian cell.

42. The cell of claim 41 that is selected from among baby hamster kidney cells (BHK-21) or 293 cells and CHO cells.

43. The cell of claim 39 that is a yeast cell.

44. The cell of claim 43 that is a *Pichia sp.* cell.

45. A modified FVII polypeptide that is produced by and the cell of any of claims 39-44.

46. A pharmaceutical composition, comprising a therapeutically effective concentration or amount of a modified FVII polypeptide of any of claims 1-33 and 45, or a nucleic acid molecule of claim 34 or a vector of any of claims 35-38 or a cell of any of claims 39-44, in a pharmaceutically acceptable vehicle.

47. The pharmaceutical composition of claim 46 that is formulated for local, systemic, or topical administration.

48. The pharmaceutical composition of claim 46 or claim 47 that is formulated for oral, nasal, pulmonary buccal, transdermal, subcutaneous, intraduodenal, enteral, parenteral, intravenous, or intramuscular administration.

49. The pharmaceutical composition of any of claims 46-48 that is formulated for controlled- release.

50. The pharmaceutical composition of any of claims 46-49 that is formulated for single-dosage administration.

55. A modified FVII polypeptide of any of claims 1-33 and 45 for use in treating a disease or condition that is treated by administration of FVII or a pro-coagulant.

56. Use of a modified FVII polypeptide of any of claims 1-33 and 45 in the preparation of a medicament for treatment of a disease or condition that is treated by administration of FVII or a pro-coagulant.

57. The modified FVII polypeptide of claim 55 or the use of claim 56, wherein the disease or condition is treated by administration of a zymogen or active form of FVII.

58. The modified FVII polypeptide of clam 55 or claim 57 or the use of claim 56 or claim 57, wherein the disease or condition to be treated is selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, factor VII deficiency, bleeding disorders, surgical bleeding, or bleeding resulting from trauma.

59. The modified FVII polypeptide or use of claim 58, wherein the hemophilia is hemophilia A or hemophilia B or hemophilia C.

60. The modified FVII polypeptide or use of claim 58, wherein the hemophilia is congenital or acquired.

61. The modified FVII polypeptide or use of claim 58, wherein the disease or condition is due to a bleeding complication due to surgery or trauma.

62. The modified FVII polypeptide or use of claim 61, wherein the bleeding is manifested as acute haemarthroses, chronic haemophilic arthropathy, haematomas, haematuria, central nervous system bleedings, gastrointestinal bleedings, or cerebral haemorrhage.

63. The modified FVII polypeptide or use of claim 61, wherein the surgery is heart surgery, angioplasty, lung surgery, abdominal surgery, spinal surgery, brain surgery, vascular surgery, dental surgery, or organ transplant surgery.

64. The modified FVII polypeptide or use of claim 63, wherein the transplant surgery is selected from among transplantation of bone marrow, heart, lung, pancreas, and liver.

65. The modified FVII polypeptide or use of any of claims 55-64, wherein the subject has autoantibodies to factor VIII or factor IX.

66. The modified FVII polypeptide or use of any of claims 55-64 in combination with one or more additional coagulation factors.

67. The modified FVII polypeptide or use of claim 66, wherein the one or more additional coagulation factors are selected from among plasma purified or recombinant coagulation factors, procoagulants, such as vitamin K, vitamin K derivative and protein C inhibitors, plasma, platelets, red blood cells and corticosteroids.

68. A kit, comprising the pharmaceutical composition of any one of claims 46-50, a device for administration of the composition and, optionally, instructions for administration.

Using the above protocol, the the pharmacokinetic properties of wild-type FVIIa and two FVIIa variants:CB728, CB735 and CB945 were assessed. The results are set forth in Table 14. CB735 and CB945 exhibited improved pharmacokinetic parameters compared to wild-type FVIIa.

Table 14. Mouse Pharmacokinetic Parameters of FVIIa Variants

CB#	Mutation (mature FVII numbering)	IV Dose (mg/kg)	Plasma $AUC_{0\text{-}inf}$ (μg.min/mL)/Dose	Half-Life (min)	Cl (mL/min/kg)	Vd (mL/kg)	N
CB553	WT	0.1	606	35.1	2.02	98.8	5
CB553	WT	1.0	798	50.2	1.55	118	2
CB728	Gla Swap FIX	0.1	207	19.9	4.85	140	2
CB735	K341D	0.1	2817	106	0.14	22.0	1
CB945	M156Q/K192D	0.1	2430	78.1	0.41	46.3	1

E. Pharmacokinetic properties of CB558

The half-life of a modified FVIIa polypeptide that exhibited increased resistance to TFPI (CB-558; containing a ~~K297E~~ K197E mutation) was measured and compared with that of an unmodified recombinant human FVIIa (rhFVIIa) protein (NovoSeven®, Novo Nordisk) in a pharmacokinetic study similar to that described above, with some modifications. Fifteen male CD-1 mice were injected with a 0.5mg/kg intravenous bolus dose of CB-558, and 15 mice were injected with a 0.5mg/kg intravenous bolus dose of rhFVIIa. At 5, 15, 30, 60 and 120 min post-injection, three mice from each injection protocol were euthanized using CO_2 asphyxiation and approximately 1.0 mL of blood was drawn into a 1.0 mL syringe via a percutaneous cardiac puncture. Each syringe was pre-loaded with sufficient sodium citrate to achieve a final concentration of 3.2% in 1mL of blood. The blood samples were then centrifuged at 9000 rpm for 8 min at 4°C. The plasma was removed to labeled individual 1.5 ml tubes (Eppendorf), snap frozen in liquid nitrogen and stored at -80°C.

To determine the coagulant activity and the half-life of the active FVIIa polypeptides, the plasma samples were assessed at Machaon Diagnostics, Inc. (Oakland, CA) using a FVIIa-dependant clotting assay (FVII:C) and an automated hemostasis instrument (AMAX 190plus, Trinity Biotech). Briefly, the frozen plasma

which contains the Q366V mutation, has a catalytic activity of between 1.5 and 5 times that of wild-type FVIIa.

Table 16. Catalytic activity of FVIIa variants: TF-Dependent Indirect Assay with FVIIa polypeptides from 293-F cells

ID	Mutation (mature FVII numbering)	Mutation (Chymotrypsin numbering)	k_{cat}/K_M ($M^{-1}s^{-1}$)	k_{cat}/K_M (% WT)	Assay Format
CB553	WT	WT	3.42×10^7	100	linear
CB554	D196K	D60K	1.10×10^7	23	hyperbolic
CB555	D196R	D60R	2.25×10^7	46	hyperbolic
CB556	D196A	D60A	2.58×10^7	53	hyperbolic
CB557	K197D	K60aD	3.05×10^7	63	hyperbolic
CB558	K197AE	K60aE	1.54×10^7	32	hyperbolic
CB559	K197EA	K60aA	3.67×10^7	75	hyperbolic
CB560	K197L	K60aL	1.51×10^7	31	hyperbolic
CB561	K197Y	K60aY	5.16×10^7	106	hyperbolic
CB562	K199TD	K60cD	4.62×10^7	95	hyperbolic
CB563	K199TE	K60cE	3.63×10^7	74	hyperbolic
CB564	K199TA	K60cA	5.56×10^7	114	hyperbolic
CB565	T239A	T99A	1.66×10^7	34	hyperbolic
CB566	R290D	R147D	5.80×10^6	12	hyperbolic
CB567	R290E	R147E	6.18×10^6	13	hyperbolic
CB568	R290A	R147A	8.25×10^6	17	hyperbolic
CB569	K341R	K192R	3.95×10^7	81	hyperbolic
CB579	D196R/R290E	D60R/R147E	2.31×10^6	5	hyperbolic
CB580	D196K/R290E	D60K/R147E	7.81×10^4	0	hyperbolic
CB581	D196R/R290D	D60R/R147D	2.91×10^6	6	hyperbolic
CB586	D196R/ K197E/ K199E	K60cE/K60aE/D60R	7.97×10^6	16	hyperbolic
CB587	D196K/ K197E/ K199E	K60cE/K60aE/D60K	7.22×10^6	15	hyperbolic
CB588	D196R/ K197E/ K199E/R290E	K60cE/K60aE/D60R/R147E	3.66×10^5	1	hyperbolic
CB589	D196R/ K197M/ K199E	K60cE/K60aM/D60R	1.81×10^7	37	hyperbolic
CB590	D196R/ K197M/ K199E/R290E	K60cE/K60aM/D60R/R147E	2.88×10^5	1	hyperbolic
CB591	L305V/S314E/L337A/F374Y	L163V/S170bE/K188A/F225Y	6.73×10^7	138	hyperbolic
CB592	M298Q	M156Q	1.40×10^8	409	linear
CB593	V158D/E296V/M298Q	V21D/E154V/M156Q	1.67×10^8	487	linear
CB594	V158D/E296V/M298Q/ K337A	V21D/E154V/M156Q/K188A	5.18×10^8	1061	hyperbolic
CB595	K197I	K60aI	5.31×10^7	109	hyperbolic
CB596	K197V	K60aV	5.15×10^7	106	hyperbolic
CB597	K197F	K60aF	7.20×10^7	148	hyperbolic
CB598	K197W	K60aW	6.25×10^7	128	hyperbolic
CB599	K197M	K60aM	7.83×10^7	160	hyperbolic
CB600	D196F	D60F	2.35×10^7	48	hyperbolic
CB601	D196Y	D60Y	6.93×10^7	142	hyperbolic
CB602	D196W	D60W	3.40×10^7	70	hyperbolic
CB603	D196L	D60L	8.57×10^7	176	hyperbolic
CB604	D196I	D60I	7.99×10^7	164	hyperbolic
CB605	G237W	G97W	8.63×10^7	177	hyperbolic

CB853	G237T238insA	G97T98insA			10000.0	>4.5
CB854	G237T238insS	G97T98insS			10000.0	>4.5
CB855	G237T238insV	G97T98insV	10000.0	>4.4		
CB856	G237T238insAS	G97T98insAS			10000.0	>4.5
CB857	G237T238insSA	G97T98insSA			10000.0	>4.5
CB858	D196K197insK	D60K60ainsK			9329.6	4.2
CB859	D196K197insR	D60K60ainsR			4322.6	1.9
CB860	D196K197insY	D60K60ainsY	2053.3	0.9		
CB862	D196K197insA	D60K60ainsA			7414.3	3.3
CB863	D196K197insM	D60K60ainsM			7299.4	3.3
CB864	K197I198insE	K60aI60binsE			10000.0	>4.5
CB865	K197I198insY	K60aI60binsY			8800.4	4.0
CB867	K197I198insS	K60aI60binsS			10000.0	>4.5
CB728	Gla swap FIX	Gla swap FIX	1005.2	0.4		

Example 13

Determination of the resistance to TFPI of FVIIa variants

The resistance of various FVIIa variants to TFPI was assessed using the assay described in Example 7, above. Table 21 provides the results of the assays. The results are expressed as the fold resistance of each FVIIa variant to TFPI compared to wild-type FVIIa.

Table 21. Inhibition of FVIIa variants by TFPI

ID	Mutation (mature FVII numbering)	Mutation (chymotrypsin numbering)	TFPI fold resistance
CB553	wt	wt	1.0
CB554	D196K	D60K	0.6
CB555	D196R	D60R	0.5
CB556	D196A	D60A	<0.3
CB557	K197D	K60aD	3.0
CB558	K197AE	K60aE	1.3
CB559	K197EA	K60aA	0.7
CB560	K197L	K60aL	16.0
CB561	K197Y	K60aY	1.5
CB562	K1997D	K60cD	0.9
CB563	K1997E	K60cE	1.3
CB564	K1997A	K60cA	0.9