Provided are modified FIX polypeptides. The modified FIX polypeptides provided have improved procoagulant therapeutic properties compared to an unmodified FIX polypeptide. For example, among the modified FIX polypeptides provided herein are those that exhibit increased coagulant activity, increased catalytic activity, increased resistance to AT-III, heparin and/or the AT-III/heparin complex, and/or improved pharmacokinetic properties, such as i) decreased clearance, ii) altered (e.g. increased or decreased) volume of distribution, iii) enhanced *in vivo* recovery, iv) enhanced total protein exposure *in vivo* (i.e., AUC), v) increased serum half-life (α-, β-, and/or γ-phase), and/or vi) increased mean resonance time (MRT). In some examples, the improved pharmacokinetic properties are a result of increased glycosylation and/or decreased binding to the low-density lipoprotein receptor-related protein (LRP). Also provided are nucleic acids encoding the modified FIX polypeptides and methods of using the modified FIX polypeptides, such as for treatment of bleeding disorders.

In one aspect, the is provided a modified Factor IX (FIX) polypeptide, comprising the amino acid replacement T343R or T343K in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide, wherein:

corresponding amino acid residues are identified by alignment of the unmodified FIX polypeptide with the polypeptide of SEQ ID NO:3;

the unmodified FIX polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325 or an active form thereof or a FIX polypeptide having at least 95% sequence identity to the polypeptide that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325;

the modified FIX polypeptide does not contain the modifications F342I/T343R/Y345T;

the modified FIX polypeptide exhibits at least one FIX activity or property that is improved compared to the unmodified FIX polypeptide that does not contain the modification; and

the activity or property is increased procoagulant activity compared to an active form of a polypeptide of any of SEQ ID NOS: 2, 3, 20 and 325.

In one aspect, there is provided nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FIX polypeptide as described herein.

In one aspect, there is provided a vector, comprising the nucleic acid molecule as described herein.

In one aspect, there is provided an isolated cell or cell culture, comprising the vector as described herein.

In one aspect, there is provided a method of producing a modified FIX polypeptide, comprising:

culturing a cell or cell culture as described herein under conditions whereby the modified FIX polypeptide is expressed; and

optionally isolating the FIX polypeptide.

In one aspect, there is provided a pharmaceutical composition, comprising a modified FIX polypeptide as described herein in a pharmaceutically acceptable vehicle.

In one aspect, there is provided a modified FIX polypeptide as described herein for use for treatment of a disease or condition that is treated by administration of FIX.

In one aspect, there is provided a use of a modified FIX polypeptide oas described herein for formulation of a medicament for treatment of a disease or condition that is treated by administration of FIX.

Among the modified FIX polypeptides provided herein are those containing two amino acid replacements in unmodified FIX polypeptide, wherein the first amino acid replacement is at a position corresponding to a position selected from among 53, 61, 64, 85, 103, 104, 105, 106, 108, 155, 158, 159, 167, 169, 172, 179, 202, 203, 204, 205, 228, 239, 241, 243, 247, 249, 251, 257, 259, 260, 262, 265, 284, 293, 312, 314, 315, 316, 317, 318, 319, 321, 333, 338, 343, 346, 345, 392, 394, 400, 403, 410, 412 and 413 in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, and the second amino acid replacement is at a position corresponding to a position selected from among 5, 53, 61, 64, 85, 155, 158, 159, 167, 239, 260, 284, 293, 312, 318, 333, 338, 346, 400, 403, 410, 412 and 413 in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3.

In some examples, the first or the second amino acid replacement is replacement with an amino acid residue selected from among alanine (Ala, A); arginine (Arg, R); asparagine (Asn, N); aspartic acid (Asp, D); cysteine (Cys, C); glutamic acid (Glu, E); glutamine (Gln, Q); glycine (Gly, G); histidine (His, H); isoleucine (Ile, I); leucine (Leu, L); lysine (Lys, K); methionine (Met, M); phenylalanine (Phe, F); proline (Pro, P); serine (Ser, S); threonine (Thr, T); tryptophan (Trp, W); tyrosine (Tyr, Y); and valine (Val, V), providing the replacing

Provided are modified FIX polypeptides. The modified FIX polypeptides provided have improved procoagulant therapeutic properties compared to an unmodified FIX polypeptide. For example, among the modified FIX polypeptides provided herein are those that exhibit increased coagulant activity, increased catalytic activity, increased resistance to AT-III, heparin and/or the AT-III/heparin complex, and/or improved pharmacokinetic properties, such as i) decreased clearance, ii) altered (e.g. increased or decreased) volume of distribution, iii) enhanced *in vivo* recovery, iv) enhanced total protein exposure *in vivo* (i.e., AUC), v) increased serum half-life (α-, β-, and/or γ-phase), and/or vi) increased mean resonance time (MRT). In some examples, the improved pharmacokinetic properties are a result of increased glycosylation and/or decreased binding to the low-density lipoprotein receptor-related protein (LRP). Also provided are nucleic acids encoding the modified FIX polypeptides and methods of using the modified FIX polypeptides, such as for treatment of bleeding disorders.

In one aspect, there is provided a modified Factor IX (FIX) polypeptide, comprising the amino acid replacement T343R or T343K in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, or the same replacement at a corresponding amino acid residue in the primary sequence of an unmodified FIX polypeptide, wherein:

corresponding amino acid residues are identified by alignment of the unmodified FIX polypeptide with the polypeptide of SEQ ID NO:3;

the unmodified FIX polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325 or a FIX polypeptide having at least 95% sequence identity to the polypeptide that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325;

the modified FIX polypeptide does not contain the modifications F342I/T343R/Y345T;

the modified FIX polypeptide exhibits at least one FIX activity or property that is improved compared to the unmodified FIX polypeptide that does not contain the modification; and

the activity or property is increased procoagulant activity compared to an active form of a polypeptide of any of SEQ ID NOS: 2, 3, 20 and 325.

In one aspect, there is provided an isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FIX polypeptide as described herein.

In one aspect, there is provided a vector, comprising the isolated nucleic acid molecule as described herein.

In one aspect, there is provided an isolated cell or cell culture, comprising the vector as described herein.

In one aspect, there is provided a method of producing a modified FIX polypeptide, comprising:

culturing a cell or cell culture as described herein under conditions whereby the modified FIX polypeptide is expressed; and

optionally isolating the FIX polypeptide.

In one aspect, there is provided a pharmaceutical composition, comprising a modified FIX polypeptide as described herein in a pharmaceutically acceptable vehicle.

In one aspect, there is provided a modified FIX polypeptide as described herein for use for treatment of a disease or condition that is treated by administration of FIX.

In one aspect, there is provided the use of a modified FIX polypeptide as described herein for formulation of a medicament for treatment of a disease or condition selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, and bleeding disorders..

Among the modified FIX polypeptides provided herein are those containing two amino acid replacements in unmodified FIX polypeptide, wherein the first amino acid replacement is at a position corresponding to a position selected from among 53, 61, 64, 85, 103, 104, 105, 106, 108, 155, 158, 159, 167, 169, 172, 179, 202, 203, 204, 205, 228, 239, 241, 243, 247, 249, 251, 257, 259, 260, 262, 265, 284, 293, 312, 314, 315, 316, 317, 318, 319, 321, 333, 338, 343, 346, 345, 392, 394, 400, 403, 410, 412 and 413 in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, and the second amino acid replacement is at a position corresponding to a position selected from among 5, 53, 61, 64, 85, 155, 158, 159, 167, 239, 260, 284, 293, 312, 318, 333, 338, 346, 400, 403, 410, 412 and 413 in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3.

In some examples, the first or the second amino acid replacement is replacement with an amino acid residue selected from among alanine (Ala, A); arginine (Arg, R); asparagine (Asn, N); aspartic acid (Asp, D); cysteine (Cys, C); glutamic acid (Glu, E); glutamine (Gln, Q); glycine (Gly, G); histidine (His, H); isoleucine (Ile, I); leucine (Leu, L); lysine (Lys, K); methionine (Met, M); phenylalanine (Phe, F); proline (Pro, P); serine (Ser, S); threonine (Thr, T); tryptophan (Trp, W); tyrosine (Tyr, Y); and valine (Val, V), providing the replacing

CLAIMS:

1. A modified Factor IX (FIX) polypeptide, comprising the amino acid replacement T343R or T343K in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide, wherein:

corresponding amino acid residues are identified by alignment of the unmodified FIX polypeptide with the polypeptide of SEQ ID NO:3;

the unmodified FIX polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325 or an active form thereof or a FIX polypeptide having at least 95% sequence identity to the polypeptide that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325;

the modified FIX polypeptide does not contain the modifications F342I/T343R/Y345T;

the modified FIX polypeptide exhibits at least one FIX activity or property that is improved compared to the unmodified FIX polypeptide that does not contain the modification; and

the activity or property is increased procoagulant activity compared to an active form of a polypeptide of any of SEQ ID NOS: 2, 3, 20 and 325.

2. The modified FIX polypeptide of claim 1, comprising the amino acid replacement T343R.

3. The modified FIX polypeptide of claim 1, comprising the amino acid replacements R338E/T343R.

4. The modified FIX polypeptide of any of claims 1-3, further comprising an amino acid replacement is selected from among replacements corresponding to R318Y, R318E, R318F or R318W with reference to a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3.

5. The modified FIX polypeptide of any of claims 1-4, comprising an amino acid replacement at residue E410 or at an amino acid residue corresponding to 410 in an unmodified FIX polypeptide, wherein the replacement amino acid is N or S.

6. The modified FIX polypeptide of claim 5, wherein the amino acid replacement is N.

7. The modified FIX polypeptide of any of claims 1-6, comprising an amino acid replacement at residue 403 of a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3 or at amino acid residues corresponding to residue 403 in an unmodified FIX polypeptide, wherein the replacement is E.

8. The modified FIX polypeptide of claim 1, comprising the amino acid replacements R318Y, R338E, T343R, R403E and E410N in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3 or the same replacements at corresponding amino acid residues in an unmodified FIX polypeptide.

9. The modified FIX polypeptide of any of claims 1-8, wherein the unmodified polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325.

10. The modified FIX polypeptide of any of claims 1-9, further comprising the amino acid replacement Y155F or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

11. The modified FIX polypeptide claim 1, further comprising the amino acid replacement Y155F or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

12. The modified FIX polypeptide of any of claims 1-11, comprising an amino acid replacement at an amino acid residue selected from among D203, F205 and K228, or at an amino acid residue corresponding to amino acid residue D203, F205 or K228 in an unmodified FIX polypeptide.

13. The modified FIX polypeptide of claim 12, comprising an amino acid replacement selected from among D203N, F205T and K228N, or the same amino acid replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

14. The modified FIX polypeptide of any of claims 1-13 that comprises an amino acid replacement selected from among A103N, D104N, N105S, K106S, K228N, I251S, N260S and N346D, or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

15. The modified FIX polypeptide of any of claims 1-14, comprising an amino acid replacement at an amino acid residue selected from among K247, N249, R403 and E410, or at an amino acid residue corresponding to amino acid residue K247, N249, R403 or E410 in an unmodified FIX polypeptide.

16. The modified FIX polypeptide of claim 15, comprising an amino acid replacement selected from among K247N, N249S, R403E and E410N or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

17. The modified FIX polypeptide of any of claims 1-16, comprising one or more modifications that introduces and/or eliminates one or more glycosylation sites compared to the unmodified FIX polypeptide.

18. The modified FIX polypeptide of claim 17, wherein the modification introduces one or more glycosylation sites.

19. The modified FIX polypeptide of any of claims1-18, wherein the improved property is increased procoagulant activity compared with the unmodified FIX polypeptide.

20. The modified FIX polypeptide of any of claims1-19, wherein the unmodified FIX polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:2, 3, 20 or 325.

21. The modified FIX polypeptide of claim 1, comprising amino acid replacements selected from among R338E/T343R/E410N; Y155F/R338E/T343R/E410N; Y155F/K247N/N249S/T343R/E410N; Y155F/T343R/R403E/E410N; K247N/N249S/T343R/R403E/E410N; Y155F/K247N/N249S/T343R/R403E/E410N; K247N/N249S/R338E/T343R/E410N; Y155F/K247N/N249S/R338E/T343R/E410N; K247N/N249S/R338E/T343R/R403E; Y155F/K247N/N249S/R338E/T343R/R403E; Y155F/K247N/N249S/R338E/T343R; K247N/N249S/R338E/T343R/R403E/E410N; Y155F/K247N/N249S/R338E/T343R/R403E/E410N; Y155F/K247N/N249S/T343R/R403E; Y155F/I251S/R338E/T343R/R403E; Y155F/R338E/T343R/R403E/E410S; R338E/T343R/R403E; Y155F/R338E/T343R/R403E; Y155F/R338E/T343R/R403E/E410N; R338E/T343R/R403E/E410N and R338E/T343R.

22. The modified FIX polypeptide of claim 21, comprising amino acid replacements selected from among K247N/N249S/R338E/T343R/R403E/E410N, R338E/T343R/E410N and R338E/T343R.

23. A modified FIX polypeptide of claim 1, comprising a sequence of amino acids set forth in any of SEQ ID NOS: 209, 215, 268, 332, 335, 351, 352, 361-363, 365, 367, 370, 371, 377, 387-392, 396, 399, 401 and 402.

24 The modified FIX polypeptide of claim 23, wherein the sequence of amino acid residues consists of the sequence set forth in any of SEQ ID NOS: 209, 215, 268, 332, 335, 351, 352, 361-363, 365, 367, 370, 371, 377, 387-392, 396, 399, 401 and 402.

25. The modified FIX polypeptide of any of claims 1-24 that is a mature polypeptide.

26. The modified FIX polypeptide of any of claims 1-24 that is a two-chain polypeptide.

27. The modified FIX polypeptide of any of claims 1-24 that is a single-chain polypeptide.

28. The modified FIX polypeptide of any of claims 1-27 that is activated.

29. The modified FIX polypeptide of any of claims 1-28 that is hyperglycosylated.

30. The modified FIX polypeptide of any of claims 1-28, wherein only the primary sequence is modified.

31. The modified FIX polypeptide of any of claims 1-28 that comprises a chemical modification or a post-translational modification.

32. The modified FIX polypeptide of claim 31, wherein the modified FIX polypeptide is glycosylated, carboxylated, hydroxylated, sulfated, phosphorylated, albuminated, or conjugated to a polyethylene glycol (PEG) moiety.

33. The modified FIX polypeptide of any of claims 1-32 that contains only 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 modifications.

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

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

36. The vector of claim 35, wherein the vector is a prokaryotic vector, viral vector, or a eukaryotic vector.

37. The vector of claim 35, wherein the vector is a mammalian vector.

38. The vector of claim 35, that is a viral vector is selected from among an adenovirus, an adeno-associated-virus, a retrovirus, a herpes virus, a lentivirus, a poxvirus, and a cytomegalovirus.

39. An isolated cell or cell culture, comprising the vector of any of claims 35-38.

40. The cell or cell culture of claim 39, that is a eukaryotic cell.

41. The cell or cell culture of claim 40, wherein the eukaryotic cell is a mammalian cell.

42. A method of producing a modified FIX polypeptide, comprising:

culturing a cell or cell culture of any of claims 39-41 under conditions whereby the modified FIX polypeptide is expressed; and

optionally isolating the FIX polypeptide.

43. A pharmaceutical composition, comprising a modified FIX polypeptide of any of claims 1-33 in a pharmaceutically acceptable vehicle.

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

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

46. The pharmaceutical composition of any of claims 43-45 that is formulated for controlled-release.

47. The pharmaceutical composition of any of claims 43-46 that is formulated for single-dosage administration.

48 A modified FIX polypeptide of any of claims1-33 for use for treatment of a disease or condition that is treated by administration of FIX.

49. Use of a modified FIX polypeptide of any of claims 1-33 for formulation of a medicament for treatment of a disease or condition that is treated by administration of FIX

50. The modified FIX polypeptide of claim 48 or use of claim 49, wherein the FIX is active FIX (FIXa).

51. The modified FIX polypeptide or use of any of claims 48-50, wherein the disease or condition to be treated is selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, and bleeding disorders.

52. The modified FIX polypeptide or use of any of claims 48-51, wherein the disease or disorder is hemophilia B.

CLAIMS:

1. A modified Factor IX (FIX) polypeptide, comprising the amino acid replacement T343R or T343K in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3, or the same replacement at a corresponding amino acid residue in the primary sequence of an unmodified FIX polypeptide, wherein:

corresponding amino acid residues are identified by alignment of the unmodified FIX polypeptide with the polypeptide of SEQ ID NO:3;

the unmodified FIX polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325 or a FIX polypeptide having at least 95% sequence identity to the polypeptide that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325;

the modified FIX polypeptide does not contain the modifications F342I/T343R/Y345T;

the modified FIX polypeptide exhibits at least one FIX activity or property that is improved compared to the unmodified FIX polypeptide that does not contain the modification; and

the activity or property is increased procoagulant activity compared to an active form of a polypeptide of any of SEQ ID NOS: 2, 3, 20 and 325.

2. The modified FIX polypeptide of claim 1, comprising the amino acid replacement T343R.

3. The modified FIX polypeptide of claim 1, comprising the amino acid replacements R338E/T343R.

4. The modified FIX polypeptide of claim 1, comprising the amino acid replacement T343K with reference to a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3.

5. The modified FIX polypeptide of any of claims 1-4, comprising an amino acid replacement at residue E410 or at an amino acid residue corresponding to 410 in an unmodified FIX polypeptide, wherein the replacement amino acid is N or S.

6. The modified FIX polypeptide of claim 5, wherein the amino acid replacement is N.

7. The modified FIX polypeptide of any of claims 1-6, comprising an amino acid replacement at residue 403 of a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3 or at amino acid residues corresponding to residue 403 in an unmodified FIX polypeptide, wherein the replacement is E.

8. The modified FIX polypeptide of claim 1, comprising the amino acid replacements R338E, T343R, R403E and E410N in a mature FIX polypeptide having a sequence set forth in SEQ ID NO:3 or the same replacements at corresponding amino acid residues in an unmodified FIX polypeptide.

9. The modified FIX polypeptide of any of claims 1-8, wherein the unmodified polypeptide comprises a sequence of amino acids set forth in any of SEQ ID NOS: 2, 3, 20 and 325.

10. The modified FIX polypeptide of any of claims 1-9, further comprising the amino acid replacement Y155F or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

11. The modified FIX polypeptide of claim 1, further comprising the amino acid replacement Y155F or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

12. The modified FIX polypeptide of any of claims 1-11, comprising an amino acid replacement at an amino acid residue selected from among D203, F205 and K228, or at an amino acid residue corresponding to amino acid residue D203, F205 or K228 in an unmodified FIX polypeptide.

13. The modified FIX polypeptide of claim 12, comprising an amino acid replacement selected from among D203N, F205T and K228N, or the same amino acid replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

14. The modified FIX polypeptide of any of claims 1-13 that comprises an amino acid replacement selected from among A103N, D104N, N105S, K106S, K228N, I251S, N260S and N346D, or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

15. The modified FIX polypeptide of any of claims 1-14, comprising an amino acid replacement at an amino acid residue selected from among K247, N249, R403 and E410, or at an amino acid residue corresponding to amino acid residue K247, N249, R403 or E410 in an unmodified FIX polypeptide.

16. The modified FIX polypeptide of claim 15, comprising an amino acid replacement selected from among K247N, N249S, R403E and E410N or the same replacement at a corresponding amino acid residue in an unmodified FIX polypeptide.

17. The modified FIX polypeptide of any of claims 1-16, comprising one or more modifications that introduces and/or eliminates one or more glycosylation sites compared to the unmodified FIX polypeptide.

18. The modified FIX polypeptide of claim 17, wherein the modification introduces one or more glycosylation sites.

19. The modified FIX polypeptide of any of claims 1-18, wherein the improved property is increased procoagulant activity compared with the unmodified FIX polypeptide.

20. The modified FIX polypeptide of any of claims 1-19, wherein the unmodified FIX polypeptide consists of the sequence of amino acids set forth in SEQ ID NO:2, 3, 20 or 325.

21. The modified FIX polypeptide of claim 1, comprising amino acid replacements selected from among R338E/T343R/E410N; Y155F/R338E/T343R/E410N; Y155F/K247N/N249S/T343R/E410N; Y155F/T343R/R403E/E410N; K247N/N249S/T343R/R403E/E410N; Y155F/K247N/N249S/T343R/R403E/E410N; K247N/N249S/R338E/T343R/E410N; Y155F/K247N/N249S/R338E/T343R/E410N; K247N/N249S/R338E/T343R/R403E; Y155F/K247N/N249S/R338E/T343R/R403E; Y155F/K247N/N249S/R338E/T343R; K247N/N249S/R338E/T343R/R403E/E410N; Y155F/K247N/N249S/R338E/T343R/R403E/E410N; Y155F/K247N/N249S/T343R/R403E; Y155F/I251S/R338E/T343R/R403E; Y155F/R338E/T343R/R403E/E410S; R338E/T343R/R403E; Y155F/R338E/T343R/R403E; Y155F/R338E/T343R/R403E/E410N; R338E/T343R/R403E/E410N and R338E/T343R.

22. The modified FIX polypeptide of claim 21, comprising amino acid replacements selected from among K247N/N249S/R338E/T343R/R403E/E410N, R338E/T343R/E410N and R338E/T343R.

23. A modified FIX polypeptide of claim 1, comprising a sequence of amino acids set forth in any of SEQ ID NOS: 209, 215, 268, 332, 335, 351, 352, 361-363, 365, 367, 370, 371, 377, 387-392, 396, 399, 401 and 402.

24. The modified FIX polypeptide of claim 23, wherein the sequence of amino acid residues consists of the sequence set forth in any of SEQ ID NOS: 209, 215, 268, 332, 335, 351, 352, 361-363, 365, 367, 370, 371, 377, 387-392, 396, 399, 401 and 402.

25. The modified FIX polypeptide of any of claims 1-24 that is a mature polypeptide.

26. The modified FIX polypeptide of any of claims 1-24 that is a two-chain polypeptide.

27. The modified FIX polypeptide of any of claims 1-24 that is a single-chain polypeptide.

28. The modified FIX polypeptide of any of claims 1-27 that is activated.

29. The modified FIX polypeptide of any of claims 1-28 that is hyperglycosylated.

30. The modified FIX polypeptide of any of claims 1-28, wherein only the primary sequence is modified.

31. The modified FIX polypeptide of any of claims 1-28 that comprises a chemical modification or a post-translational modification.

32. The modified FIX polypeptide of claim 31, wherein the modified FIX polypeptide is glycosylated, carboxylated, hydroxylated, sulfated, phosphorylated, albuminated, or conjugated to a polyethylene glycol (PEG) moiety.

33. The modified FIX polypeptide of any of claims 1-32 that contains up to 10 amino acid replacements.

34. An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FIX polypeptide of any of claims 1-33.

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

36. The vector of claim 35, wherein the vector is a prokaryotic vector, viral vector, or a eukaryotic vector.

37. The vector of claim 35, wherein the vector is a mammalian vector.

38. The vector of claim 35, 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.

39. An isolated cell or cell culture, comprising the vector of any of claims 35-38.

40. The cell or cell culture of claim 39, that is a eukaryotic cell.

41. The cell or cell culture of claim 40, wherein the eukaryotic cell is a mammalian cell.

42. A method of producing a modified FIX polypeptide, comprising:

culturing a cell or cell culture of any of claims 39-41 under conditions whereby the modified FIX polypeptide is expressed; and

optionally isolating the FIX polypeptide.

43. A pharmaceutical composition, comprising a modified FIX polypeptide of any

of claims 1-33 in a pharmaceutically acceptable vehicle.

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

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

46. The pharmaceutical composition of any of claims 43-45 that is formulated for controlled-release.

47. The pharmaceutical composition of any of claims 43-46 that is formulated for single-dosage administration.

48. A modified FIX polypeptide of any of claims 1-33 for use for treatment of a disease or condition that is treated by administration of FIX.

49. Use of a modified FIX polypeptide of any of claims 1-33 for formulation of a medicament for treatment of a disease or condition selected from among blood coagulation disorders, hematologic disorders, hemorrhagic disorders, hemophilias, and bleeding disorders.

50. The modified FIX polypeptide of claim 48 or use of claim 49, wherein the FIX is active FIX (FIXa).

51. The modified FIX polypeptide or use of any of claims 48-50, wherein the disease or disorder is hemophilia B.