

WHAT IS CLAIMED IS:

1. A Factor IX (FIX) fusion protein comprising a FIX polypeptide and at least one XTEN which is inserted within the FIX polypeptide at an insertion site corresponding to an amino acid selected from the group consisting of amino acid 103 of SEQ ID NO: 2, amino acid 105 of SEQ ID NO: 2, amino acid 142 of SEQ ID NO: 2, amino acid 149 of SEQ ID NO: 2, amino acid 162 of SEQ ID NO: 2, amino acid 166 of SEQ ID NO: 2, amino acid 174 of SEQ ID NO: 2, amino acid 224 of SEQ ID NO: 2, amino acid 226 of SEQ ID NO: 2, amino acid 228 of SEQ ID NO: 2, amino acid 413 of SEQ ID NO: 2, and any combination thereof, and wherein the FIX fusion protein exhibits procoagulant activity.
2. The FIX fusion protein of claim 1, wherein the insertion site corresponds to an amino acid selected from the group consisting of amino acid 149 of SEQ ID NO: 2, amino acid 162 of SEQ ID NO: 2, amino acid 166 of SEQ ID NO: 2, amino acid 174 of SEQ ID NO: 2 and any combination thereof.
3. The FIX fusion protein of claim 1 or 2, wherein the XTEN comprises at least about 5 amino acids, at least about 6 amino acids, at least about 12 amino acids, at least about 36 amino acids, at least about 42 amino acids, at least about 72 amino acids, at least about 144 amino acids, or at least about 288 amino acids.
4. The FIX fusion protein of any one of claims 1 to 3, which further comprises a second XTEN.
5. The FIX fusion protein of claim 4, wherein the XTEN is inserted within the FIX polypeptide at an insertion site corresponding to amino acid 166 of SEQ ID NO: 2, and wherein the second XTEN is fused to the C-terminus of the FIX polypeptide.
6. The FIX fusion protein of any one of claims 1 to 5, further comprising an Fc domain.
7. The FIX fusion protein of claim 6, comprising a second Fc domain.

8. The FIX fusion protein of claim 7, which comprises two polypeptide chains, wherein the first polypeptide chain comprises the FIX polypeptide fused to the Fc domain, and the second polypeptide chain comprises the second Fc domain, wherein the first Fc domain and the second Fc domain are associated by a covalent bond.

9. The FIX fusion protein of any one of claims 1 to 8, wherein the FIX polypeptide is a R338L FIX variant.

10. An isolated polynucleotide comprising a sequence encoding the FIX fusion protein of any one of claims 1 to 9.

11. An expression vector comprising the polynucleotide of claim 10.

12. A host cell comprising the polynucleotide of claim 10 or the vector of claim 11.

13. A composition comprising the FIX fusion protein of any one of claims 1 to 9, the polynucleotide of claim 10, the expression vector of claim 11, or the host cell of claim 12, and a pharmaceutically acceptable carrier.

14. A method of preventing, treating, ameliorating, or managing a clotting disease or condition in a patient in need thereof comprising administering an effective amount of the FIX fusion protein of any one of claims 1 to 9, the polynucleotide of claim 10, the expression vector of claim 11, the host cell of claim 12, or the composition of claim 13.

15. A Factor IX (FIX) fusion protein comprising a first chain and a second chain, wherein:

- a. the first chain comprises:
 - i. a FIX polypeptide;
 - ii. at least one XTEN, wherein the at least one XTEN is inserted within the FIX polypeptide at an insertion site corresponding to amino acid 166 of SEQ ID NO: 2, and wherein the at least one XTEN comprises an amino acid sequence having at least about 72 amino acids; and

- iii. a first Fc domain, wherein the first Fc domain is fused to the FIX polypeptide of the at least one XTEN; and
 - b. the second chain comprises a second Fc domain
- wherein the first Fc domain and the second Fc domain are associated by a covalent bond; and wherein the FIX fusion protein exhibits procoagulant activity.