CLAIMS

1. A chimeric protein comprising

(i) a first polypeptide, which comprises

(a) a Factor VIII ("FVIII") protein,

(b) an XTEN of the first polypeptide, and

(c) a first Fc region,

wherein the FVIII protein has a FVIII activity; and

(ii) a second polypeptide, which comprises

(a) a von Willebrand Factor ("VWF") fragment comprising an amino acid sequence at least 99% identical to the amino acid sequence set forth in amino acids 764 to 1240 of SEQ ID NO: 21,

(b) an XTEN of the second polypeptide,

(c) a 10-50 amino acid cleavable linker comprising an a2 region of FVIII which comprises the amino acid sequence of Glu720 to Arg740 of the FVIII corresponding to SEQ ID NO: 65, wherein the a2 region is capable of being cleaved by thrombin, and

(d) a second Fc region,

wherein the VWF fragment binds to the FVIII protein;

wherein the XTEN of the second polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 58;

wherein the XTEN of the first polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 8;

wherein the first Fc region is associated with the second Fc region by a disulfide bond; and

wherein the half-life of the chimeric protein is extended compared to a FVIII protein without the VWF fragment.

2. A chimeric protein comprising

(i) a first polypeptide, which comprises

(a) a Factor VIII ("FVIII") protein,

(b) an XTEN of the first polypeptide, and

(c) a first Fc region,

wherein the FVIII protein has a FVIII activity; and

(ii) a second polypeptide, which comprises

(a) a von Willebrand Factor ("VWF") fragment comprising an amino acid sequence at least 99% identical to the amino acid sequence set forth in amino acids 764 to 1240 of SEQ ID NO: 21,

(b) an XTEN of the second polypeptide,

(c) a 10-50 amino acid cleavable linker comprising an a2 region of FVIII which comprises the amino acid sequence of Glu720 to Arg740 of the FVIII corresponding to SEQ ID NO: 65, wherein the a2 region is capable of being cleaved by thrombin, and

(d) a second Fc region,

wherein the VWF fragment binds to the FVIII protein,

wherein the VWF fragment contains an amino acid other than cysteine substituted for a residue corresponding to residues 1099 and 1142 of SEQ ID NO: 21;

wherein the XTEN of the second polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 58;

wherein the XTEN of the first polypeptide comprises the amino acid sequence as set forth in SEQ ID NO: 8;

wherein the first Fc region is associated with the second Fc region by a disulfide bond; and

wherein the half-life of the chimeric protein is extended compared to a FVIII protein without the VWF fragment.

3. The chimeric protein of claim 1 or 2, wherein the FVIII protein is a dual chain FVIII isoform.

4. The chimeric protein of claim 3, wherein the dual chain FVIII isoform comprises a first chain comprising a heavy chain of FVIII and a second chain comprising a light chain of FVIII, wherein the heavy chain and the light chain are associated with each other by a metal bond.

5. The chimeric protein of claim 1 or 2, wherein the FVIII protein is a single chain FVIII isoform.

6. The chimeric protein of any one of claims 1, 2, or 5, wherein the FVIII protein has an amino acid sequence that is at least 99% identical to amino acids 1 to 1438 of SEQ ID NO: 67, and wherein the FVIII protein has clotting activity.

7. The chimeric protein of claim 6, wherein the XTEN of the first polypeptide is inserted immediately downstream of the residue corresponding to residue 745 of SEQ ID NO: 67.

8. The chimeric protein of any one of claims 1-7, wherein the second polypeptide comprises a D' domain and a D3 domain of VWF fused to the second Fc region by the XTEN of the second polypeptide in-between,

wherein the XTEN sequence contains less than 288 amino acid residues, and

wherein the XTEN of the second polypeptide is fused to the second Fc region by the cleavable linker.

9. The chimeric protein of claim 2, wherein the VWF fragment contains an alanine residue substituted for the residues corresponding to residues 1099 and 1142 of SEQ ID NO: 21.

10. The chimeric protein of any one of claims 1-9, wherein the first Fc region and the second Fc region are identical.

11. The chimeric protein of claim 10, wherein the first Fc region and the second Fc region are derived from human IgG1.

12. The chimeric protein of claim 8, wherein the VWF fragment further comprises the D1 domain, the D2 domain, or the D1 and D2 domains of VWF.

13. The chimeric protein of claim 12, wherein:

    (i) the first polypeptide comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 70; and

    (ii) the second polypeptide comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 197.

14. The chimeric protein of claim 13, wherein:

    (i) the first polypeptide comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 70; and

    (ii) the second polypeptide comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 197.

15. The chimeric protein of any of claims 1-14, wherein the chimeric protein is obtainable by a method of making the chimeric protein comprising

    (a) transfecting a host cell comprising a polynucleotide or a set of polynucleotides encoding the chimeric protein, and

    b) culturing the host cell in a culture medium under a condition suitable for expressing the chimeric protein, wherein the chimeric protein is expressed,

    wherein the polynucleotide or the set of polynucleotides comprises the nucleic acid sequence according to SEQ ID NO 172 encoding for the first polypeptide.

16. The chimeric protein of any of claims 1-15, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 173.

17. The chimeric protein of any one of claims 1-11, wherein the VWF fragment consists of the D' domain and the D3 domain.

18. A polynucleotide or a set of polynucleotides encoding the chimeric protein of any one of claims 1 to 14 and 17.

19. A vector or a set of vectors comprising the polynucleotide or the set of polynucleotides of claim 18 and one or more promoters operably linked to the polynucleotide or the set of polynucleotides.

20. A host cell comprising the polynucleotide or the set of polynucleotides of claim 18 or the vector or the set of vectors of claim 19.

21. A stable cell line comprising the host cell of claim 20.

22. A pharmaceutical composition comprising the chimeric protein of any one of claims 1 to 11 and 15 to 17 and a pharmaceutically acceptable carrier.

23. The chimeric protein of any one of claims 1 to 11 and 15 to 17 for use in the treatment of a bleeding disease or condition in a subject in need thereof.

24. The pharmaceutical composition of claim 22 for use in the treatment of a bleeding disease or condition in a subject in need thereof.

25. The chimeric protein of any one of claims 1 to 11 and 15 to 17 for use in the treatment of hemophilia A in a subject in need thereof.

26. The pharmaceutical composition of claim 22 for use in the treatment of hemophilia A in a subject in need thereof.