WHAT IS CLAIMED IS:

1. A chimeric protein comprising (i) a von Willebrand Factor (VWF) protein comprising the D' domain and the D3 domain of VWF, (ii) an XTEN sequence, and (iii) a FVIII protein, wherein the VWF fragment and the XTEN sequence are linked by an optional linker, wherein the VWF fragment or the XTEN sequence is linked to or associated with the FVIII protein.

2. A chimeric protein comprising a formula, which comprises:

(a) V-X-FVIII,

(b) FVIII-X-V,

(c) V-X:FVIII,

(d) X-V:FVIII,

(e) FVIII:V-X, or

(f) FVIII:X-V,

wherein V comprises a VWF fragment,

X comprises one or more XTEN sequences,

FVIII comprises a FVIII protein;

(-) is a peptide bond or one or more amino acids; and

(:) is a covalent bond or a non-covalent bond.

3. The chimeric protein of claim 1 or 2, wherein the XTEN sequence is linked to the FVIII protein by a linker.

4. The chimeric protein of claim 3, wherein the linker is a cleavable linker.

5. The chimeric protein of any one of claims 1 to 4, which comprises a single polypeptide chain comprising the VWF fragment, the XTEN sequence and the FVIII protein.

6. The chimeric protein of any one of claims 1 to 4, which comprises a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain comprises FVIII and the second polypeptide chain comprises the VWF fragment and the XTEN sequence.

7. The chimeric protein of any one of claims 1 to 6, further comprising (iv) an Ig constant region or a portion thereof linked to either the VWF fragment, the XTEN sequence, or the FVIII protein, or any combination thereof.

8. A chimeric protein comprising a formula, which comprises:

(g) V-L2-X-L1-F1:FVIII-L3-F2;

(h) V-L2-X-L1-F1:F2-L3-FVIII;

(i) F1-L1-X-L2-V: FVIII-L3-F2;

(j) F1-L1-X-L2-V:F2-L3-FVIII;

(k) V-L2-X-L1-F1-L4-FVIII-L3-F2;

(l) F2-L3-FVIII-L4-F1-L1-X-L2-V;

(m) FVIII-L3-F2-L4-V-L2-X-L1-F1; and

(n) F1-L1-X-L2-V-L4-F2-L3-FVIII,

wherein V comprises a VWF fragment,

each of L1, L2, and L3 comprises an optional linker,

L4 is an optional linker,

FVIII comprises a FVIII protein,

X comprises one or more XTEN sequences,

F1 comprises an optional Ig constant region or a portion thereof,

F2 comprises an optional additional Ig constant region or a portion thereof;

(-) is a peptide bond or one or more amino acids; and

(:) is a covalent bond or a non-covalent bond.

9. The chimeric protein of any one of claims 7 or 8, wherein the Ig constant region or a portion thereof extends a half-life of the VWF fragment.

10. The chimeric protein of any one of claims 7 to 9, wherein the Ig constant region or a portion thereof comprises a first Fc region, which is linked to the XTEN sequence or the VWF fragment.

11. The chimeric protein of claim 10, wherein the Ig constant region or a portion thereof is linked to the XTEN sequence by a linker.

12. The chimeric protein of claim 12, wherein the linker comprises a cleavable linker.

13. The chimeric protein of any one of claims 7 to 12, further comprising an additional Ig constant region or a portion thereof.

14. The chimeric protein of claim 13, wherein the additional Ig constant region or a portion thereof comprises an additional Fc region.

15. The chimeric protein of claim 14, wherein the additional Ig constant region or a portion thereof extends the half-life of a FVIII protein.

16. The chimeric protein of any one of claims 13 to 15, wherein the additional Ig constant region or a portion thereof is linked to the FVIII protein.

17. The chimeric protein of claim 16, wherein the second Fc region is further linked to the VWF fragment by a linker.

18. The chimeric protein of claim 17, wherein the linker is a processable linker.

19. The chimeric protein of any one of claims 8 to 18, wherein L4 is a processable linker.

20. The chimeric protein of any one of claims 7 to 19, wherein the additional Ig constant region or a portion thereof is associated with the Ig constant region or a portion thereof.

21. The chimeric protein of claim 20, wherein the additional Ig constant region or a portion thereof is associated with the Ig constant region or a portion thereof by a covalent bond.

22. The chimeric protein of claim 21, wherein the covalent bond is a disulfide bond.

23. The chimeric protein of any one of claims 1 to 22, wherein the VWF fragment is associated with the FVIII protein by a non-covalent bond.

24. The chimeric protein of any one of claims 1 to 23, wherein the half-life of the FVIII protein, is extended compared to a FVIII protein without the VWF fragment or compared to wild type FVIII.

25. The chimeric protein of claim 24, wherein the half-life of the FVIII is extended at least about 1.5 times, at least about 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times, at least about 7 times, at least about 8 times, at least about 9 times, at least about 10 times, at least about 11 times, or at least about 12 times longer than a FVIII protein without the VWF fragment or compared to wild type FVIII..

26. The chimeric protein of claim 24, wherein the half-life of the Factor VIII is at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours, at least about 24 hours, at least about 25 hours, at least about 26 hours, at least about 27 hours, at least about 28 hours, at least about 29 hours, at least about 30 hours, at least about 31 hours, at least about 32 hours, at least about 33 hours, at least about 34 hours, at least about 35 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, or at least about 108 hours.

27. A chimeric protein comprising (i) a FVIII protein, (ii) an XTEN sequence, and (iii) an Ig constant region or a portion thereof, wherein the XTEN sequence is linked to the FVIII protein by an optional linker at the N-terminus or C terminus of the FVIII protein or is inserted between two amino acids of at least one or more insertion sites in the FVIII protein and wherein the Ig constant region or a portion thereof is linked to or associated with the FVIII protein or the XTEN sequence.

28. The chimeric protein of claim 27, wherein the XTEN sequence and the Ig constant region or a portion thereof extends the half-life of the FVIII protein.

29. The chimeric protein of claim 27 or 28, wherein the VWF binding site is located in the A3 domain or the C2 domain of the FVIII protein or both the A3 domain and the C2 domain.

30. The chimeric protein of claim 29, wherein the VWF binding site comprises the amino acid sequence corresponding to amino acids 1669 to 1689 and 2303 to 2332 of SEQ ID NO: 4.

31. The chimeric protein of any one of claims 27 to 30, wherein the half-life of the FVIII protein is extended compared to a FVIII protein without the Ig constant region or a portion thereof or a FVIII protein without the XTEN sequence.

32. The chimeric protein of claim 31, wherein the half-life of the FVIII protein is extended at least about 1.5 times, at least about 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times, at least about 7 times, at least about 8 times, at least about 9 times, at least about 10 times, at least about 11 times, or at least about 12 times longer than a FVIII protein without the Ig constant region or a portion thereof or a FVIII protein without the XTEN sequence or wild-type FVIII.

33. The chimeric protein of claim 31, wherein the half-life of the FVIII protein is at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours, at least about 14 hours, at least about 15 hours, at least about 16 hours, at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, or at least about 108 hours.

34. The chimeric protein of any one of claims 27 to 33, wherein the Ig constant region or a portion thereof comprises a first Fc region.

35. The chimeric protein of any one of claims 27 to 34, further comprising an additional Ig constant region or a portion thereof.

36. The chimeric protein of claim 35, wherein the additional Ig constant region or a portion thereof comprises a second Fc region, which is linked to or associated with the first Fc region.

37. The chimeric protein of claim 36, wherein the second Fc region is associated with the first Fc region by a covalent bond.

38. The chimeric protein of claim 36, wherein the first Fc region is linked to the second Fc region by a linker.

39. The chimeric protein of claim 38, wherein the linker is a processable linker.

40. The chimeric protein of any one of claims 27 to 34, which comprises a single polypeptide chain comprising the FVIII protein, the XTEN sequence, and the Ig constant region or a portion thereof.

41. The chimeric protein of any one of claims 27 to 34, which comprises a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain comprises a heavy chain of the FVIII protein, the second polypeptide chain comprises a light chain of the FVIII protein and the XTEN sequence and the Ig constant region or a portion thereof.

42. The chimeric protein of any one of claims 35 to 39, which comprises a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain comprises the FVIII protein, the XTEN sequence, and the Ig constant region and the second polypeptide chain comprises the additional Ig constant region or a portion thereof.

43. The chimeric protein of any one of claims 35 to 39, which comprises a first polypeptide chain, a second polypeptide chain, and a third polypeptide chain, wherein the first polypeptide chain comprises a heavy chain of the FVIII protein and the XTEN sequence, the second polypeptide chain comprises a light chain of the FVIII protein and the Ig constant region or a portion thereof, and the third polypeptide chain comprises the additional Ig constant region or a portion thereof.

44. The chimeric protein of any one of claims 35 to 39, which comprises a single chain polypeptide comprising the FVIII protein, the XTEN sequence, the Ig constant region or a portion thereof, and the additional Ig constant region or a portion thereof.

45. A chimeric protein comprising (i) a FVIII protein, (ii) an XTEN sequence, (iii) a VWF fragment, and (iv) an Ig constant region or a portion thereof, which comprises the D' domain and the D3 domain of VWF, wherein the XTEN sequence is linked to the FVIII protein by an optional linker at the N-terminus or C terminus of the FVIII protein or inserted immediately downstream of one or more insertion sites in the FVIII protein, the VWF fragment is linked to or associated with the FVIII protein or the XTEN sequence, and the Ig constant region or a portion thereof is linked to the FVIII protein, the XTEN sequence, the VWF fragment, or any combinations thereof.

46. A chimeric protein comprising a formula, which comprises:

(1) FVIII(X1)-L1-F1:V-L2-X2-L3-F2;

(2) FVIII(X1)-L1-F1:F2-L3-X2-L2-V;

(3) F1-L1-FVIII(X1):V-L2-X2-L3-F2;

(4) F1-L1-FVIII(X1);F2-L3-X2-L2-V;

(5) FVIII(X1)-L1-F1-L4-V-L2-X2-L3-F2;

(6) FVIII(X1)-L1-F1-L4-F2-L3-X2-L2-V;

(7) F1-L1-FVIII(X1)-L4-V-L2-X2-L3-F2, or

(8) F1-L1-FVIII(X1)-L4-F2-L3-X2-L2-V,

wherein FVIII(X1) comprises a FVIII protein and an XTEN sequence, wherein the XTEN sequence is linked to the N-terminus or C-terminus of the FVIII protein or inserted immediately downstream of one or more amino acids ("one or more insertion site") in the FVIII protein;

each of L1, L2, or L3 comprises an optional linker;

L4 is a linker;

X2 comprises one or more XTEN sequences;

F1 comprises an Ig constant region or a portion thereof;

F2 comprises an optional additional Ig constant region or a portion thereof, and

V comprises a VWF fragment;

(-) is a peptide bond or one or more amino acids; and

(:) comprises a covalent bond or a non-covalent bond.

47. The chimeric protein of claim 45 or 46, wherein the VWF fragment does not bind to a VWF clearance receptor.

48. The chimeric protein of any one of claims 45 to 47, wherein the VWF fragment is capable of protecting the FVIII protein from cleavage by one or more protease, protecting the FVIII protein from activation, stabilizing the heavy chain and/or the light chain of the FVIII protein, or preventing clearance of the FVIII protein by one or more scavenger receptors.

49. The chimeric protein of any one of claims 45 to 48, wherein the Ig constant region or a portion thereof inhibits or prevents endogenous VWF from binding to the FVIII protein by shielding or blocking a VWF binding site on the FVIII protein.

50. The chimeric protein of claim 49, wherein the VWF binding site is located in the A3 domain or the C2 domain of the FVIII protein or both the A3 domain and the C2 domain.

51. The chimeric protein of claim 49 or 50, wherein the VWF binding site comprises the amino acid sequence corresponding to amino acids 1669 to 1689 and 2303 to 2332 of SEQ ID NO: 4.

52. The chimeric protein of any one of claims 45 to 51, wherein a half-life of the FVIII protein is extended compared to a FVIII protein without the VWF fragment.

53. The chimeric protein of claim 52, wherein the half-life of the FVIII protein is extended at least about 1.5 times, at least about 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times, at least about 7 times, at least about 8 times, at least about 9 times, at least about 10 times, at least about 11 times, or at least about 12 times longer than wild type FVIII.

54. The chimeric protein of claim 52, wherein the half-life of the FVIII protein is at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours, at least about 14 hours, at least about 15 hours, at least about 16 hours, at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, or at least about 108 hours.

55. The chimeric protein of any one of claims 45 to 54, which comprises a single polypeptide chain comprising the FVIII protein, the XTEN sequence, the VWF fragment, and the Ig constant region or a portion thereof.

56. The chimeric protein of any one of claims 45 to 54, wherein the Ig constant region or a portion thereof comprises a first Fc region.

57. The chimeric protein of any one of claims 45 to 54, wherein the Ig constant region or a portion thereof is linked to the VWF fragment by an optional linker.

58. The chimeric protein of claim 57, wherein the linker comprises a cleavable linker.

59. The chimeric protein of claim 45 to 50, which further comprises an additional Ig constant region or a portion thereof, which is linked to the FVIII protein, the Ig constant region or a portion thereof, the VWF fragment, or any combinations thereof by an optional linker.

60. The chimeric protein of claim 59, wherein the additional Ig constant region or a portion thereof is linked to the FVIII protein by an optional linker.

61. The chimeric protein of claim 59 or 60, wherein the Ig constant region or a portion thereof is a second Fc region.

62. The chimeric protein of any one of claims 8 to 26, 42 to 44, and 46 to 61, wherein the Ig constant region or a portion thereof and the additional Ig constant region or a portion thereof are identical or different.

63. The chimeric protein of any one of claims 46 to 62, which comprises a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain comprises the FVIII protein, the XTEN sequence, and the Ig constant region or a portion thereof and the second polypeptide chain comprises the VWF fragment and the additional Ig constant region or a portion thereof.

64. The chimeric protein of any one of claims 46 to 62, which comprises a first polypeptide chain, a second polypeptide chain, and a third polypeptide chain, wherein the first polypeptide chain comprises a heavy chain of the FVIII protein and the XTEN sequence, the second polypeptide chain comprises a light chain of the FVIII protein and the Ig constant region or a portion thereof, and the third polypeptide chain comprises the VWF fragment and the additional Ig constant region or a portion thereof.

65. The chimeric protein of any one of claims 46 to 62, which comprises a first polypeptide chain, a second polypeptide chain, and a third polypeptide chain, wherein the first polypeptide chain comprises a heavy chain of the FVIII protein, the second polypeptide chain comprises a light chain of the FVIII protein, the XTEN sequence, and the Ig constant region or a portion thereof, and the third polypeptide chain comprises the VWF fragment and the additional Ig constant region or a portion thereof.

66. The chimeric protein of any one of claims 46 to 62, wherein a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain comprises a heavy chain of the FVIII protein and the XTEN sequence and the second polypeptide chain comprises a light chain of the FVIII protein, the Ig constant region or a portion thereof, the VWF fragment, and the additional Ig constant region or a portion thereof.

67. The chimeric protein of any one of claims 63 to 66, which further comprises an additional XTEN sequence linked to the VWF fragment or to the additional Ig constant region or a portion thereof.

68. The chimeric protein of any one of claims 1 to 26, wherein the FVIII protein is linked to an XTEN sequence at the C-terminus or the N-terminus of the FVIII protein or inserted immediately downstream of one or more amino acids in the FVIII protein or any combinations thereof.

69. The chimeric protein of any one of claims 27 to 68, wherein the FVIII protein is linked to at least two XTEN sequences, at least three XTEN sequences, at least four XTEN sequences, at least five XTEN sequences, or at least six XTEN sequences.

70. The chimeric protein of any one of claims 1 to 69, wherein the FVIII protein comprises one or more domains of FVIII selected from the group consisting of an A1 domain, a1 acidic region, an A2 domain, a2 acidic region, a B domain, an A3 domain, a3 acidic region, a C1 domain, a C2 domain, one or more fragments thereof, and any combinations thereof.

71. The chimeric protein of any one of claims 27 to 70, wherein the one or more insertion sites in the FVIII protein is located within one or more domains of the FVIII protein selected from the group consisting of the A1 domain, the a1 acidic region, the A2 domain, the a2 acidic region, the A3 domain, the B domain, the C1 domain, the C2 domain, and any combinations thereof or between one or more domains of the FVIII protein selected from the group consisting of the A1 domain and a1 acidic region, the a1 acidic region and A2 domain, the A2 domain and a2 acidic region, the a2 acidic region and B domain, the B domain and A3 domain, the A3 domain and C1 domain, the C1 domain and C2 domain, and any combinations thereof or between two domains of the FVIII protein selected from the group consisting of the A1 domain and a1 acidic region, the a1 acidic region and A2 domain, the A2 domain and a2 acidic region, the a2 acidic region and B domain, the B

domain and A3 domain, the A3 domain and C1 domain, the C1 domain and C2 domain, and any combinations thereof.

72. The chimeric protein of any one of claims 27 to 71, wherein the one or more insertion sites in the FVIII protein are one or more amino acids selected from the group consisting of the amino acid residues in Table 7, Table 8, Table 9 and Table 10.

73. The chimeric protein of claim 72, wherein the XTEN sequence inserted at the insertion site corresponding to amino acids 3R of SEQ ID NO: 4 further comprises an amino acid sequence of ATR.

74. The chimeric protein of any one of claims 27 to 71, wherein the one or more insertion sites in the FVIII protein are located immediately downstream of one or more amino acids selected from the group consisting of:

(1) amino acid 3, (2) amino acid 18, (3) amino acid 22,
(4) amino acid 26, (5) amino acid 32, (6) amino acid 40,
(7) amino acid 60, (8) amino acid 65, (9) amino acid 81,
(10) amino acid 116, (11) amino acid 119, (12) amino acid 130,
(13) amino acid 188, (14) amino acid 211, (15) amino acid 216,
(16) amino acid 220, (17) amino acid 224, (18) amino acid 230,
(19) amino acid 333, (20) amino acid 336, (21) amino acid 339,
(22) amino acid 375, (23) amino acid 399, (24) amino acid 403,
(25) amino acid 409, (26) amino acid 416, (26) amino acid 442,
(28) amino acid 487, (29) amino acid 490, (30) amino acid 494,
(31) amino acid 500, (32) amino acid 518, (33) amino acid 599,
(34) amino acid 603, (35) amino acid 713, (36) amino acid 745,
(37) amino acid 1656, (38) amino acid 1711, (39) amino acid 1720,
(40) amino acid 1725, (41) amino acid 1749, (42) amino acid 1796,
(43) amino acid 1802, (44) amino acid 1827, (45) amino acid 1861,
(46) amino acid 1896, (47) amino acid 1900, (48) amino acid 1904,

(49) amino acid 1905, (50) amino acid 1910, (51) amino acid 1937,
(52) amino acid 2019, (53) amino acid 2068, (54) amino acid 2111,
(55) amino acid 2120, (56) amino acid 2171, (57) amino acid 2188,
(58) amino acid 2227, (59) amino acid 2277, and
(60) two or more combinations thereof.

75. The chimeric protein of any one of claims 1 to 74, wherein the FVIII protein comprises B domain or a portion thereof.

76. The chimeric protein of claim 75, wherein the FVIII protein is SQ B domain deleted FVIII.

77. The chimeric protein of any one of claims 1 to 76, wherein the FVIII protein comprises single chain FVIII.

78. The chimeric protein of claim 77, wherein the single chain FVIII contains at least one amino acid substitution at a residue corresponding to residue 1648, residue 1645, or both of full-length mature Factor VIII polypeptide (SEQ ID NO: 4) or residue 754, residue 751, or both of SQ BDD Factor VIII (SEQ ID NO: 6).

79. The chimeric protein of claim 78, wherein the amino acid substitution is an amino acid other than arginine.

80. The chimeric protein of any one of claims 1 to 76, wherein the FVIII protein comprises a heavy chain of FVIII and a light chain of Factor VIII, wherein the heavy chain and the light chain are associated with each other by a metal bond.

81. The chimeric protein of any one of claims 1 to 80, wherein the FVIII protein has a low affinity to or does not bind to a low-density lipoprotein receptor-related protein (LRP).

82. The chimeric protein of claim 81, wherein the FVIII protein contains at least one amino acid substitution that lowers the affinity to or eliminates the binding to the LRP.

83. The chimeric protein of claim 82, wherein the at least one amino acid substitution is at a residue corresponding to residue 471, residue 484, residue 487, residue 490, residue 497,

residue 2092, residue 2093 or two or more combinations thereof of full-length mature FVIII.

84. The chimeric protein of claim 83, wherein the amino acid substitution at residue 471, 484, or 497 is an amino acid other than Arginine, the amino acid substitution at residue 487 is an amino acid other than Tyrosine, the amino acid substitution at residue 2092 is an amino acid other than Lysine, or the amino acid substitution at residue 2093 is an amino acid other than phenylalanine.

85. The chimeric protein of any one of claims 1 to 84, wherein the FVIII protein contains at least one amino acid substitution, which induces the FVIII protein to be more stable than a FVIII protein without the substitution.

86. The chimeric protein of claim 85, wherein the A2 domain and the A3 domain of the FVIII protein are associated to each other by a covalent bond.

87. The chimeric protein of claim 85 or 86, wherein the at least one amino acid substitution is at a residue corresponding to residue 664, residue 1826, residue 662, or residue 1828 of full-length mature FVIII, or two or more combinations thereof.

88. The chimeric protein of claim 87, wherein the FVIII protein contains (a) cysteine at the residue corresponding to residue 664 of full-length mature FVIII and cysteine at the residue corresponding to residue 1826 of full-length mature FVIII or (b) cysteine at the residue corresponding to residue 662 of full-length mature FVIII and cysteine at the residue corresponding to residue 1828 of full-length mature FVIII.

89. The chimeric protein of any one of claims 1 to 26 and 45 to 88, wherein the VWF fragment is not amino acids 764 to 1274 of SEQ ID NO: 2.

90. The chimeric protein of any one of claims 1 to 26 and 45 to 89, wherein the amino acid sequence of the D' domain is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 764 to 866 of SEQ ID NO: 2.

91. The chimeric protein of any one of claims 1 to 26 and 45 to 90, wherein the amino acid sequence of the D3 domain is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 867 to 1240 of SEQ ID NO: 2.

92. The chimeric protein of any one of claims 1 to 26 and 45 to 91, wherein the VWF fragment is a monomer.

93. The chimeric protein of any one of claims 1 to 26 and 45 to 91, wherein the VWF fragment comprises at least two VWF fragments, at least three VWF fragments, at least four VWF fragments, at least five VWF fragments, or at least six VWF fragments.

94. The chimeric protein of any one of claims 1 to 26 and 45 to 93, wherein the VWF fragment comprises an amino acid at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 764 to 1240 of SEQ ID NO: 2.

95. The chimeric protein of claim 94, wherein the VWF fragment consists essentially of or consists of amino acids 764 to 1240 of SEQ ID NO: 2.

96. The chimeric protein of any one of claims 1 to 26 and 45 to 95, wherein the VWF fragment contains at least one amino acid substitution at a residue corresponding to residue 1099, residue 1142, or both residues 1099 and 1142 of SEQ ID NO: 2.

97. The chimeric protein of claim 96, wherein the VWF fragment contains an amino acid other than cysteine substituted for a residue corresponding to residue 1099, residue 1142, or both residues 1099 and 1142 of SEQ ID NO: 2.

98. The chimeric protein of any one of claims 1 to 26 and 45 to 97, wherein the VWF fragment further comprises the D1 domain, the D2 domain, or the D1 and D2 domains of VWF.

99. The chimeric protein of any one of claims 1 to 27 and 45 to 98, wherein the VWF fragment further comprises a VWF domain selected from the group consisting of the A1 domain, the A2 domain, the A3 domain, the D4 domain, the B1 domain, the B2 domain, the B3 domain, the C1 domain, the C2 domain, the CK domain, one or more fragments thereof, and any combinations thereof.

100. The chimeric protein of any one of claims 1 to 27 and 45 to 99, wherein the VWF fragment consists essentially of or consists of: (1) the D' and D3 domains of VWF or fragments thereof; (2) the D1, D', and D3 domains of VWF or fragments thereof; (3) the D2, D', and D3 domains of VWF or fragments thereof; (4) the D1, D2, D', and D3

domains of VWF or fragments thereof; or (5) the D1, D2, D', D3, and A1 domains of VWF or fragments thereof.

101. The chimeric protein of any one of claims 1 to 27 and 45 to 100, wherein the VWF fragment further comprises a signal peptide of VWF or FVIII which is operably linked to the VWF fragment.

102. The chimeric protein of any one of claims 1 to 101, wherein one or more of the linkers have a length of at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1400, 1600, 1800, or 2000 amino acids.

103. The chimeric protein of any one of claims 1 to 101, wherein one or more of the linkers have a length of about 1 to about 2000 amino acids.

104. The chimeric protein of claim 103, wherein one or more of the linkers have a length of at least about 20, 35, 42, 48, 73, 75, 95, 98, 144, 288, 324, 333, 576, or 864 amino acids.

105. The chimeric protein of any one of claims 1 to 104, wherein one or more of the linkers comprise a Gly/Ser peptide.

106. The chimeric protein of claim 105, wherein the Gly/Ser peptide has a formula of $(Gly_4Ser)_n$ (SEQ ID NO: 139) or $Ser(Gly_4Ser)_n$ (SEQ ID NO: 140), wherein n is a positive integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

107. The chimeric protein of claim 106, wherein the $(Gly_4Ser)_n$ linker is $(Gly_4Ser)_3$ (SEQ ID NO: 63) or $(Gly_4Ser)_4$ (SEQ ID NO: 138).

108. The chimeric protein of any one of claims 1 to 107, wherein the XTEN sequence is selected from the group consisting of AE42, AE72, AE864, AE576, AE288, AE144, AG864, AG576, AG288, and AG144.

109. The chimeric protein of claim 108, wherein the XTEN sequence is selected from the group consisting of SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO:

39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43, SEQ ID NO: 44, and SEQ ID NO: 127.

110. The chimeric protein of claim 109, wherein the XTEN sequence is AE288 or AG288.

111. The chimeric protein of any one of claims 1 to 110, wherein the linker comprises at least one first cleavage site at the N-terminus of the linker, at least one second cleavage site at the C-terminus of the linker, or both.

112. The chimeric protein of any one of claims 1 to 111, wherein the linker comprises 20 amino acids, 35 amino acids, 48 amino acids, 73 amino acids, or 95 amino acids.

113. The chimeric protein of claim 112, wherein the linker is 48 amino acids thrombin cleavage linker.

114. The chimeric protein of claim 112, wherein the linker is 35 amino acids thrombin cleavage linker.

115. The chimeric protein of claim 111, wherein the one or more of the cleavage sites is TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 8).

116. The chimeric protein of claim 111, wherein one or more of the cleavage sites is cleaved by a protease selected from the group consisting of factor XIa, factor XIIa, kallikrein, factor VIIa, factor IXa, factor Xa, factor IIa (thrombin), Elastase-2, Granzyme-B, TEV, Enterokinase, Protease 3C, Sortase A, MMP-12, MMP-13, MMP-17, and MMP-20.

117. The chimeric protein of claim 111 or 116, wherein one or more of the cleavage sites comprise an amino acid sequence selected from the group consisting of RRRR (SEQ ID NO: 9), RKRRKR (SEQ ID NO: 10), RRRRS (SEQ ID NO: 11), TQSFNDFTR (SEQ ID NO: 12), SVSQTSKLTR (SEQ ID NO: 13), DFLAEGGGVR (SEQ ID NO: 14), TTKIKPR (SEQ ID NO: 15), LVPRG (SEQ ID NO: 16), ALRPR (SEQ ID NO: 17), KLTRAET (SEQ ID NO: 18), DFTRVVG (SEQ ID NO: 19), TMTRIVGG (SEQ ID NO: 20), SPFRSTGG (SEQ ID NO: 21), LQVRIVGG (SEQ ID NO: 22), PLGRIVGG (SEQ ID NO: 23), IEGRTVGG (SEQ ID NO: 24), LTPRSLLV (SEQ ID NO: 25), LGPVSGVP (SEQ ID NO: 26), VAGDSLEE (SEQ ID NO: 27), GPAGLGGA (SEQ ID NO: 28),

GPAGLRGA (SEQ ID NO: 29), APLGLRLR (SEQ ID NO: 30), PALPLVAQ (SEQ ID NO: 31), ENLYFQG (SEQ ID NO: 32), DDDKIVGG (SEQ ID NO: 33), LEVLFQGP (SEQ ID NO: 34), and LPKTGSES (SEQ ID NO: 35).

118. The chimeric protein of any one of claims 111 to 117, wherein the first cleavage site and the second cleavage site are identical or different.

119. The chimeric protein of any one of claims 1 to 118, which is polysialylated, pegylated, or hesylated.

120. A polynucleotide or a set of polynucleotides encoding the chimeric protein of any one of claims 1 to 120.

121. The polynucleotide of claim 120, further comprising a polynucleotide chain, which encodes PC5 or PC7.

122. A vector comprising the polynucleotide of claim 120 or 121 and one or more promoter operably linked to the polynucleotide or the set of polynucleotides.

123. The vector of claim 122, further comprising an additional vector, which comprises a polynucleotide chain encoding PC5 or PC7.

124. A host cell comprising the polynucleotide of any one of claims 120 or 121 or the vector of claim 122 or 123.

125. The host cell of claim 124, which is a mammalian cell.

126. The host cell of claim 125, wherein the mammalian cell is selected from the group consisting of HEK293 cell, CHO cell, and BHK cell.

127. A pharmaceutical composition comprising the chimeric protein of any one of claims 1 to 119, the polynucleotide of claim 120 or 121, the vector of claim 122 or 123, or the host cell of any one of claims 124 to 125, and a pharmaceutically acceptable carrier.

128. The composition of claim 127, wherein the FVIII protein has extended half-life compared to wild type FVIII protein.

129. The composition of claim 127 or 128, wherein the half-life of the FVIII protein is extended at least about 1.5 times, at least about 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times, at least about 7 times, at least about 8 times, at least about 9 times, at least about 10 times, at least about 11 times, or at least about 12 times longer than wild type FVIII.

130. The composition of claim 128 or 129, wherein the half-life of Factor VIII is at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours, at least about 24 hours, at least about 25 hours, at least about 26 hours, at least about 27 hours, at least about 28 hours, at least about 29 hours, at least about 30 hours, at least about 31 hours, at least about 32 hours, at least about 33 hours, at least about 34 hours, at least about 35 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, or at least about 108 hours.

131. The composition of any one of claims 127 to 130, which is administered by a route selected from the group consisting of topical administration, intraocular administration, parenteral administration, intrathecal administration, subdural administration and oral administration.

132. The composition of claim 131, wherein the parenteral administration is intravenous or subcutaneous administration.

133. The composition of any one of claims 127 to 132, which is used to treat a bleeding disease or condition in a subject in need thereof.

134. The composition of claim 133, wherein the bleeding disease or condition is selected from the group consisting of a bleeding coagulation disorder, hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, bleeding in the iliopsoas sheath and any combinations thereof.

135. The composition of claim 133 or 134, wherein the subject is scheduled to undergo a surgery.

136. The composition of any one of claims 133 to 135, wherein the treatment is prophylactic or on-demand.

137. A method of preventing or inhibiting binding of a FVIII protein with endogenous VWF comprising adding an effective amount of the chimeric protein of any one of claims 1 to 26 and 45 to 119, the polynucleotide of claim 120 or 121, the vector of claim 122 or 123, the host cell of any one of claims 124 to 126, or the composition of any one of claims 127 to 136 to a subject in need thereof, wherein the VWF fragment binds to the FVIII protein and thus prevents or inhibits binding of endogenous VWF.

138. A method of extending or increasing half-life of a FVIII protein, wherein the method comprises adding an effective amount of the chimeric protein of any one of claims 1 to 26 and 45 to 119, the polynucleotide of claim 120 or 121, the vector of claim 122 or 123, the host cell of any one of claims 124 to 126, or the composition of any one of claims 127 to 136 to a subject in need thereof, wherein the VWF fragment binds to the FVIII protein and thus extends or increases half-life of the FVIII protein.

139. A method of preventing or inhibiting clearance of a FVIII protein from a cell, wherein the method comprises adding an effective amount of the chimeric protein of any one of claims 1 to 26 and 45 to 119, the polynucleotide of claim 120 or 121, the vector of claim 122 or 123, the host cell of any one of claims 124 to 126, or the composition of any one of claims 127 to 136 to a cell comprising a FVIII protein or a polynucleotide encoding the FVIII protein, wherein the protein having VWF activity binds to the FVIII protein.

140. The method of any one of claims 137 to 139, wherein the subject is an animal.

141. The method of claim 140, wherein the animal is a human.

142. The method of claim 140, wherein the subject is suffering from hemophilia A.

143. A method of treating a bleeding disease or disorder in a subject in need thereof comprising administering an effective amount of the chimeric protein of any one of claims 1 to 26 and 45 to 119, the polynucleotide of claim 120 or 121, the vector of claim

122 or 123, the host cell of any one of claims 124 to 126, or the composition of any one of claims 127 to 136, wherein the bleeding disease or disorder is selected from the group consisting of a bleeding coagulation disorder, hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, and bleeding in the illiopsoas sheath.

144. The method of claim 143, wherein the treatment is prophylactic or on-demand.

145. The method of claim 143 or 144, wherein the effective amount is 0.1 μg/kg to 500 mg/kg.

146. The method of any one of claims 143 to 145, wherein the chimeric protein of any one of claims 1 to 119, the polynucleotide of claim 120 or 121, the vector of claim 122 or 123, the host cell of any one of claims 124 to 126, or the composition of any one of claims 127 to 136 is administered by a route selected from the group consisting of topical administration, intraocular administration, parenteral administration, intrathecal administration, subdural administration and oral administration.

147. The method of claim 146, wherein the parenteral administration is selected from the group consisting of intravenous administration, subcutaneous administration, intramuscular administration, and intradermal administration,

148. A method of making a chimeric protein, comprising transfecting one or more host cell with the polynucleotide of claim 120 or 121 or the vector of claim 122 or 123 and expressing the chimeric protein in the host cell.

149. The chimeric protein of any one of claims 27-119, wherein the XTEN insertion site is immediately downstream of residue 745 corresponding to the mature FVIII protein (SEQ ID NO: 4).

150. The chimeric protein of any one of claims 27-119, where the XTEN insertion sites are immediately downstream of residue 1656 and residue 1900 of the FVIII protein.

151. The chimeric protein of any one of claims 27-119, wherein the XTEN insertion sites are immediately downstream of residues 26, 1656, and 1900 of the FVIII protein.

152. The chimeric protein of any one of claims 27-119, wherein the XTEN insertion sites are immediately downstream of residues 403 and 745 of the FVIII protein.

153. The chimeric protein of any one of claims 27-119, wherein the XTEN insertion sites are immediately downstream of residues 745 and 1900 of the FVIII protein.

154. The chimeric protein of any one of claims 27-119, wherein the XTEN insertion sites are immediately downstream of residues 18 and 745 of the FVIII protein.

155. The chimeric protein of any one of claims 149-154, wherein the FVIII protein is a dual chain FVIII isoform.

156. The chimeric protein of any one of claims 149-154, wherein the FVIII protein is a single chain FVIII isoform.

157. The chimeric protein of any one of claims 149-156, comprising one XTEN.

158. The chimeric protein of any one of claims 149-156, comprising two XTENs.

159. The chimeric protein of any one of claims 149-156, comprising three XTENS are inserted.

160. The chimeric protein of any one of claims 149-157, wherein the XTEN is SEQ ID NO: 39 (AE288).

161. The chimeric protein of any one of claims 149-156 and 158, wherein the XTENs are SEQ ID NOs: 38 and 37 (AG144 and AE144).

162. The chimeric protein of any one of claims 149-156, and 159 wherein the XTENs are SEQ ID NOs: 37, 38 and 37 (AE144, AG144, and AE144).

163. The chimeric protein of any one of claims 149-156 and 157, wherein the XTENs are SEQ ID NOs: 38 and 39(AE144 and AE288).

164. The host cell of claim 124, wherein the PC5 or PC7 cleaves the D1D2 domains of VWF.

165. The chimeric protein of any one of claims 1 to 27, which comprises at least two XTENs, at least three XTENs, at least four XTENs, at least five XTENs, or at least six XTENs.

CLAIMS

1. An invention not claimed in any divisional application.