WHAT IS CLAIMED IS:

1. A chimeric protein comprising a Factor VIII ("FVIII") protein and an adjunct moiety (AM), which are linked by a covalent bond, wherein the adjunct moiety inhibits or prevents endogenous VWF from binding to the FVIII protein.

2. The chimeric protein of claim 1, wherein the covalent bond prevents dissociation of the adjunct moiety from the FVIII protein in the presence of endogenous VWF.

3. The chimeric protein of claim 1 or 2, wherein the covalent bond is a peptide bond.

4. The chimeric protein of any one of claims 1 to 3, wherein the covalent bond is a disulfide bond.

5. The chimeric protein of any one of claims 1 to 4, wherein the covalent bond is a linker between the FVIII protein and the adjunct moiety.

6. The chimeric protein of any one of claims 1-5, wherein the adjunct moiety prevents the FVIII protein from being cleared through a VWF clearance pathway.

7. The chimeric protein of claim any one of claims 1 to 6, wherein the adjunct moiety inhibits or prevents endogenous VWF from binding to the FVIII protein by shielding or blocking a VWF binding site on the FVIII protein.

8. The chimeric protein of claim 7, 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.

9. The chimeric protein of claim 8, wherein the VWF binding site is the amino acid sequence corresponding to amino acids 1669 to 1689 and 2303 to 2332 of SEQ ID NO: 16.

10. The chimeric protein of any one of claims 1 to 9, wherein the chimeric protein does not comprise a FVIII half-life limiting factor.

11. The chimeric protein of claim 10, wherein the FVIII half-life limiting factor comprises a full-length VWF protein or a mature VWF protein.

12. The chimeric protein of any one of claims 1 to 11, wherein the half-life of the FVIII protein is extendable beyond the half-life limitation of the FVIII protein in the presence of endogenous VWF.

13. The chimeric protein of any one of claims 1 to 12, wherein the adjunct moiety has at least one VWF-like FVIII protecting property.

14. The chimeric protein of claim 13, wherein the VWF-like FVIII protecting property comprises protecting the FVIII protein from one or more protease cleavages, 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.

15. The chimeric protein of any one of claims 1 to 14, wherein the adjunct moiety comprises a polypeptide, a non-polypeptide moiety, or both.

16. The chimeric protein of claim 15, wherein the polypeptide comprises an amino acid sequence of at least about 40, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, at least about 110, at least about 120, at least about 130, at least about 140, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, or at least about 1000 amino acids in length.

17. The chimeric protein of any one of claims 1 to 16, wherein the adjunct moiety comprises a VWF fragment, an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, or any combinations thereof.

18. The chimeric protein of claim 17, wherein the non-polypeptide moiety comprises polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof, or any combinations thereof.

19. The chimeric protein of claim 17, wherein the adjunct moiety comprises a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the VWF fragment is associated with the FVIII protein by a non-covalent bond in addition to the covalent bond.

20. The chimeric protein of claim 17 or 19, wherein the VWF fragment is a monomer.

21. The chimeric protein of claim 19 or 20, wherein the VWF fragment comprises two, three, four, five, or six VWF fragments linked to one or more of each other.

22. The chimeric protein of any one of claims 1-21, wherein the VWF fragment comprises at least one heterologous moiety (H1) and an optional linker between the VWF fragment and the heterologous moiety (H1).

23. The chimeric protein of claim 22, wherein the at least one heterologous moiety (H1) linked to the VWF fragment comprises a polypeptide, a non-polypeptide moiety, or both.

24. The chimeric protein of claim 22 or 23, wherein the heterologous moiety (H1) comprises a moiety that extends the half-life of the FVIII protein.

25. The chimeric protein of claim 24, wherein the heterologous moiety (H1) comprises an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, or any combinations thereof.

26. The chimeric protein of claim 24, wherein the non-polypeptide moiety comprises polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof, or any combinations thereof.

27. The chimeric protein of claim 25, wherein the heterologous moiety (H1) comprises a first Fc region.

28. The chimeric protein of claim 24, wherein the heterologous moiety (H1) comprises an amino acid sequence comprising at least about 50 amino acids, at least about 100 amino acids, at least about 150 amino acids, at least about 200 amino acids, at least about 250 amino acids, at least about 300 amino acids, at least about 350 amino acids, at least about 400 amino acids, at least about 450 amino acids, at least about 500 amino acids, at least about 550 amino acids, at least about 600 amino acids, at least about 650 amino acids, at least about 700 amino acids, at least about 750 amino acids, at least about 800 amino acids, at least about 850 amino acids, at least about 900 amino acids, at least about 950 amino acids, or at least about 1000 amino acids.

29. The chimeric protein of claim 22, wherein the chimeric protein comprises a linker between the VWF fragment and the heterologous moiety (H1), which is a cleavable linker.

30. The chimeric protein of claim 29, wherein the cleavable linker comprises one or more cleavable site.

31. The chimeric protein of any one of claims 29 or 30 wherein the cleavable linker is capable of being 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.

32. The chimeric protein of claim 29, wherein the cleavable linker comprises TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 56).

33. The chimeric protein of any one of claims 29 to 32, wherein the cleavable linker comprises one or more cleavage sites comprising an amino acid sequence selected from the group consisting of RRRR (SEQ ID NO: 52), RKRRKR (SEQ ID NO: 53), RRRRS (SEQ ID NO: 54), TQSFNDFTR (SEQ ID NO: 47), SVSQTSKLTR (SEQ ID NO: 48), DFLAEGGGVR (SEQ ID NO: 49), TTKIKPR (SEQ ID NO: 50), LVPRG (SEQ ID NO: 55), ALRPRVVGGA (SEQ ID NO: 51), KLTRAET (SEQ ID NO: 29), DFTRVVG (SEQ ID NO: 30), TMTRIVGG (SEQ ID NO: 31), SPFRSTGG (SEQ ID NO: 32), LQVRIVGG (SEQ ID NO: 33), PLGRIVGG (SEQ ID NO: 34), IEGRTVGG (SEQ ID NO: 35), LTPRSLLV (SEQ ID NO: 36), LGPVSGVP (SEQ ID NO: 37), VAGDSLEE (SEQ ID NO: 38), GPAGLGGA (SEQ ID NO: 39), GPAGLRGA (SEQ ID NO: 40), APLGLRLR (SEQ ID NO: 41), PALPLVAQ (SEQ ID NO: 42), ENLYFQG (SEQ ID NO: 43), DDDKIVGG (SEQ ID NO: 44), LEVLFQGP (SEQ ID NO: 45), and LPKTGSES (SEQ ID NO: 46).

34. The chimeric protein of any one of claims 1 to 33, wherein the FVIII protein comprises FVIII and at least one heterologous moiety (H2).

35. The chimeric protein of claim 34, wherein the heterologous moiety (H2) is capable of extending the half-life of the FVIII protein.

36. The chimeric protein of claim 34 or 35, wherein the heterologous moiety (H2) comprises a polypeptide, a non-polypeptide moiety, or both.

37. The chimeric protein of claim 34 or 35, wherein the heterologous moiety (H2) comprises an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, or any combinations thereof.

38. The chimeric protein of claim 34 or 35, wherein the non-polypeptide moiety comprises polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof, or any combinations thereof.

39. The chimeric protein of claim 34, wherein the heterologous moiety (H2) comprises a second Fc region.

40. The chimeric protein of any one of claims 1 to 39, which comprises a first polypeptide chain comprising the VWF fragment, a first heterologous moiety, and a linker and a second polypeptide chain comprising the FVIII protein and a second heterologous moiety, wherein the first polypeptide chain and the second polypeptide chain are linked to each other by a covalent bond.

41. The chimeric protein of claim 40, wherein the first heterologous moiety and the second heterologous moiety are linked to each other by the covalent bond, wherein the covalent bond prevents replacement of the VWF fragment in the first polypeptide chain with endogenous VWF in vivo.

42. The chimeric protein of claim 41, wherein the covalent bond is a disulfide bond.

43. The chimeric protein of any one of claims 34 to 42, wherein the FVIII protein is linked to the second heterologous moiety (H2) by a linker

44. The chimeric protein of claim 43, wherein the linker between the FVIII protein and the second heterologous moiety is a cleavable linker.

45. The chimeric protein of claim 34 to 44, wherein the first heterologous moiety (H1) and the second heterologous moiety (H2) are linked by a linker.

46. The chimeric protein of claim 45, wherein the linker is a scFc linker.

47. The chimeric protein of claim 46, wherein the scFc linker is a processable linker.

48. The chimeric protein of claims 1-47 comprising a formula selected from the group consisting of:

(a) V-L1-H1-L3-C-L2-H2,

(b) H2-L2-C-L3-H1-L1-V,

(c) C-L2-H2-L3-V-L1-H1,

(d) H1-L1-V-L3-H2-L2-C,

(e) H1-L1-V-L3-C-L2-H2,

(f) H2-L2-C-L3-V-L1-H1,

(g) V-L1-H1-L3-H2-L2-C,

(h) C-L2-H2-L3-H1-L1-V,

(i) H2-L3-H1-L1-V-L2-C,

(j) C-L2-V-L1-H1-L3-H2,

(k) V-L2-C-L1-H1-L3-H2, and

(l) H2-L3-H1-L1-C-L2-V,

wherein V comprises a VWF fragment comprising the D' domain and the D3 domain of VWF;

L1 is an optional linker;

L2 is an optional linker;

L3 in (a) to (f) is an optional linker,

L3 in (g) to (l) is an optional scFc linker,

Each of H1 and H2 comprises an optional heterologous moiety;

C comprises a FVIII protein; and

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

49. The chimeric protein of claims 1-47 comprising a formula selected from the group consisting of:

(m) V-L1-H1: H2-L2-C,

(n) V-L1-H1:C-L2-H2;

(o) H1-L1-V:H2-L2-C;

(p) H1-L1-V:C-L2-H2;

(q) V:C-L1-H1:H2;

(r) V:H1-L1-C:H2;

(s) H2:H1-L1-C:V,

(t) C:V-L1-H1:H2, and

(u) C:H1-L1-V:H2,

wherein V is a VWF fragment comprising the D' domain and the D3 domain of VWF;

L1 is an optional linker;

L2 is an optional linker;

H1 is a first heterologous moiety;

H2 is a second heterologous moiety;

C is a FVIII protein;

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

(:) is a covalent bond between the H1 and the H2.

50. The chimeric protein of claim 48 and 49, wherein the VWF fragment and the FVIII protein are associated with each other by a non-covalent bond in addition to the covalent bond, the peptide bone, or the one or more amino acids

51. The chimeric protein of claim 48 and 49, wherein the VWF fragment inhibits or prevents binding of endogenous VWF to the FVIII protein.

52. The chimeric protein of any one of claims 49 to 51, wherein the covalent bond between the H1 and the H2 is a disulfide bond.

53. The chimeric protein of any one of claims 48 to 52, wherein H1 comprises a polypeptide, a non-polypeptide moiety, or both.

54. The chimeric protein of claim 53, wherein H1 comprises an immunoglobulin constant region or a portion thereof, albumin or fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, or any combinations thereof.

55. The chimeric protein of claim 53 or 54, wherein H1 comprises a first Fc region.

56. The chimeric protein of claim 53, wherein the non-polypeptide moiety comprises polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof, or any combinations thereof.

57. The chimeric protein of any one of claims 48 to 56, wherein H2 comprises a polypeptide, a non-polypeptide moiety, or both.

58. The chimeric protein of claim 57, wherein H2 comprises an immunoglobulin constant region or a portion thereof, albumin or fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, or any combination thereof.

59. The chimeric protein of any one of claims 48 to 58, wherein H2 comprises a second Fc region.

60. The chimeric protein of claim 59, wherein the non-polypeptide moiety comprises polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof, or any combinations thereof.

61. The chimeric protein of claim 60, wherein the covalent bond is a disulfide bond.

62. The chimeric protein of any one of claims 1 to 61, wherein the FVIII protein comprises a third heterologous moiety (H3).

63. The chimeric protein of any one of claims 1 to 62, wherein the FVIII protein comprises a fourth heterologous moiety (H4).

64. The chimeric protein of any one of claims 1 to 63, wherein the FVIII protein comprises a fifth heterologous moiety (H5).

65. The chimeric protein of any one of claims 1 to 64, wherein the FVIII protein comprises the sixth heterologous moiety (H6).

66. The chimeric protein of any one of claims 61 to 65, wherein one or more of the third heterologous moiety (H3), the fourth heterologous moiety (H4), the fifth heterologous moiety (H5), the sixth heterologous moiety (H6) are capable of extending the half-life of the FVIII protein.

67. The chimeric protein of any one of claims 1 to 66, wherein the third heterologous moiety (H3), the fourth heterologous moiety (H4), the fifth heterologous moiety (H5), and the sixth heterologous moiety (H6) are linked to the C terminus or N terminus of FVIII or inserted between two amino acids of FVIII.

68. The chimeric protein of any one of claims 1 to 67, wherein one or more of the third heterologous moiety (H3), the fourth heterologous moiety (H4), the fifth heterologous moiety (H5), or the sixth heterologous moiety (H6) comprises an amino acid sequence comprising at least about 50 amino acids, at least about 100 amino acids, at least about 150 amino acids, at least about 200 amino acids, at least about 250 amino acids, at least about 300 amino acids, at least about 350 amino acids, at least about 400 amino acids, at least about 450 amino acids, at least about 500 amino acids, at least about 550 amino acids, at least about 600 amino acids, at least about 650 amino acids, at least about 700 amino acids, at least about 750 amino acids, at least about 800 amino acids, at least about 850 amino acids, at least about 900 amino acids, at least about 950 amino acids, or at least about 1000 amino acids.

69. The chimeric protein of any one of claims 1 to 68, which 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 wild-type FVIII.

70. The chimeric protein of any one of claims 1 to 69, 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.

71. The chimeric protein of any one of claims 22 to 70, wherein the linker between the FVIII protein and the second heterologous moiety or the linker between the VWF fragment and the first heterologous moiety further comprises a first cleavage site (P1) at the N-terminal region of the linker, a second cleavage site (P2) at the C-terminal region of the linker, or both.

72. The chimeric protein of any one of claims 22 to 71, wherein the linker between the FVIII protein and the second heterologous moiety, the linker between the VWF fragment and the first heterologous moiety, or both comprises TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 56).

73. The chimeric protein of any one of claims 22 to 71 wherein the linker between the FVIII protein and the second heterologous moiety, the linker between the VWF fragment and the first heterologous moiety, or both are 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.

74. The chimeric protein of any one of claims 22 to 73, wherein the linker between the FVIII protein and the second heterologous moiety, the linker between the VWF fragment and the first heterologous moiety, or both comprise an amino acid sequence selected from the group consisting of RRRR (SEQ ID NO: 52), RKRRKR (SEQ ID NO: 53), RRRRS (SEQ ID NO: 54), TQSFNDFTR (SEQ ID NO: 47), SVSQTSKLTR (SEQ ID NO: 48), DFLAEGGGVR (SEQ ID NO: 49), TTKIKPR (SEQ ID NO: 50), LVPRG (SEQ ID NO: 55), ALRPRVVGGA (SEQ ID NO: 51), KLTRAET (SEQ ID NO: 29), DFTRVVG (SEQ ID NO: 30), TMTRIVGG (SEQ ID NO: 31), SPFRSTGG (SEQ ID NO: 32), LQVRIVGG (SEQ ID NO: 33), PLGRIVGG (SEQ ID NO: 34), IEGRTVGG (SEQ ID NO: 35), LTPRSLLV (SEQ ID NO: 36), LGPVSGVP (SEQ ID NO: 37), VAGDSLEE (SEQ ID NO: 38), GPAGLGGA (SEQ ID NO: 39), GPAGLRGA (SEQ ID NO: 40), APLGLRLR (SEQ ID NO: 41), PALPLVAQ (SEQ ID NO: 42), ENLYFQG (SEQ ID NO: 43), DDDKIVGG (SEQ ID NO: 44), LEVLFQGP (SEQ ID NO: 45), and LPKTGSES (SEQ ID NO: 46).

75. The chimeric protein of any one of claims 71 to 74, wherein the first enzymatic cleavage site and the second enzymatic cleavage site are identical or different.

76. The chimeric protein of any one of claims 5 to 75, wherein one or more of the linker between the FVIII protein and the adjunct moiety, the linker between the FVIII protein and the second heterologous moiety, and the linker between the VWF fragment and the first heterologous moiety have a length of about 1 to about 2000 amino acids.

77. The chimeric protein of any one of claims 5 to 75, wherein one or more of the linker between the FVIII protein and the adjunct moiety, the linker between the FVIII protein and the second heterologous moiety, and the linker between the VWF fragment and the

first heterologous moiety 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.

78. The chimeric protein of any one of claims 5 to 77, wherein one or more of the linker between the FVIII protein and the adjunct moiety, the linker between the FVIII protein and the second heterologous moiety, and the linker between the VWF fragment and the first heterologous moiety comprise a gly/ser peptide.

79. The chimeric protein of claim 78, wherein the gly/ser peptide has a formula of (Gly4Ser)n or S(Gly4Ser)n, wherein n is a positive integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, or 100.

80. The chimeric protein of claim 79, wherein the (Gly4Ser)n linker is (Gly4Ser)3 or (Gly4Scr)4.

81. The chimeric protein of any one of claims 5 to 80, wherein the linker between the FVIII protein and the adjunct moiety is a cleavable linker.

82. The chimeric protein of claim 81, wherein the cleavable linker comprises one or more thrombin cleavage sites.

83. The chimeric protein of claim 81 or 82, wherein the cleavable linker comprises TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 56).

84. The chimeric protein of any one of claims 81 to 83, wherein cleavable linker 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.

85. The chimeric protein of any one of claims 81 to 83, wherein the cleavable linker comprise an amino acid sequence selected from the group consisting of RRRR (SEQ ID NO: 52), RKRRKR (SEQ ID NO: 53), RRRRS (SEQ ID NO: 54), TQSFNDFTR (SEQ ID NO: 47), SVSQTSKLTR (SEQ ID NO: 48), DFLAEGGGVR (SEQ ID NO: 49), TTKIKPR (SEQ ID NO: 50), LVPRG (SEQ ID NO: 55), ALRPRVVGGA (SEQ ID NO: 51), KLTRAET (SEQ ID NO: 29), DFTRVVG (SEQ ID NO: 30), TMTRIVGG (SEQ ID NO: 31), SPFRSTGG (SEQ ID NO: 32), LQVRIVGG (SEQ ID NO: 33), PLGRIVGG (SEQ ID NO: 34), IEGRTVGG (SEQ ID NO: 35), LTPRSLLV (SEQ ID NO: 36), LGPVSGVP (SEQ ID NO: 37), VAGDSLEE (SEQ ID NO: 38), GPAGLGGA (SEQ ID NO: 39), GPAGLRGA (SEQ ID NO: 40), APLGLRLR (SEQ ID NO: 41), PALPLVAQ (SEQ ID NO: 42), ENLYFQG (SEQ ID NO: 43), DDDKIVGG (SEQ ID NO: 44), LEVLFQGP (SEQ ID NO: 45), and LPKTGSES (SEQ ID NO: 46).

86. The chimeric protein of any one of claims 5 to 85, wherein the linker between the FVIII protein and the adjunct moiety further comprises a sortase recognition motif.

87. The chimeric protein of claim 86, wherein the sortase recognition motif comprises the sequence of LPXTG (SEQ ID NO: 106 ).

88. The chimeric protein of any one of claims 19 to 87, wherein the VWF fragment comprises the D' domain and the D3 domain of VWF.

89. The chimeric protein of claim 88, wherein the VWF fragment inhibits or prevents binding of endogenous VWF to a FVIII protein.

90. The chimeric protein of claim 88 or 89, wherein the amino acid sequence of the D' domain of the VWF fragment 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 88 to 90, wherein the amino acid sequence of the D3 domain of the VWF fragment 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 88 to 91, 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.

93. The chimeric protein of any one of claims 88 to 91, wherein in the sequence of the VWF fragment, an amino acid other than cysteine is substituted for a residue corresponding to residue 1099, residue 1142, or both residues 1099 and 1142 of SEQ ID NO: 2.

94. The chimeric protein of any one of claims 88 to 93, wherein the sequence of the VWF fragment comprises amino acids 764 to 1240 of SEQ ID NO: 2.

95. The chimeric protein of any one of claims 88 to 94, wherein the VWF fragment further comprises the D1 domain, the D2 domain, or the D1 and D2 domains of VWF.

96. The chimeric protein of any one of claims 88 to 95, 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.

97. The chimeric protein of any one of claims 88 to 95, 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.

98. The chimeric protein of any one of claims 88 to 97, further comprising a signal peptide of VWF, which is operably linked thereto.

99. The chimeric protein of any one of claims 19 to 98, wherein the VWF fragment is pegylated, glycosylated, hesylated, or polysialylated.

100. The chimeric protein of any one of claims 1 to 99, wherein the FVIII protein comprises one or more domains of FVIII selected from the group consisting of the A1

domain, the A2 domain, the B domain, the A3 domain, the C1 domain, the C2 domain, one or more fragment thereof, and any combinations thereof.

101. The chimeric protein of claim 100, wherein the FVIII protein comprises the A1 domain, the A2 domain, the A3 domain, and the C1 domain, and the optional C2 domain.

102. The chimeric protein of claim 100 or 101, wherein the FVIII protein comprises the B domain or a portion thereof.

103. The chimeric protein of any one of claims 100 to 102, which comprises an amino acid sequence at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 16 or SEQ ID NO: 18.

104. The chimeric protein of any one of claims 100 to 103, wherein the FVIII protein is SQ B domain deleted FVIII.

105. The chimeric protein of any one of claims 100 to 104, wherein the FVIII protein comprises single chain FVIII.

106. The chimeric protein of claim 105, 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: 16) or residue 754, residue 751, or both of SQ BDD Factor VIII (SEQ ID NO: 18).

107. The chimeric protein of claim 106, wherein the amino acid substitution is an amino acid other than Arginine.

108. The chimeric protein of any one of claims 1 to 107, wherein the FVIII protein comprises a first chain and a second chain, the first chain comprises a heavy chain of FVIII and the second chain comprises a light chain of Factor VIII, wherein the heavy chain and the light chain are associated with a metal bond.

109. A polynucleotide encoding the chimeric protein of any one of claims 1 to 108.

110. The polynucleotide of claim 110, further comprising an additional polynucleotide sequence, which encodes PC5, PC7, or furin.

111. The polynucleotide of claim 109 or 110, further comprising an additional polynucleotide sequence, which encodes a D1 domain and D2 domain of VWF.

112. A vector or vectors comprising the polynucleotide of any one of claims 109 to 111 and one or more promoter operably linked to the polynucleotide or the set of polynucleotides.

113. The vector or vectors of claim 112, further comprising an additional vector, which comprises a second polynucleotide chain encoding PC5, PC7, or furin.

114. The vector or vectors of claim 112 or 113, further comprising an additional vector, which comprises a polynucleotide sequence encoding a D1 domain and a D2 domain of VWF.

115. A host cell comprising the polynucleotide of any one of claims 109 to 111 or the vector of any one of claims 112 to 114.

116. The host cell of claim 115 comprising an additional vector encoding PC5, PC7, or furin.

117. The host cell of claim 115 or 116, further comprising an additional vector, which comprises a polynucleotide sequence encoding a D1 domain and a D2 domain of VWF.

118. The host cell of claim 115 or 118, which is a mammalian cell.

119. The host cell of claim 118, wherein the mammalian cell is selected from the group consisting of HEK293 cell, CHO cell, and BHK cell.

120. A pharmaceutical composition comprising the chimeric protein of any one of claims 1 to 108, the polynucleotide of claim 109 or 111, the vector of claim 112 or 114, or the host cell of any one of claims 115 and 118 and a pharmaceutically acceptable carrier.

121. The composition of any one of claims 120, wherein the half-life of the FVIII protein of the chimeric protein is extended in FVIII/VWF double knock out ("DKO") mice compared to the half-life of the FVIII protein of the chimeric protein without the VWF fragment.

122. The composition of claim 120 or 121, which the half-life of 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, at least about 12 times, at least 20 times, at least 30 times, or at least 40 times longer than wild type FVIII.

123. The composition of claim 120 or 122, wherein the half-life of Factor VIII is at least 6 hours, at least 7 hours at least 9 hours, at least 10 hours, at least 11 hours, at least 12 hours, at least 15 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 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.

124. The composition of any one of claims 120 to 123, 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.

125. The composition of claim 124, wherein the parenteral administration is intravenous or subcutaneous administration.

126. The composition of any one of claims 120 to 125, which is used to treat a bleeding disease or condition in a subject in need thereof.

127. The composition of claim 126, 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 illiopsoas sheath and any combinations thereof.

128. The composition of claim 126 or 127, wherein the subject is scheduled to undergo a surgery.

129. The composition of any one of claims 126 or 127, wherein the treatment is prophylactic or episodic.

130. A method of preventing or inhibiting interaction of a FVIII protein with endogenous VWF comprising adding to a subject in need thereof an effective amount of the chimeric protein of any one of claims 1 to 108, the polynucleotide of any one of claims 109 to 111, the vector of any one of claims 112 to 114, the host cell of any one of claims 115 to 119, or the composition of any one of claims 120 to 129, wherein the VWF fragment inhibits or prevents interaction of the FVIII protein with endogenous VWF.

131. A method of removing or reducing a half-life limiting factor of a FVIII protein, wherein the method comprises adding an effective amount of the chimeric protein of any one of claims 1 to 108, the polynucleotide of any one of claims 109 to 111, the vector of any one of claims 112 to 114, the host cell of any one of claims 115 to 119, or the composition of any one of claims 120 to 129, wherein the chimeric protein or the chimeric protein encoded by the polynucleotide, the vector, or expressed by the host cell prevents or inhibits interaction of the FVIII protein with endogenous VWF.

132. A method of extending or increasing the 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 108, the polynucleotide of any one of claims 109 to 111, the vector of any one of claims 112 to 114, the host cell of any one of claims 115 to 119, or the composition of any one of claims 120 to 129, wherein the VWF fragment of the chimeric protein prevents or inhibits interaction of the FVIII protein with endogenous VWF.

133. The method of claim 132, 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 about4 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 about10 times, at least about 11 times, or at least about 12 times longer than wild-type FVIII.

134. The method of claim 133, 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 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.

135. A method of treating a bleeding disease or condition in a subject in need thereof comprising administering an effective amount of the chimeric protein of any one of claims 1 to 108, the polynucleotide of any one of claims 109 to 111, the vector of any one of claims 112 to 114, the host cell of any one of claims 115 to 119, or the composition of any one of claims 120 to 129, 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, bleeding in the illiopsoas sheath, and any combinations thereof.

136. The method of claim 135, wherein the treatment is prophylactic or on demand (episodic).

137. The method of any one of claims 130 to 136, wherein the effective amount is 0.1 μg/kg to 500 mg/kg.

138. The method of any one of claims 130 to 137, wherein the chimeric protein, the polynucleotide, the host cell, or the composition is administered by a route selected from the group consisting of topical administration, intraocular administration, parenteral administration, intrathecal administration, subdural administration and oral administration.

139. The method of claim 138, wherein the parenteral administration is selected from the group consisting of intravenous administration, subcutaneous administration, intramuscular administration, and intradermal administration,

140. The method of any one of claims 130 to 139, wherein the subject is a human.

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

142. A method of making a chimeric protein, comprising transfecting one or more host cell with the polynucleotide of any one of claims 109 to 111 or the vector of any one of claims 112 to 114, and expressing the VWF fragment or the chimeric protein in the host cell.

143. The method of claim 142, wherein the vector further comprises a polynucleotide encoding a processing enzyme.

144. The method of claim 143, wherein the processing enzyme is PACE.

145. The method of claim 144, wherein PACE cleaves the D1D2 domains of the VWF fragment.

146. The method of claim 142 and 143, wherein further comprising transfecting one or more host cell with a polynucleotide sequence expressing a D1 domain and a D2 domain of VWF.

147. A method of constructing the chimeric protein of any one of claims 1 to 108 comprising ligating the adjunct moiety with the FVIII protein by a covalent bond in the presence of a sortase enzyme.

CLAIMS

1. A chimeric protein comprising a Factor VIII (FVIII) protein and an adjunct moiety (AM), which are linked by a covalent bond, wherein the adjunct moiety inhibits or prevents endogenous VWF from binding to the FVIII protein.

2. The chimeric protein of claim 1, wherein the covalent bond prevents dissociation of the adjunct moiety from the FVIII protein in the presence of endogenous VWF.

3. The chimeric protein of claim 1 or claim 2, wherein the adjunct moiety prevents the FVIII protein from being cleared through a VWF clearance pathway or wherein the adjunct moiety inhibits or prevents endogenous VWF from binding to the FVIII protein by shielding or blocking a VWF binding site on the FVIII protein.

4. The chimeric protein of any one of claims 1 to 3, wherein the adjunct moiety comprises a polypeptide, a non-polypeptide moiety or both.

5. The chimeric protein of any one of claims 1 to 4, wherein the adjunct moiety comprises a VWF fragment, an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof or any combination thereof.

6. The chimeric protein of any one of claims 1 to 4, wherein the adjunct moiety comprises a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the VWF fragment is associated with the FVIII protein by a non-covalent bond in addition to the covalent bond.

7. The chimeric protein of claim 5 or claim 6, wherein the VWF fragment comprises a monomer or two, three, four, five or six monomers linked to one or more of each other.

8. The chimeric protein of claim 6 or claim 7, wherein the VWF fragment comprises at least one first heterologous moiety (H1) and an optional linker between the VWF fragment and the heterologous moiety (H1).

9. The chimeric protein of claim 8, wherein the heterologous moiety (H1) comprises a moiety that extends the half-life of the FVIII protein.

10. The chimeric protein of claim 9, wherein the heterologous moiety (H1) comprises an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof or any combination thereof.

11. The chimeric protein of claim 10, wherein the heterologous moiety (H1) comprises a first Fc region.

12. The chimeric protein of any one of claims 8 to 11, wherein the chimeric protein comprises a linker between the VWF fragment and the heterologous moiety (H1), said linker being cleavable.

13. The chimeric protein of any one of claims 1 to 12, wherein the FVIII protein comprises FVIII and at least one second heterologous moiety (H2).

14. The chimeric protein of claim 13, wherein the heterologous moiety (H2) is capable of extending the half-life of the FVIII protein.

15. The chimeric protein of claim 13 or claim 14, wherein the heterologous moiety (H2) comprises an immunoglobulin constant region or a portion thereof, albumin or a fragment thereof, an albumin binding moiety, a PAS sequence, a HAP sequence, transferrin or a fragment thereof, polyethylene glycol (PEG), polysialic acid, hydroxyethyl starch (HES), a derivative thereof or any combination thereof.

16. The chimeric protein of claim 13, wherein the heterologous moiety (H2) comprises a second Fc region.

17. The chimeric protein of any one of claims 13 to 16, wherein the FVIII protein is linked to the heterologous moiety (H2) by a linker.

18. The chimeric protein of claim 17, wherein the linker between the FVIII protein and the heterologous moiety (H2) is a cleavable linker.

19. The chimeric protein of any one of claims 13 to 18, wherein the first heterologous moiety (H1) and the second heterologous moiety (H2) are linked by a linker.

20. The chimeric protein of claim 19, wherein the linker is a scFc linker.

21. The chimeric protein of any one of claims 6 to 20, wherein the amino acid sequence of the D' domain of the VWF fragment is at least 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to amino acids 764 to 866 of SEQ ID NO: 2.

22. The chimeric protein of any one of claims 6 to 21, wherein the amino acid sequence of the D3 domain of the VWF fragment is at least 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to amino acids 867 to 1240 of SEQ ID NO: 2.

23. The chimeric protein of any one of claims 6 to 22, 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.

24. The chimeric protein of any one of claims 6 to 22, wherein in the sequence of the VWF fragment an amino acid other than cysteine is substituted for a residue corresponding to residue 1099, residue 1142 or both residues 1099 and 1142 of SEQ ID NO: 2.

25. The chimeric protein of any one of claims 6 to 22, wherein the sequence of the VWF fragment comprises amino acids 764 to 1240 of SEQ ID NO: 2.

26. The chimeric protein of any one of claims 6 to 25, wherein the VWF fragment further comprises the D1 domain, the D2 domain or the D1 and D2 domains of VWF.

27. The chimeric protein of any one of claims 6 to 26, wherein the VWF fragment is PEGylated, glycosylated, HESylated or polysialylated.

28. The chimeric protein of any one of claims 1 to 27, wherein the FVIII protein lacks the entire B domain or a portion thereof.

29. The chimeric protein of claim 28, which comprises an amino acid sequence at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 16 or SEQ ID NO: 18.

30. The chimeric protein of claim 28 or claim 29, wherein the FVIII protein is an SQ B domain deleted FVIII.

31. The chimeric protein of any one of claims 28 to 30, wherein the FVIII protein comprises a single chain FVIII.

32. The chimeric protein of any one of claims 1 to 30, wherein the FVIII protein comprises a first chain and a second chain, the first chain comprises a heavy chain of FVIII and the second chain comprises a light chain of FVIII, wherein the heavy chain and the light chain are associated with a metal bond.

33. A polynucleotide encoding the chimeric protein of any one of claims 1 to 32.

34. A vector comprising the polynucleotide of claim 33 and one or more promoters operably linked to the polynucleotide.

35. A host cell comprising the polynucleotide of claim 33 or the vector of claim 34.

36. The host cell of claim 35, which is a mammalian cell selected from the group consisting of HEK293 cell, CHO cell and BHK cell.

37. A pharmaceutical composition comprising the chimeric protein of any one of claims 1 to 32, the polynucleotide of claim 33, the vector of claim 34 or the host cell of claim 35 or claim 36 and a pharmaceutically acceptable carrier.

38. A method of making a chimeric protein, said method comprising transfecting one or more host cells with the polynucleotide of claim 33 or the vector of claim 34, and expressing the chimeric protein in the host cell.