Claims

1. A covalently linked complex comprising von Willebrand factor or variants thereof (VWF) and Factor VIII or variants thereof (Factor VIII), which complex comprises a half-life extending moiety, with the proviso that it is not a heterodimeric Fc fusion with one Fc monomer linked to VWF and the other Fc monomer linked to Factor VIII, wherein the covalent link is not provided by the half-life extending moiety.

~~2. The covalently linked complex of claim 1, wherein the covalent link is not provided by the half-life extending moiety.~~

~~3~~2. The covalently linked complex of claim 1 ~~or claim 2~~, wherein Factor VIII is modified so that it forms a disulphide bridge with VWF.

~~4~~3. The covalent complex of claim ~~3~~ 2, wherein Factor VIII is modified by substitution of a naturally occurring amino acid with a cysteine residue or the insertion of a cysteine residue which forms a disulphide bridge with a cysteine residue in VWF.

~~5~~4. The complex of claim ~~4~~ 3, wherein the naturally occurring amino acid that is substituted in Factor VIII is selected from an amino acid in the Factor VIII a3 domain.

~~6~~5. The complex of claim ~~4~~ 3 or claim ~~5~~ 4, wherein the naturally occurring amino acid that is substituted in Factor VIII is located within amino acids 1653 to 1660 or within amino acids 1667 to 1674 or within amino acids 1675 to 1688 of the FVIII a3 domain or a cysteine is introduced into the sequence of amino

acids 1653 to 1660 or amino acids 1667 to 1674 or amino acids 1675 to 1688 of the FVIII a3 domain.

~~7~~6. The complex of claim ~~3~~ 2, wherein the naturally occurring amino acid that is substituted in Factor VIII is in the C-terminal domain.

~~8~~7. The complex of any of claims 1 to ~~7~~ 6, wherein VWF is modified by substitution of a naturally occurring amino acid with a cysteine residue or the insertion of a cysteine residue which forms a disulphide bridge with a cysteine residue introduced into Factor VIII.

~~9~~8. The complex of claim ~~8~~ 7, wherein the naturally occurring amino acid in VWF is an amino acid in the D' or D3 domain, or wherein the insertion of a cysteine residue is in the D' or D3 domain.

~~10~~9. The complex of claim ~~8~~ 7 or claim ~~9~~ 8, wherein a cysteine residue is inserted into the TIL´domain, the E´ domain, the D3 domain, the C8-3 domain, the TIL-3 domain or the E-3 domain or the naturally occurring amino acid in VWF that is substituted with a cysteine residue is a residue in the TIL´domain, the E´ domain, the D3 domain, the C8-3 domain, the TIL-3 domain or the E-3 domain.

~~11~~10. The complex of any of claims 1 to ~~10~~ 9, wherein the VWF comprises or consists of the FVIII binding domain.

~~12~~11. The complex of any previous claim, wherein Factor VIII is modified to comprise one or more domains of VWF.

~~13~~12. The complex of claim ~~12~~ 11, wherein Factor VIII is modified to comprise the C-terminal domain CK of VWF.

~~14~~13. The complex of claim ~~13~~ 12, wherein the Factor VIII is modified to also comprise VWF domains C6, or C5 and C6, C3 to C6, or any one or more of domains C1 to C6, or variants thereof.

~~15~~14. The complex of any of claims ~~12~~ 11 to ~~14~~ 13, wherein the Factor VIII comprises residues 2724 to 2812 of SEQ ID NO: 2 or a variant thereof, provided that cysteine residue 2773 (or equivalent thereof) is preserved.

~~16~~15. The complex of any of claims ~~13~~ 12 to ~~15~~ 14, wherein the C-terminal VWF domain is attached to Factor VIII by a cleavable linker.

~~17~~16. The complex of claim ~~16~~ 15, wherein the cleavable linker comprises one of the thrombin cleavage sites of Factor VIII.

~~18~~17. The complex of claim ~~16~~ 15 or claim ~~17~~ 16, wherein the linker sequence comprises additional amino acid residues providing a peptide of sufficient length to permit the intramolecular interaction of Factor VIII and VWF via the a3 and D´D3 domains, respectively.

~~19~~18. The complex of any of claims ~~12~~ 11 to ~~18~~ 17, wherein the Factor VIII is modified at its C-terminus or at its N-terminus, or within the B-domain of Factor VIII, or partially or completely replacing, the B-domain of Factor VIII.

~~20~~19. The complex of claim ~~12~~ 11 or claim ~~19~~ 18, wherein Factor VIII is modified to comprise the D´D3 domain of VWF or fragments thereof.

~~21~~20. The complex of claim ~~20~~ 19, wherein the Factor VIII is modified by replacing its B domain partially or completely by the VWF D´D3 domain or fragments or variants thereof.

~~22~~21. The complex of claim ~~21~~ 20, wherein the Factor VIII comprises within its B domain or instead of its B domain or instead of part of its B domain residues 746 to 1241 of SEQ ID NO: 2 or variants or fragments thereof.

~~23~~22. The complex of any of claims ~~19~~ 18 to ~~21~~ 20, wherein the Factor VIII is expressed as a two-chain molecule with the VWF D´D3 domain representing the aminoterminus of the Factor VIII light chain.

~~24~~23. The complex of any of claims ~~19~~ 18 to ~~22~~ 21, wherein an additional linker sequence is introduced between the D´D3 region of VWF and the Factor VIII light chain domains.

~~25~~24. The complex of any previous claim, wherein the Factor VIII is a genetically engineered Factor VIII.

~~26~~25. The complex of claim ~~25~~ 24, wherein the engineered Factor VIII has full or partial B-domain deletion, is a mutated Factor VIII, or a fusion polypeptide with a half-life extending moiety.

~~27~~26. The complex of any previous claim, wherein the VWF is a half-life extended form of VWF.

~~28~~27. The complex of claim ~~26~~ 25, wherein the half-life extended form of VWF is a genetically engineered fusion protein of VWF with a half-life extending moiety.

~~29~~28. The complex of any of claims ~~26~~ 25 to ~~29~~ 27, wherein the half-life extending moiety is selected from albumin or variants or fragments thereof, immunoglobulin constant region and portions and variants thereof, e.g. the Fc fragment or variants thereof, solvated random chains with large hydrodynamic volume (for example XTEN or PAS), afamin or variants thereof, alpha-fetoprotein or variants thereof, Vitamin D binding protein or variants thereof, transferrin or

variants thereof, carboxyl-terminal peptide (CTP) of human chorionic gonadotropin-ß subunit, polypeptides or lipids capable of binding under physiological conditions to albumin or immunoglobulin constant regions.

~~30~~29. The complex of any of claim~~s~~ 1~~, 2~~ or ~~27~~ 26, wherein the plasma half-life of VWF is extended by chemical modification, e.g. attachment of polyethylene glycol (PEGylation), glycosylated PEG, hydroxyl ethyl starch (HESylation), polysialic acids, heparosan polymers, elastin-like polypeptides or hyaluronic acid.

~~31~~30. The complex of any of claims 1 to ~~30~~ 29, wherein the VWF is expressed as a monomer or wherein the VWF is expressed as a dimer.

~~32~~31. The complex of any of claims 1 to ~~30~~ 29, wherein the VWF forms a multimer.

~~33~~32. The complex of claim 1 or claim ~~30~~ 29, wherein the covalent link is obtained by use of one or more chemically synthetized cross-linkers.

~~34~~33. A complex according to any previous claim, characterized in that the Factor VIII and VWF are connected by more than one covalent disulfide bond or peptide or proteinaceous linker.

~~35~~34. A method of producing the covalent complex of Factor VIII and VWF of any of claims 1 to ~~32~~ 31 or claim ~~34~~ 33, comprising co-expressing the Factor VIII and VWF in a eukaryotic cell line.

~~36~~35. A covalent complex of any of claims 1 to ~~34~~ 33 for use in the treatment or prophylaxis of a bleeding disorder.

~~37~~36. The complex of claim ~~36~~ 35, wherein the bleeding disorder is hemophilia A or von Willebrand disease.

~~38~~37. A pharmaceutical composition comprising the complex of any of claims 1 to ~~34~~ 33.

38. Use of the covalent complex of any of claims 1 to 33 in the preparation of a medicament in the treatment or prophylaxis of a bleeding disorder.

39. The use of claim 38, wherein the bleeding disorder is hemophilia A or von Willebrand disease.