useful for the detection and purification of human FVIII and/or FVIII-like polypeptides from solutions such as blood or conditioned media.

In US Pat. No. 7,033,590 FIX/FIXa activating antibodies and antibody derivatives are used for increasing the amidolytic activity of FIXa, and for treating blood coagulation disorders such as hemophilia A and hemorrhagic diathesis.

In US Pat. No. 7,084,109 FVIIa antagonists are disclosed. These antagonists are peptides that inhibit FVIIa activity and are said to be useful for prevention of arterial thrombosis in combination with thrombolytic therapy.

The listing or discussion of a prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

There remains a great need in the art for a low molecular weight peptide with procoagulant activity for treatment of patients with hemophilia A (FVIII deficiency). The present invention provides novel low molecular weight peptides with procoagulant activity which can be used for the non-intravenous treatment of hemophilia A. The present prevention also provides these novel peptides for the treatment of a deficiency in FV, FVII, FX and/or FXI.

SUMMARY OF THE INVENTION

One aspect of the invention provides a peptide or peptide derivative comprising:
(i) WDLYFEIVW (SEQ ID NO: 1); or
(ii) a variant amino acid sequence comprising one, two, three or four L-amino acid substitutions in WDLYFEIVW (SEQ ID NO: 1 ); or
(Hi) the retro-inverso variant of the peptide or peptide derivative of either one of parts (i) and (ii),
wherein said peptide or peptide derivative has procoagulant activity.

For the avoidance of doubt, the sequence WDLYFEIVW (SEQ ID NO: 1 ) may be represented as the L-amino acids Trp-Asp-Leu-Tyr-Phe-Glu-Ile-Val-Trp using the three letter code for amino acids. The retro-inverso variant of WDLYFEIVW (SEQ ID NO: 1 ) is wviefyldw and comprises D-amino acids.

Another aspect of the invention provides a peptide or peptide derivative comprising:
(i) an amino acid sequence comprising imfwydcye; or
(ii) a variant amino acid sequence comprising one, two, three, four, five or six amino acid substitutions in imfwydcye,
wherein said peptide or peptide derivative has procoagulant activity.

For the avoidance of doubt, the sequence cimfwydcye may be represented as D-amino acids ile-met-phe-trp-tyr-asp-cys-tyr-glu using the three letter code for amino acids.

Another aspect of the invention provides a dual peptide comprising a peptide or peptide derivative of the first or second aspects of the invention conjugated to a further peptide or peptide derivative of the first or second aspects of the invention, wherein the two peptides/derivatives may be the same as or different from each other and wherein the dual peptide has procoagul ant activity.

Another aspect of the invention provides a pharmaceutical composition comprising the peptide or peptide derivative of the first or second aspects of the invention or the dual peptide of the third aspect of the invention.

Another aspect of the invention provides a peptide or peptide derivative of the first or second aspects or a dual peptide of the third aspect of the invention for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

Another aspect of the invention provides a use of a peptide or peptide derivative of the first or second aspects or a dual peptide of the third aspect of the invention in the manufacture of a medicament for the treatment of a deficiency in FV, FVII, FVIII, FX and/or FXI in a patient.

Another aspect of the invention provides a method of treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI comprising administering a therapeutically effective amount of the pharmaceutical composition of the fourth aspect.

Another aspect of the invention provides a peptide or peptide derivative which has procoagulant activity, wherein the peptide or peptide derivative is not FVIII or a fragment thereof and, wherein the procoagulant activity is a thrombin generation time of 25, 50 or 100 µM of peptide, peptide derivative or dual peptide equivalent to that of at least 100 mU/mL Factor Eight Inhibitor Bypassing Activity (FEIBA), preferably at least 300 mU/mL FEIBA, more preferably at least 900 mU/mL FEIBA, most preferably at least 1200 mU/mL FEIBA in the Defined Intrinsic Thrombin Generation Assay.

Another aspect of the invention provides a peptide or peptide derivative which has procoagulant activity, wherein the peptide or peptide derivative is not FVIII or a fragment thereof and, wherein the procoagulant activity is a thrombin generation time of 25, 50 or 100 µM of peptide, peptide derivative or dual peptide in a Defined Intrinsic Thrombin Generation Assay peaking within 30 minutes, preferably within 15 minutes and most preferably within 10 minutes.

Another aspect of the invention provides a peptide or peptide derivative which has procoagulant activity, wherein the peptide or peptide derivative is not FVIII or a fragment thereof and, wherein the peptide or peptide derivative can at least partially compensate for the absence of biologically active FVIII when administered in an animal model of severe human hemophilia A.

One aspect of the invention provides use of a therapeutically effective amount of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

DESCRIPTION OF FIGURES

Figure 1: Effect of therapeutics approved for treatment of hemophilia on peak thrombin generation and thrombin peak time in a defined Dual-pathway thrombin generation assay

Figure 2: Effect of A01 on FVIII -/- mouse bleeding model - blood loss

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

The term "amino acid" within the scope of the present invention is intended to include all naturally occurring L α-amino acids. The one and three letter abbreviations for naturally occurring amino acids are used herein (Lehninger, Biochemistry, 2d ed., Worth Publishers, New York, 1995: 71-92). The term

38. The pharmaceutical composition of Claim 36 suitable for intravenous administration.

39. The peptide or peptide derivative of Claim 1 for use in medicine.

40. The peptide or peptide derivative of Claim 10 for use in medicine.

41. The peptide or peptide derivative of Claim 1 for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

42. The peptide or peptide derivative of Claim 10 for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

43. Use of a peptide or peptide derivative of Claim 1 in the manufacture of a medicament for the treatment of a deficiency in FV, FVII, FVIII, FX and/or FXI.

44. Use of a peptide or peptide derivative of Claim 10 in the manufacture of a medicament for the treatment of a deficiency in FV, FVII, FVIII, FX and/or FXI.

45. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 33, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

46. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 34, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

47. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 35, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

48. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 36, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

49. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 37, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

50. Use of a therapeutically effective amount of the pharmaceutical composition of Claim 38, in the manufacture of a medicament for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

51. The peptide or peptide derivative of Claim 41 , wherein the patient has inhibitor antibodies against FV, FVII, FVIII, FX and/or FXI.

52. The use of Claim 43, wherein the patient has inhibitor antibodies against FV, FVII, FVIII, FX and/or FXI.

53. The method of Claim 45, wherein the patient has inhibitor antibodies against FV, FVII, FVIII, FX and/or FXI.

54. A method of making the peptide or peptide derivative of Claim 1 by solid phase synthesis.

55. A method of making the peptide or peptide derivative of Claim 10 by solid phase synthesis.

56. A peptide or peptide derivative which has procoagulant activity, wherein the peptide or peptide derivative is not FVIII or a fragment thereof and, wherein the procoagulant activity is a thrombin generation time of 25, 50 or 100 μM of peptide, peptide derivative or dual peptide equivalent to that of at least 100 mU/mL Factor Eight Inhibitor Bypassing Activity (FEIBA), preferably at least 300 mll/mL FEIBA, more preferably at least 900 mU/mL FEIBA, most preferably at least 1200 mU/mL FEIBA in the Defined Intrinsic Thrombin Generation Assay.

57. A peptide or peptide derivative which has procoagulant activity, wherein the peptide or peptide derivative is not FVIII or a fragment thereof and, wherein the procoagulant activity is a thrombin generation time of 25, 50 or 100 μM of peptide, peptide derivative or dual peptide in a Defined Intrinsic Thrombin