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~~DISCLOSURE

A first aspect of the ~~invention~~disclosure 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

(iii) 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.

A second aspect of the ~~invention~~disclosure 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.

In another aspect, there is provided a peptide or peptide derivative comprising:

(i) WDLYFEIVW (SEQ ID NO: 322); or

(ii) a variant amino acid sequence comprising one, two, three or four L-amino acid substitutions in WDLYFEIVW (SEQ ID NO: 322), said variant amino acid sequence comprising $X_1X_2X_3YX_4EX_5X_6X_7$, wherein X_1 is W, L or P, X_2 is D or S, X_3 is L or F, X_4 is F, Phg, L, Ebw, Pff, Thi, 1Ni, Hfe, Ece or Cha, X_5 is I or F, X_6 is S, V or G and X_7 is W or L (SEQ ID NO:323); or

(iii) 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 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.

A third aspect of the ~~invention~~disclosure provides a dual peptide comprising a peptide or peptide derivative as disclosed herein~~of the first or second aspects of the invention~~ conjugated to a further peptide or peptide derivative as disclosed herein~~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 procoagulant activity.

A fourth aspect of the ~~invention~~disclosure provides a pharmaceutical composition comprising the peptide or peptide derivative as disclosed herein~~of the first or second aspects of the invention~~ or the dual peptide of the third aspect of the ~~invention~~disclosure.

A fifth aspect of the ~~invention~~disclosure provides a peptide or peptide derivative as disclosed herein~~of the first or second aspects~~ or a dual peptide of the third aspect of the ~~invention~~disclosure for treating a patient having a deficiency in FV, FVII, FVIII, FX and/or FXI.

A sixth aspect of the ~~invention~~disclosure provides a use of a peptide or peptide derivative as disclosed herein~~of the first or second aspects~~ or a dual peptide of the third aspect of the ~~invention~~disclosure in the manufacture of a medicament for the treatment of a deficiency in FV, FVII, FVIII, FX and/or FXI in a patient.

A seventh aspect of the ~~invention~~disclosure 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.

An eighth aspect of the ~~invention~~disclosure 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.

A ninth aspect of the ~~invention~~disclosure 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.

A tenth aspect of the ~~invention~~disclosure 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.

In another aspect, there is provided a method of making the peptide or peptide derivative as disclosed herein by solid phase synthesis.

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