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(54) Title: FVIIl-INDEPENDENT FIX-MUTANT PROTEINS FOR HEMOPHILIA A TREATMENT

(57) **Abstract:** The present invention relates to recombinant blood coagulation factor IX (rFIX) mutants having factor VIII (FVIII) independent factor X (FX) activation potential. Five full length FIX proteins with combinations of mutations of amino acids important for functional activity of FIX and FIX wild type were cloned and expressed in HEK 293 cells. The proteins were tested by an activated partial thromboplastin time (aPTT) assay in FVIII-depleted plasma as well as in FVIII-inhibited patient plasma. In FVIII-depleted plasma functional activity of the FIX mutants was calculated as increased FVIII equivalent activity. The mutant proteins had increased FVIII equivalent activity. In FVIII-inhibited patient plasma the FEIBA equivalent activity was calculated for analysis of FVIII independent FX activation potential. The proteins had also increased FEIBA equivalent activity. Furthermore, the pre-activated FIX proteins had an increased activity in FIX-depleted plasma containing FVIII inhibitors. Therefore these FIX mutants are alternatives as bypassing agents for treatment of FVIII inhibitor patients.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N9/64 A61K38/36

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B. RELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOLKMAN JOOST A ET AL: "Insertion loop 256-268 in coagulation factor IX restricts enzymatic activity in the absence but not in the presence of factor VIII" BIOCHEMISTRY, vol. 39, no. 25, 27 June 2000 (2000-06-27), pages 7398-7405, XP002487244 ISSN: 0006-2960 abstract page 7401 page 7403, left-hand column, paragraph 3 figure 1	1,6-9, 13-15
Y		2-5, 10-12

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[X] Further documents are listed in the continuation of Box C. **D** See patent family annex.

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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl. Fax (+31-70) 340-3016	Surdej , **Patrick**

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(^Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication where appropriate of the relevant passages	Relevant to claim No
X	CHRISTOPHE OLIVIER D ET AL: "Blood coagulation factor IX residues glu78 and Arg94 provide a link between both epidermal growth factor-like domains that is crucial in the interaction with factor VIII light chain" JOURNAL OF BIOLOGICAL CHEMISTRY, vol . 273, no. 1 , 2 January 1998 (1998-01-02), pages 222-227, XP002487245 ISSN: 0021-9258 abstract page 224 - page 225	1,6-9, 13-15
Y		2-5, 10-12
X	SICHLER KATRIN ET AL: "Physiological fIXa activation involves a cooperative conformational rearrangement of the 99-1 oop." JOURNAL OF BIOLOGICAL CHEMISTRY, vol . 278, no. 6 , 7 February 2003 (2003-02-07), pages 4121-4126, XP002487246 ISSN: 0021-9258 abstract page 4125 - page 4126	1,6-9, 13-15
Y		2-5, 10-12
P ,X	HARTMANN RUDOLF ET AL: "Variants of recombinant factor IX with enhanced functional properties" BLOOD, vol. 110, no. 11, Part 1 , November 2007 (2007-11), page 791A, XP009101449 & 49TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; ATLANTA, GA, USA; DECEMBER 08 -11, 2007 ISSN: 0006-4971 the whole document	1-15