Title: FACTOR VIII COMPOSITIONS AND METHODS

Abstract: The present invention provides methods of increasing the half-life and/or specific activity of factor VIII. More specifically, the invention provides methods of increasing the half-life and/or specific activity of factor VIII by substituting one or more amino acids in the A2 domain. It further provides methods for producing such factor VIII mutants. The invention also provides polynucleotides encoding the mutant factor VIII, and methods of treating hemophilia using the polypeptides and polynucleotides of the invention.

**Declarations under Rule 4.17:**
- as to applicant's entitlement to claim the priority of the earlier application (Rule 4.17(ii)) for all designations
- as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

**Published:**
- with international search report

**(88) Date of publication of the international search report:**

10 November 2005

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/755 C12N15/12 A61K38/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classificiation system followed by classification symbols)
IPC 7 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, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

X SAENKO E L ET AL: "The future of recombinant coagulation factors.
JOURNAL OF THROMBOSIS AND HAEMOSTASIS:
JTH. MAY 2003,
vol. 1, no. 5, May 2003 (2003-05), pages 922-930, XP002320944
ISSN: 1538-7933
in particular pages 926-927
the whole document

1-26, 28-32

Further documents are listed in the continuation of box C.

Date of the actual completion of the international search
11 March 2005

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Form PCT/ISA/210 (second sheet) (January 2004)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>X</td>
<td>ANANYEVA N M ET AL: &quot;Catabolism of the coagulation factor VIII: can we prolong lifetime of f VIII in circulation?&quot; TRENDS IN CARDIOVASCULAR MEDICINE. AUG 2001, vol. 11, no. 6, August 2001 (2001-08), pages 251-257, XP002320945 ISSN: 1050-1738 the whole document</td>
<td>1-26, 28-32</td>
</tr>
<tr>
<td>X</td>
<td>WO 02/060951 A (THE AMERICAN NATIONAL RED CROSS; SAENKO, EVGENI, L; SARAFANOV, ANDREY) 8 August 2002 (2002-08-08) in particular, example 4 and claims the whole document</td>
<td>1-26, 28-32</td>
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</tbody>
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INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2.☐ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-25, 28, 29, 30, 32 (partially), claims 26, 31 (entirely)

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-25, 28, 29, 30, 32 (partially), claims 26, 31 (entirely)

   A mutant factor VIII comprising an amino acid substitution at position Lys466, wherein the mutant fVIII has procoagulant activity, and polynucleotide encoding said mutant fVIII, embodiments thereof and method of treating hemophilia comprising administering to a patient said mutant fVIII or said polynucleotide, pharmaceutically acceptable composition comprising said mutant fVIII or polynucleotide; method of increasing the specific activity of factor VIII.

2. claims: 1-12, 25, 28 (partially), 27 (entirely)

   A mutant factor VIII comprising an amino acid substitution at position Arg471, wherein the mutant fVIII has procoagulant activity, and polynucleotide encoding said mutant fVIII, embodiments thereof and method of treating hemophilia comprising administering to a patient said mutant fVIII or said polynucleotide, pharmaceutically acceptable composition comprising said mutant fVIII or polynucleotide.

3. claims: 13-24, 29, 30, 32 (partially)

   A mutant factor VIII comprising an amino acid substitution at position Lys477, wherein the mutant fVIII has procoagulant activity, and polynucleotide encoding said mutant fVIII, embodiments thereof and method of treating hemophilia comprising administering to a patient said mutant fVIII or said polynucleotide, pharmaceutically acceptable composition comprising said mutant fVIII or polynucleotide; method of increasing the specific activity of factor VIII.

4. claims: 13-24, 29, 30, 32 partially)

   A mutant factor VIII comprising an amino acid substitution at position His478, wherein the mutant fVIII has procoagulant activity, and polynucleotide encoding said mutant fVIII, embodiments thereof and method of treating hemophilia comprising administering to a patient said mutant fVIII or said polynucleotide, pharmaceutically acceptable composition comprising said mutant fVIII or polynucleotide; method of increasing the specific activity of factor VIII.

5. claims: 29, 32 (partially)
Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys380, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

6. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Ser488, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

7. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Arg489, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

8. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Arg490, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

9. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Leu491, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

10. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys493, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

11. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys496, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

12. claims: 29, 32 (partially)
Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position His497, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

13. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position His499, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

14. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys512, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

15. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys523, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.

16. claims: 29, 32 (partially)

Method for increasing the specific activity of factor VIII comprising substituting an amino acid for a residue at position Lys556, wherein the resulting factor VIII has procoagulant activity, embodiment thereof.
## INTERNATIONAL SEARCH REPORT

**Patent document cited in search report** | **Publication date** | **Patent family member(s)** | **Publication date**
---|---|---|---
WO 02060951 A | 08-08-2002 | CA 2434097 A1 | 08-08-2002
WO 02060951 A2 | 08-08-2002 |