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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

[Continued on next page]

(54) Title: HYBRID FACTOR VIII POLYPEPTIDES FOR USE TO TREAT HEMOPHILIA A

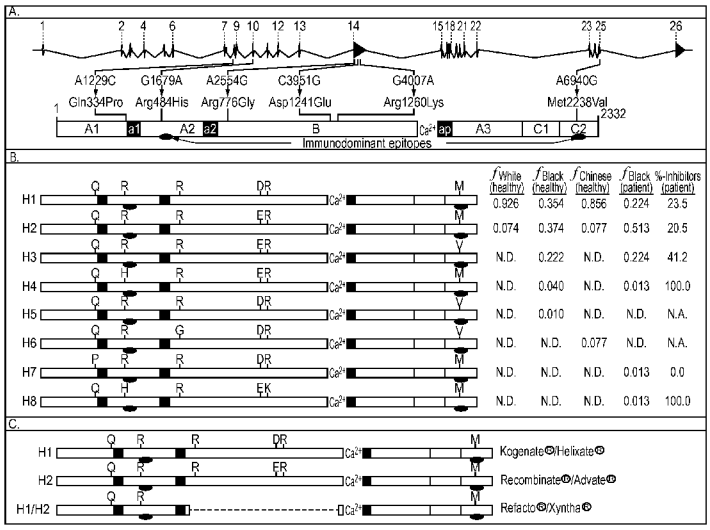

FIG. 1

(57) Abstract: Hybrid recombinant FVIII polypeptides (hrFVIII) comprising non-naturally occurring combinations of amino acid modifications, cDNAs encoding such hrFVIII, expression vectors comprising nucleic acids encoding such hrFVIII, cells comprising expression vectors comprising nucleic acids encoding such hrFVIII, and methods of treating subjects having hemophilia A by administering to the subject such hrFVIII are disclosed herein. The non- naturally occurring amino acid modifications occur at sites of naturally occurring nonsynonymous-Single Nucleotide Polymorphisms (ns-SNP). The hrFVIII can be full length, having a B-domain deletion (BDD), having a B-domain deletion 2 (BDD-2), or having a B-domain deletion 3 (BDD-3). Methods of making the hrFVIIIs, cDNAs, expression vectors, cells are also disclosed.

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4 June 2015

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/59787

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/37, A61K 35/14 (2015.01)
CPC - C07K 14/755
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 38/37, A61K 35/14 (2015.01)
CPC - C07K 14/755

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/14.1, 530/383

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
pubWEST; PatBase; Google Scholar
search terms - factor VIII, FVIII, hrFVIII, rFVIII, recombinant, recombin*, nonsynonym$, non, synonym$, human, Glu113Asp, Gln334Pro, Ala387Thr, Arg484His, Arg776Gly, Arg1107Trp, Asp1241Glu, Arg1260Lys, Leu1462Pro or Ile1668Val or His1919Asn or Glu2004Lys

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0297494 A1 (HOWARD et al.) 22 November 2012 (22.11.2012) para [0010]; [0014]; [0031]; [0032]; [0046]; [0047]; [0050]; SEQ ID NOs: 3, 7; claim 1.	1-9, 12-14
A	US 2010/0256062 A1 (HOWARD et al.) 07 October 2010 (07.10.2010) para [0025]; [0039], [0066]; [0450].	1-9, 12-14

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2015 (20.03.2015)	10 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/59787

Box No. 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.: 10, 11, 15-20, 26, 27
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-9 and 12-14, directed to a hybride recombinant factor VIII polypeptide (hrFVIII).
Group II, claims 21-25, directed to a method of treating a subject having hemophilia A, comprising, administering a hrFVIII.

The inventions listed as Groups I-II do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

--continued on extra 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 additional fees, this Authority did not invite payment of additional fees.

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.:
1-9, 12-14

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

continuation of Box No III:

Special technical features
Group I includes the special technical feature of a cell comprising an expression vector having a complementary DNA (cDNA) encoding a hrFVIII, which is not required by Group II.
Group II includes the special technical feature of a method of treatment comprising administering an effective amount of a hrFVIII peptide, which is not required by Group I.

Shared technical features
Groups I and II share the common technical features of a hybride recombinant factor VIII polypeptide (hrFVIII) having non-naturally occurring combinations of amino acid modifications, wherein the amino acid modifications occur at sites of naturally occurring nonsynonymous-single nucleotide polymorphisms. Groups I and II further share the common feature of a cell/method for treatment of a subject having hemophilia A. However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2010/0256062 A1 to Howard et al., (hereinafter Howard).

Howard teaches a hybride recombinant factor VIII polypeptide (hrFVIII) having non-naturally occurring combinations of amino acid modifications, wherein the amino acid modifications occur at sites of naturally occurring nonsynonymous-single nucleotide polymorphisms (para [0039], [0066] 'In FIG. 2, the five SNP's (W255C, R484H, R776G, D1241E, and M2238V) are illustrated. Combinations of these four SNP's correspond to six haplotypes'; [0450] FVIII replacement product(s)...Recombinate vary at only 1 amino acid residue, position 1241, i.e. the site of a naturally-occurring biallelic polymorphisms, D1241E, which is encoded by 1 (C92714G) of the 4 nsSNPs found in the human F8. Since Refacto lacks the B-domain, the location of D1241E, and has the same allele as Recombinate and Kogenate at the three additional nsSNP sites (i.e., R484H, R776G and M2238V), are referred to as representing a hybrid haplotype designated H1/H2'; [0495] 'four non-synonymous human F8 SNPs--which have common minor alleles conferring the amino acid substitutions R484H, R776G, E1241D and M2238V'; these taught substitutions are non-naturally occurring modifications as evidenced by the present application claim 5). Howard further teaches a method of treating a subject having hemophilia A (para [0025]).

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Groups I-II lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

Note: Claims 10, 11, 15-20, 26 and 27 have been held as unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).