Title: NEW POLYNUCLEOTIDES AND POLYPEPTIDES OF THE ERYTHROPOIETIN GENE

Abstract: The present invention relates to new polynucleotides deriving from the nucleotide sequence of the EPO gene and comprising new SNPs, new polypeptides derived from the natural EPO protein and comprising at least one mutation caused by the SNPs of the invention as well as their therapeutic uses.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12O1/68 G01N33/68 C07K14/505 C07K16/00 C12N15/85
C12N15/63 A61K38/21 A61P9/00 A61P31/12 A61P35/00
A61P37/00
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 7 C12Q C12N C07K G01N A61K A61P

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, SEQUENCE SEARCH, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>WO 00 68376 A (GENENTECH INC ; HENNER DENNIS J (US); DESAUVAGE FREDERIC (US)) 16 November 2000 (2000-11-16)</td>
<td>1-3, 6, 9-12, 17, 18, 21, 22</td>
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<td>Y</td>
<td>* see especially SEQ ID NO:1, nucleotide 1082 * abstract; claims 1-33; figures 1B,3; examples 1-10</td>
<td>4, 5, 7, 8, 13-16, 19, 20, 23-35</td>
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<td>Y</td>
<td>WO 99 38890 A (GRODBERG JENNIFER ; BETH ISRAEL HOSPITAL (US); SYTKOWSKI ARTHUR J (US) 5 August 1999 (1999-08-05)</td>
<td>4, 5, 7, 8, 13-16, 19, 20, 23-35</td>
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<td>abstract page 15, line 3 - page 20, line 5 page 26, line 10 - page 28, line 14 page 31, line 1 - page 50, line 20; claims 1, 2, 5, 6, 9, 10, 12-14, 17; figure 10C; examples 3-5</td>
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X
Further documents are listed in the continuation of box C.

X
Patent family members are listed in annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance to the invention
"E" earlier document 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

30 May 2003

Name and mailing address of the ISA

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Authorized officer

Knehr, M

Form PCT/ISA210 (second sheet) (July 1998)
<table>
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<td>P,X</td>
<td>VILALTA A ET AL.: &quot;Rabbit EPO gene and cDNA: Expression of rabbit EPO after intramuscular injection of pDNA&quot; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 284, June 2001 (2001-06), pages 823-827, XP002188195 * see especially Fig.1A and B, Rabbit’ sequence, amino acid residue no.105 * the whole document</td>
<td>4,5, 13-15, 49,52-59</td>
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# INTERNATIONAL SEARCH REPORT

## Box I  Observations where certain claims were found unsearchable (Continuation of item 1 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. **X** Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 23–33 are directed to a therapeutic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the gene’s expression products as related to the underlying polymorphisms.

2. **X** Claims Nos.: 36–48, 50, 51  
   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:
   
   see FURTHER INFORMATION sheet PCT/ISA/210

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

## Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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.:

### 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 (1)) (July 1998)
Continuation of Box I.2

Claims Nos.: 36-48, 50, 51

Present claims 36-48, 50 and 51, relate to methods as well as therapeutic compounds resulting from such methods, defined by reference to a desirable characteristic or property, namely in possessing some biological activity being substantially similar to the activity of the GI04S-mutated erythropoietin gene product (claims 36-47), and further, in possessing some alterations resulting in binding with higher affinity to the erythropoietin receptor as compared with binding of the wild-type erythropoietin (claims 48, 50 and 51). Without comprising clear essential technical features allowing the person skilled in the art to understand what exactly is meant with '...substantially similar to the activity of the GI04S-mutated erythropoietin gene product...'. or '...helices A, B, C and D having cellular proliferative functional characteristics atleast equal to that of the wild-type human erythropoietin and capable of binding to an erythropoietin receptor, havinf at least one alteration...resulting in binding with higher affinity to the erythropoietin receptor than that of the wild-type human erythropoietin...', it is without saying that such terms could be interpreted in any possible way. Thus, they are not fulfilling the requirements of giving a clear teaching about the content and the scope of these claims, and especially, how to execute the teaching of these claims succesfully. In fact, these claims cover all possible methods and deriving compounds having these characteristics or properties without giving any clue in form of technical features how to do so, in contrast to the requirements of Article 6 PCT (need for support) and/or Article 5 PCT (need for disclosure). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT) since an attempt is made to define the methods and deriving compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, by lacking any technical feature making these claims clear, supported and disclosed, no search has been carried out for claims 36-48, 50 and 51.

In addition, a limited search has been executed for claims 1-35, 49, and 52-59, since it is not clear how and to what extent '...all or part of the sequence...' within the context of a polynucleotide or polypeptide sequence should be interpreted and be limited. From the description and the examples given, it appears that what is meant, is a mutated form of the erythropoietin gene and its encoded gene product, provided they comprise at least one of the polymorphisms as claimed. However, present claims 1-35, comprising the wording '...or part of...' relate to an extremely large number of possible gene or polypeptide fragments. In fact, the claims contain so many possible permutations that a lack of clarity and/or conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of these claims impossible. Consequently, the search has been limited and
carried out to those parts of these claims which do appear to be clear and/or concise and/or supported, namely a mutated erythropoietin gene and its encoded gene product, comprising at least one of the polymorphisms as claimed, as well as methods of genotyping and screening relying on such a mutated gene.

Finally, related to claims 49, and 52-59, again, the claims contain so many possible permutations that a lack of clarity and/or conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the whole scope of these claims impossible. Consequently, the search has been limited and carried out to those parts of these claims which do appear to be clear and/or concise and/or supported, namely the features as disclosed within the application and within dependent claims 53-59, thus to a erythropoietin molecule being specifically modified by the G104S polymorphism.

The applicant’s attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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<td>AU 4704700 A</td>
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