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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: FORMATION OF NOVEL ERYTHROPOIETIN CONJUGATES USING TRANSGLUTAMINASE

(57) Abstract: The invention provides biologically active erythropoietin (EPO) conjugate compositions wherein a transglutaminase reaction is employed to covalently and site specifically conjugate the EPO molecule to a non-antigenic hydrophilic polymer that can also be covalently linked to an organic molecule either of which modification increases the circulating serum half-life of the composition.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/16670

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 38/00, 38/52; C07K 1/00 US CL : 514/2; 530/350; 435/68.1; 424/94.5, 185.1, 280.1 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) U.S. : 514/2; 530/350; 435/68.1; 424/94.5, 185.1, 280.1 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 practicable, search terms used) EAST, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,904,584 (SHAW) 27 Feb. 1990 (27.02.1990), entire document, particularly claims 1-3.	1-48
Y	US 6,010,871 (TAKAHARA et al.) 04 Jan. 2000 (04.01.2000), entire document, particularly column 4, line 23 - column 8, line 29, and claims 1, and 5.	1-48
Y	US 4,806,524 (KAWAGUCHI et al.) 21 Feb. 1989 (21.02.1989), entire document, particularly claims 1, and 2.	1-48
Y	US 6,340,742 B1 (BURG et al.) 22 Jan. 2002 (22.01.2002), entire document, particularly abstract, column 1, line 65 - column 2, line 61, and claims 1-89.	1-48
Y	US 2004/0082765 A1 (NAKAMURA et al.) 29 Apr. 2004 (29.04.2004), entire document, particularly paragraph 11-15, and claims 1-8.	1-48
Y	US 6,322,996 B1 (SATO et al.) 27 Nov. 2001 (27.11.2001), entire document, particularly column 1, line 50 - column 9, line 44, and claims 1-10.	1-48
A	DALE, G. et al. Stimulated platelets use serotonin to enhance their retention of procoagulant proteins on the cell surface. NATURE, Vol. 10, pages 175-179 (2002). Entire document.	1-48
A	FISHER, J.W. Erythropoietin: Physiology and Pharmacology Update. EXP. BIOL. MED. Jan. 2003, 228(1): 1-14. Entire document.	1-48
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* 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 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 04 November 2004 (04.11.2004)		Date of mailing of the international search report 27 JAN 2005
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. (703) 305-3230		Authorized officer Anand Desai Telephone No. (571) 272-1600

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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.:
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:
Please See Continuation 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.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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, claim(s) 1, 3-9 in part, 10, 12-20 in part, and 21, 41, 42, 44, 45, and 46, drawn to erythropoietic conjugate comprising a modified glutamine residue.

Group II, claim(s) 2, 3-9 in part, 11, 12-20 in part, 22, 43, 47, and 48, drawn to an erythropoietic conjugate comprising a modified lysine residue.

Group III, claim(s) 23-26 in part, 27, and 30 in part, drawn to a method of preparing an erythropoietic conjugate with a mammalian transglutaminase.

Group IV, claim(s) 23-26 in part, 28, 29, and 30 in part, drawn to a method of preparing an erythropoietic conjugate comprising a modified glutamine residue.

Group V, claim(s) 31-34 in part, 35, and 38 in part, drawn to a method of preparing an erythropoietic conjugate comprising a modified lysine residue with a mammalian transglutaminase.

Group VI, claim(s) 31-34 in part, 36, 37, and 38 in part, drawn to a method of preparing an erythropoietic conjugate comprising a modified lysine residue with a prokaryotic transglutaminase.

Group VII, claim(s) 39, and 40, drawn to a method of treating anemia comprising administering a therapeutically effective amount of an erythropoietic conjugate.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking groups I-VII appears to be that they all relate to erythropoietin conjugates. However, Burg et al. U.S. 6,340,742 B1 teaches erythropoietin conjugates that increase production of reticulocytes and red blood cells. The erythropoietin conjugates have an increased circulating half-life, plasma residence time, decreased clearance, and increased clinical activity in vivo. Burg et al. also teaches the method of treatment for anemia using the erythropoietin conjugate.

Therefore, the technical feature linking the inventions of groups I-VII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is to erythropoietic conjugate comprising a modified glutamine residue

The special technical feature of Group II is to an erythropoietic conjugate comprising a modified lysine residue.

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The special technical feature of Group III is a method of preparing an erythropoietic conjugate with a mammalian transglutaminase.

The special technical feature of Group IV is a method of preparing an erythropoietic conjugate comprising a modified glutamine residue.

The special technical feature of Group V is a method of preparing an erythropoietic conjugate comprising a modified lysine residue with a mammalian transglutaminase.

The special technical feature of Group VI is a method of preparing an erythropoietic conjugate comprising a modified lysine residue with a prokaryotic transglutaminase.

The special technical feature of Group VII is a method of treating anemia comprising administering a therapeutically effective amount of an erythropoietic conjugate.

Accordingly, Groups I-VII are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.