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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

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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.

(54) Title: METHOD FOR RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ACTIVATION AND CONTROL THEREOF

(57) Abstract: An improved blood substitute composition comprising a blood substitute and a renin-angiotensin-aldosterone system inhibitor. A method of treating a patient having a disorder requiring a blood transfusion comprising administering a free hemoglobin based blood substitute and a renin-angiotensin-aldosterone system inhibitor. A renin-angiotensin-aldosterone system activator comprising hemoglobin or hemoglobin and a peroxide. A method of increasing the activity of angiotensin converting enzyme comprising incubation with hemoglobin or hemoglobin and peroxide. A method according of activating the renin-angiotensin-aldosterone system comprising contacting in vivo a free hemoglobin based blood substitute with a peroxide wherein the product induces the production of angiotensin I metabolites which comprise metabolites capable of affecting the vascular tone and/or stimulating aldosterone production.

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/00 A61K35/14 A61K38/42 A61K45/06 A61P7/08

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)

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, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; September 1995 (1995-09), DE MACEDO I L ET AL: "[Nonimmune fetal edema]" XP002456822 Database accession no. NLM8668826 abstract & REVISTA MÉDICA DE PANAMÁ SEP 1995, vol. 20, no. 3, September 1995 (1995-09), pages 92-97, ISSN: 0379-1629</p> <p style="text-align: center;">----- -/--</p>	1-9

☒ 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 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

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& document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/022028

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DESRAME J ET AL: "Syndrome hemolytique et uremique secondaire a la gemcitabine : a propos de six observations et revue de la litterature"</p> <p>REVUE DE MEDECINE INTERNE, CMR, ASNIERES, FR,</p> <p>vol. 26, no. 3, March 2005 (2005-03),</p> <p>pages 179-188, XP004786934</p> <p>ISSN: 0248-8663</p> <p>page 182, column 2, paragraph 4</p> <p>page 181, column 1, paragraph 4</p> <p>-----</p>	1-9
X	<p>NESHER G ET AL: "Valvular dysfunction in antiphospholipid syndrome: Prevalence, clinical features, and treatment"</p> <p>SEMINARS IN ARTHRITIS AND RHEUMATISM,</p> <p>vol. 27, no. 1, August 1997 (1997-08),</p> <p>pages 27-35, XP004680835</p> <p>ISSN: 0049-0172</p> <p>page 28, column 2</p> <p>-----</p>	1-9
X	<p>FRANCIS R C E ET AL: "Effect of angiotensin II and endothelin-1 receptor blockade on the haemodynamic and hormonal changes after acute blood loss and after retransfusion in conscious dogs."</p> <p>ACTA PHYSIOLOGICA SCANDINAVICA APR 2004,</p> <p>vol. 180, no. 4, April 2004 (2004-04),</p> <p>pages 319-328, XP002456820</p> <p>ISSN: 0001-6772</p> <p>abstract</p> <p>-----</p>	1-9
X	<p>BARTOSZ MALGORZATA ET AL: "Antioxidant and prooxidant properties of captopril and enalapril"</p> <p>FREE RADICAL BIOLOGY AND MEDICINE,</p> <p>vol. 23, no. 5, 1997, pages 729-735,</p> <p>XP002457241</p> <p>ISSN: 0891-5849</p> <p>abstract</p> <p>-----</p>	1-26
X	<p>ALAYASH ABDU I: "Oxidative mechanisms of hemoglobin-based blood substitutes"</p> <p>ARTIFICIAL CELLS BLOOD SUBSTITUTES AND IMMOBILIZATION BIOTECHNOLOGY,</p> <p>vol. 29, no. 6, November 2001 (2001-11),</p> <p>pages 415-425, XP009091583</p> <p>ISSN: 1073-1199</p> <p>the whole document</p> <p>-----</p>	1-26

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MOISAN STEVE ET AL: "Mechanism of the acute pressor effect and bradycardia elicited by diaspirin crosslinked hemoglobin in anesthetized rats" CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, vol. 76, no. 4, April 1998 (1998-04), pages 434-442, XP009091573 ISSN: 0008-4212 abstract</p>	1-26
X	<p>ALAYASH ABDU I: "Oxygen therapeutics: can we tame haemoglobin?" NATURE REVIEWS. DRUG DISCOVERY FEB 2004, vol. 3, no. 2, February 2004 (2004-02), pages 152-159, XP002457242 ISSN: 1474-1776 the whole document</p>	1-26
X	<p>BUEHLER PAUL W ET AL: "Toxicities of hemoglobin solutions: in search of in-vitro and in-vivo model systems" TRANSFUSION (MALDEN), vol. 44, no. 10, October 2004 (2004-10), pages 1516-1530, XP002457243 ISSN: 0041-1132 the whole document</p>	1-26
X	<p>HEMOLINK STUDY GROUP GREENBURG ET AL: "Use of an oxygen therapeutic as an adjunct to intraoperative autologous donation to reduce transfusion requirements in patients undergoing coronary artery bypass graft surgery" JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS, COLLEGE, CHICAGO, IL, US, vol. 198, no. 3, March 2004 (2004-03), pages 373-383, XP005290068 ISSN: 1072-7515 page 381, column 1 abstract</p>	1-26
X	<p>CYR M ET AL: "Anomaly of the des-Arg9-bradykinin metabolism associated with severe hypotensive reactions during blood transfusions: A preliminary study" TRANSFUSION (BETHESDA), vol. 39, no. 10, October 1999 (1999-10), pages 1084-1088, XP002457244 ISSN: 0041-1132 the whole document</p>	1-9

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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:
Although claims 1-9,16-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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 reportcovers 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 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.