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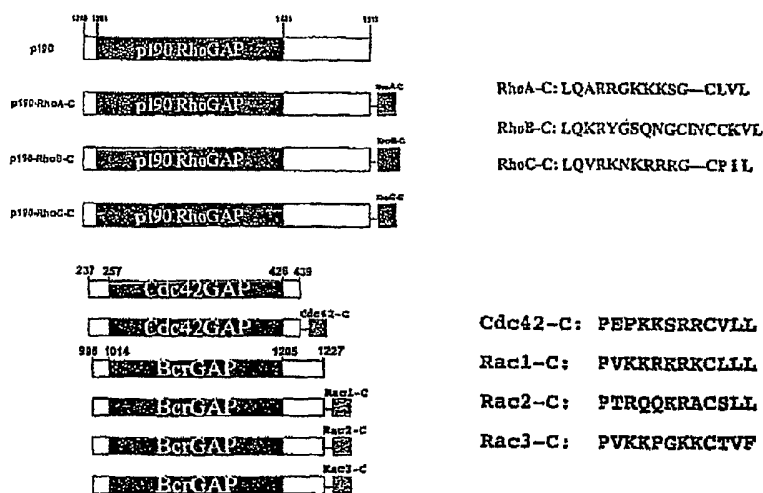
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[Continued on next page]

(54) Title: MOBILIZATION OF HEMATOPOIETIC CELLS



(57) Abstract: Improved methods and pharmaceutical compositions are provided herein for mobilizing hematopoietic progenitor cells from bone marrow into peripheral blood, comprising the administration of an effective amount of an inhibitor of GTPases, such as Rac1 and Rac2 alone or in combination. Specifically, methods are disclosed for mobilizing hematopoietic stem cells into a subject's peripheral blood. In particular, embodiments of the method involve inhibition of both Rac1 and Rac2 GTPases to increase the numbers of hematopoietic stem cells into a subject's peripheral blood of a subject. The subject's blood can be processed and used to repopulate the destroyed lymphohematopoietic system of a recipient and may in the future be utilized to repair a variety of non-hematopoietic tissues. Therefore, hematopoietic stem cells mobilized into a subject's peripheral blood by the method of the invention is useful as a source of donor cells in bone marrow transplantation for the treatment of a variety of disorders, including cancer, anemia, autoimmunity and immunodeficiency. They can also be used for increasing white blood cell survival and for chemotherapy.

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# INTERNATIONAL SEARCH REPORT

International Application No PCT/US2004/026459
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K38/00 A61K31/7088 A61K31/04 C12N5/06 C12N15/62 C07K14/47		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K C12N 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) BIOSIS, EMBASE, WPI Data, EPO-Internal, PAJ		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YANG F -C ET AL: "Rac and Cdc42 GTPases control hematopoietic stem cell shape, adhesion, migration, and mobilization" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 98, no. 10, 8 May 2001 (2001-05-08), pages 5614-5618, XP002312312 ISSN: 0027-8424 page 5614, left-hand column, paragraph 2 page 5615, last paragraph -page 5616, right-hand column, paragraph 2 ---	1-59
A	WO 03/011277 A (ANORMED INC ; MACFARLAND RONALD TREVOR (CA); HENSON GEOFFREY W (US); B) 13 February 2003 (2003-02-13) page 4, line 25 -page 26, line 16 example 3 claims 1-29 --- -/--	1-42
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <span style="margin-left: 200px;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</span>		
° 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 *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	
11 January 2005	23/02/2005	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Perez, C	

## INTERNATIONAL SEARCH REPORT

Intel Patent Application No  
PCT/US2004/026459

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 117 850 A (BLEICHER PAUL ET AL) 12 September 2000 (2000-09-12) column 1, line 53 -column 2, line 31 examples 1-11 claims 1-22 ---	1-42
A	WO 01/78761 A (GIANNI ALESSANDRO MASSIMO ; IACOBELLI MASSIMO (IT); FERRO LAURA (IT);) 25 October 2001 (2001-10-25) page 2, line 28 -page 4, last line example 6 claims 1-13 ---	1-42
A	WO 01/93900 A (GIANNI ALESSANDRO MASSIMO ; APPLIED RESEARCH SYSTEMS (NL)) 13 December 2001 (2001-12-13) page 3, line 1 -page 14, line 33 example EXAMPLE claims 1-50 ---	1-42
A	WO 99/40783 A (HADASIT MED RES SERVICE ; FIBACH EITAN (IL); FRIEDMAN MARK M (IL); GAM) 19 August 1999 (1999-08-19) page 4, line 20 -page 8, line 5 examples 1-5 claims 1-35 ---	1-42
A	CA 2 467 557 A (KYOWA HAKKO KOGYO KK) 30 May 2003 (2003-05-30) page 7, line 10 -page 14, line 18 claims 1-40 ---	1-42
P,X	GU YI ET AL: "Hematopoietic cell regulation by Rac1 and Rac2 guanosine triphosphatases." SCIENCE, vol. 302, no. 5644, 17 October 2003 (2003-10-17), pages 445-449, XP002312006 Washington DC ISSN: 0036-8075 the whole document ---	1-59
P,A	GAO YUAN ET AL: "Rational design and characterization of a Rac GTPase-specific small molecule inhibitor" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 101, no. 20, 18 May 2004 (2004-05-18), pages 7618-7623, XP002312007 ISSN: 0027-8424 the whole document ---	1-42
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/026459

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WANG LEI ET AL: "A novel strategy for specifically down-regulating individual Rho GTPase activity in tumor cells."                      JOURNAL OF BIOLOGICAL CHEMISTRY,                      vol. 278, no. 45,                      7 November 2003 (2003-11-07), pages                      44617-44625, XP002312008                      ISSN: 0021-9258                      the whole document</p> <p style="text-align: center;">-----</p>	43-59

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/026459

## 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:  
  
Although claims 1-59 are directed to or embrace methods 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.: 1-42 partially  
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(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:

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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-42 partially

Present claims 1-42 refer to a product, namely a GTPase/Rac1/Rac2 inhibitor or an active agent capable of inhibiting GTPases, defined by nothing more than a result to be achieved, i.e. its capacity to inhibit GTPase in general or Rac1 or Rac2 in particular, without providing any true characterization of the compounds themselves. Moreover the scope of said claims embrace methods referring to all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for methods using only a very limited number of said GTPase inhibitors.

Consequently said claims are contrary to both Article 6 PCT for lack of clarity and technical support, and Article 5 PCT for lack of sufficient 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. Consequently, the search has been carried out for the methods referring to GTPases inhibitors which appear to be clear in the sense of Article 6 PCT, supported and disclosed, namely :

- the antisense oligonucleotides that specifically hybridize with nucleic acids encoding rac1 and rac2 described in paragraph '0108!,
- the specific small inhibitor NSC23776 used in example 6,
- and the isolated fusion (chimeric) polypeptides comprising a Rho GAP domain peptide and a C-terminus targeting peptide as referred to in claims 43-59, and supported by example 4.

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.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/026459

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