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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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(54) Title: METHODS FOR DIAGNOSIS AND TREATMENT OF DISEASES ASSOCIATED WITH ALTERED EXPRESSION OF PIK3R1

(57) Abstract: The present invention relates to novel sequences for use in diagnosis and treatment of lymphoma and leukemia. In addition, the present invention describes the use of novel compositions for use in screening methods.

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/IB 02/04123

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 C12N15/63 C12N5/10 C07K14/47 C07K16/18 C12Q1/68  
 G01N33/50 C12N15/11

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 G01N 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)

EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, SEQUENCE SEARCH, 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	WO 98 20126 A (ONYX PHARMA INC) 14 May 1998 (1998-05-14) claims 1-10,17,20	1-9, 12-16
X	SKOLNIK E Y ET AL: "Cloning of PI3 kinase-associated p85 utilizing a novel method for expression/cloning of target proteins for receptor tyrosine kinases" CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 65, no. 1, 5 April 1991 (1991-04-05), pages 83-90, XP002100383 ISSN: 0092-8674 the whole document	1-5,15, 16

 Further documents are listed in the continuation of box C.

 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
- \*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.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

9 July 2003

Date of mailing of the international search report

21/07/2003

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## INTERNATIONAL SEARCH REPORT

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PCT/IB 02/04123

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRUMAN DAVID A ET AL: "Structural organization and alternative splicing of the murine phosphoinositide 3-kinase p85-alpha gene." GENOMICS, vol. 37, no. 1, 1996, pages 113-121, XP002246862 ISSN: 0888-7543 page 114, right-hand column page 115, left-hand column ---	1-5, 15, 16
X	SUN MEI ET AL: "Phosphatidylinositol-3-OH kinase (PI3K)/AKT2, activated in breast cancer, regulates and is induced by estrogen receptor alpha (ERalpha) via interaction between ERalpha and PI3K." CANCER RESEARCH, vol. 61, no. 16, 15 August 2001 (2001-08-15), pages 5985-5991, XP002246863 ISSN: 0008-5472 page 5986; figure 4 ---	1-5, 15, 16
X	BAI RENYUAN Y ET AL: "NPM-ALK associated with anaplastic large-cell lymphoma activates the PI3-kinase/Akt antiapoptotic signaling pathway." BLOOD, vol. 96, no. 11 Part 1, 16 November 2000 (2000-11-16), page 469a XP008019458 42nd Annual Meeting of the American Society of Hematology; San Francisco, California, USA; December 01-05, 2000 ISSN: 0006-4971 the whole document ---	10-16, 19
X	LIN XIONGBIN ET AL: "Overexpression of phosphatidylinositol 3-kinase in human lung cancer." LANGENBECK'S ARCHIVES OF SURGERY, vol. 386, no. 4, July 2001 (2001-07), pages 293-301, XP002246865 ISSN: 1435-2443 page 295; table 1 ---	11, 15, 16
	-/--	

## INTERNATIONAL SEARCH REPORT

 Interna plication No  
 PCT/IB 02/04123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SNYDER R C ET AL: "Increased levels of the p85alpha regulatory subunit of phosphatidylinositol 3-OH kinase in cell lysates of juvenile myelomonocytic leukemia cells." BLOOD, vol. 90, no. 10 SUPPL. 1 PART 1, 15 November 1997 (1997-11-15), page 411A XP008019234 39th Annual Meeting of the American Society of Hematology; San Diego, California, USA; December 5-9, 1997 ISSN: 0006-4971 the whole document ---	10,11, 18,19
X	BORLADO LUIS R ET AL: "Increased phosphoinositide 3-kinase activity induces a lymphoproliferative disorder and contributes to tumor generation in vivo." FASEB JOURNAL, vol. 14, no. 7, May 2000 (2000-05), pages 895-903, XP002246866 ISSN: 0892-6638 the whole document ---	10,11, 18,19
X	WO 01 00881 A (COWSERT LEX M ; MONIA BRETT P (US); ISIS PHARMACEUTICALS INC (US)) 4 January 2001 (2001-01-04) claims 20,21 ---	13
X	HOFMANN WOLF-K ET AL: "Altered apoptosis pathways in mantle cell lymphoma detected by oligonucleotide microarray." BLOOD, vol. 98, no. 3, 1 August 2001 (2001-08-01), pages 787-794, XP002246867 ISSN: 0006-4971 table 1 ---	17
P,X	WO 02 40637 A (BUTLER MADELINE M ; COWSERT LEX M (US); MONIA BRETT P (US); DEAN NI) 23 May 2002 (2002-05-23) SEQ ID NO:1 of the present application the whole document ---	1-19
P,X	WO 01 81346 A (ICOS CORP) 1 November 2001 (2001-11-01) the whole document ---	1-19
P,X	WO 01 83481 A (IMP CANCER RES TECHNOLOGY LTD ; HAYAKAWA MASAHIKO (JP); OHTA MITSUA) 8 November 2001 (2001-11-08) the whole document ---	1-19
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## INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/IB 02/04123

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HARRIS N L ET AL: "New approaches to lymphoma diagnosis." HEMATOLOGY / THE EDUCATION PROGRAM OF THE AMERICAN SOCIETY OF HEMATOLOGY. AMERICAN SOCIETY OF HEMATOLOGY. EDUCATION PROGRAM. UNITED STATES 2001, 2001, pages 194-220, XP002246868 ISSN: 1520-4391 the whole document -----	1-19

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/04123

## 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.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
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:  
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 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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the use of expression profiling of Pik3r1 for the evaluation of lymphoma drugs.

Although claims 12, 13, and 14 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.

## Continuation of Box I.2

Present claim 15 relates to polypeptides defined by reference to a desirable characteristic or property, namely polypeptides which specifically bind to a protein comprising an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO : 1, SEQ ID NO : 3, Genbank accession number U50413, and Genbank accession number M61906.

The claim covers all polypeptides 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 only antibodies. 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). An attempt is made to define the polypeptides 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, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to antibodies

Present claims 12-14 relate to compounds defined by reference to a desirable characteristic or property, namely inhibiting the activity of a Pik3r1 protein.

The claims cover all compounds 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 only a very limited number of such compounds. 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). An attempt is made to define the 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, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds listed on page 3 lines 19-24 of the description.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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/IB 02/04123

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9820126	A	14-05-1998	AU 735357 B2	05-07-2001
			AU 5079198 A	29-05-1998
			CA 2239463 A1	14-05-1998
			EP 0877806 A1	18-11-1998
			JP 2000506396 T	30-05-2000
			WO 9820126 A1	14-05-1998
			US 6133419 A	17-10-2000
WO 0100881	A	04-01-2001	US 6100090 A	08-08-2000
			AU 6952800 A	31-01-2001
			CA 2378227 A1	04-01-2001
			EP 1190099 A1	27-03-2002
			JP 2003503371 T	28-01-2003
			WO 0100881 A1	04-01-2001
WO 0240637	A	23-05-2002	AU 3653302 A	27-05-2002
			WO 0240637 A2	23-05-2002
WO 0181346	A	01-11-2001	AU 5566701 A	07-11-2001
			BR 0110371 A	17-06-2003
			CA 2406278 A1	01-11-2001
			EP 1278748 A2	29-01-2003
			NO 20025104 A	10-12-2002
			WO 0181346 A2	01-11-2001
			US 2002161014 A1	31-10-2002
			US 6518277 B1	11-02-2003
WO 0183481	A	08-11-2001	AU 5260901 A	12-11-2001
			CA 2407573 A1	08-11-2001
			EP 1277754 A1	22-01-2003
			WO 0183481 A1	08-11-2001