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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

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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: INHIBITORS OF TIP-1 FOR TREATMENT TISSUE DAMAGE

(57) Abstract: The present invention relates to the use of agents that reduce cellular levels of HTLV1 Tax Interacting Protein-1 (TIP-1) or act to inhibit or alter the functional effects of TIP-1 to treat, prevent or limit tissue damage. The agents are particularly useful for preventing damage that may occur as a result of the ageing process and in the treatment of cancer. The invention also concerns the diagnosis, and treatment (including prophylactic treatment) of, cancer and to a method for the identification of cancer targets involved in the process of tumour invasion.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/7105 A61K48/00 G01N33/574 A61P35/00 A61P17/00		
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 A61K A61P G01N		
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, Sequence Search, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 177 796 A (MITSUBISHI PHARMA CORP) 6 February 2002 (2002-02-06) see abstract, claim 1, '0014! and '0088!	1,6-18, 20,21
A	REYNAUD C. ET AL.: "The PDZ protein TIP-1 interacts with the Rho effector rhotekin and is involved in Rho signaling to the serum response element." J.BIOL. CHEM., vol. 275, no. 43, 27 October 2000 (2000-10-27), pages 33962-22968, XP002296886 see abstract and fig.1 ----- -/--	1-25, 27-36
☒ 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. *&* document member of the same patent family		
Date of the actual completion of the international search 9 February 2005		Date of mailing of the international search report 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 Merckling-Ruiz, V

INTERNATIONAL SEARCH REPORT

International Application No
PC1/GB2004/002383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VAN AELST L. AND SYMONS M.: "Role of Rho family GTPases in epithelial morphogenesis." GENES AND DEVELOPMENT, vol. 16, 2002, pages 1032-1054, XP002296887 see the whole document	1-25, 27-36
A	RIENTO K. AND RIDLEY A.: "ROCKs : multifunctional kinases in cell behaviour." NATURE REVIEWS MOLECULAR CELL BIOLOGY., vol. 4, no. 6, June 2003 (2003-06), pages 446-456, XP009036656 see the whole document	1-25, 27-36
A	WO 03/014303 A (RABINOWITZ JOSHUA D ; ARBOR VITA CORP (US); LU PETER S (US); CARRICK D) 20 February 2003 (2003-02-20) see claims 27-28, table 12 and examples 2 and 3	1-25, 27-36
X	Biosis abstract No. PREV199598550556, Hofmann-Wellenhof et. al. , Melanoma Research vol.5 No.5 pages 311-319 (1995) XP002296889	21,24
Y	abstract	21-25, 27-36
Y	WO 99/66946 A (UNIV PENNSYLVANIA ; EL DEIRY WAFIK S (US)) 29 December 1999 (1999-12-29) see abstract and examples	21-25, 27-36
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Y	FILATOV L. ET AL.: "Chromosomal instability is correlated with telomere erosion and inactivation of G2 checkpoint function in human fibroblasts expressing human papilloma virus type 16 E6 oncoprotein." ONCOGENE, vol. 16, 1998, pages 1825-1838, XP002296888 see abstract and page 1826	21-25, 27-36
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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	WO 01/15739 A (COWSERT LEX M ; ROBERTS M LUISA (US); ISIS PHARMACEUTICALS INC (US)) 8 March 2001 (2001-03-08)	1,6, 8-18,20, 21
Y	see tables 7 to 9, page 7 lines 10-11, example 2 and claims 21-22	1,6-18, 20,21,27
E	EP 1 452 589 A (MIGRAGEN AG) 1 September 2004 (2004-09-01) see claim 22, paragraphs '0001! and '0025!	1,6,8-16
P,X	WO 2004/022541 A (THOUIN ERYK ; LUBELL WILLIAM D (CA); MCKERRACHER LISA (CA)) 18 March 2004 (2004-03-18) see pages 56-57, 132-133 and claim 1	1,6-18, 20,21
X	EP 0 956 865 A (YOSHITOMI PHARMACEUTICAL) 17 November 1999 (1999-11-17)	1,6, 8-18,20, 21
Y	see abstract and claims 22,29,49 and 61	1,6-18, 20,21,27
Y	SOMLYO A V ET AL: "Rho-kinase inhibitor retards migration and in vivo dissemination of human prostate cancer cells" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 269, no. 3, 24 March 2000 (2000-03-24), pages 652-659, XP002277882 ISSN: 0006-291X see abstract	1,6-18, 20,21,27
Y	SAWADA K. ET AL.: "Lysophosphatidic acid induces focal adhesion assembly through Rho/Rho-associated kinase pathway in human ovarian cancer cells." GYNECOLOGIC ONCOLOGY, vol. 87, 2002, pages 252-259, XP002313601 see abstract	1,6-18, 20,21,27

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

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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:
2. ☒ Claims Nos.: 26
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:

see additional 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(part), 2-3, 4-5(part), 8-17(part), 19, 20-21(part), 23-25, 27(part), 29-36

compounds which directly inhibit TIP-1 expression or activity and their use as a medicament, or in screening or diagnostic assays.

2. claims: 1(part), 6(part), 8-18(part), 20-21(part), 27(part)

compounds which directly inhibit RhoA expression or activity and their use as a medicament, or in screening or diagnostic assays.

3. claims: 1(part), 6(part), 7, 8-18(part), 20-21(part), 27(part)

compounds which directly inhibit ROCK expression or activity and their use as a medicament, or in screening or diagnostic assays.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 26

Claim 26 relates to compounds defined by the screening method used to identify them. Such a definition so lacks clarity and support in the application that this claim cannot be searched.

Present claims 17, 21 and 27, referring to "TIP-1 induced proteins" relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. 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 those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as defined in claim 18.

As for invention 3 (inhibitors of ROCK and their use in as a medicament or diagnostic agent), the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the inhibitor Y-27632 and to the general concept of inhibitors or antagonists of ROCKs.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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