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(54) Title: THERAPEUTIC USE AND IDENTIFICATION OF MODULATORS OF A HEDGEHOG SIGNALLING PATHWAY OR ONE OF ITS TARGET PATHWAYS

(57) Abstract: Use of a modulator of a Hedgehog signalling pathway, or a modulator of a pathway which is a target of the Hedgehog signalling pathway in the preparation of a medicament for treatment of a disease or disorder associated with a T-cell mediated disease or disorder.

WO 2002/080952 A3

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/01666

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K38/00 A61K31/00 A61K33/00 A61K39/395 G01N33/50 C12Q1/68 A61P37/02		
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 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, MEDLINE, BIOSIS, WPI Data, PAJ, EMBASE		
<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	WO 00 74706 A (DALLMAN MARGARET JANE ;LORANTIS LTD (GB); HOYNE GERARD FRANCIS (GB) 14 December 2000 (2000-12-14)	1-18,20, 22-28
Y	the whole document	1-18,20, 22-28
X	WO 99 10364 A (HUMAN GENOME SCIENCES INC ;DUAN ROXANNE (US); RUBEN STEVEN M (US)) 4 March 1999 (1999-03-04)	1-17, 22-24, 26-28
Y	the whole document	1-17, 22-28
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> 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  <p style="text-align: center;">9 July 2003</p>		Date of mailing of the international search report  <p style="text-align: center;">29. 10. 2003</p>
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  <p style="text-align: center;">Lechner, O.</p>

## 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.
Y	SALDANHA G: "The Hedgehog signalling pathway and cancer." THE JOURNAL OF PATHOLOGY. ENGLAND APR 2001, vol. 193, no. 4, April 2001 (2001-04), pages 427-432, XP008015850 ISSN: 0022-3417 the whole document	1-18,20, 22-28
Y	----- LENDECKEL U ET AL: "Inhibition of alanyl-aminopeptidase suppresses the activation-dependent induction of glycogen synthase kinase-3beta (GSK-3beta) in human T cells." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. UNITED STATES 24 JUN 2000, vol. 273, no. 1, 24 June 2000 (2000-06-24), pages 62-65, XP002237295 ISSN: 0006-291X the whole document -----	1-18,20, 22-28

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 02/01666

## 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:
  
2.  Claims Nos.: 1-18, 20, 22-28 (all only 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 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:

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.:  
1-17, 22-25 (all partially), 18, 20, 21, 26-28, 48

### 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

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Continuation of Box I.2

Claims Nos.: 1-18, 20, 22-28 (all only partially)

Present claims 1-16, 22-28 relate to products defined by reference to a desirable characteristic or property, namely modulator of a Hedgehog signalling pathway, or a modulator of a pathway which is a target of the (Sonic, Indian or Desert) Hedgehog signalling/Wnt signalling pathway, an inhibitor or upregulator of the biological activity of these pathways and growth factor receptor agonists.

The claims cover 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 only a very limited number of such products. 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 products 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.

Present claims 1-18 and 20 relate to an extremely large number of possible compounds etc., i.e. derivatives, variants, mimetics, homologues, analogues (all of them without any functional limitation), agents of the cAMP signalling pathway and antibodies.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, products etc. 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.

Present claims 1-18, 20, 22-28 relate to an extremely large number of ill defined pathologic conditions/diseases circumscribed by a (patho)physiological mechanism, result to be achieved etc., i.e. T-cell mediated disease or infection, disorder associated with increased or decreased T-cell apoptosis, modification of (peripheral) T-cell, activation/proliferation/apoptosis, modulation of the Notch signalling pathway, inflammatory diseases, proliferative disorders, viral infections, infectious or genetic immunodeficiencies, cerebellar degeneration, myelodysplastic syndromes, ischemic injuries, toxin-induced diseases, wasting diseases, tumor induced aberrations to the T-cell system etc. This does not allow any practical application in the form of a defined, real treatment of a pathological condition

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

(disease).

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the diseases 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.

Present claim 21 relates to an extremely large number of possible small molecules. In fact, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

The subject matter of claim 48 relates to the "use of a modulator identifiable by a method according to any one of claims 29-47 " and, thus, do(es) not fulfil the requirements of Article 6, PCT. No meaningful search is possible, since it would require a minimum of structural information: The functional feature "modulators of Hedgehog signalling" etc. may be an inherent known or unknown feature of any known and unknown organic or inorganic compound.

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 compositions comprising and the use of the specific molecules disclosed in claims 17 and 18 for treating the specific, well characterized pathologic conditions/diseases listed in claims 22-25 as well as the general concept of influencing T-cell mediated immune responses by modulating the Hedgehog and its target pathways.

Claims 14-18, 20 and 22-25 were interpreted to refer to any of the preceding claims, as the use of a claim for treating a disease would have made no sense.

The subject matter of claims 21 and 48 has not been searched (vide supra).

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-17, 22-25 (all partially), 18, 20, 21, 26-28, 48

Use of HIP, cyclopamine, Frzb, Cerberus, WIF-1, Xnr-3, Gremlin, Follistatin, Ptc, Cos2, PKA, antibodies modulating a Hedgehog signalling pathway or one of its target signalling pathways for treating pathologic conditions/diseases involving T-cells and compositions thereof.

1.1. claims: 1-17, 22-25 (all partially), 18

Use of HIP, cyclopamine, Frzb, Cerberus, WIF-1, Xnr-3, Gremlin, Follistatin, Ptc, Cos2, PKA for treating pathologic conditions/diseases involving T-cells

1.2. claims: 1-17, 22-25 (all partially) 20

Use of antibodies modulating a Hedgehog signalling pathway or one of its target signalling pathways for treating pathologic conditions/diseases involving T-cells

1.3. claims: 26-28

Composition for use in the treatment of pathologic conditions/diseases involving T-cells

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2. claims: 1-17, 22-25 (all partially), 19, 26-28

Use of a member of the TGF-beta family, interleukins, an FLT-3 ligand or a member of the BMP superfamily for treating pathologic conditions/diseases involving T-cells

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3. claims: 29-47, 49-56

Methods for detecting modulators of Hedgehog signalling

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## INTERNATIONAL SEARCH REPORT

International Application No

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