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(71) Applicant (for all designated States except US): CURIS,
INC. [US/US]; 61 Moulton Street, Cambridge, MA 02138
(US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): BUMCROT, David,
A. [US/US]; 30 Leicester Road, Belmont, MA 02478 (US).

(74) Agents: HALSTEAD, David, P. et al.; Fish & Neave
IP group of Ropes & Gray LLP, One International Place,
Boston, MA 02110-2624 (US).

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AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,

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GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
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MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
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FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

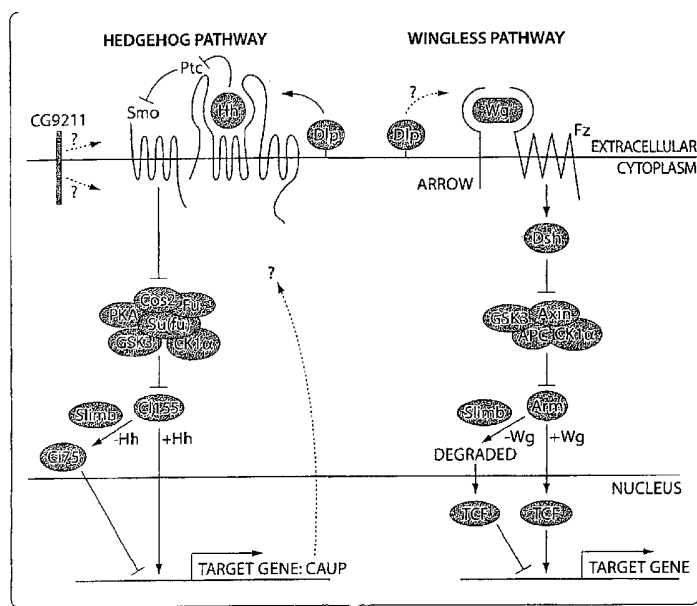
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(88) Date of publication of the international search report:
12 January 2006

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: RNA INTERFERENCE MODULATORS OF HEDGEHOG SIGNALING AND USES THEREOF



(57) Abstract: The instant application relates to methods and reagent for modulating the Hedgehog signaling pathway using RNA interference technology (RNAi). The application provides potential targets of the Hedgehog RNAi, methods to identify additional Hedgehog signaling pathway components, methods to inhibit Hedgehog signaling targets using siRNA, and their uses in the treatment of a number of disease conditions.

WO 2005/097207 A3

INTERNATIONAL SEARCH REPORT

International Application No
 /US2005/009739

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/11 A61K48/00 C12N5/06 A61P25/00 A61P35/00

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 C12N A61K

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, BIOSIS, WPI Data, 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.
P,X	SANCHEZ PILAR ET AL: "Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 101, no. 34, 24 August 2004 (2004-08-24), pages 12561-12566, XP002352148 ISSN: 0027-8424 abstract; figure 3	1-71
P,X	US 2004/072345 A1 (ALTABA ARIEL RUIZ I ET AL) 15 April 2004 (2004-04-15) paragraphs '0057! - '0059!, '0225! - '0230! ----- -/--	1-71

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.

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15/11/2005

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

Renggli-Zulliger, N

INTERNATIONAL SEARCH REPORT

national Application No

T/US2005/009739

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUM LAWRENCE ET AL: "Identification of Hedgehog pathway components by RNAi in <i>Drosophila</i> cultured cells." SCIENCE (WASHINGTON D C), vol. 299, no. 5615, 28 March 2003 (2003-03-28), pages 2039-2045, XP002352150 ISSN: 0036-8075	1,2,26, 27,30, 31, 40-42, 44,50, 56,66
Y	the whole document	3-25,28, 29, 32-39, 43, 45-49, 51-55, 57-65, 67-71
Y	----- MICHELSON ALAN M: "Running interference for hedgehog signaling." SCIENCE'S STKE 'ELECTRONIC RESOURCE! : SIGNAL TRANSDUCTION KNOWLEDGE ENVIRONMENT. 22 JUL 2003, vol. 2003, no. 192, 22 July 2003 (2003-07-22), page PE30, XP002352149 ISSN: 1525-8882 the whole document	3-25,28, 29, 32-39, 43, 45-49, 51-55, 57-65, 67-71
Y	----- MCMANUS MICHAEL T ET AL: "Gene silencing in mammals by small interfering RNAs" NATURE REVIEWS GENETICS, vol. 3, no. 10, October 2002 (2002-10), pages 737-747, XP002352198 ISSN: 1471-0056 the whole document	3-25,28, 29, 32-39, 43, 45-49, 51-55, 57-65, 67-71
Y	----- WO 2004/020599 A (CURIS, INC; DUDEK, HENRYK, K; KARAVANOV, IRINA; PEPICELLI, CARMEN; RUB) 11 March 2004 (2004-03-11) the whole document	3-25,28, 29, 32-39, 43, 45-49, 51-55, 57-65, 67-71
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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.
A	<p>THAYER S P ET AL: "Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 425, no. 23, 23 October 2003 (2003-10-23), pages 851-856, XP002987278 ISSN: 0028-0836 abstract</p>	1-71
A	<p>BELLUSCI S ET AL: "INVOLVEMENT OF SONIC HEDGEHOG (SHH) IN MOUSE EMBRYONIC LUNG GROWTH AND MORPHOGENESIS" DEVELOPMENT, COMPANY OF BIOLOGISTS, CAMBRIDGE,, GB, vol. 124, no. 1, 1997, pages 53-63, XP000877451 ISSN: 0950-1991 abstract</p>	1-71
A	<p>DAHMANE N ET AL: "Activation of the transcription factor Gli1 and the Sonic hedgehog signalling pathway in skin tumors" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 389, 23 October 1997 (1997-10-23), pages 876-881, XP002133796 ISSN: 0028-0836 abstract</p>	1-71
A	<p>RUIZ I ALTABA ARIEL ET AL: "Hedgehog-Gli signaling in brain tumors: Stem cells and paradevelopmental programs in cancer." CANCER LETTERS, vol. 204, no. 2, 20 February 2004 (2004-02-20), pages 145-157, XP002352151 ISSN: 0304-3835 the whole document</p>	1-71
A	<p>RUIZ I ALTABA ARIEL ET AL: "Gli and Hedgehog in cancer: Tumours, embryos and stem cells." NATURE REVIEWS CANCER, vol. 2, no. 5, May 2002 (2002-05), pages 361-372, XP002352152 ISSN: 1474-175X the whole document</p>	1-71

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2005/009739

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

International application No.
PCT/US2005/009739

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 53-55, 60-61 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 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
T/US2005/009739

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2004072345	A1	15-04-2004	NONE	
WO 2004020599	A	11-03-2004	AU 2003265853 A1	19-03-2004