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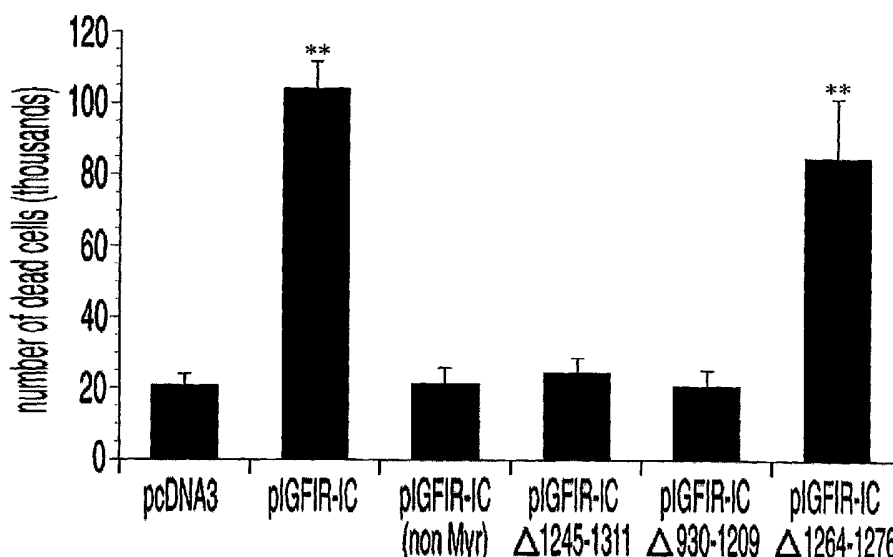
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- (72) Inventors; and
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- (74) Agents: SPAIN, Astrid, R. et al.; Campbell & Flores LLP, 7th Floor, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).
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[Continued on next page]

(54) Title: NON-APOPTOTIC FORMS OF CELL DEATH AND METHODS OF MODULATION



(57) Abstract: The invention is directed to methods for identifying molecules that modulate paraptosis, a newly identified non-apoptotic form of programmed cell death. The invention also provides a method of inhibiting paraptosis by preventing association of caspase-9 and an endogenous paraptosis-mediating molecule. In one embodiment, the invention provides a method of inhibiting paraptosis by preventing association of caspase-9 and the Insulin-Like Growth Factor I Receptor (IGFIR). The invention further is directed to therapeutic methods for treatment of pathologies associated with aberrant levels of paraptosis such as neural cell death disorders and neoplastic disorders. Also provided by the present invention are methods of identifying endogenous paraptosis-mediating molecules.



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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 (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/48261

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/50 C12Q1/37 C07K14/71 C12N9/64 A61P25/00
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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 G01N C12Q C07K C12N

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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 63 218681 A (MITSUBISHI KASEI CORP) 12 September 1988 (1988-09-12) abstract	10-12
A	--- TURMAINE M ET AL: "NONAPOPTOTIC NEURODEGENERATION IN A TRANSGENIC MOUSE MODEL OF HUNTINGTON'S DISEASE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 14, 5 July 2000 (2000-07-05), pages 8093-8097, XP000990139 ISSN: 0027-8424 cited in application abstract page 8095, column 2, line 8 -page 8096, column 2, line 12 --- -/--	1-14

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	*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
E earlier document but published on or after the international filing date	*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
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)	*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.
O document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 1 July 2002	Date of mailing of the international search report 17/07/2002
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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 Vanmontfort, D
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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.
A	RESNICOFF M ET AL: "The insulin -like growth factor I receptor protects tumor cells from apoptosis in vivo" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 55, no. 11, 1995, pages 2463-2469, XP002124515 ISSN: 0008-5472 abstract page 2467, column 2, line 19 -page 1468, column 2, line 25 ---	1-14
A	MAJNO G ET AL: "APOPTOSIS ONCOSIS AND NECROSIS AN OVERVIEW OF CELL DEATH" AMERICAN JOURNAL OF PATHOLOGY, PHILADELPHIA, PA, US, vol. 146, no. 1, January 1995 (1995-01), pages 3-15, XP000884170 ISSN: 0002-9440 cited in application the whole document ---	1-14
A	US 5 958 872 A (O'CONNOR ROSEMARY ET AL) 28 September 1999 (1999-09-28) the whole document ---	1-14
P,X	SPERANDIO SABINA ET AL: "An alternative, nonapoptotic form of programmed cell death." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 26, 19 December 2000 (2000-12-19), pages 14376-14381, XP002204088 December 19, 2000 ISSN: 0027-8424 the whole document ---	1-14
P,X	SPERANDIO S ET AL: "A proteomic approach to the characterization of non-apoptotic programmed cell death." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 869 XP001083701 31st Annual Meeting of the Society for Neuroscience; San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295 abstract ---	1-14
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/48261

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	OPPENHEIM RONALD W ET AL: "Programmed cell death of developing mammalian neurons after genetic deletion of caspases." JOURNAL OF NEUROSCIENCE, vol. 21, no. 13, 1 July 2001 (2001-07-01), pages 4752-4760, XP001084981 ISSN: 0270-6474 abstract -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
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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.: 10-12
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.2

Claims Nos.: 10-12

Present claims 10-12 relate to an extremely large number of possible compounds. 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 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 those compounds mentioned in the description at pages 16 (lines 16-22).

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/US 01/48261

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
JP 63218681	A	12-09-1988	NONE	
US 5958872	A	28-09-1999	EP 0923642 A1	23-06-1999
			JP 2000509370 T	25-07-2000
			WO 9737010 A1	09-10-1997