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[Continued on next page]

(54) Title: REAGENTS AND METHODS FOR IDENTIFYING AND MODULATING EXPRESSION OF TUMOR SENESCENCE GENES

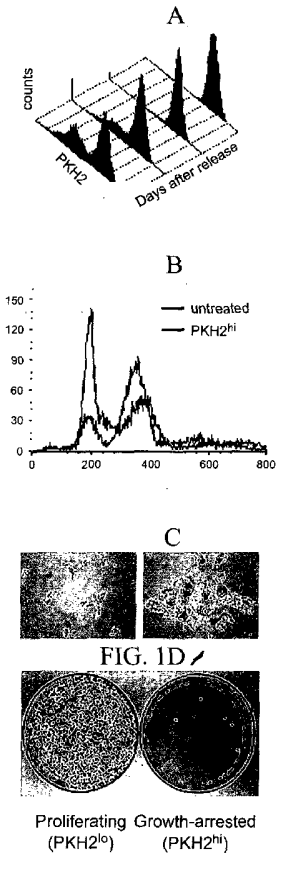

FIG. 1D

(57) Abstract: This invention identifies tumor senescence genes induced by treatment with cytotoxic agents. The invention provides reagents and methods for identifying compounds that induce expression of these cellular genes and produce cellular senescence, particularly senescence in tumor cells. The invention also provides reagents that are recombinant mammalian cells containing recombinant expression constructs that express a reporter gene under the transcriptional control of a promoter for a gene the expression of which is modulated in senescent cells, and methods for using such cells to identify compounds that modulate expression of these cellular genes.

WO 2002/061134 A3

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INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/US 01/50574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

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

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, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 10479 A (LEXICON GENETICS) 4 March 1999 (1999-03-04) page 7, line 10 -page 11, line 5; claims 1-18 page 29 ---	1-83, 86-94, 97-107
Y	GONOS EFSTATHIOS S ET AL: "Cloning and identification of genes that associate with mammalian replicative senescence" EXPERIMENTAL CELL RESEARCH, SAN DIEGO, CA, US, vol. 240, no. 1, 10 April 1998 (1998-04-10), pages 66-74, XP002207761 ISSN: 0014-4827 the whole document --- -/--	1-83, 86-94, 97-107

[X] Further documents are listed in the continuation of box C.

[X] 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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2003	11/07/2003

Name and mailing address of the ISA	Authorized officer
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	Moreno de Vega, C

INTERNATIONAL SEARCH REPORT

Int I Application No
PCT/US 01/50574

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHANG B-D ET AL: "EFFECTS OF P21WAF1/CIP1/SDI1 ON CELLULAR GENE EXPRESSION: IMPLICATIONS FOR CARCINOGENESIS, SENESCENCE, AND AGE-RELATED DISEASES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 8, April 2000 (2000-04), pages 4291-4296, XP000921392 ISSN: 0027-8424 the whole document	1-83, 86-94, 97-107
X	CHANG B D ET AL: "ROLE OF P53 AND P21 WAF1/CIP1 IN SENESCENCE-LIKE TERMINAL PROLIFERATION ARREST INDUCED IN HUMAN TUMOR CELLS BY CHEMOTHERAPEUTIC DRUGS" ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 18, August 1999 (1999-08), pages 4808-4818, XP000922555 ISSN: 0950-9232 the whole document	1-83, 86-94, 97-107
Y	CHANG BEY-DIH ET AL: "A senescence-like phenotype distinguishes tumor cells that undergo terminal proliferation arrest after exposure to anticancer agents." CANCER RESEARCH, vol. 59, no. 15, 1 August 1999 (1999-08-01), pages 3761-3767, XP002245658 ISSN: 0008-5472 the whole document	1-83, 86-94, 97-107
X	PRIMLANO THOMAS ET AL: "Activation of accelerated senescence by the cancer chemopreventive agent N-(4-hydroxyphenyl)retinamide (4-HPR) in prostate carcinoma cell lines." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 852 XP001152963 91st Annual Meeting of the American Association for Cancer Research.;San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X the whole document	1-83, 86-94, 97-107
X	WO 00 61751 A (BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS) 19 October 2000 (2000-10-19) the whole document	1-83, 86-94, 97-107

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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 01/50574

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	KRAMER DEBORA L ET AL: "Polyamine depletion in human melanoma cells leads to G1 arrest associated with induction of p21WAF1/CIP1/SDI1, changes in the expression of p21-regulated genes, and a senescence-like phenotype." CANCER RESEARCH, vol. 61, no. 21, 1 November 2001 (2001-11-01), pages 7754-7762, XP001152964 ISSN: 0008-5472 the whole document	1-83, 86-94, 97-107

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 01/50574

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.: 84, 85, 95, 96
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.: 84, 85, 95, 96

Present claims 84, 85, 95, 96 relate to an extremely large number of possible compounds and methods using them. Said compounds are very unclearly defined by a method for their identification. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is not to be found, however, for the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the claimed scope is impossible.

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

Int nal Application No
PCT/US 01/50574

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1240323 A2	18-09-2002
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