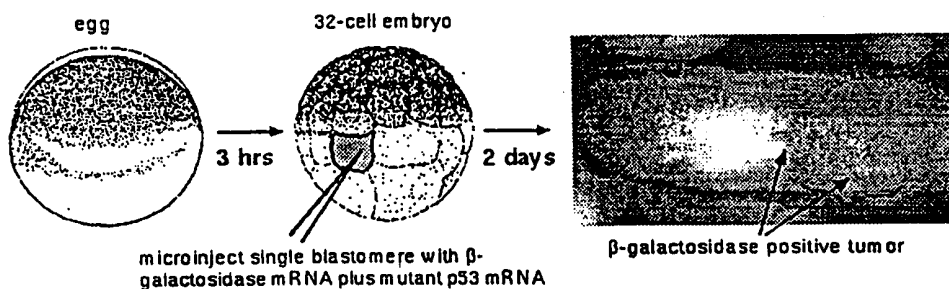




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : G01N 33/50, 33/68</p>	<p>A3</p>	<p>(11) International Publication Number: WO 99/01763</p> <p>(43) International Publication Date: 14 January 1999 (14.01.99)</p>
<p>(21) International Application Number: PCT/US98/13797</p> <p>(22) International Filing Date: 1 July 1998 (01.07.98)</p> <p>(30) Priority Data: 60/051,549 2 July 1997 (02.07.97) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/051,549 (CIP) Filed on 2 July 1997 (02.07.97)</p> <p>(71) Applicant (for all designated States except US): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): VIZE, Peter, D. [US/US]; 903 Shelley Avenue, Austin, TX 78703 (US). WALLINGFORD, John, B. [US/US]; 903 Shelley Ave, Austin, TX 78703 (US).</p> <p>(74) Agent: HIGHLANDER, Steven, L.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 25 March 1999 (25.03.99)</p>

(54) Title: p53 AS A REGULATOR OF CELL DIFFERENTIATION



(57) Abstract

The present invention involves the role of p53 in the differentiation of embryonic tissues. More particularly, the present invention provides methods of the blocking of p53 function in embryonic tissues, and the use of these tissues as screening tools for substances that are capable of overcoming the p53-related block in differentiation, both *in vitro* and *in vivo*. The similarities between undifferentiated embryonic cells and tumor cells is evident, and thus these assays serve as a model for possible cancer therapeutics. In addition, methods for identifying additional cellular components that interact p53 or p53-related pathways are provided.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/13797

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 G01N33/50 G01N33/68				
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 6 G01N C07K 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)				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 91 13150 A (MEDICAL RES COUNCIL ;LUDWIG INST CANCER RES (GB)) 5 September 1991 see page 23, line 7 - line 13 see page 30, line 12 - line 20 see claim 20	1,2,7,8, 23,26		
A	WO 97 11367 A (CIBA GEIGY AG ;CHENE PATRICK (FR); HOCHKEPPEL HEINZ KURT (CH)) 27 March 1997 see the whole document	1-27		
A	EP 0 518 650 A (UNIV JOHNS HOPKINS ;PHARMAGENICS INC (US)) 16 December 1992 see the whole document	1-27		
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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 :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
"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 <div style="text-align: center; font-size: 1.2em;">13 October 1998</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">07. 01. 99</div>		
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 <div style="text-align: center; font-size: 1.2em;">Hoekstra, S</div>		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/13797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 14777 A (WU LELIA ;BISCHOFF JAMES R (US); ONYX PHARMACEUTICALS (US)) 1 June 1995 see page 5 - page 11 ---	1-27
A	WO 93 20238 A (UNIV JOHNS HOPKINS) 14 October 1993 see the whole document ---	14
A	MOMAND J ET AL: "THE MDM-2 ONCOGENE PRODUCT FORMS A COMPLEX WITH THE P53 PROTEIN AND INHIBITS P53-MEDIATED TRANSACTIVATION" CELL, vol. 69, no. 7, 26 June 1992, pages 1237-1245, XP000673412 see the whole document ---	1-27
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/13797

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.:
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 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.:

1-27

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

1. Claims: 1-27

Methods for screening agents that inhibit a p53 related block of embryonic cell differentiation, comprising blocking p53 function and contacting the cell with candidate agents and subsequent monitoring of differentiation.

2. Claims: 28-33

Method for identifying genes involved in p53-mediated embryonic cell differentiation comprising a dominant negative mutant of p53 regulated by a developmentally regulated promoter in *D. melanogaster* cells, mutagenising the cells and assessing a trait normally regulated by said promoter and subsequently identifying the mutated cellular product.

3. Claims: 34-56

Method for identifying genes involved in p53-mediated embryonic cell differentiation comprising a dominant negative mutant of p53 regulated by an inducible promoter in pluripotent embryonic cells, mutagenising the cells and assessing a trait normally regulated by said promoter and subsequently identifying the mutated cellular product.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/13797

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