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60/895,606 19 March 2007 (19.03.2007) US
- (63) **Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:**  
US 60/853,208 (CON)  
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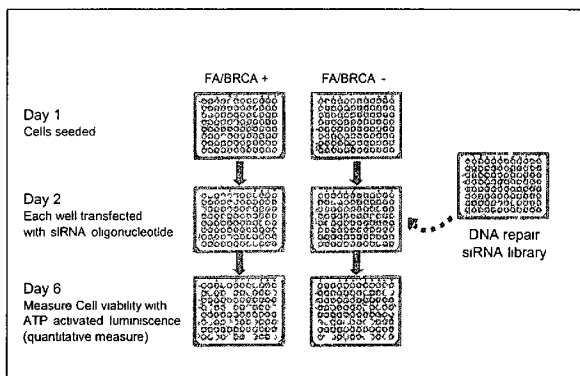
Binney Street, Boston, MA 021 15-6084 (US). **DNAR, INC** [US/US]; 8 Saint Mary's Street, Boston, MA 02215 (US). **OREGON HEALTH AND SCIENCE UNIVERSITY** [US/US]; Technology & Research Collaborations, Mailcode: AD120, 2525 SW 1st Ave, Suite 120, Portland, OR 97201 (US).

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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FT, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,

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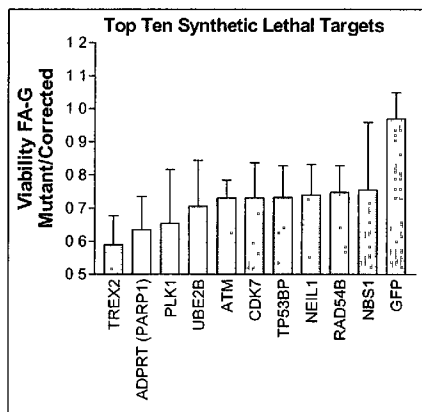
(54) **Title:** DNA DAMAGE REPAIR INHIBITORS AND METHODS FOR TREATING CANCER

a)



(57) **Abstract:** This present invention relates compositions and methods of treating cancer and methods of accessing/monitoring the responsiveness of a cancer cell to a therapeutic compound, specific for a DNA repair pathway. A method for treating cancer is provided, which includes: a) determining whether the cancer cell is deficient in a DNA repair pathway (eg. Fanconi anemia) and b) administering a DNA damaging agent or inhibitor specific for at least one different DNA repair pathway than that identified in step (a) (eg. mismatch repair or non-homologous endjoining repair pathways).

b)



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IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, ZA, ZM, ZW.

**(84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, 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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# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. 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)  
 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 , EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/012524 A (UNIV SHEFFIELD [GB]; HELLEDAY THOMAS [SE]) 10 February 2005 (2005-02-10)	1-15, 25-42
Y	page 2, line 15 - page 6, line 7 page 10 - page 17 claims 1-32	16-24
X	WO 2005/053662 A (KUDOS PHARM LTD [GB]; INST OF CANCER RES [GB]; ASHWORTH ALAN [GB]; JAC) 16 June 2005 (2005-06-16)	1-15, 25-42
Y	page 1 - page 5 pages 9,11,13-, column 17 pages 26-27 claims 1-67	16-24

Further documents are listed in the continuation of Box C.

See patent family 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.
- \*&1 document member of the same patent family

Date of the actual completion of the international search

3 June 2008

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20/06/2008

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/022439

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCCABE NUALA ET AL: "Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition." CANCER RESEARCH 15 AUG 2006, vol . 66, no. 16, 15 August 2006 (2006-08-15) , pages 8109-8115, XP002482543 ISSN: 1538-7445 cited in the application	1-15 , 25-42
Y	the whole document	16-24
X	BRYANT H E ET AL: "Inhibition of poly(ADP-ribose) polymerase activates ATM which is required for subsequent homologous recombination repair" NUCLEIC ACIDS RESEARCH 2006 GB, vol . 34, no. 6, 2006 , pages 1685-1691 , XP002482544 ISSN: 0305-1048 1362-4962	1-15 , 25-42
Y	the whole document	16-24
X	CURTIN NICOLA J ET AL: "Novel poly(ADP-ribose) polymerase-1 inhibitor, AG14361, restores sensitivity to temozolomide in mismatch repair-deficient cells." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 FEB 2004, vol . 10, no. 3, 1 February 2004 (2004-02-01) , pages 881-889, XP002482545 ISSN: 1078-0432	1-15, 25-42
Y	the whole document	16-24
X	wo 03/039327 A (DANA FARBER CANCER INST. INC [US] ; UNIV OREGON HEALTH & SCIENCE [US] ; D) 15 May 2003 (2003-05-15)	9-21 , 28-43
Y		1-8, 22-27
X	MADHUSUDAN ET AL: "The emerging role of DNA repair proteins as predictive prognostic and therapeutic targets in cancer" CANCER TREATMENT REVIEWS, SAUNDERS, US, vol . 31, no. 8, 1 December 2005 (2005-12-01) , pages 603-617, XP.005168388 ISSN: 0305-7372	25-43
Y		1-24

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/022439

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERNSTEIN C ET AL: "DNA REPAIR/PRO-APOPTOTIC DUAL-ROLE PROTEINS IN FIVE MAJOR DNA REPAIR PATHWAYS: FAIL-SAFE PROTECTION AGAINST CARCINOGENESIS" MUTATION RESEARCH, AMSTERDAM, NL, vol . 511, no. 2, 1 June 2002 (2002-06-01 ), pages 145-178, XP009045915 ISSN: 0027-5107	28-43
Y	the whole document	1-27
Y	TANIGUCHI TOSHIYASU ET AL: "Convergence of the fanconi anemia and ataxia telangiectasia signaling pathways ." CELL 17 MAY 2002, vol . 109, no. 4, 17 May 2002 (2002-05-17) , pages 459-472 , XP002482546 ISSN: 0092-8674 the whole document	1-43
Y	HO GARY P H ET AL: "Phosphorylation of FANCD2 on two novel sites is required for mitomycin C resistance. " MOLECULAR AND CELLULAR BIOLOGY SEP 2006, vol . 26, no. 18, September 2006 (2006-09) , pages 7005-7015, XP002482547 ISSN: 0270-7306 the whole document	1-43
X <sub>5</sub> P	KENNEDY RICHARD D ET AL: "Fanconi anemia pathway-deficient tumor cells are hypersensitive to inhibition of ataxia telangiectasia mutated. " THE JOURNAL OF CLINICAL INVESTIGATION MAY 2007, vol . 117, no. 5, May 2007 (2007-05) , pages 1440-1449 , XP002482548 ISSN: 0021-9738 the whole document	1-43
X,P	WANG XIAOZHE ET AL: "Chkl-mediated phosphorylation of FANCE is required for the Fanconi anemia/BRCA pathway. " MOLECULAR AND CELLULAR BIOLOGY APR 2007, vol . 27, no. 8, April 2007 (2007-04) , pages 3098-3108, XP002482549 ISSN: 0270-7306 the whole document	1-43
x,P	wo 2006/127978 A (DANA FARBER CANCER INST INC [US] ; D ANDREA ALAN D [US] ; TANIGUCHI TOSH) 30 November 2006 (2006-11-30) the whole document	1-43

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/022439

Box No. 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 1-8, 11-15 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 No. 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 allsearchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No <b>PCT/US2007/022439</b>
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005012524    A	10-02-2005	AU 2004261779 A1	10-02--2005
		BR PI0412909 A	26-09--2006
		CA 2533423 A1	10-02--2005
		CN 1856572 A	01-11--2006
		CN 1856313 A	01-11--2006
		EP 1649017 A1	26-04--2006
		GB 2419882 A	10-05--2006
		JP 2006528618 T	21-12--2006
		KR 20060052877 A	19-05--2006
		US 2007179160 A1	02-08--2007
WO 2005053662    A	16-06-2005	AU 2004294790 A1	16-06-2005
		BR PI0417056 A	06-02-2007
		CA 2547077 A1	16-06-2005
		EP 1684736 A1	02-08-2006
		OP 2007516241 T	21-06-2007
		KK 20060123403 A	01-12-2006
WO. 03039327    A	15-05-2003	AU 2000280389 A1	19-05-2003
		CA 2465949 A1	15-05-2003
		EP 1451343 A2	01-09-2004
WO 2006127978    A	30-11-2006	AU 2006249807 A1	30-11-2006
		CA 2609751 A1	30-11-2006
		EP 1904088 A2	02-04-2008