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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, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, IT, 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).
- Published:**
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- 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.



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(54) Title: POLYMORPHISM IN THE HUMAN NBS1 GENE USEFUL IN DIAGNOSTIC OF INHERITED PREDISPOSITION TO CANCER

(57) Abstract: The present invention relates to methods and kits for determining a predisposition and surveillance protocols for developing cancer, e.g., prostate and/or breast cancer due to germline mutation of the NBS 1 gene.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL2004/000044

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 C12N15/63 A01K67/027 A61K48/00 A61P43/00

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 C12Q 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, EMBASE, 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	<p>GORSKI BOHDAN ET AL: "GERMLINE 657DEL5 MUTATION IN THE NBS1 GENE IN BREAST CANCER PATIENTS" INTERNATIONAL JOURNAL OF CANCER, vol. 106, no. 3, 16 May 2003 (2003-05-16), pages 379-381, XP008040558 ISSN: 0020-7136 the whole document</p> <p style="text-align: center;">-/--</p>	<p>1, 2, 8, 11, 24-26, 34-37, 39, 40, 43-62</p>

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

23 March 2005

Date of mailing of the international search report

31/03/2005

Name and mailing address of the ISA

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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.
	<p>-& GORSKI B ET AL: "GERMLINE 657DEL5 MUTATION IN THE NBS1 GENE IN BREAST CANCER PATIENTS" INTERNET ABSTRACT, 'Online! 16 May 2003 (2003-05-16), XP002314494 ISSN: 0020-7136 Retrieved from the Internet: URL:http://www3.interscience.wiley.com/cgi-bin/abstract/104533362/ABSTRACT> 'retrieved on 2005-01-21! Indicates the online publication date of XP0008040558. abstract</p> <p>-----</p>	
X	<p>WO 99/55716 A (VIRGINIA MASON RES CENTER) 4 November 1999 (1999-11-04)</p> <p>page 4, line 1 - line 4 page 5, line 29 - line 30 page 40, line 1 - line 5 page 28, line 20 - line 28 page 29, line 10 - page 31 table 1 figure 1B figure 2A</p>	<p>1-9,11, 13-24, 26-28, 34-37, 39,40, 60,61</p>
Y	<p>-----</p>	25,43-46
X	<p>VARON R ET AL: "NIBRIN, A NOVEL DNA DOUBLE-STRAND BREAK REPAIR PROTEIN, IS MUTATED IN NIJMEGEN BREAKAGE SYNDROME" CELL, CELL PRESS, CAMBRIDGE, NA, US, vol. 93, 1 May 1998 (1998-05-01), pages 467-476, XP002921650 ISSN: 0092-8674</p>	<p>1-9,11, 13-24, 26,28, 34-37, 39,40, 60,61</p>
Y	<p>-----</p>	25,43-62
X	<p>MASER RICHARD S ET AL: "An alternative mode of translation permits production of a variant NBS1 protein from the common Nijmegen breakage syndrome allele" NATURE GENETICS, vol. 27, no. 4, April 2001 (2001-04), pages 417-421, XP002313420 ISSN: 1061-4036 the whole document</p> <p>-----</p>	<p>1-9,11, 13-23, 38-40</p>
	<p>-----</p> <p style="text-align: center;">-/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/PL2004/000044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PLISIECKA-HALASA J ET AL: "Nijmegen breakage syndrome gene (NBS1) alterations and its protein (nibrin) expression in human ovarian tumours." ANNALS OF HUMAN GENETICS, vol. 66, no. 5-6, November 2002 (2002-11), pages 353-359, XP008041446 ISSN: 0003-4800	1,2,8, 11,24, 26, 34-37, 39,40
Y	the whole document	25,43-62
X	VARON R ET AL: "Mutations in the Nijmegen Breakage Syndrome gene (NBS1) in childhood acute lymphoblastic leukemia (ALL)." CANCER RESEARCH. 1 MAY 2001, vol. 61, no. 9, 1 May 2001 (2001-05-01), pages 3570-3572, XP002313421 ISSN: 0008-5472	1,2,8, 11,24, 26, 34-37, 39,40
Y	the whole document	25,43-62
X	RESNICK IGOR B ET AL: "657de15 mutation in the gene for Nijmegen breakage syndrome (NBS1) in a cohort of Russian children with lymphoid tissue malignancies and controls." AMERICAN JOURNAL OF MEDICAL GENETICS. 15 JUL 2003, vol. 120A, no. 2, 15 May 2003 (2003-05-15), pages 174-179, XP002313422 ISSN: 0148-7299	1,2,8, 11,24, 26, 34-37, 39,40
Y	the whole document -& RESNICK IGOR B ET AL: "657de15 mutation in the gene for Nijmegen breakage syndrome (NBS1) in a cohort of Russian children with lymphoid tissue malignancies and controls." INTERNET ABSTRACT, 'Online! 15 May 2003 (2003-05-15), XP002313423 ISSN: 0148-7299 Retrieved from the Internet: URL:http://www3.interscience.wiley.com/cgi-bin/abstract/104531847/ABSTRACT> 'retrieved on 2005-01-12! Indicates the online publication date of XP002313422. abstract	25,43-62
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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>KANG JIAN ET AL: "Targeted disruption of NBS1 reveals its roles in mouse development and DNA repair" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 21, no. 6, 15 March 2002 (2002-03-15), pages 1447-1455, XP002313424 ISSN: 0261-4189 the whole document</p>	
A	<p>CEROSALETTI KAREN M ET AL: "Retroviral expression of the NBS1 gene in cultured Nijmegen breakage syndrome cells restores normal radiation sensitivity and nuclear focus formation" MUTAGENESIS, vol. 15, no. 3, May 2000 (2000-05), pages 281-286, XP008041328 ISSN: 0267-8357 the whole document</p>	
P,X	<p>CYBULSKI C ET AL: "NBS1 is a prostate cancer susceptibility gene." CANCER RESEARCH, vol. 64, no. 4, 15 February 2004 (2004-02-15), pages 1215-1219, XP002313426 ISSN: 0008-5472 the whole document</p>	<p>1,2,8, 11, 24-26, 34-37, 39,40, 43-62</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/PL2004/000044

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 27 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the compounds used for such treatment and their alleged effects.
2. Claims Nos.: 10, 12, 29, 30-33, 41, 42, 63
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 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 27 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the compounds used for such treatment and their alleged effects.

Continuation of Box II.2

Claims Nos.: 10,12,29,30-33,41,42,63

Due to the fact that claim 10 only relates to an antibody which specifically recognizes an epitope of a protein variant of NBS1 associated with an increased inherited predisposition to cancer which is considered not to be supported by the underlying application (Art. 6 PCT) and due to the fact that no such antibodies are exemplified in the underlying application, a meaningful search for claim 10 was not possible.

Claim 12 refers to a nucleic acid molecule defined by a desirable characteristic or property, namely being able to cleave the polynucleotide of claim 1. This functional feature is considered to be unclear (Art. 6 PCT) because the application does not disclose any distinctive structural feature associated to it. This unclear technical feature therefore entails doubts as to the subject-matter covered by that claim. Due to the fact that no such nucleic acid molecule is exemplified in the underlying application, the lack of clarity in the present case is such as to render a meaningful search impossible.

Although claim 29 is directed to methods of making a pharmaceutical composition, the method claimed comprise the additional steps of identifying the compound to which the pharmaceutical composition relate, i.e. the steps of the methods of any one of claims 17-23. The steps of identifying a compound with a desirable characteristic or property is however not technically related to a method of formulating a pharmaceutical composition. Claim 29 therefore represents a combination of two different and irreconcilable types of process claims, so that the subject matter for which protection is sought is not clearly defined (Art. 6 PCT). Furthermore the compound the pharmaceutical composition relates to is not clearly defined because the compound is only defined by reference to a desirable characteristic or property (see also reasoning below). Claim 29 therefore is considered to lack clarity to such an extent that a meaningful search was not possible.

Present claims 30-33,41,42 relate to compounds wherein the compounds are only defined by reference to desirable characteristics or properties. However, a functional features only defining the result to be achieved in connection with an indefinite structural feature, as is the case here, cannot assist in rendering a claim clear (Art. 6 PCT), since it still leaves open what exactly the subject-matter is for which patent protection is sought. Due to the fact that no such compounds are exemplified in the underlying application, the lack of clarity in the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

present case is such as to render a meaningful search impossible.

Claim 63 refers to a protocol which is only defined by its intended use. In this case, the intended use cannot assist in rendering the claim clear, since it does not clearly define the subject matter for which patent protection is claimed. The intended limitations are therefore not clear from this claim, contrary to the requirements of Art. 6 PCT. The lack of clarity is such, that a meaningful search was not possible for this claim.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/PL2004/000044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955716	A	AU 3762499 A	16-11-1999
		WO 9955716 A1	04-11-1999
		US 6458534 B1	01-10-2002
