UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/483,554	06/7/95	SKOLNICK	M 24894-109347

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18N2/0327

EXAMINER	
RAZZAQUE, A	
ART UNIT	**PAPER NUMBER**
1819	15

DATE MAILED: 03/27/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 2/5/97

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-84 is/are pending in the application.

Of the above, claim(s) 39-43, 69-76, 78-84 is/are withdrawn from consideration.

☑ Claim(s) 1, 2, 4-8, 20-22, 26, 27, 44, 45, 47, 48 is/are allowed.

☑ Claim(s) 3, 9-19, 23-25, 28-30, 31-38, 46, 49-68, 77 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-410-238/40050

DETAILED ACTION

Applicants' election with traverse of restriction requirement in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the applicants believe that the claims are sufficiently related and fall into 5 or 7 groups as mentioned in Paper No.14. Applicants argue that there is no undue burden on the Examiner for searching the claimed subject matter, therefore, inclusion of the subject matter as applicants proposed would be precise. These arguments are not persuasive. Applicants regrouping include claims 77-84 in group I, which is not proper because claims 78-84 are drawn to a transgenic animal for screening potential cancer therapeutic, while claims 1-38, 44-45 are drawn to an isolated DNA encoding a BRCA1 polypeptide, a vector containing the BRCA1 gene, transformed cells with the recombinant vector, method of producing BRCA1 polypeptide and primers for determining the BRCA1 gene. The transgenic animals are quite different from a gene, vector, method of production and a primer-directed identification of a gene. Transgenic animals are not required to make or use the compositions of I. DNA (class 435) does not make animals (class 800) obvious. Further searches are required for transgenic animal art and for in vivo testing, all classified separately.

Claims 1-84 are pending. However, due to applicants election and in view of a notification published in the *Official Gazette* on 26, 1996 which establishes guidelines for treatment of product and process claims in light of *In re Ochiai* and *In re Brouwer*, claims 1-38, 44 and 45 in group I will be rejoined with claims 46-48, 49-68 and 77, and will be examined in this Office

action. Claims 39-43 and claims 78-84 are withdrawn from consideration. The requirement is still deemed proper and is therefore made **FINAL.**

Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 46 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10-14, 16-19 and 28-30 of copending Application No. 08/488011. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain overlapping subject matter. The claims of the instant invention are drawn to a method for identifying a mutant BRCA1 nucleotide sequence comprising comparing the nucleotide sequence of the suspected mutant BRCA1 allele with the wild-type BRCA1 sequence, while the claims of '011 are drawn to a method of screening which encompasses the steps of comparing the BRCA1 sequence from a tissue sample of a

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subject with that of the wild-type BRCA1 sequence. The various ways of comparing the sequences in both sets of claims are the same. Therefore, the claimed methods are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 46 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10-14, 16-19 and 29-30 of copending Application No. 08/487,002. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain overlapping subject matter. The claims of the instant invention are drawn to a method for identifying a mutant BRCA1 nucleotide sequence comprising comparing the nucleotide sequence of the suspected mutant BRCA1 allele with the wild-type BRCA1 sequence, while the claims of '002 are drawn to a method of screening which encompasses the steps of comparing the BRCA1 sequence from a tissue sample of a subject with that of the wild-type BRCA1 sequence. The various ways of comparing the sequences in both sets of claims are the same. Therefore, the claimed methods are obvious variants. OK

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 3, 9-19, 23-25, 28-30, 33-35, 38, 49-68 and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA (SEQ ID:1) coding for a BRCA1 polypeptide (SEQ ID: 2) and a method of supplying a wild-type BRCA1 gene function, does not reasonably provide enablement for all allelic variants of SEQ ID:1, for all mutants of SEQ ID: 1 or 2 and for an in vivo method of supplying a wild-type gene function in host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to any allelic variant of SEQ ID:1 and any mutant of SEQ ID:1 or 2 including deletion, insertion, nonsense mutation, missense mutation, but the specification is not enabling for such broad claims pertaining to this invention. The specification does not provide adequate information how to make such numerous types of mutants and use each and every kind of mutant of the BRCA1 gene. The specification does not teach what kinds of insertion sequence would be used to make an insertion mutant and, similarly, what specific sequences or how many base pairs would be deleted to make a deletion mutant. The specification does not teach what would be the rationality of making such deletion or insertion mutants and also for making numerous other types of mutants of the BRCA1 gene. There is no evidence that all of these mutants would be useful in the art.

Regarding the method of supplying a wild-type BRCA1 gene function (claim 49-68) to a cell which has lost said gene function or has altered gene function by virtue of a mutation in the BRCA1 gene, the specification is only enabling for a method of supplying gene function in vitro. Specification has not provided guidelines for achieving gene therapy when a BRCA1 gene containing vector is inserted into a host such that there is suppression of a tumor or that the gene has caused a physiological change in the host. The specification describes that the wild-type BRCA1 gene or a part thereof when introduced into a mutant cell, it recombines with the endogenous mutant BRCA1 gene, and results in the correction of the BRCA1 gene mutation. However, the specification does show any example of such correction of mutations using the desired BRCA1 gene. The specification does not teach what would be the efficiency of such corrections and whether the result would be a suppression of a tumor cell growth. Mere description of a process is not sufficient for artisan to practice the invention without undue experimentation. In vivo gene function, i.e. gene therapy causing a beneficial physiological change in the host would require sufficient expression of a desired gene. Applicants have not provided any evidence of expression of the isolated BRCA1 gene in vivo and has not shown any correlation of its expression to any physiological change in the host.

Achievement of a beneficial physiological effect based on a desired gene expression in vivo is highly unpredictable because of problems of gene transfer and sufficient level of gene expression in vivo in different species including human. In this regard, recent reviews indicate

that expression of a desired therapeutic gene is usually low in vivo, depends on the gene, and requires an accurate and efficient delivery system (Targeted Gene Therapy, 1995, Vol. 9, p. 190, col.1). Recent reviews also teach that efficient delivery and expression of foreign DNA has not been achieved by any method. For example, Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (Science, 1995, Vol. 269, p.1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (Science, 1995, Vol. 269, p.1054, col. 3). According to the art, "The actual vectors - how we're going to practice our trade - have not been discovered" (Science, 1995, Vol. 269, p. 1055, col. 2). Miller and Vile also review the types of vectors available for in vivo gene transfer and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (Targeted Gene Therapy ,1995, Vol. 9, p. 198, col. 1). In the instant application, applicants have not shown any evidence of any level of expression in vivo or evidence of any recombinational events causing a physiological change in the host. Applicant does not teach how much expression of a desired BRCA1 gene would make a beneficial physiological change to the host. There is no evidence that applicants have overcome the above mentioned obstacles and undue experimentation would be required to practice the invention as claimed.

Claim 77 is drawn to a method of screening potential cancer therapeutics by growing a transformed cells containing an altered BRCA1 gene in the presence of a potential cancer therapeutic, but it is not clear whether the altered BRCA1 gene is causing cancer. Specific cells can be transformed with any normal or abnormal gene and can be tested for growth in presence of a desired substance, but applicants are meaning to identify the cancer therapeutics. Rejection of this can be overcome by amending the claim to read "an altered BRCA1 gene causing cancer".

For the reasons discussed above it would require undue experimentation for one skilled in the art to make and use the claimed compositions and methods, particularly given the quantity of experimentation, the unpredictability of the art and the breadth of the claims.

Claims 16-19, 31-38, 52, 53 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 17 are indefinite because it is not clear whether an isolated 15 nucleotide contains a mutation or not, as these are dependent on claims 10 and 11, respectively. OK

Claim 31-38 are indefinite in their recitation of "recombinant host cells" or "recombinant BRCA1 polypeptide". This term has no specific meaning, and encompasses natural recombinants. Because DNA constantly undergoes recombination in cells or living organisms, many skilled in the OK

art consider all DNA sequences "recombinant" in cells (Watson et al., p. 313). Therefore, it is not clear what limitation is intended by the word "recombinant".

Claims 52 and 53 are indefinite in their use of the term " substantially homologous", which is contrary to its art-recognized definition. "Homology" is understood to refer to qualitative evolutionary relationships rather than quantitative measures of sequence similarity. While similar sequences may in fact be homologous, there is no way to ascertain whether any two given sequences are derived from a common ancestral gene. See MPEP 608.01(o). For purposes of experimentation, "homologous" is interpreted to mean "similar". OK

Claim 77 is indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The claim should read comparison of growth rate of cells transformed with an altered BRCA1 gene causing cancer with that of normal cells. OK

The claims are free of the prior art. At the time of the instant invention, the prior art did not teach or suggest an isolated BRCA1 gene or portion thereof with specific mutations and there production along with gene function in vitro.

Claims 1, 2, 4-8, 20-22, 26-27, 44-45 and 47-48 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdur Razzaque whose telephone number is (703) 305-4061. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Abdur Razzaque

March 18, 1997

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
08/483554	1819	15

APPLICANT(S): Skolnick et al

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG.	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R: E. Marshall (1995) Science 269: 1050-1055

S: Vile et al (1995) Targeted Gene Therapy 9: 190-199.

T: ~~Ed~~ Molecular Biology of the Gene, 4th edition, Vol. 1 Eds. J. D. Watson et al., 1987, P. 313

U:

EXAMINER: Abdel Razzaq | DATE: 3/25/97 | 181

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

Form PTO 948 (Rev. 10-94) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 483574

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date)_____; are
A.___ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B.__X__ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - ___ Not black solid lines. Fig(s)_____
   - ___ Color drawings are not acceptable until petition is granted. Fig(s) _____
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - X Photographs are not acceptable until petition is granted. Fig(s) _____
   - ___ Photographs not properly mounted (must use brystol board or photographic double-weight paper). Fig(s)_____
   - ___ Poor quality (half-tone). Fig(s)_____
3. GRAPHIC FORMS. 37 CFR 1.84 (d)
   - ___ Chemical or mathematical formula not labeled as separate figure. Fig(s)_____
   - ___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s)_____
   - ___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s)_____
4. TYPE OF PAPER. 37 CFR 1.84(c)
   - ___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)_____
   - X Erasures, ~~alterations, overwritings, interlineations~~, cracks, creases, and folds copy machine marks not accepted. Fig(s) _____
   - ___ Mylar, velum paper is not acceptable (too thin). Fig(s) _____
5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:
   - 21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
   - 21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
   - 21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
   - 21.0 cm. by 29.7 cm. (DIN size A4)
   - ___ All drawing sheets not the same size. Sheet(s)_____
   - ___ Drawing sheet not an acceptable size. Sheet(s) _____
6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Paper size	21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm X 33.1 cm. (8 1/2 X 13 inches)	21.6 cm. X 27.9 cm. (8 1/2 X 11 inches)	21.0 cm. X 29.7 cm. (DIN Size A4)
T	5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5cm.
L	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	2.5 cm.
R	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.5 cm.
B	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm.

Margins do not conform to chart above.
Sheet(s)_____
___Top (T) ___Left (L) ___Right(R) ___Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   - ___ All views not grouped together. Fig(s)_____
   - ___ Views connected by projection lines or lead lines. Fig(s)_____
   - Partial views. 37 CFR 1.84(h) 2
   - ___ View and enlarged view not labled separatly or properly. Fig(s)_____
   - Sectional views. 37 CFR 1.84 (h) 3
   - ___ Hatching not indicated for sectional portions of an object. Fig(s)_____
   - ___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)_____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ___ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)_____
9. SCALE. 37 CFR 1.84(k)
   - ___ Scale not large enough to show mechanism with crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)_____
   - ___ Indication such as "actual size" or scale 1/2" not permitted. Fig(s)_____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - X Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s) 1-10
11. SHADING. 37 CFR 1.84(m)
    - ___ Solid black shading areas not permitted. Fig(s)_____
    - ___ Shade lines, pale, rough and blurred. Fig(s)_____
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - ___ Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(l) Fig(s)_____
    - ___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(l) Fig(s)_____
    - ___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)_____
    - ___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)_____
13. LEAD LINES. 37 CFR 1.84(q)
    - ___ Lead lines cross each other. Fig(s)_____
    - ___ Lead lines missing. Fig(s)_____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)_____
15. NUMBER OF VIEWS. 37 CFR 1.84(u)
    - ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)_____
    - ___ View numbers not preceded by the abbreviation Fig. Fig(s)_____
16. CORRECTIONS. 37 CFR 1.84(w)
    - ___ Corrections not made from prior PTO-948. Fig(s)_____
17. DESIGN DRAWING. 37 CFR 1.152
    - ___ Surface shading shown not appropriate. Fig(s)_____
    - ___ Solid black shading not used for color contrast. Fig(s)_____

COMMENTS:

ATTACHMENT TO PAPER NO. 15 REVIEWER _____ DATE 8/7/02

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