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(54) Title: METHODS AND COMPOSITIONS FOR DETERMINING METHYLATION PROFILES

(57) Abstract: METHODS AND COMPOSITIONS FOR DETERMINING METHYLATION PROFILESABSTRACT OF THE DISCLOSURE Methods and compositions for determining the methylation profile of individuals and using the profiles to identify clones with desired traits.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/35970

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/68; C12P 19/34; C07H 21/02, 21/04
US CL : 435/6, 91.2; 536/23.1, 24.3
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)
U.S. : 435/6, 91.2; 536/23.1, 24.3

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 practicable, search terms used)
WEST, PubMED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	YAN, P.S. et al. "CpG Island Arrays: An Application toward Deciphering Epigenetic Signatures of Breast Cancer", Clin. Cancer Res., April 2000, vol. 6, pp. 1432-1438; see Abstract; page 1433; Fig. 1	1, 5, 7-10, 12, 18, 19, 23, 25, 27 --- 2-6, 11, 13-17, 20-22, 26, 28-30
Y	US 6,331,393 B1 (LAIRD et al.) 18 December 2001; Fig. 2, 3; col. 7, lines 26-56	3

☐ 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 application or patent 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

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/35970

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim 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. ☐ Claim 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:
Please See Continuation 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.: 1-30

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

C) Parent individual is a fungus (claim 50).
D) Parent individual is a prokaryote (claim 51).

The following claim(s) are generic: 1, 43.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each of the organisms, tissues or cells represents unique features and properties of methylation patterns.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-30, drawn to a special technical feature of a method of determining a methylation profile of a cell, tissue or organism by providing a population of randomly cleaved DNA from the cell or organism, the DNA comprising the first and second portions, separating the second portion into two sub-portions, quantifying the relative amount of a specific sequence in at least two samples selected from the group consisting of the first portion, the methylated sub-portion and the methylated sub-portion, determining the methylation profile.

Group II, claim(s) 31-42, drawn to a special technical feature of a polynucleotide microarray hybridizing to first and second labeled DNA portions.

Group III, claim(s) 43-62, drawn to a special technical feature of a method for producing an epigenetically uniform or diverse population of progeny from one or more parent individuals, the metho comprising the steps of:
a. determining the genomic methylation profile of sexually or asexually propagated progeny of a parent individual; and
b. selecting progeny exhibiting a uniform or diverse methylation profile, thereby producing an epigenetically uniform population from one or more parent individuals.

Group IV, claim(s) 63 and 64, drawn to a special technical feature of a method of associating heterosis with a methylation profile, the method comprising,
crossing individuals to produce progeny;
determining the methylation profile of the individuals and the progeny; and
comparing a trait of the progeny with the methylation profiles of the individuals, thereby associating appearance of the trait with a the methylation profle.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Yan et al. (Clin. Cancer Res., vol. 6, pp. 1432-1438, April 2000), teach polynucleotide microarrays hybridizing to different DNA populations (page 1433, fourth paragraph; Fig. 1), therefore the is no contribution over prior art from the claims.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Group I.

A) Organism is a plant (claim 13).
B) Organism is a fungus (claim 14).
C) Organism is a prokaryote (claims 15-17).
D) Organism is an animal (claims 18 and 19).
E) Cell is a stem cell (claim 20).
F) Cell is a transgenic cell (claims 21 and 27).
G) Tissue is blood (claims 22 and 27).
H) Tissue is biopsy tissue (claim 23 and 27).
I) Tissue is resected tissue (claim 24 and 27).
J) Tissue is normal (claims 25 and 27).
K) Tissue is precancerous (claim 26).

Group III

A) Parent individual is a plant (claim 48).
B) Parent individual is an animal (claim 49).