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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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20 July 2006

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.

(54) Title: GENE EXPRESSION SIGNATURES, METHODS AND COMPOSITIONS FOR DIAGNOSING DISORDERS OF THE LUNG

(57) Abstract: A minimally invasive sample procurement method for obtaining airway epithelial cell RNA that can be analyzed by expression profiling, e.g., by array-based gene expression profiling, is disclosed. These methods can be used to identify patterns of gene expression that are diagnostic of lung disorders, e.g., cancer, to identify subjects at risk for developing lung disorders and to custom design an array, e.g., a microarray, for the diagnosis or prediction of lung disorders or susceptibility to lung disorders. Arrays and informative genes are also disclosed for this purpose.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/18492

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) : G01N 30/00

US CL : 435/6

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

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)
STN - caplus, medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO02/086443 (AZIZ et al.) 31 October 2002, entire document	1-2, 4-15, 17
Y	KITARA et al. "Alterations in gene expression during colorectal carcinogenesis revealed by cDNA microarrays after laser-capture microdissection of tumor tissues and normal epithelia" Cancer Research, 2001, 61: 3544-3549.	1-17
A	WO03/040325 (AGEE et al.), 15 May 2003, p. 12, 190, 735-744	1-17

☐ 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

Date of the actual completion of the international search

20 January 2006 (20.01.2006)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/18492

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:

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:
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 additional fees, this Authority did not invite payment of any 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.: 1-17, species TAT, tyrosine aminotransferase

- 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.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-17, drawn to a method of diagnosing a lung cancer.

Group II, claim(s) 18-21, drawn to a method of treating a lung cancer.

Group III, claim(s) 22, drawn to a substrate with immobilized polymers.

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: TAT, KIAA0436, KIAA0978, CHERP, SERPINA1, LOC84549, USP4, HBG1, K-ALPHA-1, KIAA0326, 76P, C16QBP, KCNE1, NXF1, CLDN3, CGGBP1, RAGE, DKFZP586D2223, VEGF, NFYC, RABAC1, TM4SF7, SSA2, FLJ13291, GPRC5C, DECR2, NEUROD6, LOC51657, LMCD1, WARS2, DKFZP434N1235, EIF4EBP1 as recited in Figures 1A and 1B up to an including BCOR, FLJ10895, FLJ20311, GMPPB, FLJ13096, RGS17, UBQLN3, MCM3APAS, PER3, OR2W1, PPIE, LOC90806, FGFR3, SLCO4C1, LTZS1, PKNOX1 as recited in Figure 8E. The species include approximately 1196 separate gene sequences across 78 figures as recited in Figures 1A-1N, 2A-2F, 3A-3D, 4A-4P, 5A-5F, 6A-6R, 7A-7L and 8A-8E as recited in claims 1 and 18-22.

The inventions listed as Groups I-III 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:

The first broadest product claimed, the substrate with immobilized polymers, of Group III does not provide a contribution over the prior art. Crowley-Weber et al. (2002, Carcinogenesis, vol. 23, no. 12, pp. 2063-2080) analyze the expression of multiple genes expressed by a cancerous cell line using a cDNA microarray that included a panel of multiple genes included in Figures 1-8, including a) epidermal growth factor receptor (EGFR), b) Peroxiredoxin 4, c) Thioredoxin reductase I, d) glutamate-cysteine ligase, e) cytochrome P450, subfamily I (dioxin-inducible), polypeptide I (glaucoma 3, primary infantile) (CYP1B1), f) metallothionein 1G, g) metallothionein 1H, h) retinoblastoma-binding protein 8 (RBBP8) (see Table III of Crowley-Weber, starting p. 2069).

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: For the reasons listed above, the inventions of groups I-III lack a special technical feature in view of the prior art.