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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

[Continued on next page]

(54) Title: LIPOCALIN-TYPE PROSTAGLANDIN D2 SYNTHASE AS A BIOMARKER FOR LUNG CANCER PROGRESSION AND PROGNOSIS

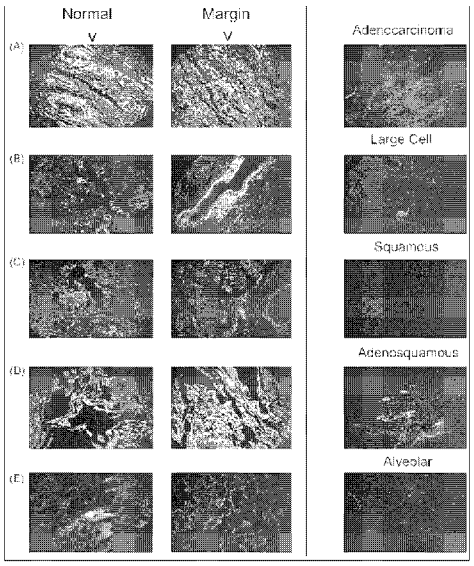

Fig. 1

(57) Abstract: A PGD(2) receptor (DP) deficiency enhances tumor progression accompanied by abnormal vascular expansion. In tumors, angiogenic endothelial cells highly express DP receptor, and its deficiency accelerates vascular leakage and angiogenesis. Administration of a synthetic DP agonist, BW245C, markedly suppresses tumor growth as well as tumor hyperpermeability in WT mice, but not in DP-deficient mice. In a corneal angiogenesis assay and a modified Miles assay, host DP deficiency potentiates angiogenesis and vascular hyperpermeability under COX-2-active situation, whereas exogenous administration of BW245C strongly inhibits both angiogenic properties in WT mice. In an in vitro assay, BW245C does not affect endothelial migration and tube formation, processes that are necessary for angiogenesis; however, it strongly improves endothelial barrier function via an increase in intracellular cAMP production. PGD(2)/DP receptor is a newly identified regulator of tumor vascular permeability, indicating DP agonism can be exploited as a therapy for the treatment of cancer.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/12, A61K 31/4166, A61K 31/4172 (2012.01)
USPC - 514/396, 514/678, 514/724
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(8) - A61K 31/12, A61K 31/4166, A61K 31/4172 (2012.01)
USPC - 514/396, 514/678, 514/724

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/360, 514/675

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar
Search terms: non small cell lung cancer, non small cell lung carcinoma, NSCLC, prostaglandin D2 receptor, PGD2 receptor, PTGDR, agonist, Lipocalin-type prostaglandin D2 synthase, L-PGDS, LPGDS, BW245C, BW868C, adenovirus, SV40, enhancer, gene therapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	MURATA et al., Role of prostaglandin D2 receptor DP as a suppressor of tumor hyperpermeability and angiogenesis in vivo. Proc Natl Acad Sci U S A, 16 December 2008, Vol 105, No 50, pp20009-14. Abstract; p 20009, right col, para 2	1, 2 ---------- 3, 11, 17, 18
Y	RAGOLIA et al., Diminished lipocalin-type prostaglandin D2 synthase expression in human lung tumors. Lung Cancer, October 2010 (published online 7 February 2010), Vol 70, No 1, pp 103-109. Abstract; p 107, left col, para 1	3, 11-18
Y	US 2006/0115829 A1 (MAO et al.) 1 June 2006 (01.06.2006) para [0020], [0022]-[0023], [0063], [0066], [0074]	12-18
Y	Uniprot Accession No P41222, 1 February 1995 [online]. [Retrieved on 16 January 2012]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/P41222.txt?version=106>	14

☐ Further documents are listed in the continuation of Box C. ☐

* 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 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	Date of mailing of the international search report
17 January 2012 (17.01.2012)	25 JAN 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/41751

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:
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: claims 1-3 and 11-18, directed to a method of treating a non-small cell lung cancer, comprising administering an effective amount of a prostaglandin D.sub.2 (PGD.sub.2) receptor agonist or L-PGDS inducer in a pharmaceutically acceptable form in sufficient quantity.

Group II: claims 4-10, 19 and 20, directed to a method of diagnosing, staging or predicting outcome of a non-small cell lung cancer tumor, comprising testing cells of the tumor for at least one of indicia or mRNA level corresponding to the lipocalin-type prostaglandin D synthase gene, gene product and PGD.sub.2 level, and scoring the test result with respect to non-cancer lung cells.

- Please see extra sheet for continuation -

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 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.:
1-3 and 11-18

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

International application No.
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Continuation of Box III: Lack of Unity of Invention

The inventions listed as Groups I - II 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 special technical feature of the Group I claims is a method of treating a non-small cell lung cancer - not required by the claims of Group II. The special technical feature of the Group II claims is a method of diagnosing, staging or predicting outcome of a non-small cell lung cancer - not required by the claims of Group I.

The inventions of Groups I and II share the technical feature of an evaluation of the expression or activity of L-PGDS or its product, PGD.sub.2., in association with non-small cell lung cancer. This common technical element does not represent an improvement over the prior art of the article entitled "Immunohistochemical Expression of Cyclooxygenase Isoenzymes and Downstream Enzymes in Human Lung Tumors" by Ermert et al., which discloses wherein "To elucidate the role of arachidonic acid metabolism via the cyclooxygenase pathway in different human lung tumors, expression of cyclooxygenase isoenzymes (Cox-1 and Cox-2) and downstream enzymes of prostanoid metabolism was investigated in human non-small cell lung cancer and normal human lung tissue by immunohistochemical techniques" "Adenocarcinomas were also positive for prostaglandin D.sub.2 synthase" (abstract) "we found an increase in PGD-S staining intensity in vascular endothelial cells of tumor-associated vessels in comparison to pulmonary vessels of normal lung tissue" (pg. 1607, col 2, para 1).

Therefore, the inventions of Group I and Group II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.