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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

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))*

(88) Date of publication of the international search report:
18 March 2010

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(54) Title: COMPOSITIONS AND METHODS FOR TREATING PULMONARY HYPERTENSION

(57) Abstract: Provided herein are methods and materials for treating pulmonary hypertension (PH) in a subject. Also provided herein is a method of diagnosing whether a has PH by detecting a PH marker. A PKG pulmonary hypertension marker has been identified and may be useful in predicting PH disease progression and assessing a subject's response to PH therapy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/47241

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/45; C12N 9/12 (2010.01)
USPC - 424/94.5, 435/194
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)
USPC: 424/94.5, 435/194

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/94.5, 94.1, 435/194, 193, 183

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (PGPB,USPT,USOC,EPAB,JPAB)
Google (Patents, Scholar, and Web)
Search Terms Used: treat pulmonary hypertension protein kinase inhaled ascorbate sildenafil

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0213399 A1 (MESSADEK) 13 September 2007 (13.09.2007), para [0017], [0043], [0051], [0062]-[0065], [0072], [0095], [0110], [0254], [0330], [0381]	1-3 and 18-27
Y	US 2005/0085486 A1 (GONZALEZ-CADAVID et al.) 21 April 2005 (21.04.2005), Abstract, para [0078], [0176]	1-3 and 18-27

☐ 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
06 January 2010 (06.01.2010)	26 JAN 2010
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 09/47241

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.

Please see extra 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 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.:
claims 1-3 and 18-27

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.
PCT/US 09/47241

Box No. III 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 Claims 1-3 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is a peroxynitrate scavenger and the peroxynitrate scavenger is selected from the group consisting of uric acid, a plant extracted proanthocyanidin, ascorbate, trolox, glutathione (GSH), Mn (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP), flavonoid, ebselen, catchol (1,2dihydroxybenzene), kaempferol, galangin, caffeic acid, o-coumaric acid, p-coumaric acid, gallic acid, and ferolic acid.

Group II Claims 1, 2 and 4 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is proanthocynidin and wherein the proanthocynidin is extracted from an arborescent or herbaceous plant species.

Group III Claims 1, 2, and 5-7 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG -effector agent to a subject in need thereto wherein the PKG-effector agent is a superoxide scavenger and the superoxide scavenger is selected from the group consisting of manganese (III) tetrakis (l-methyl-4-pyridyl) porphyrin pentachloride (MnTMPyP), l-oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine (TEMPOL), and NAD(P)H:quinone oxidoreductase 1.

Group IV Claims 1, 2, and 8 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is an NADPH oxidase inhibitor the NADPH oxidase inhibitor is selected from the group consisting of apocynin and diphenylene iodonium.

Group V Claims 1, 2 and 9 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is a peroxidase activator and the peroxidase activator is selected from the group consisting of iron, copper, melatonin, N-acetylcysteine, and 4-hydrobenzoic acid.

Group VI Claims 1, 2, and 10-12 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is a catalase activator and the catalase activator increases catalase expression.

Group VII Claims 1, 2, and 13 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG -effector agent to a subject in need thereto wherein the PKG-effector agent is a flavonoid and the flavonoid is selected from the group consisting of quercetin, rutin, morin, acacetin, hispidulin, hesperidin, and naringin.

Group VIII Claims 1, 2, 14, and 15 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is an NOS inhibitor and the NOS inhibitor is selected from the group consisting of N omega-nitro-L-arginine, N omega-monomethyl-L-arginine, l-NG monomethyl arginine (l-NMMA), a caveolin-l peptide, ARL 17477, and KLYP956.

Group IX Claims 1, 2, 16, and 17 are directed to a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is a PKG activator and the PKG activator is selected from the group consisting of phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3), cyclic guanosine 3', 5' monophosphate (cGMP), 8-pCPT-cGMP (cGMP derivative), and a cGMP phosphodiesterase inhibitor.

Group X Claims 28 and 29 are directed to a method of diagnosing pulmonary hypertension in a subject, comprising providing one or more antibodies that bind to nitrated PKG, contacting the one or more antibodies with a sample from the subject, and identifying the subject as having pulmonary hypertension if the one or more antibodies bind to nitrated PKG and is/are detected in the sample.

Group XI Claim 30 is directed to a kit comprising: (a) a sample collecting means; (b) means for determining the presence of a PH-marker in the sample; and (c) a control sample, wherein the control sample does not have a PH-marker.

Claims 18-27 are generic for any of Groups I-IX.

Groups I-IX have the shared technical feature of a method of treating pulmonary hypertension in a subject, comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is selected from the group consisting of a peroxynitrate scavenger, a superoxide scavenger, flavonoid, NOS inhibitor, a PKG activator, a NADPH oxidase inhibitor, a superoxide dismutase activator, a peroxidase activator, a catalase activator, and combinations thereof. However, this is not an improvement over the prior art of US 6127356 A to Crapco et al. (3 October 2000) that specifically teaches a method of treating pulmonary hypertension in a subject (col 29 ln 24-26) , comprising administering a PKG-effector agent to a subject in need thereto wherein the PKG-effector agent is a superoxide scavenger (col 16 ln 21-25). Groups X and XI have no shared technical feature with Groups I-IX nor with each other.