

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:

PCT/US2012/020459

(22) International Filing Date:

6 January 2012 (06.01.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/430,927	7 January 2011 (07.01.2011)	US
61/545,091	7 October 2011 (07.10.2011)	US
61/563,174	28 December 2011 (28.12.2011)	US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

(88) Date of publication of the international search report:

4 October 2012

(54) Title: COMPOUNDS THAT MODULATE OXIDATIVE STRESS

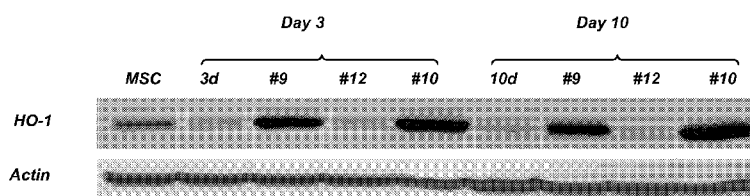


FIG. 9

(57) Abstract: The present invention provides methods of identifying compounds that selectively induce an oxidative stress response in a biological sample. The present invention further provides methods of treating a subject having a disease associated with oxidative stress using compounds that selectively induce an oxidative stress response in the subject. The invention further provides methods of selectively inducing an oxidative stress response in a cell.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/20459

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68 (2012.01)

USPC - 435/6.13

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: 435/6.13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6.1; 506/10; 506/15 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar

Search Terms Used: HMOX1, NfκB, NQO1, NRF2, oxidative stress, cell stress, ER stress

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7,306,905 B2 (Ron et al.) 11 December 2007 (11.12.2007) col 2, ln 53-59, col 4, ln 10-26, col 6, ln 50-57, col 8, ln 64-67	1-3
A	US 2010/0304384 A1 (Valdivieso Amate et al.) 02 December 2010 (02.12.2010). Entire document.	1-3
A	Han et al. 'Oxidative preconditioning apoptosis in L-cells' J Biol Chem., 2001, Vol 276(28) pp 26357-26364. Entire document.	1-3

☐ 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

27 June 2012 (27.06.2012)

Date of mailing of the international search report

06 JUL 2012

Name and mailing address of the ISA/US

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P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/20459

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.: 4-40 and 59-61
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:
--See Attached 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.:
1-3

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.

Attachment to Box III:

Lack of unity invention:

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, drawn to a method of identifying compounds that decrease oxidative stress by selectively inducing oxidative stress response in a biological sample, the method comprising:

- (a) contacting the biological sample with one or more compounds;
- (b) determining whether the one or more compounds induce an oxidative stress response in the biological sample, wherein induction of the oxidative stress response comprises inducing expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2;
- (c) determining whether the one or more compounds activate a cellular stress response in the biological sample, wherein activation of the cellular stress response comprises inducing expression of a cellular stress gene other than an oxidative stress-responsive gene, wherein the cellular stress gene is an ER stress-responsive gene, a genotoxic stress-responsive gene, a heat stress-responsive gene, or a cold stress-responsive gene; and
- (d) selecting for the one or more compounds that induce the oxidative stress response but do not significantly activate the cellular stress response in the biological sample; wherein the one or more compounds that are selected for are identified as decreasing oxidative stress by selectively inducing oxidative stress response.

Group II: claims 41-58, drawn to a method of treating a subject having a disease associated with oxidative stress, the method comprising:

- (a) identifying the subject having the disease associated with oxidative stress; and
- (b) administering to the subject a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene and does not significantly increase production of reactive oxygen species in the subject; thereby treating the subject having the disease.

Group III: claims 62-63, drawn to a method of reducing ischemic damage in a subject, the method comprising:

- (a) identifying the subject having ischemic damage; and
- (b) administering to the subject a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene and does not significantly increase production of reactive oxygen species in the subject; thereby reducing ischemic damage in the subject.

Group IV: claims 64-68, drawn to a method of reducing inflammation associated with transplantation in a subject, the method comprising:

- (a) identifying the subject having inflammation associated with transplantation; and
- (b) administering to the subject a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene and does not significantly increase production of reactive oxygen species in the subject; thereby reducing inflammation in the subject.

Group V: claims 69-70, drawn to a method of improving graft viability in a graft recipient, the method comprising:

- (a) identifying the graft recipient; and
- (b) administering to the graft recipient a compound that decreases oxidative stress by selectively inducing oxidative stress response in the graft recipient, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene and does not significantly increase production of reactive oxygen species in the graft recipient; thereby improving graft viability in the graft recipient.

Group VI: claim 71, drawn to a method of maintaining an arteriovenous fistula in a subject, the method comprising:

- (a) identifying the subject having the arteriovenous fistula; and
- (b) administering to the subject a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene and does not significantly increase production of reactive oxygen species in the subject; thereby maintaining the arteriovenous fistula in the subject.

The inventions listed as Groups I through VI 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 inventions of Group I-V do not include the inventive concept of a method of maintaining an arteriovenous fistula in a subject, as required by Group VI.

The inventions of Group I-IV do not include the inventive concept of a method of improving graft viability in a graft recipient, as required by Group V.

The inventions of Group I-III do not include the inventive concept of a method of reducing inflammation associated with transplantation in a subject, as required by Group IV.

The inventions of Group I-II do not include the inventive concept of a method of reducing ischemic damage in a subject, as required by Group III.

=====Continued in Next Sheet=====

Continuation of Prior Sheet:

The inventions of Group I do not include the inventive concept of a method of treating a subject having a disease associated with oxidative stress, as required by Group II.

The inventions of Group II-VI do not include the inventive concept of a method of identifying compounds that decrease oxidative stress as required by Group I.

The inventions of Groups I-VI share the technical feature of a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive gene. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 7,306,905 B2 to Ron et al. (hereinafter 'Ron'). Ron discloses a compound that decreases oxidative stress by selectively inducing oxidative stress response in the subject, wherein the compound induces expression of an oxidative stress-responsive gene that is responsive to transcription factor Nrf2, but does not significantly induce expression of a cellular stress gene other than an oxidative stress-responsive (col 4, ln 10-26 and col 8, 64-67, a method for screening a plurality of test substances useful for the prevention or treatment of a disease involving an oxidative stress, which comprises i) testing each of the test substances for its ability to activate the expression of heme oxygenase-1 and ii) identifying the test substance which activates the expression of heme oxygenase-1, thereby to identify a test substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress; heme oxygenase-1 is a Nrf2 responsive gene. Additionally, the method comprises determining whether the substance promotes resistance to cell stress consisting of ER stress). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Groups II-VI share the technical feature of treating a subject having a disease associated with oxidative stress comprising a compound that does not significantly increase production of reactive oxygen species in the subject. Ron teaches a method of treating a subject having a disease associated with oxidative stress (col 4, ln 10-26 and col 9, ln 1-14) comprising a compound that does not significantly increase production of reactive oxygen species in the subject (col 1, ln 39-60 and col 8, 64-67; cell stress includes oxidative stress such as ROS). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I through VI therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Continuation of Section 4:

Claims 4-40 and 59-61 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).