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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,
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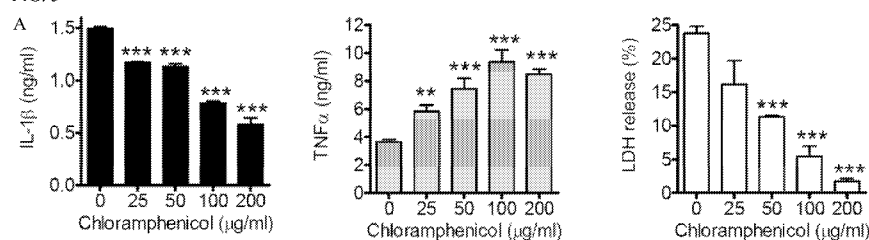
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10 May 2012

(54) Title: MITOCHONDRIAL APOPTOSIS-INDUCED INFLAMMATION

FIG. 5



(57) Abstract: Disclosed is a method of treating inflammation, an inflammatory disease, an inflammatory disease condition and/or an autoimmune disease in a subject in need thereof. The method can comprise providing a composition comprising a mitochondrial apoptosis inhibitor or an oxidative nucleotide and administering the composition to the subject to treat the inflammation, the inflammatory disease, the inflammatory disease condition and/or the autoimmune disease. Said method is based on the mitochondria acting as a unifying point that integrates diverse NLRP3 stimuli and that mitochondrial dysfunction and apoptosis of macrophages are critical steps in various danger signal-induced NLRP3 inflammasome activation.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45893

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00; A61P 17/00; A61P 29/00 (2012.01)

USPC - 514/12.2; 514/18.7

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 38/00; A61P 17/00; A61P 29/00 (2012.01)

USPC: 514/12.2; 514/18.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC: 514/1.9; 514/6.9; 514/16.6; 514/17.8; 514/863

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

WEST (PGPB,USPT,EPAB,JPAB); Google Scholar: esp@cnr: mitochondria, inhibitor, apoptosis, inflammation, Bcl-2, Mcl-1, Bcl-xL, Bcl-w, Bfl-1, nfh, XIAP, Boo Diva, Nr13, IP3R, vMIA, MitoQ, IL-1 beta, mitochondrial, induced, IL-1 beta, diabetes, inflammatory disease, Cedars, Kenichi Shimada, Moshe Arditi

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	WO 2006/041835 A2 (HARLAN et al.) 20 April 2006 (20.04.2006) pg 1, ln 4-5; pg 5, ln 8-11; pg 5, ln 30-pg 6, 11; pg 6, ln 1; pg 6, ln 11; pg 7, ln 8-21	1-3 and 6-7 ----- 4-5
Y	DONATH et al. Mechanisms of Beta-Cell Death in Type 2 Diabetes. Diabetes. December 2005, Vol 54, Suppl 2, Pages S108-S113: fig 2-3; abstract; pg S108, col 2, para 1; S109, col 1, para 2 to col 2, para 1; S110, col 1, para 3, col 2, para 2 to S111, col 1, para 1; S111, col 2, para 2 to S112, col 1, para 1	4-5
A	US 2004/0034030 A1 (RICHARDSON et al.) 19 February 2004 (19.02.2004) para [0046], [0049], [0206], [0207], [0216], [0260], [0273], [0334], [0335], [0397].	1

☐ 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45893

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 1-7, drawn to a method comprising: providing a composition comprising a mitochondrial apoptosis inhibitor, and administering the composition to a subject in need of treatment for inflammation to treat the inflammation.

Group II: Claims 8-14, drawn to a method comprising: providing a composition comprising an oxidative nucleotide, and administering the composition to a subject in need of treatment for inflammation to treat the inflammation.

-----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.:
1-7

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.

Continuation of Box (III): Lack of Unity

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:

Group I does not include the inventive concept of a composition comprising an oxidative nucleotide, as required by Group II.

Group II does not include the inventive concept of a composition comprising a mitochondrial apoptosis inhibitor, as required by Group I.

Groups I-II share the technical feature of a method comprising: providing a composition, and administering the composition to a subject in need of treatment for inflammation to treat the inflammation. However, this shared technical feature does not represent a contribution over prior arts, specifically, US 2004/0034030 A1 to Richardson et al. (hereinafter "Richardson") teaches a method, comprising:
--providing a composition (claim 27 - diabetes is an inflammatory disease, para [0334], [0335], [0397]), and
--administering the composition to a subject in need of treatment for inflammation to treat the inflammation (claim 27; para [0334], [0335], [0397]).

Richardson further discloses a method comprising inhibiting mitochondrial apoptosis in a subject in need of treatment for inflammation to treat the inflammation (para [0046]-[0049], [0206], [0207], [0216]-"Inhibiting mitochondrial-derived apoptosis"; [0259], [0260], [0273]). As said shared technical feature was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

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