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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: COPPER-DEPENDENT NON-TRADITIONAL PRO-INFLAMMATORY CYTOKINE EXPORT AND METHODS,
COMPOSITIONS AND KITS RELATING THERETO

(57) Abstract: The present invention relates to the discovery that non-traditional export of certain pro-inflammatory cytokines lack-
ing a signal sequence from a cell can be inhibited by copper chelation and/or administration to the cell of a truncated form of S100A13
lacking the basic residue portion. Further, copper chelation inhibits, *inter alia*, neointima formation, macrophage infiltration and
associated inflammation, cell proliferation, secretion, macrophage infiltration and associated inflammation, cell proliferation, se-
cretion of extracellular matrix, intimal thickening, adventitial angiogenesis, restenosis, and the like, associated with vascular vessel
injury. Thus, the present invention provides novel methods for preventing and treating, and for identifying novel compounds also
useful as therapeutics for, such conditions.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27247

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/20, 33/34

US CL : 424/85.2, 630; 514/6,836

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. : 424/85.2, 630; 514/6,836

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)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,159,988 (NAIK et al) 12 December 2000 (12.12.2000), column 16, lines 15-17.	1, 2 and 5
Y	LANDRISCINA et al. S100A13 Participates in the Release of Fibroblast Growth Factor 1 in Response to Heat Shock in vitro. Journal of Biological Chemistry, June 2001, Vol. 276, No. 25, pages 22544-22552.	6-10,13



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

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INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 3 and 4
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:
Claims 3 and 4 were not searched because these claims depend on themselves.
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.: 6-10 and 13
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.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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BOX II. 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 claim(s) 1, 2 and 5 drawn to the special technical feature of a method of inhibiting interleukin-1 alpha release from a cell by the administering an effective amount of an IL-1 release inhibitor.

Group II, claim(s) 6-10 drawn to the special technical feature of a method of inhibiting neointima formation following vessel injury by inhibiting IL-1 release using copper chelator.

Group III, claim(s) 11-12, drawn to the special technical feature of a method of inhibiting secretion of extracellular matrix following arterial wall injury by inhibiting export of IL-1 by using copper chelator.

Group IV, claim(s) 13, drawn to the special technical feature of a method of inhibiting adventitial angiogenesis associated with arterial wall injury by inhibiting export of IL-1 by using copper chelator.

Group V, claim(s) 14-15, drawn to the special technical feature of a method identifying a compound useful for inhibiting adventitial angiogenesis associated with arterial wall injury in a mammal.

Group VI, claim(s) 16, drawn to the special technical feature of a compound identified by claim 14.

Group VII, claim(s) 17, drawn to the special technical feature of a kit for inhibiting the release of IL-1 from a cell.

Group VIII, claim(s) 18, drawn to the special technical feature of a kit for treating a condition mediated by stress-induced release of IL-1 from a cell.

Group IX, claim(s) 19, drawn to the special technical feature of a kit for inhibiting neointima formation following vessel injury in a mammal.

Group X, claim(s) 20, drawn to the special technical feature of a kit for inhibiting restenosis following vessel injury in a mammal.

The inventions listed as groups I-IX 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 feature for the following reasons; Claims 1, 2 and 5 at least are anticipated by Naik et al. (U.S. Patent NO: 6, 159, 988). Consequently, the special technical feature which links Group I and II, does not provide contribution over the prior art, so the unity of invention is lacking.

Inventions I- V are directed to non equivalent methods and are different from each other. Invention VI is directed to a compound. Inventions VII-X are directed to different kits used for different purposes. Invention I is a method of inhibiting interleukin-1 alpha release from a cell by the administering an effective amount of an IL-1 release inhibitor. Similarly, Invention II is a method of inhibiting neointima formation following vessel injury by inhibiting IL-1 release using copper chelator. Invention III is a method of inhibiting secretion of extracellular matrix following arterial wall injury by inhibiting export of IL-1 by using copper chelator. Invention IV is a method of inhibiting adventitial angiogenesis associated with arterial wall injury by inhibiting export of IL-1 by using copper chelator. Invention V is a method identifying a compound useful for inhibiting adventitial angiogenesis associated with arterial wall injury in a mammal. Invention VI is directed to a compound. Inventions VII-X are directed to different kits used for different purposes.

The claims of these groups are directed to different inventions, which are not linked to form a single general inventive concept under PCT Rule 13.1. The claims in the different groups lack the same or corresponding special technical features. In particular, each group is directed to different compounds, kits and /or methods. Accordingly, the claims are not so linked by a

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special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept and lack of unity is deemed proper.

Continuation of B. FIELDS SEARCHED Item 3:

STN search: CAPLUS, MEDLINE, CANCERLIT, BIOSIS, EMBASE, USPATFUL

WEST search: USPAT

search terms: interleukin-1 alpha, IL-1 alpha, release, inhibit, copper chelate