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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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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: PHOSPHORYLATED GLYOXALASE I AND ITS USE

(57) Abstract: The present invention relates to a phosphorylated form of mammalian glyoxalase I. The present invention relates further to the use of phosphorylated mammalian glyoxalase I to modulate MG-modification of proteins (AGE formation) and consequent cell death, especially upon stress such as oxidative stress, or upon TNF treatment.



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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/01118

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/88 A61K38/51

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 7 C12N A61K

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 practical, search terms used)

BIOSIS, PAJ, EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, EMBASE, SCISEARCH, LIFESCIENCES

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 017, no. 388 (C-1086), 21 July 1993 (1993-07-21) & JP 05 068571 A (SAGAMI CHEM RES CENTER), 23 March 1993 (1993-03-23) abstract ---	1,2
Y	INOUE Y ET AL: "SEXUAL RESPONSE OF SACCHAROMYCES-CEREVISIAE PHOSPHORYLATION OF YEAST GLYOXALASE I BY A CELL EXTRACT OF MATING FACTOR-TREATED CELLS" JOURNAL OF BIOCHEMISTRY (TOKYO), vol. 108, no. 1, 1990, pages 4-6, XP001005285 ISSN: 0021-924X cited in application the whole document, in particular paragraph bridging pages 5 and 6 --- -/--	1,2



Further documents are listed in the continuation of box C.



Patent family members are listed in 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 document 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
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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

25 November 2002

Date of mailing of the international search report

11/12/2002

Name and mailing address of the ISA

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Bassias, I

INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/EP 02/01118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GUY G R ET AL: "INTERLEUKIN 1 AND TUMOR NECROSIS FACTOR ACTIVATE COMMON MULTIPLE PROTEIN KINASES IN HUMAN FIBROBLASTS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 22, 1991, pages 14343-14352, XP000999253 ISSN: 0021-9258 cited in application the whole document ---	1-10
Y	RANGANATHAN SULABHA ET AL: "Cloning and characterization of human colon glyoxalase-I." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 8, 1993, pages 5661-5667, XP000999251 ISSN: 0021-9258 cited in application the whole document ---	1-10
Y	KIM NAM-SOON ET AL: "Human glyoxalase I: cDNA cloning, expression, and sequence similarity to glyoxalase I from Pseudomonas putida." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 15, 1993, pages 11217-11221, XP000999259 ISSN: 0021-9258 the whole document, in particular Fig. 2 ---	1-10
A	THORNALLEY PAUL J: "Advances in glyoxalase research: Glyoxalase expression in malignancy, anti-proliferative effects of methylglyoxal, glyoxalase I inhibitor diesters and S-D-lactoylglutathione, and methylglyoxal-modified protein binding and endocytosis by the advanced glycation endproduct receptor." CRITICAL REVIEWS IN ONCOLOGY-HEMATOLOGY, vol. 20, no. 1-2, 1995, pages 99-128, XP001000228 ISSN: 1040-8428 the whole document ---	
A	SAKAMOTO HIROSHI ET AL: "Glyoxalase I is involved in resistance of human leukemia cells to antitumor agent-induced apoptosis." BLOOD, vol. 95, no. 10, 15 May 2000 (2000-05-15), pages 3214-3218, XP002170378 ISSN: 0006-4971 the whole document ---	
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	VAN HERREWEGHE FRANKY ET AL: "Tumor necrosis factor-induced modulation of glyoxalase I activities through phosphorylation by PKA results in cell death and is accompanied by the formation of a specific methylglyoxal-derived AGE." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 99, no. 2, 22 January 2002 (2002-01-22), pages 949-954, XP002222256 http://www.pnas.org January 22, 2002 ISSN: 0027-8424 the whole document -----	

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 02/01118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

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.:
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 3-9 relate inter alia to INHIBITORS of specific molecules (PKA) or biochemical reactions (phosphorylation). Inhibitors embrace an extremely large number of possible compounds/products or even physical conditions such as heat/cold. Inhibitors must be defined by structural features, not by their activity (note that e.g., sulfuric acid is a very strong inhibitor of all polypeptides). In fact, the claims contain so many options, that a lack of clarity (and conciseness) within the Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Inhibitors like S-p-bromobenzylglutathione diester or H89 have been used in the application. Only those two inhibitors are considered to be clear and sufficiently disclosed. Consequently, the search relating to inhibitors has been limited to S-p-bromobenzylglutathione diester and H89.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Information on patent family members

PCT/EP 02/01118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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JP 05068571 A 23-03-1993 NONE