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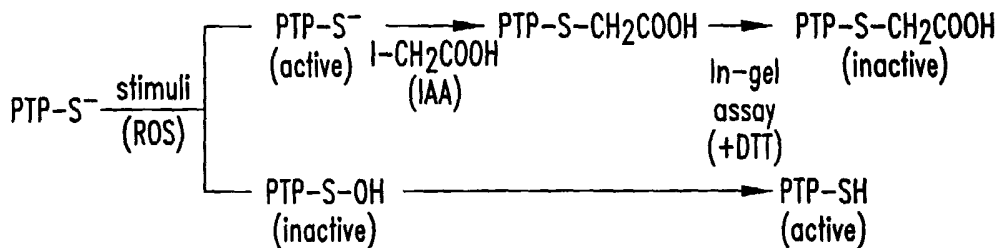
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- (74) Agents: MENGES, A. V. et al.; Uexküll & Stolberg, Be-selerstrasse 4, 22607 Hamburg (DE).
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(54) Title: REVERSIBLE OXIDATION OF PROTEIN TYROSINE PHOSPHATASES



(57) Abstract: The invention relates to a method of identifying any protein tyrosine phosphatase (PTP) that undergoes reversible modification of PTP active site invariant cysteine within a cell, such that the phosphatase is transiently protected from irreversible active site invariant cysteine-directed PTP inactivating agents. Methods related to regulation of PTPs by reactive oxygen species (ROS) in a cellular environment are provided. Multiple PTPs are shown to be reversibly oxidized and inactivated following treatment of cells with H₂O₂ or with physiological stimuli that promote ROS formation, and inhibition of PTP function is shown to contribute to ROS-induced mitogenesis. Transient oxidation of the PTP catalytic site invariant cysteine is exploited in methods to identify which of multiple candidate PTPs are components of a given biological signal transduction pathway, without a requirement for first specifically purifying any particular candidate PTP.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01446

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12Q1/42		
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 C12Q		
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, EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DENU JOHN M ET AL: "Specific and reversible inactivation of protein tyrosine phosphatase by hydrogen peroxide: Evidence for a sulfenic acid intermediate and implications for redox regulation." BIOCHEMISTRY, vol. 37, no. 16, 21 April 1998 (1998-04-21), pages 5633-5642, XP002247280 ISSN: 0006-2960 p. 5635, left-hand column, section "14Ccarboxymethylation experiments" and p. 5637, right-hand column, second paragraph.	1-50
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> 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 *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 11 July 2003		Date of mailing of the international search report 31/07/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Jacques, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/01446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HERRLICH P ET AL: "REDOX REGULATION OF SIGNAL TRANSDUCTION IN MAMMALIAN CELLS" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 59, no. 1, 1 January 2000 (2000-01-01), pages 35-41, XP000960762 ISSN: 0006-2952 the whole document ---	1-50
A	GROSS S ET AL: "Inactivation of protein-tyrosine phosphatases as mechanism of UV-induced signal transduction" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 274, no. 37, 10 September 1999 (1999-09-10), pages 263782-6386, XP002162918 ISSN: 0021-9258 the whole document ---	1-50
A	WO 01 20021 A (BOEHMER FRANK ;HERRLICH PETER (DE); KARLSRUHE FORSCHZENT (DE)) 22 March 2001 (2001-03-22) the whole document ---	1-50
A	BURKE T R ET AL: "PROTEIN-TYROSINE PHOSPHATASES: STRUCTURE, MECHANISM AND INHIBITOR DISCOVERY" BIOPOLYMERS, NEW YORK, NY, US, vol. 47, no. 3, 1998, pages 225-241, XP001069403 ISSN: 0006-3525 the whole document -----	1-50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/01446

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.: 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:
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

Claims Nos.: 4

Present claim 4 relates to the protein tyrosine phosphatase as presented in figure 8. However as the copy of the said figure is totally unreadable, a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear namely claims 1-3, 5-50.

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/01446

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0120021	A	22-03-2001	DE	10035472 A1	15-03-2001
			WO	0120021 A2	22-03-2001
