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Previous Correction:
see Notice of 20 March 2008

(54) Title: INHIBITORS OF USP1 DEUBIQUITINATING ENZYME COMPLEX

(57) Abstract: The invention provides compositions and methods used to inhibit USP1 deubiquitinase activity and to identify new inhibitors of USP1 deubiquitinase. The inhibitors can be used to treat or prevent cancer, bone marrow failure, and damage to cells or DNA resulting from genotoxic agents such as antineoplastic agents, including chemotherapeutic agents and radiation. The inhibitors include siRNA directed at inhibiting the expression of USP1 or UAF1, a protein which forms a heterodimeric complex with USP1. The inhibitors can be used to enhance cell survival if administered either before or after radiation exposure. Methods are also provided to enhance chemotherapy or radiotherapy of cancer and to enhance DNA repair. Transgenic knockout animals and knockdown cells are provided, whose USP1 expression is impaired.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/14378

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12N 9/64(2006.01)

USPC: 435/226

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. : 435/226

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEQ ID NO: 3 & 4

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NIJMAN et al, The deubiquitinating enzyme USP1 regulates the Fanconi anemia pathway. Mol Cell. February 4, 2005 Vol 17, No. 3, pages 331-9.	1



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

24 April 2008 (24.04.2008)

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Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

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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:
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 additional fees, this Authority did not invite payment of any 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.: 1-6

- 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. |

INTERNATIONAL SEARCH REPORT

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The inventions listed as Groups I-V(A)-(O) 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: The technical feature linking Groups I-V(A)-(O) appears to be that they all relate to USP1 deubiquitinases. However, USP1 deubiquitinases were known in the art. Moreover, Nijman et al, 2005 teach a method for identifying inhibitors of a USP1 deubiquitinase which anticipates Claim 7 (Fig 2H). Therefore Groups I-V(A)-(O) share no special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Furthermore, the methods of Groups II-V do not use the same reagents or produce the same results and said methods do not comprise all of the methods for making or using the products of Groups I. Accordingly, Groups I-V(A)-(O) are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

NIJMAN et al, The deubiquitinating enzyme USP1 regulates the Fanconi anemia pathway. Mol Cell. February 4, 2005 Vol 17, No. 3, pages 331-9.

INTERNATIONAL SEARCH REPORT

International application No.

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BOX III. 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, Claims 1-6, drawn to a composition comprising the USP1 deubiquitinase of SEQ ID NO: 3, a proliferating cell nuclear antigen (PCNA) polypeptide, and, optionally, the UAF1 polypeptide of SEQ ID NO: 4.

Group II, Claims 7-25, drawn to a method for identifying modulators of USP1 deubiquitinase.

Group III, Claims 26-27, drawn to a method for identifying a cytoprotective agent using a USP1 deubiquitinase.

Group IV, Claims 28-29, drawn to a method for diagnosing cancer by measuring levels of cellular components.

Group V, Claim 30, drawn to a method for diagnosing cancer by measuring binding of UAF1 to USP1.

For each of Inventions I-V above, restriction to one of the following is also required under 35 USC 121. Therefore, election is required of one of Inventions I-V and one of Inventions (A)-(O).

If Invention II is elected, elect one of:

- (A.) In vivo
- (B.) In a cellular system
- (C.) In vitro

If Invention II is elected, also elect one of:

- (D.) A PCNA substrate
- (E.) A FANCD2 substrate
- (F.) A ubiquitin-7-4-methylcoumarin substrate

If Invention II is elected, also elect one of:

- (G.) Complexed with UAF1
- (H.) Not complexed with UAF1

If Invention III is elected, elect one of:

- (I.) UV light
- (J.) Ionizing radiation
- (K.) Anti-neoplastic agent

If Invention IV is elected, elect one of:

- (L.) Measuring USP1 and UAF1
- (M.) Measuring USP1, UAF1, and FANCD2
- (N.) Protein
- (O.) mRNA