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(54) Title: METHODS FOR SCREENING SUBSTANCES CAPABLE OF MODULATING THE REPLICATION OF AN INFLUENZA VIRUS

(57) Abstract: The present invention relates to methods for screening substances capable of modulating the replication of an influenza virus. More particularly, the present invention relates to methods for screening a plurality of substances capable of modulating the replication of an influenza virus in a host cell comprising the step consisting of identifying a substance that modulates the specific interaction of a host cell protein with a viral protein required for viral replication as depicted in table 1 or identifying a substance that modulates the specific interaction of a first host cell protein as depicted in table 1 with a second host cell protein present in cellular network of the first host cell protein or identifying a substance that modulates the expression of a host cell protein as depicted in table 1, or identifying a substance that modulates the activity of a host cell protein as depicted in table 1



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INTERNATIONAL SEARCH REPORT

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| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. G01N33/68<br>ADD.   |   |  |
|--|---|--|
| According to International Patent Classification (IPC) or to both national classification and IPC  |   |  |
| <b>B. FIELDS SEARCHED</b>  |   |  |
| Minimum documentation searched (classification system followed by classification symbols)<br>G01N  |   |  |
| 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)<br>EPO-Internal, BIOSIS, EMBASE, WPI Data   |   |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>  |   |  |
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
| 3 A  | SHAPIRA SAGI D ET AL: "A Physical and Regulatory Map of Host-Influenza Interactions Reveals Pathways in H1N1 Infection",<br>CELL,<br>vol. 139, no. 7, December 2009 (2009-12),<br>pages 1255-1267, XP002660295,<br>ISSN: 0092-8674  | 1  |
| 3 A  | MI SHUOFU ET AL: "Na <sup>+</sup> /K <sup>+</sup> -ATPase beta 1 subunit interacts with M2 proteins of influenza A and B viruses and affects the virus replication",<br>SCIENCE CHINA-LIFE SCIENCES,<br>vol. 53, no. 9, September 2010 (2010-09),<br>pages 1098-1105, XP002660296,<br>ISSN: 1674-7305<br>the whole document | 1  |
| -/--   |   |  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.   |   | <input checked="" type="checkbox"/> 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<br>"E" earlier application or patent but published on or after the international filing date<br>"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)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"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<br>"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<br>"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<br>"&" document member of the same patent family |
| Date of the actual completion of the international search<br><br>19 July 2012  |   | Date of mailing of the international search report<br><br>26. 11. 2012   |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016   |   | Authorized officer<br><br>Marinoni J-C   |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/059189

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| 2         | <p>A PRUSTY BHUPESH K ET AL: "Genome-wide RNAi screen for viral replication in mammalian cell culture", METHODS IN MOLECULAR BIOLOGY, HUMANA PRESS INC, NJ, US</p> <p>vol. 721, no. Part 5<br/>1 January 2011 (2011-01-01), pages 383-395, XP009150907,<br/>ISSN: 1064-3745<br/>Retrieved from the Internet:<br/>URL:10.1007/978-1-61779-037-9_24</p>       | 1                     |
| 2         | <p>A NAVRATIL VINCENT ET AL: "When the human viral infectome and disease networks collide: towards a systems biology platform for the aetiology of human diseases", BMC SYSTEMS BIOLOGY, BIOMED CENTRAL LTD, LO,</p> <p>vol. 5, no. 1,<br/>21 January 2011 (2011-01-21), page 13,<br/>XP021090532,<br/>ISSN: 1752-0509, DOI:<br/>10.1186/1752-0509-5-13</p> | 1                     |
| 2         | <p>A KARLAS A ET AL: "Genome-wide RNAi screen identifies human host factors crucial for influenza virus replication", NATURE, NATURE PUBLISHING GROUP, LONDON, GB,</p> <p>vol. 463, 11 February 2010 (2010-02-11), pages 818-822, XP002569908,<br/>ISSN: 0028-0836, DOI: 10.1038/NATURE08760<br/>[retrieved on 2010-01-17]</p>                              | 1                     |
|           | <p>A EMMOTT EDWARD ET AL: "Quantitative Proteomics Using SILAC Coupled to LC-MS/MS Reveals Changes in the Nucleolar Proteome in Influenza A Virus-Infected Cells", JOURNAL OF PROTEOME RESEARCH,</p> <p>vol. 9, no. 10, October 2010 (2010-10), pages 5335-5345, XP002660297,<br/>ISSN: 1535-3893</p>   | 1                     |
| 3         | <p>A WATANABE TOKIKO ET AL: "Cellular Networks Involved in the Influenza Virus Life Cycle", CELL HOST &amp; MICROBE,</p> <p>vol. 7, no. 6, June 2010 (2010-06), pages 427-439, XP002660298,<br/>ISSN: 1931-3128</p>   | 1                     |
| 1         | -/--  |                       |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/059189

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| 3         | A<br>LIAO TSAI-LING ET AL: "Ubiquitination and deubiquitination of NP protein regulates influenza A virus RNA replication",<br>EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL,<br>vol. 29, no. 22, November 2010 (2010-11),<br>pages 3879-3890, XP002660299,<br>ISSN: 0261-4189<br>-----                                       | 1                     |
| 3         | A<br>COOMBS KEVIN M ET AL: "Quantitative Proteomic Analyses of Influenza Virus-Infected Cultured Human Lung Cells",<br>JOURNAL OF VIROLOGY,<br>vol. 84, no. 20, October 2010 (2010-10),<br>pages 10888-10906, XP002660300,<br>-----  | 1                     |
| 5         | A<br>WO 2009/127693 A1 (INST NAT SANTE RECH MED [FR]; LOTTEAU VINCENT [FR])<br>22 October 2009 (2009-10-22)<br>-----   | 1                     |
| 3         | A<br>STERTZ SILKE ET AL: "Uncovering the global host cell requirements for influenza virus replication via RNAi screening",<br>MICROBES AND INFECTION,<br>vol. 13, no. 5, Sp. Iss. SI,<br>May 2011 (2011-05), pages 516-525,<br>XP002660301,<br>ISSN: 1286-4579<br>-----   | 1                     |
| 2         | A<br>LINHUI HAO ET AL: "Drosophila RNAi screen identifies host genes important for influenza virus replication",<br>NATURE, NATURE PUBLISHING GROUP, LONDON, GB,<br>vol. 454, no. 7206,<br>14 August 2008 (2008-08-14), pages 890-893, XP002629478,<br>ISSN: 0028-0836, DOI: 10.1038/NATURE07151<br>[retrieved on 2008-07-09]<br>----- | 1                     |
| 5         | A<br>WO 2007/146057 A2 (WISCONSIN ALUMNI RES FOUND [US]; KAWAOKA YOSHIHIRO [US] WISCONSIN ALUM)<br>21 December 2007 (2007-12-21)<br>-----  | 1                     |
| 5         | A,P<br>WO 2011/076873 A1 (MAX PLANCK GESELLSCHAFT [DE]; MACHUY NIKOLAUS [DE]; KARLAS ALEXANDER []) 30 June 2011 (2011-06-30)<br>the whole document<br>-----  | 1                     |
| 1         |  |                       |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2012/059189

## 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:

see additional 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 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(partially)

### 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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claim: 1(partially)

A method for screening a plurality of substances capable of modulating the replication of an influenza virus in a host cell comprising the step consisting of identifying a substance that modulates the specific interaction of ABCD4 (host cell protein) with NS1 (viral protein required for replication) as in table 1

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## 2-318. claim: 1(partially)

Same as in invention 1, with the other host protein/viral protein pairs disclosed in table 1. Invention 2=ABCD4/NS2, Invention 3=ACTN1/M1, invention 4=ADAR/NS1, ... , invention 318=ZYX/NS1

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## 319. claim: 1(partially)

A method for screening a plurality of substances capable of modulating the replication of an influenza virus in a host cell comprising the step consisting of identifying a substance that modulates the specific interaction of ABCD4 (first host cell protein) with a second host protein present in cellular network of ABCD4 (the first host cell protein)

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## 320-563. claim: 1(partially)

Same as in invention 319 with the first host cell protein being ACTN1 (invention 320), ADAR (invention 321), .... , ZYX (invention 563).

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## 564. claim: 1(partially)

A method for screening a plurality of substances capable of modulating the replication of an influenza virus in a host cell comprising the step consisting of identifying a substance that modulates the expression of ABCD4 (a host cell protein)

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## 565-808. claim: 1(partially)

Same as in invention 564 with the host cell protein being ACTN1 (invention 565), ADAR (invention 566), ... , ZYX (invention 808).

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## 809. claim: 1(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method for screening a plurality of substances capable of modulating the replication of an influenza virus in a host cell comprising the step consisting of identifying a substance that modulates the activity of ABCD4 (a host cell protein).

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810-1053. claim: 1(partially)

Same as in invention 809 with the host cell protein being ACTN1 (invention 810), ADAR (invention 811), ... , ZYX (invention 1053).

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059189

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| WO 2009127693 A1                       | 22-10-2009       | EP 2269074 A1           | 05-01-2011       |
|  |                  | JP 2011517779 A         | 16-06-2011       |
|  |                  | US 2011091994 A1        | 21-04-2011       |
|  |                  | WO 2009127693 A1        | 22-10-2009       |
|  |                  | WO 2009127913 A1        | 22-10-2009       |
| -----                                  |                  |                         |                  |
| WO 2007146057 A2                       | 21-12-2007       | US 2009017444 A1        | 15-01-2009       |
|  |                  | WO 2007146057 A2        | 21-12-2007       |
| -----                                  |                  |                         |                  |
| WO 2011076873 A1                       | 30-06-2011       | AU 2010334799 A1        | 12-07-2012       |
|  |                  | CA 2784547 A1           | 30-06-2011       |
|  |                  | EP 2516645 A1           | 31-10-2012       |
|  |                  | WO 2011076873 A1        | 30-06-2011       |
| -----                                  |                  |                         |                  |