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*C07K 16/30* (2006.01) *A61K 39/395* (2006.01)

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CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,  
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,  
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,  
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,  
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- before the expiration of the time limit for amending the  
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## (54) Title: BIOLOGICAL INHIBITORS OF ROR1 CAPABLE OF INDUCING CELL DEATH

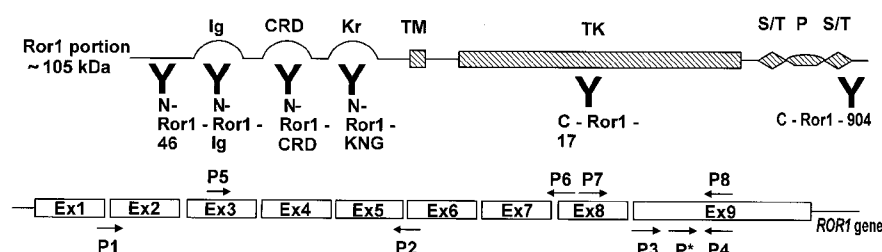


Fig. 1

(57) Abstract: The invention relates to antibodies and siRNA molecules for inducing cell death by the specific binding of ROR1, domains thereof or nucleotide molecules encoding ROR1. There are also provided methods involving and uses of the antibodies and siRNA molecules of the invention.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2010/007524

## 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.:

### 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

International application No  
PCT/EP2010/007524

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07K16/28 C07K16/30 C12N15/113 A61K39/395  
ADD.

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)  
C07K C12N

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)

EPO-Internal, BIOSIS, EMBASE, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                            | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2008/076868 A2 (ABBOTT LAB [US];<br>DAVIDSON DONALD J [US]; HASKELL CATHERINE<br>J [US]) 26 June 2008 (2008-06-26)         | 1-7,<br>13-31         |
| A         | the whole document                                                                                                            | 8-12                  |
| X         | WO 2005/100605 A1 (UNIV CALIFORNIA [US];<br>SLAMON DENNIS J [US]; WILSON CINDY A [US];<br>DERIN) 27 October 2005 (2005-10-27) | 1-31                  |
|           | the whole document                                                                                                            |                       |
|           | -----<br>-/--                                                                                                                 |                       |



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 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

28 July 2011

Date of mailing of the international search report

03/08/2011

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Morawetz, Renate

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/007524

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                    | Relevant to claim No. |
| X                                                    | AMIR H DANESHMANESH ET AL: "Ror1, a cell surface receptor tyrosine kinase is expressed in chronic lymphocytic leukemia and may serve as a putative target for therapy",<br>INTERNATIONAL JOURNAL OF CANCER, JOHN WILEY & SONS, INC, UNITED STATES, SWITZERLAND, GERMANY,<br>vol. 123, no. 5,<br>1 September 2008 (2008-09-01), pages 1190-1195, XP002622341,<br>ISSN: 0020-7136, DOI:<br>DOI:10.1002/IJC.23587<br>[retrieved on 2008-06-10]                           | 1-7,27                |
| A                                                    | the whole document                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 8-26,<br>28-31        |
| X                                                    | -----<br>WO 2007/146957 A2 (IRM LLC [BM]; WARMUTH MARKUS [US]; FOSTER KARIN [US] IRM LLC; WARMUTH) 21 December 2007 (2007-12-21)<br>the whole document                                                                                                                                                                                                                                                                                                                | 1-31                  |
| X                                                    | -----<br>BASKAR SIVASUBRAMANIAN ET AL: "Unique cell surface expression of receptor tyrosine kinase ROR1 in human B-cell chronic lymphocytic leukemia",<br>CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US,<br>vol. 14, no. 2,<br>15 January 2008 (2008-01-15), pages 396-404, XP009135221,<br>ISSN: 1078-0432, DOI:<br>DOI:10.1158/1078-0432.CCR-07-1823<br>the whole document                                                             | 1-31                  |
| A                                                    | -----<br>LAPALOMBELLA ROSA ET AL: "Lenalidomide treatment promotes CD154 expression on CLL cells and enhances production of antibodies by normal B cells through a PI3-kinase-dependent pathway",<br>BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US,<br>vol. 115, no. 13,<br>24 November 2009 (2009-11-24), pages 2619-2629, XP009146859,<br>ISSN: 0006-4971, DOI:<br>DOI:10.1182/BLOOD-2009-09-242438<br>[retrieved on 2009-11-24]<br>the whole document<br>-----<br>-/-- | 1-31                  |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2010/007524

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                 | Relevant to claim No. |
| A                                                    | <p>FUKUDA TETSUYA ET AL: "Antisera induced by infusions of autologous Ad-CD154-leukemia B cells identify ROR1 as an oncofetal, antigen and receptor for Wnt5a",<br/>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), NATIONAL ACADEMY OF SCIENCE, US, vol. 105, no. 8, 26 February 2008 (2008-02-26), pages 3047-3052, XP009135222, ISSN: 0027-8424, DOI: DOI:10.1073/PNAS.0712148105 [retrieved on 2008-02-19] the whole document</p> | 1-31                  |
| X                                                    | <p>-----</p> <p>MACKEIGAN JEFFREY P ET AL: "Sensitized RNAi screen of human kinases and phosphatases identifies new regulators of apoptosis and chemoresistance", NATURE CELL BIOLOGY, NATURE PUBLISHING GROUP, GB, vol. 7, no. 6, 1 June 2005 (2005-06-01), pages 591-600, XP002425115, ISSN: 1465-7392, DOI: DOI:10.1038/NCB1258 the whole document</p>                                                                                                          | 1-31                  |
| X,P                                                  | <p>-----</p> <p>ANIRUDDHA CHOUDHURY ET AL: "Silencing of ROR1 and FMOD with siRNA results in apoptosis of CLL cells", BRITISH JOURNAL OF HAEMATOLOGY, WILEY-BLACKWELL PUBLISHING LTD, GB, vol. 151, no. 4, 31 August 2010 (2010-08-31), pages 327-335, XP002622344, ISSN: 0007-1048, DOI: DOI:10.1111/J.1365-2141.2010.08362.X [retrieved on 2010-08-31] the whole document</p>                                                                                    | 1-31                  |
| X,P                                                  | <p>-----</p> <p>WO 2010/124188 A1 (US OF AMERICA AS REPRESENTED B [US]; RADER CHRISTOPH [US]; BASKAR SIVA) 28 October 2010 (2010-10-28) the whole document</p> <p>-----</p> <p style="text-align: center;">-/--</p>                                                                                                                                                                                                                                                | 1-31                  |

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2010/007524

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                              |                       |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                           | Relevant to claim No. |
| X                                                    | J. W. TYNER ET AL: "RNAi screen for rapid therapeutic target identification in leukemia patients", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 106, no. 21, 26 May 2009 (2009-05-26), pages 8695-8700, XP55003694, ISSN: 0027-8424, DOI: 10.1073/pnas.0903233106 the whole document including supporting information<br>-----                      | 1-31                  |
| A                                                    | TAKAYAMA K ET AL: "Suppression of tumor angiogenesis and growth by gene transfer of a soluble form of vascular endothelial growth factor receptor into a remote organ", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 60, no. 8, 15 April 2000 (2000-04-15), pages 2169-2177, XP002312417, ISSN: 0008-5472 the whole document<br>----- | 1-31                  |
| A                                                    | HEANEY D L ET AL: "SOLUBLE RECEPTORS IN HUMAN DISEASE", JOURNAL OF LEUKOCYTE BIOLOGY, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, US, vol. 64, no. 2, 1 August 1998 (1998-08-01), pages 135-146, XP008005930, ISSN: 0741-5400 the whole document<br>-----                                                                                     | 1-31                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/007524

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date         |
|-------------------------------------------|---------------------|----------------------------|-----------------------------|
| WO 2008076868                             | A2                  | 26-06-2008                 | NONE                        |
| WO 2005100605                             | A1                  | 27-10-2005                 | AU 2005233564 A1 27-10-2005 |
|                                           |                     | CA 2563333 A1              | 27-10-2005                  |
|                                           |                     | EP 1735461 A1              | 27-12-2006                  |
|                                           |                     | JP 2007532111 A            | 15-11-2007                  |
|                                           |                     | US 2008318212 A1           | 25-12-2008                  |
| WO 2007146957                             | A2                  | 21-12-2007                 | NONE                        |
| WO 2010124188                             | A1                  | 28-10-2010                 | NONE                        |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 4(completely); 1-3, 5-7, 13-31(partially)

A biological inhibitor of ROR1 capable of inducing cell death in a cell expressing ROR1, wherein the inhibitor is an antibody; and subject-matter related thereto.

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2. claims: 8-12(completely); 1-3, 5-7, 13-31(partially)

A biological inhibitor of ROR1 capable of inducing cell death in a cell expressing ROR1, wherein the inhibitor is an interfering nucleic acid molecule; and subject-matter related thereto.

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3. claims: 1-3, 5-7, 13-31(all partially)

A biological inhibitor of ROR1 capable of inducing cell death in a cell expressing ROR1, wherein the inhibitor is a soluble receptor; and subject-matter related thereto.

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