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- (81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, 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, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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- with international search report (Art. 21(3))
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26 October 2012



WO 2012/107728 A3

(54) **Title:** FRMD4A ANTAGONISTS AND THEIR USES

(57) **Abstract:** An antagonist of FERM domain-containing protein 4A (FRMD4A) and/or of the Hippo pathway for use in a method of treating a cancer in a mammalian subject, wherein the cancer is selected from: squamous cell carcinoma (SCC), an epithelial cancer, an adenocarcinoma and a carcinoma is disclosed, as well as related methods of treatment of cancer, methods of screening and generating such antagonists, including anti-FRMD4A antibodies.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/000137

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07K16/30 C07K16/18 A61K31/7088 C12N15/113
 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 A61K 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 practicable, 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	MITCHELL O ET AL: "P88 FRMD4A is a potential marker of tumour stem cells in Human Head and Neck Squamous Cell Carcinoma (HNSCC)", BRITISH JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY, CHURCHILL LIVINGSTONE, EDINBURGH, GB, vol. 48, 1 May 2010 (2010-05-01), page S47, XP027057061, ISSN: 0266-4356 [retrieved on 2010-05-01]	1
Y	the whole document	1-7, 12-24, 26-29, 35-38
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 5 June 2012	Date of mailing of the international search report 14/08/2012
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Chapman, Rob
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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2012/000137

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MILENA R KALU EROVI ET AL: "Organogallium(III) complexes as apoptosis promoting anticancer agents for head and neck squamous cell carcinoma (HNSCC) cell lines", JOURNAL OF INORGANIC BIOCHEMISTRY, ELSEVIER INC, US, vol. 105, no. 2, 25 October 2010 (2010-10-25), pages 164-170, XP028133398, ISSN: 0162-0134, DOI: 10.1016/J.JINORGBIO.2010.10.013 [retrieved on 2010-10-30] the whole document</p>	<p>1-7, 12-24, 26-29, 35-38</p>
A	<p>J. IKENOUCI ET AL: "FRMD4A regulates epithelial polarity by connecting Arf6 activation with the PAR complex", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 107, no. 2, 12 January 2010 (2010-01-12), pages 748-753, XP055028924, ISSN: 0027-8424, DOI: 10.1073/pnas.0908423107 the whole document</p>	<p>1-7, 12-24, 26-29, 35-38</p>
T	<p>S. J. GOLDIE ET AL: "FRMD4A upregulation in human squamous cell carcinoma promotes tumor growth and metastasis and is associated with poor prognosis", CANCER RESEARCH, 7 May 2012 (2012-05-07), XP055028922, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-12-0423 the whole document</p>	
X	<p>2010 International PhD Student's Cancer Conference IFOM-IEO Campus Milan 19-21st May 2010 Abstract Book of Conference 'Keynote Lecture and Oral Presentations' p.151 XP007920686</p>	<p>1</p>
Y	<p>the whole document</p>	<p>1-7, 12-24, 26-29, 35-38</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2012/000137

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.:

5-7, 29(completely); 1-4, 12-24, 26-28, 35-38(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. claims: 5-7, 29(completely); 1-4, 12-24, 26-28, 35-38(partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is an antibody

2. claims: 8-11, 25(completely); 1-4, 12-24, 26-28, 35-38(partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is a nucleic acid

3. claims: 1-4, 12-24, 26-28, 35-38(all partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is an aptamer

4. claims: 1-4, 12-24, 26-28, 35-38(all partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is an affinity protein

5. claims: 1-4, 12-24, 26-28, 35-38(all partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is a hyaluronic acid

6. claims: 1-4, 12-24, 26-28, 35-38(all partially)

An antagonist of FRMD4A and/or the Hippo pathway for use in a method of treating cancer, wherein the antagonist is 17-DMAG

7. claims: 30, 31

An isolated peptide consisting of SEQ ID NO:3, 5, or 6

8. claims: 32-34

Methods for screening antibodies that bind FRMD4A
