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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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description (Rules 13bis.4(d)(i) and 48.2(a)(viii))
- with sequence listing part of description (Rule 5.2(a))

- (88) **Date of publication of the international search report:**
7 May 2015

(54) **Title:** ANTIBODIES AND ASSAYS FOR DETECTION OF FOLATE RECEPTOR 1

(57) **Abstract:** The invention generally relates to antibodies that bind to human folate receptor and diagnostic assays for folate receptor 1-based therapies. Methods of using the antibodies to monitor therapy are further provided.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/53512

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395, C07K 16/28 (2015.01)

CPC - A61K 47/48384, A61K 47/48561, C07K 16/28

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(8) - A61K 39/395, C07K 16/28 (2015.01)

CPC - A61K 47/48384, A61K 47/48561, C07K 16/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C07K 16/32

(keyword limited; terms below)

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

PatBase, PubWEST(USPT, PGPB, EPAB, JPAB), Google Science

Search terms: FOLR1, folate receptor 1, folate receptor alpha, antibody, antibodies, huMov19, DM4, sulfo-SPDB, IMGN853, conjugat, N-glycosylated

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROBERTS et al., Role of individual N-linked glycosylation sites in the function and intracellular transport of the human alpha folate receptor. Arch Biochem Biophys, 15 March 1998, Vol 351, No 2, pages 227-235. Especially abstract; p 228, col 1, para 3; pg 228, col 2, last para; p 229, Fig. 1	1
A	US 2012/0009181 A1 (AB et al.) 12 January 2012 (12.01.2012) para [0002], [0004], [0011], [0297]	2-5, 15-17, 87-89
A	US 2007/0048315 A1 (PRESTA) 01 March 2007 (01.03.2007) SEQ ID NO: 14	2-4, 5/(2-4), 87-89
A	US 2009/0156788 A1 (PRESTA) 18 June 2009 (18.06.2009) SEQ ID NO: 14	2-4, 5/(2-4), 87-89
A	US 2011/0002942 A1 (PRESTA) 06 January 2011 (06.01.2011) SEQ ID NO: 14	2-4, 5/(2-4), 87-89
A	US 2013/0039916 A1 (PRESTA) 14 February 2013 (14.02.2013) SEQ ID NO: 14	2-4, 5/(2-4), 87-89
A	WO 2008/103473 A1 (PRESTA) 28 August 2008 (28.08.2008) SEQ ID NO: 14	2-4, 5/(2-4), 87-89
A	US 2012/0282637 A1 (HUBER et al.) 08 November 2012 (08.11.2012) SEQ ID NO: 6	2-5, 15-17, 87-89
A	WO 2011/042548 A1 (HUBER et al.) 14 April 2011 (14.04.2011) SEQ ID NO: 6	2-4, 5/(2-4), 87-89
A	WO 2007/020965 A1 (SEKIKAWA et al.) 22 February 2007 (22.02.2007) SEQ ID NO: 2	2-4, 5/(2-4), 87-89
A	US 2008/0171014 A1 (WU et al.) 17 July 2008 (17.07.2008) SEQ ID NOs: 33 and 35	2-5, 15-17, 87-89

☒ Further documents are listed in the continuation of Box C.

* 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 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

03 February 2015 (03.02.2015)

Date of mailing of the international search report

24 FEB 2015

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/53512

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0256127 A1 (BOURHIS et al.) 20 October 2011 (20.10.2011) SEQ ID NO: 22	5/1, 15-17
A	F9RS38, UniProtKB/TrEMBL Accession No F9RS38_9VIBR, 28 November 2012 [online]. [Retrieved on 3 February2015]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/F9RS38.txt?version=5 > Entire document	5/1, 15-17
A	US 2011/0038867 A1 (PINCELLI et al.) 17 February 2011 (17.02.2011) SEQ ID NO: 6	5/1, 15-17
A	US 7,465,449 A (VIOLETTE et al.) 16 December 2008 (16.12.2008) SEQ ID NO: 34	5/1, 15-17
A	US 8,153,126 A (VIOLETTE et al.) 10 April 2012 (10.04.2012) SEQ ID NO: 34	5/1, 15-17
A	US 2012/0251532 A1 (VIOLETTE et al.) 04 October 2012 (04.10.2012) SEQ ID NO: 34	5/1, 15-17
A	US 2009/0087478 A1 (HANSEN et al.) 02 April 2009 (02.04.2009) SEQ ID NO: 7	5/1, 15-17
A	H0DED6, UniProtKB/TrEMBL Accession No. H0DED6_9STAP, 28 November 2012 [online]. [Retrieved on 3 February2015]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/H0DED6.txt?version=5 > Entire document	5/1, 15-17
A	US 2004/0031072 A1 (LA ROSA et al.) 12 February 2004 (12.02.2004) SEQ ID NO: 221094	5/1, 15-17
A	R5I4W9, UniProtKB/TrEMBL Accession No. R5I4W9_9FIRM, 24 July 2013 [online]. [Retrieved on 3 February2015]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/R5I4W9.txt?version=1 > Entire document	5/1, 15-17
A	US 2007/0071675 A1 (WU et al.) 29 March 2007 (29.03.2007) SEQ ID NO: 1	5/1, 15-17
A	US 7,915,388 A (WU et al.) 29 March 2011 (29.03.2011) SEQ ID NO: 33	5/1, 15-17
A	US 2007/0253950 A1 (JACOBSEN) 01 November 2007 (01.11.2007) SEQ ID NO: 22	5/1, 15-17
A	US 2007/0286858 A1 (CLANCY et al.) 13 December 2007 (13.12.2007) SEQ ID NO: 22	5/1, 15-17

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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.: 6-7, 10-14, 18-86
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:
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 1-5, 8-9, 15-17 and 87-89, drawn to an antibody or antigen-binding fragment thereof that specifically binds to an epitope of FOLR1 and methods of using said antibody. Group I+ will be searched without fee to the extent that it reads on antibody muFRIHC2-1. It is believed that claims 1-5, 15-17, and 87-89, limited to antibody muFRIHC2-1 (muFRIHC2 comprises muFRIHC2-1 VH chain: SEQ ID NO: 27, muFRIHC2-1 VL chain: SEQ ID NO: 28, muFRIHC2-1 VH CDRs1-3: SEQ ID NOs: 3-5, muFRIHC2-1 VL CDRs1-3: SEQ ID NOs: 6-8) read on this first named invention. [Note that claims 8-9 are drawn to sequences for an antibody other than muFRIHC2-1]. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention being searched/examined. An exemplary election would be: antibody muFRIHC5-7 (which comprises SEQ ID NOs: 29, 30, 9-11, 12-14), i.e. claims 1-5 and 15-17.
---please see continuation on extra 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 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.: 1-5, 15-17, and 87-89, limited to antibody muFRIHC2-1 (SEQ ID NOs: 27, 28, 3-5, and 6-8)

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.

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Continuation of Box No. III Observations where unity of invention is lacking

The inventions listed as Groups I+ 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 features for the following reasons:

Special Technical Features

The special technical feature of each of the inventions of Group I+ is the specific antibody or antigen-binding fragment thereof recited therein. Each of the antibodies or fragment thereof requires specific sequences that are unique to that antibody and are not required by any of the antibodies of the other inventions.

The first named invention of Group I+ requires methods of using antibody muFRIHC2-1 fragments (SEQ ID NOs: 27 and 28) in a method for identifying a cancer as likely to respond to treatment with an antibody maytansinoid conjugate comprising the FOLR1 antibody huMov19, the maytansinoid DM4 and a sulfo-SPDB linker (IMGN853); not required by any of the other inventions of Group I+.

Common Technical Features

The feature shared by Group I+ is an antibody or antigen-binding fragment thereof that specifically binds to an epitope of FOLR1, wherein said epitope comprises at least one, at least two, or three N-glycosylated amino acids. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2012/0009181 A1 to Ab et al. (hereinafter 'Ab'). Ab discloses an antibody or antigen-binding fragment thereof that specifically binds to an epitope of FOLR1 (folate receptor 1) (para [0002] - "antibodies and immunoconjugates that bind to human folate receptor 1"; para [0011] - "The present invention provides novel antibodies that bind to human folate receptor 1, immunoconjugates comprising these antibodies, and methods of their use. The present invention further provides novel polypeptides, such as antibodies that bind human folate receptor 1, fragments of such antibodies, and other polypeptides related to such antibodies"). Ab also teaches that FOLR1 is an N-glycosylated protein expressed on plasma membrane of cells (para [0004]). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

Please note that the methods of claims 87-89 are not a common technical feature of Group I+ because the methods of claims 87-89 require SEQ ID NOs:27 and 28, sequences that represents the muFRIHC2-1 antibody of the first named invention and no other antibody of the other inventions of Group I+.

Groups I+ therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

NOTE:

Claims 6-7, 10-14, 18-86 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Claim 16 is objected to for depending on a subsequent claim. As drafted, claim 16 depends from claim 20, which is a claim that comes after claim 16. For the purposes of this ISA Search and Written Opinion, claim 16 is construed as though depending from claim 15.