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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *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))*

(88) Date of publication of the international search report:
21 August 2014

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(54) Title: FULLY HUMAN ANTIBODIES AND FRAGMENTS RECOGNIZING HUMAN C-MET

(57) Abstract: Human antibody fragments against c-Met have been identified through phage display technology. The high affinity and low immunogenicity make them very useful for both *in vivo* and *in vitro* applications. These novel human antibodies can greatly help the study of drug resistance in EGFR targeted therapies, and improve the diagnosis and treatment of cancer patients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/72668

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12P 21/08; C07K 16/00; A61K 39/00 (2014.01)
USPC - 530/387.3, 530/388.15; 530/391.1; 424/133.1,424/142.1, 424/178.1
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) - C12P 21/08; C07K 16/00; A61K 39/00; A61K 39/395 (2014.01)
USPC - 530/387.3, 530/388.15; 530/391.1; 424/133.1,424/142.1, 424/178.1; 530/387.1, 424/130.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12P 21/08; C07K 16/00; A61K 39/00; A61K 39/395 (2014.01) - see keyword below
USPC - 530/387.3, 530/388.15; 530/391.1; 424/133.1,424/142.1, 424/178.1; 530/387.1, 424/130.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: isolated, human anti-c-met, antibody, single chain, scFv, diabody, cys -diabody, minibody, triabody, chimeric, heavy chain, light chain, CDR, conjugate, cytotoxic, chemotherapeutic, gemcitabine, carboplatin, taxol, paclitaxel, purified, linker, GGGGGS, GGGGSGGGGSGGGGS, CysDB, Cys-Db

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0040629 A1 (MICHAUD et al.) 18 February 2010 (18.02.2010), Abstract, para [0006], [0032], [0064], [0066], [0090], [0096], [0106], [0114], [0161], [0186], and [0187]	1-4, 8-9, 13, 14/(1-4, 8-9, 13), 15, 16/(1-4, 8-9, 13), (17-19)/(1-4), 35, 46-47
A	US 2011/0268656 A1 (HO et al.) 03 November 2011 (03.11.2011), para [0012], [0015], [0016], [0024], [0025], [0028], [0050], [0055], and [0070]	1-4, 8-9, 13, 14/(1-4, 8-9, 13), 15, 16/(1-4, 8-9, 13), (17-19)/(1-4), 35, 46-47
A	US 2012/0058906 A1 (SMIDER et al.) 08 March 2012 (08.03.2012), para [0446], [0487], Table 41, and SEQ ID NO: 3174	1-4, 8-9, 13, 14/(1-4, 8-9, 13), 15, 16/(1-4, 8-9, 13), (17-19)/(1-4), 35, 46-47
A	US 2008/0038266 A1 (BURNIE et al.) 14 February 2008 (14.02.2008), para [0022], [0071], and SEQ ID NO: 16.	1-4, 8-9, 13, 14/(1-4, 8-9, 13), 15, 16/(1-4, 8-9, 13), (17-19)/(1-4), 35, 46-47
A	US 2004/0071696 A1 (ADAMS et al.) 15 April 2004 (15.04.2004), para [0013], Table 2, and SEQ ID NO: 6	35
A	HOLLIGER et al. "Diabodies": Small bivalent and bispecific antibody fragments. Proc Natl Acad Sci U S A. 1993, Vol. 90(14), p. 6444-8. Entire documentation, especially Abstract; pg 6444, col 2, para 1; and pg 6445, Fig 1	1-4, 8-9, 13, 14/(1-4, 8-9, 13), 15, 16/(1-4, 8-9, 13), (17-19)/(1-4), 35, 46-47

☐ 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	Date of mailing of the international search report
21 February 2014 (21.02.2014)	13 JUN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/72668

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.: 20-34, 39-45, and 48-51
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.

Groups I+, claims 1-19, 35-38, 46-47, drawn to an isolated human anti-c-Met antibody comprising a human heavy chain variable domain and a human light chain variable domain. The first invention is restricted to the first named sequence, SEQ ID NO: 1, SEQ ID NO: 9, SEQ ID NO: 17, and SEQ ID NO: 25 (wherein SEQ ID NO:17 and SEQ ID NO: 25 each comprises SEQ ID.NO: 1 and SEQ ID NO: 9; Specification: para [00097]; [000105], and [000113]). Group I+ will be searched to the extent that it reads on SEQ ID NOs: 1, 9, 17, and 25, without fee. It is believed that claims 1-4, 8-9, 13, 14/(part), 15, 16-19/(part), 35, 46-47 read on this first named invention. 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 to be searched/examined. An exemplary election would be: SEQ ID NO: 2, SEQ ID NO: 10, SEQ ID NO: 18, and SEQ ID NO: 26 (claims 1-5, 8-10, 13, 14/(part), 15, 16-19/(part), 35-36, 46-47; Specification: [00098], [000106], and [000114]).

**********Continued in the 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.:
1-4, 8-9, 13, 14/(1-4,8-9,13), 15, 16/(1-4,8-9,13), (17-19)/(1-4), 35, 46-47, limited to SEQ ID NOs: 1, 9, 17, and 25

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/US 13/72668

Continuation of:
Box No III (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 Feature
Among Groups I+, each of anti-c-Met antibody and associated scFv or cys-diabody comprising a pair of heavy chain and light chain variable domains is structurally different from all other anti-c-met antibodies comprising a different pair of heavy chain and light chain variable domains (Specification: para [00097]-[000120]).

Common Technical Features
The inventions of Groups I+ share the technical feature of an isolated human anti-c-Met antibody comprising a human heavy chain variable domain and a human light chain variable domain, and further the antibody is an scFv or cys-diabody.

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2010/0040629 A1 to MICHAUD et al. (hereinafter Michaud'); or as being obvious over Michaud, in view of US 2011/0268656 A1 to HO et al. (hereinafter 'Ho') as follows:

Michaud discloses an isolated human anti-c-Met antibody (Abstract - 'human antibodies and antigen-binding portions thereof that specifically bind to c-Met, preferably human c-Met'; para [0006] - 'an isolated antibody or antigen-binding portion thereof that specifically binds c-Met')
--- comprising a human heavy chain variable domain and a human light chain variable domain (para [0096] - 'light chain of the human anti-c-Met antibody comprises the V.sub.L a...SEQ ID NO: 4; para [0106] - 'heavy and/or light chain variants of certain of the above-listed human anti-c-Met antibodies'; para [0099] - 'heavy chain comprises the V.sub.H amino acid sequence of antibody 13.3.2 (SEQ ID NO: 2'; para [0066] - 'term "human antibody" means any antibody in which the variable and constant domain sequences are human sequences'; para [0114] - 'a human anti-c-Met monoclonal antibody that binds to c-Met a...(b) ... heavy chain variable domain ... SEQ ID NO: 2, ...14, (c) ... a light chain variable domain ...SEQ ID NO: 4,... 16').

Michaud further discloses heavy chain and light chain variable domain sequences of the human anti-c-Met antibody (para [0114] - 'a human anti-c-Met monoclonal antibody that binds to c-Met a...(b) ... heavy chain variable domain ... SEQ ID NO: 2, ...14, (c) ... a light chain variable domain ...SEQ ID NO: 4,... 16'), and wherein the antibody is a single-chain anti-c-met antibody, or an anti-c-met diabody comprising a heavy chain variable domain, a light chain variable domain, and a linker (para [0161] - anti-c-Met antibodies. ... single chain antibodies... diabodies'; para [0064] - the antibody is a single-chain antibody (scFv) ...the antibodies are diabodies, i.e., are bivalent antibodies in which V.sub.H and V.sub.L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites'); as well as methods of using the antibody for diagnosis and treatment (Abstract - 'human anti-c-Met antibodies ...methods of using the antibodies and compositions for diagnosis and treatment').

Michaud does not specifically teach wherein the diabody is a cys-diabody. Ho discloses a method for generating cys-diabody comprising heavy chain and light chain variable domains linked by different length of linkers comprising a cys amino acid (para [0024] - 'a schematic diagram of the cys-diabody (CysDB) (A)... a CysDB in VLVH orientation (B)... a CysDB in VHVL orientation (C).... VH=variable heavy domain, VL=variable light...L linker (may be 5 or 8 amino acids), GGS=cysteine tail (Gly-Gly-Cys)'; para [0025][0028]) for conjugation of different agents for in vivo diagnosis or treatment applications (para [0015] - 'diagnosing a cancer ...administering ... a cys-diabody conjugated to a diagnostic agent to a subject'; para [0016] - 'treating a cancer ...administering ...cys-diabody ... conjugated to a therapeutic agent').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Michaud and Ho, to obtain a human anti-c-met antibody that is a diabody comprising a heavy chain variable domain and a light chain variable domain and a linker, as taught by Michaud, and further wherein the diabody is a cys-diabody, based on the combination of Ho and Michaud, in order to use the method available and the sequences known in the art for generating human anti-c-met cys-diabody for facilitating further conjugation of diagnosing or therapeutic agents for diagnosing or treating disorders associated with altered expression of c-Met level with expected success and without undue experimentation.

Without a shared special technical feature, the inventions lack unity with one another.

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

Note re item 4: Claims 20-34, 39-45, and 48-51 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note:
Claims 14 and 16 are objected to as self-referring. It is assumed that claims 14 and 16 each depends upon any of claims 1-13. For the purposes of this ISR, claims 14 and 16 are construed as follows:

14. The isolated human anti- c-Met antibody of any of claims 1-13 wherein the antibody or antigen binding fragment thereof is a fully human antibody.

16. The isolated human anti- c-Met antibody of any of claims 1-13, wherein the antibody or antigen binding fragment thereof is chimeric.