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- with international search report (Art. 21(3))
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7 January 2010

(54) Title: HER2/NEU-SPECIFIC ANTIBODIES AND METHODS OF USING SAME

(57) Abstract: This invention relates to antibodies that specifically bind HER2/neu, and particularly chimeric 4D5 antibodies to HER2/neu, which have reduced glycosylation as compared to known 4D5 antibodies. The invention also relates to methods of using the 4D5 antibodies and compositions comprising them in the diagnosis, prognosis and therapy of diseases such as cancer, autoimmune diseases, inflammatory disorders, and infectious disease.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/38201

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00; C12P 21/08 (2009.01)
USPC - 424/133.1; 530/387.3

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 39/00; C12P 21/08 (2009.01)
USPC - 424/133.1; 530/387.3

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)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: HER2/neu, HER-2/neu, ErbB-2, ERBB2, antibody, substitution, L235V, Fc, light chain, variable, variant, modification, cytotoxicity, binding, increased, wild-type, immunoglobulin, N65S, F243L, Fc.gamma.RIIIA, Fc.gamma.RIIA, enhance. GenCore 6.3: SEQ ID NO: 4 and 2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2006/0018899 A1 (KAO et al.) 26 Jan 2006 (26.01.2006) para [0008], [0038], and [0080]	1, 4 ----- 5-6, 9
Y	US 2007/0036799 A1 (STAVENHAGEN et al.) 15 Feb 2007 (15.02.2007), Abstract, para [0048], [0053]-[0054], [0056], [0067], [0132], [0189], [0202], and [0216]	5-6, 9
A	US 2004/0236078 A1 (CARTER et al.) 25 Nov 2004 (25.11.2004), para [0044]	2-3

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	“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
“A” document defining the general state of the art which is not considered to be of particular relevance	“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
“E” earlier application or patent but published on or after the international filing date	“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
“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)	“&” document member of the same patent family
“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	

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/38201

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.: 13-20
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:

Group I+: claims 1-9, drawn to a polypeptide comprising a chimeric 4D5 immunoglobulin light chain comprising an N65S substitution. The first invention encompasses said polypeptide comprising a chimeric 4D5 immunoglobulin light chain comprising an N65S substitution further comprising the L235V substitution. Additional substitutions and combination(s) thereof will be searched for an additional fee. In order to have additional substitutions searched, Applicant must specify them. The exact claims searched will depend on the specifically elected substitutions.

[Note: Claims 7-8 were not searched because are not encompassed by the first named invention of Group I+ as drawn to nonelected substitutions.]

Groups II-IV: claim 10, drawn to a polypeptide of SEQ ID NO: 9, SEQ ID NO: 11, or SEQ ID NO: 13, respectively.

*****Continued in 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.:
Claims 1-6, and 9, limited to the L235V substitution.

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 09/38201

***** SUPPLEMENTAL BOX *****8

Continuation of: Box No III (unity of invention is lacking)

Group V+; claims 11-12, drawn to a polypeptide comprising a 4D5 immunoglobulin heavy chain further comprising at least one substitution. Said substitution, additional substitutions and combination(s) thereof will be searched for an additional fee. In order to have additional substitutions searched, Applicant must specify them.

The inventions listed as Groups I-V+ 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:

Groups I+ and V+ do not include the inventive concept of a polypeptide of SEQ ID NO: 9, SEQ ID NO: 11, and SEQ ID NO: 13, as required by Groups II-IV.

Group I+ does not include the inventive concept of a polypeptide comprising a 4D5 immunoglobulin heavy chain further comprising at least one substitution, as required by Group I+.

Group V+ does not include the inventive concept of a polypeptide comprising a chimeric 4D5 immunoglobulin light chain comprising an N65S substitution, as required by Group I+.

The invention of Group I+ share the technical feature of a polypeptide comprising a chimeric 4D5 immunoglobulin light chain comprising an N65S substitution. However, this shared technical feature does not represent a contribution over the prior art. Specifically, GenBank entry 1FVE_A "Chain A, X-Ray Structures Of The Antigen-Binding Domains From Three Variants Of Humanized Anti-P185-Her2 Antibody 4d5 And Comparison With Molecular Modeling" (01 OCT 2007) [Retrieved from the Internet 08 Jul 2009: <<http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?442923:PROT:5227463>>] discloses said polypeptide (1 diqmtqspss lsasvgrdvt itcrasqdn tavawyqqkp gkapklliys asflesgvps 61 rfsqSrsqtd fltisslqp edfatyyccq hytptfpgq gtkveikrtv aapsvfifpp 121 sdeqlksgta svvcllnffy preakvqwkv dnalqsgnsq esvteqdskd styslssitt 181 lskadyekhk vyacevthqg lsspvtksfn rgec). As the above polypeptide was known at the time, this cannot be considered a special technical feature that would otherwise unify the groups.

The special technical feature of the invention listed as Groups Groups II-IV is the specific nucleic acid sequence recited therein. As no significant structural similarities can readily be ascertained among the nucleic acid sequences, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

The invention of Group V+ share the technical feature of a polypeptide comprising a 4D5 immunoglobulin heavy chain. However, this shared technical feature does not represent a contribution over the prior art. Specifically, an article entitled "Humanization of an anti-p185HER2 antibody for human cancer therapy" by CARTER, et al. (Proc. Natl. Acad. Sci. USA May 1992, 89:4285-4289) discloses said polypeptide (Abstract, "Light- and heavy-chain variable regions were simultaneously humanized in one step by "gene conversion mutagenesis" ... One of seven additional human variants designed by molecular modeling (humAb4D5-8) binds the p185HER2 antigen 250-fold and 3-fold more tightly than humAb4D5-1 and mumAb4D5, respectively.") As the above polypeptide was known at the time, this cannot be considered a special technical feature that would otherwise unify the groups.

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