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(54) Title: MOUSE PRIMERS

(57) Abstract: The present invention provides primer sets for the isolation of mouse antibody variable region sequences. Further provided are antibodies comprising these regions which are useful in the development of therapeutics and, in particular, in the development of humanised antibodies.

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68 C07K16/00 C12N15/10

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)
C12Q C12N C07K

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, Sequence Search, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"PRIMER DESIGN FOR THE CLONING OF IMMUNOGLOBULIN HEAVY-CHAIN LEADER-VARIABLE REGIONS FROM MOUSE HYBRIDOMA CELLS USING THE PCR" BIOTECHNIQUES, INFORMA LIFE SCIENCES PUBLISHING, WESTBOROUGH, MA, US, vol. 11, no. 2, August 1991 (1991-08), pages 152-154,156, XP000647450 ISSN: 0736-6205 abstract page 153, left-hand column; figure 1; table 1 page 154, right-hand column, paragraph 4 page 155, left-hand column	1,2,13, 16,19

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
27 October 2006	08. 02. 2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hagenmaier, Susanne

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ORUM H ET AL: "Efficient method for constructing comprehensive murine Fab antibody libraries displayed on phage." NUCLEIC ACIDS RESEARCH. 25 SEP 1993, vol. 21, no. 19, 25 September 1993 (1993-09-25), pages 4491-4498, XP002393352 ISSN: 0305-1048 abstract page 4491, right-hand column, paragraph 1 page 4492; figure 1 page 4495; figure 3 page 4495, right-hand column, last paragraph	1,2,13, 16,19
Y	DÜBEL S ET AL: "Isolation of IgG antibody Fv-DNA from various mouse and rat hybridoma cell lines using the polymerase chain reaction with a simple set of primers." JOURNAL OF IMMUNOLOGICAL METHODS. 30 SEP 1994, vol. 175, no. 1, 30 September 1994 (1994-09-30), pages 89-95, XP002079907 ISSN: 0022-1759 abstract the whole document	1,2,13, 16,19
Y	ORLANDI R ET AL: "CLONING IMMUNOGLOBULIN VARIABLE DOMAINS FOR EXPRESSION BY THE POLYMERASE CHAIN REACTION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 86, no. 10, 1 May 1989 (1989-05-01), pages 3833-3837, XP000026475 ISSN: 0027-8424 abstract page 3833, left-hand column, last paragraph page 3835, left-hand column page 3835; figure 2 page 3837, left-hand column, last paragraph	1,2,13, 16,19

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BABCOOK J S ET AL: "A NOVEL STRATEGY FOR GENERATING MONOCLONAL ANTIBODIES FROM SINGLE, ISOLATED LYMPHOCYTES PRODUCING ANTIBODIES OF DEFINED SPECIFICITIES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 93, no. 15, 23 July 1996 (1996-07-23), pages 7843-7848, XP000608647 ISSN: 0027-8424 abstract page 7844, right-hand column, paragraph 2 - paragraph 3 page 7844, right-hand column, last paragraph page 7845; figure 2	1,2,13, 16,19
Y	GAVILONDO-COWLEY J V ET AL: "SPECIFIC AMPLIFICATION OF REARRANGED IMMUNOGLOBULIN VARIABLE REGION GENES FROM MOUSE HYBRIDOMA CELLS" HYBRIDOMA, LIEBERT, NEW YORK, NY, US, vol. 407 - 417, no. 9, January 1990 (1990-01), page 5, XP008067250 ISSN: 0272-457X abstract page 410; figure 1 page 409; table 1 page 413 - page 415	1,2,13, 16,19
Y	WO 03/054016 A (VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECHNOLOGIE VZW; MUYLDERMAN) 3 July 2003 (2003-07-03) page 15, line 12 - page 16, line 8; example 1	1,2,13, 16,19
Y	US 6 291 161 B1 (LERNER RICHARD A ET AL) 18 September 2001 (2001-09-18) column 2, line 15 - line 19 column 12, last paragraph - column 13, paragraph 2 column 20, line 48 - column 22	1,2,13, 16,19
Y	WO 00/23087 A (SUNOL MOLECULAR CORPORATION) 27 April 2000 (2000-04-27) page 89; example 23; sequence JS300 -& DATABASE Geneseq [Online] 15 August 2000 (2000-08-15), "F23.1 heavy chain PCR primer JS300." XP002393358 retrieved from EBI accession no. GSN:AAZ94969 Database accession no. AAZ94969	1,2,13, 16,19

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/001251

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 675 199 A (TAKARA SHUZO CO. LTD; TAKARA BIO INC) 4 October 1995 (1995-10-04) page 23; example 1; sequence 12 -& DATABASE Geneseq [Online] 9 May 1996 (1996-05-09), "Primer for mouse heavy chain constant region." XP002393359 retrieved from EBI accession no. GSN:AAT04162 Database accession no. AAT04162	1,2,13, 16,19
A	FORD JOHN E ET AL: "Chimeric molecules created by gene amplification interfere with the analysis of somatic hypermutation of murine immunoglobulin genes" GENE (AMSTERDAM), vol. 142, no. 2, 1994, pages 279-283, XP002393354 ISSN: 0378-1119	
A	MAYNARD J ET AL: "ANTIBODY ENGINEERING" ANNUAL REVIEW OF BIOMEDICAL ENGINEERING, ANNUAL REVIEW INCO., PALO ALTO, CA, US, vol. 2, 2000, pages 339-376, XP009039750 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.
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Box 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.: 22-24 (all completely)
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 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 fee, this Authority did not invite payment of any additional fee.

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, 13, 16 (all partially); 2, 19 (all completely)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 22-24 (all completely)

Claim 22 relates to a mouse antibody isolated according to the method of any one of claims 13-21. However, said claim 22 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the mouse antibody only in that they are obtained by the methods of claims 13-21. This sole indication does not allow the skilled person to identify any structural feature of the "antibody" which could allow its unambiguous definition. Moreover, the said indication does not even contain any information concerning the method for producing the claimed antibody since claims 13-21 relates to methods for the isolation of a nucleic acid and not to methods for producing antibodies. Also the description provides no indication whatsoever as to such an antibody. Claim 22 is, therefore, so unclear (Art. 6 PCT) that no meaningful search with respect of its subject-matter could be carried out.
Claim 23 relates to the use of an antibody according to claim 22, for the manufacture of a medicament for the treatment and/or prophylaxis of a disease involving aberrant expression or aberrant activity of an antigen recognised by said antibody. For the same reasons as set out herein above, claim 23 is so unclear (Art. 6 PCT) that no meaningful search with respect of its subject-matter could be carried out.
For the same reasons as set out herein above, present claim 24, which relates to a method of screening for and/or diagnosis or prognosis of a disease in a subject, and/or monitoring the effectiveness of therapy for said disease, wherein the antibody of claim 22 is used, so lacks clarity (Art. 6 PCT) that no meaningful search with respect of its subject-matter could be carried out.

Consequently, the subject matter of claims 22-24 was not considered for establishing the different groups of non-unitary inventions.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

Invention 1: 1,13,16 (all partially); 2,19 (all completely)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 1; or
-the specific combination of the primers of Seq.ID 1-45;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody heavy chain comprising the use of these primer sets.

Invention 2: 1,7,8,13,16 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 2; or
-the specific combination of the primer of Seq. ID 1 and the primer of Seq. ID 2; or
-the specific combination of the primers of Seq.ID 2-45;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 108;
-the specific combination of the primers of Seq.ID 103-151;
-the specific combination of the primers of Seq.ID 108-151;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody heavy chain comprising the use of these primer sets.

Inventions 3-45: 1,7,8,13,16 (all partially)

Invention 3:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 3; or
-the specific combination of the primer of Seq. ID 1 and the primer of Seq. ID 3;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 109;
-the specific combination of the primers of Seq.ID 103-151;
-the specific combination of the primers of Seq.ID 108-151;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody heavy chain comprising the use of these primer sets.
..ibidem for inventions 4-45 relating to Seq.IDs 4-45 and Seq.IDs 110-151.

Invention 46: 3,4,14,17,20 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 46; or
-the specific combination of the primer of Seq. ID 46 and at least one primer selected from the group consisting of Seq. IDs 47-93;
-the specific combination of the primers of Seq.ID 46-93;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody kappa light chain comprising the use of these primer sets.

Invention 47: 3,4,9,10,14,17,20 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 47; or
-the specific combination of the primer of Seq. ID 46 and the primer of Seq. ID 47;
-the specific combination of the primers of Seq.ID 46-93; or
-the specific combination of the primers of Seq.ID 47-93
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 157; or
-the specific combination of the primers of Seq.ID 152-203;
-the specific combination of the primers of Seq.ID 157-203
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody kappa light chain comprising the use of these primer sets.

Inventions 48-93: 3,4,9,10,14,17,20 (all partially)

Invention 48:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 48; or
-the specific combination of the primer of Seq. ID 46 and the primer of Seq. ID 48;
-the specific combination of the primers of Seq.ID 46-93; or
-the specific combination of the primers of Seq.ID 47-93
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 158; or
-the specific combination of the primers of Seq.ID 152-203;
-the specific combination of the primers of Seq.ID 157-203;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody kappa light chain comprising the use of these primer sets.
..ibidem for inventions 49-93 relating to Seq.IDs 49-93 and Seq.ID 159-203.

Invention 94: 5,6,15,18,21 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 94; or
-the primer of Seq. ID 94 and at least one primer selected from the group consisting of Seq. IDs 95-102; or
-the specific combination of the primers of Seq.ID 94-102;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody lambda light chain comprising the use of these primer sets.

Invention 95: 5,6,11,12,15,18,21 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 95; or
-the specific combination of the primer of Seq. ID 94 and the primer of Seq. ID 95;
-the specific combination of the primers of Seq.ID 94-102;
or
-the specific combination of the primers of Seq.ID 95-102
an oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 205; or
-the specific combination of the primers of Seq.ID 204-212;
or
-the specific combination of the primers of Seq.ID 205-212
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody lambda light chain comprising the use of these primer sets.

Invention 96-102: 5,6,11,12,15,18,21 (all partially)

Invention 96:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 96; or
-the specific combination of the primer of Seq. ID 94 and the primer of Seq. ID 96;
-the specific combination of the primers of Seq.ID 94-102;
or
-the specific combination of the primers of Seq.ID 95-102
an oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 206; or
-the specific combination of the primers of Seq.ID 204-212;
or
-the specific combination of the primers of Seq.ID 205-212
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody lambda light chain comprising the use of these primer sets.
..ibidem for inventions 97-102 relating to Seq.IDs 97-102 and Seq.IDs 207-212.

Inventions 103-107: 7,8,13,16,19 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 103:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 103; or
-the primer of Seq. ID 103 and at least one primer selected from the group consisting of Seq. IDs 108-151;
-the specific combination of the primers of Seq.ID 103-151;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody heavy chain comprising the use of this primer set.
..ibidem for inventions 104-107 relating to Seq.IDs 104-107.

Invention 108: 9,10,14,17,20 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 152; or
-the primer of Seq. ID 152 and at least one primer selected from the group consisting of Seq. IDs 157-203; or
-the specific combination of the primers of Seq.IDs 152-203;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody kappa light chain comprising the use of this primer set.

Inventions 109-112: 9,10,14,17,20 (all partially)

Invention 109:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 153; or
-the primer of Seq. ID 153 and at least one primer selected from the group consisting of Seq. IDs 157-203; or
-the specific combination of the primers of Seq.IDs 152-203;
a method for the isolation of a nucleic acid comprising the variable region sequence of a mouse antibody kappa light chain comprising the use of this primer set.
...ibidem for inventions 110-112 relating to Seq.IDs 154-156.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/001251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03054016 A	03-07-2003	AU 2002360068 A1	09-07-2003
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