Abstract
The present invention provides primer sets for the isolation of rat antibody variable region sequences. Further provided are antibodies comprising these region which are useful in the development of therapeutics and, in particular, in the development of humanised antibodies.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C1201/68   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)
C120  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

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>COCHET 0 ET AL: &quot;Intracellular expression and functional properties of an anti-p21Ras scFV derived from a rat hybridoma containing specific lambda and irrelevant kappa light chains.&quot; MOLECULAR IMMUNOLOGY. DEC 1998, vol. 35, no. 17, December 1998 (1998-12), pages 1097-1110, XP002398950 ISSN: 0161-5890 page 1098, left-hand column, last paragraph - right-hand column, paragraph 1 page 1098, right-hand column, last paragraph - page 1099, left-hand column, paragraph 1 page 1100, right-hand column, paragraph 3.3 page 1102; table 1</td>
<td>1, 2, 13, 16, 19</td>
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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

Date of the actual completion of the international search

31 October 2006

Date of mailing of the international search report

05. 02. 2007

Name and mailing address of the ISA

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Fax: (+31-70) 340-3518

Authorized officer

Hagenmaier, Susanne

Form PCT/ISA/10 (second sheet) (April 2006)
<table>
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<td>Y</td>
<td>&quot;PRIMER DESIGN FOR THE CLONING OF IMMUNOGLOBULIN HEAVY-CHAIN LEADER-VARIABLE REGIONS FROM MOUSE HYBRIDOMA CELLS USING THE PCR&quot; 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</td>
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<td>Y</td>
<td>DÜBEL S ET AL: &quot;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.&quot; 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</td>
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<td>ORUM H ET AL: &quot;Efficient method for constructing comprehensive murine Fab antibody libraries displayed on phage.&quot; NUCLEIC ACIDS RESEARCH. 25 SEP 1993, vol. 21, no. 19, 25 September 1993 (1993-09-25), pages 4491-4498, XP000828043 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</td>
<td>1,2,13, 16,19</td>
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<td>ORLANDI R ET AL: &quot;CLONING IMMUNOGLOBULIN VARIABLE DOMAINS FOR EXPRESSION BY THE POLYMERASE CHAIN REACTION&quot; 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</td>
<td>1,2,13, 16,19</td>
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<td>BABCOOK J S ET AL: &quot;A NOVEL STRATEGY FOR GENERATING MONOClonAL ANTIBODIES FROM SINGLE, ISOLATED LYMPHOCYTES PRODUCING ANTIBODIES OF DEFINED SPECIFICITIES&quot; 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</td>
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<td>Y</td>
<td>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</td>
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INTERNATIONAL SEARCH REPORT

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.: 22-25 (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 (completely)

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.
Continuation of Box II.2

Claims Nos.: 22-25 (all completely)

Claims 22 and 23 relate to an antibody isolated according to the method of any one of claims 13-21. However, said claims 22 and 23 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the 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. Claims 22 and 23 are, therefore, so unclear (Art. 6 PCT) that no meaningful search with respect of its subject-matter could be carried out.

Claim 24 relates to the use of an antibody according to claim 22 or 23, 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 24 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 25, 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 or 23 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 22-25 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.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

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

An oligonucleotide primer set comprising or consisting of
-at least one primer selected from the group consisting of Seq.ID 1,2,3 and 4; or
-the specific combination of the primers of Seq.ID 1-44;
a method for the isolation of a nucleic acid comprising the variable region sequence of an 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 5; or
-the specific combination of the primer of Seq. ID 5 and at least one primer selected from the group consisting of Seq. ID 1,2,3 and 4; or
-the specific combination of the primers of Seq.ID 5-44;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 114; or
-the specific combination of the primers of Seq.ID 114-153; or
-the specific combination of the primers of Seq.ID 102-153;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody heavy chain comprising the use of these primer sets.

Inventions 3-41: 1,7,8,13,16 (all partially)

Invention 3:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 6; or
-the specific combination of the primer of Seq. ID 6 and at least one primer selected from the group consisting of Seq. ID 1,2,3 and 4; or
-the specific combination of the primers of Seq.ID 5-44;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 115; or
-the specific combination of the primers of Seq.ID 114-153; or
-the specific combination of the primers of Seq.ID 102-153;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody heavy chain comprising the use of these primer sets.
..ibidem for inventions 4-41 relating to Seq.IDs 7-44 and Seq.IDs 116-153.

Invention 42: 3,4,14,17,20 (all partially)
An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 45; or
-the primer of Seq.ID 45 and at least one primer selected
from the group consisting of Seq. ID 46-92;
-the specific combination of the primers of Seq.ID 45-92;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody kappa light chain
comprising the use of these primer sets.

Invention 43: 3,4,9,10,14,17,20 (all partially)

Invention 43:
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
the primer of Seq. ID 45; or
-the specific combination of the primers of Seq.ID 45-92; or
-the specific combination of the primers of Seq.ID 46-92;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 156; or
-the specific combination of the primer of Seq. ID 156 and
the primer of Seq.ID 154 and/or Seq. ID 155; or
-the specific combination of the primers of Seq.ID 156-202; or
-the specific combination of the primers of Seq.ID 154-202;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody kappa light chain
comprising the use of these primer sets.

Invention 44-89: 3,4,9,10,14,17,20 (all partially)

Invention 44:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 47; or
-the specific combination of the primer of Seq. ID 47 and
the primer of Seq. ID 45; or
-Seq.ID 45-92; or
-Seq.ID 46-92;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 157; or
-the specific combination of the primer of Seq. ID 157 and
the primer of Seq.ID 154 and/or Seq. ID 155; or
-the specific combination of the primers of Seq.ID 156-202; or
-the specific combination of the primers of Seq.ID 154-202;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody kappa light chain
comprising the use of these primer sets.
Ibidem for inventions 45-89 relating to Seq.IDs 48-92 and
Seq.ID 158-202.

Invention 90: 5,6,15,18,21 (all partially)
An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 93; or
-the specific combination of the primer of Seq.ID 93 and at
least one primer selected from the group consisting of Seq.
ID 94-101;
-the specific combination of the primers of Seq.ID 93-101;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody lambda light chain
comprising the use of these primer sets.

Invention 91: 5,6,11,12,15,18,21 (all partially)
An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 94; or
-the specific combination of the primer of Seq. ID 94 and
the primer of Seq. ID 93; or
-the specific combination of the primers of Seq.ID 94-101;
or
-the specific combination of the primers of Seq.ID 93-101;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 204; or
-the specific combination of the primer of Seq. ID 204 and
the primer of Seq.ID 203; or
-the specific combination of the primers of Seq.ID 204-211;
or
-the specific combination of the primers of Seq.ID 203-211;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody lambda light chain
comprising the use of these primer sets.

Invention 92-98: 5,6,11,12,15,18,21 (all partially)

Invention 92: An oligonucleotide primer set comprising or consisting of
-the primer of Seq. ID 95; or
-the specific combination of the primer of Seq. ID 95 and
the primer of Seq. ID 93; or
-the specific combination of the primers of Seq.ID 94-101;
or
-the specific combination of the primers of Seq.ID 93-101;
an oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 205; or
-the specific combination of the primers of Seq.ID 204-211;
or
-the specific combination of the primers of Seq.ID 203-211;
a method for the isolation of a nucleic acid comprising the
variable region sequence of an antibody lambda light chain
comprising the use of these primer sets.
..ibidem for inventions 93-98 relating to Seq.IDs 96-101 and
Seq.IDs 206-211.
Invention 99: 7,8,13,16,19 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 102; or
-the specific combination of the primer of Seq.ID 102 and at least one primer selected from the group consisting of Seq.
ID 114-153;
-the specific combination of the primers of Seq.ID 102-153;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody heavy chain comprising the use of this primer set.

Invention 100-110: 7,8,13,16,19 (all partially)

Invention 100:
An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 103; or
-the specific combination of the primer of Seq.ID 103 and at least one primer selected from the group consisting of Seq.
ID 114-153;
-the specific combination of the primers of Seq.ID 102-153;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody heavy chain comprising the use of this primer set.
..ibidem for inventions 101-110 relating to Seq.IDs 104-113.

Invention 111: 9,10,14,17,20 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 154 and/or Seq. ID 155; or
-the specific combination of the primer of Seq.ID 154 and/or Seq. ID 155 and at least one primer selected from the group consisting of Seq. ID 156-202;
-the specific combination of the primers of Seq.ID 154-202;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody kappa light chain comprising the use of this primer set.

Invention 112: 11,12,15,18,21 (all partially)

An oligonucleotide primer set comprising or consisting of
-the primer of Seq.ID 203; or
-the specific combination of the primer of Seq.ID 203 and at least one primer selected from the group consisting of Seq. ID 204-211; or
-the specific combination of the primers of Seq.ID 203-211;
a method for the isolation of a nucleic acid comprising the variable region sequence of an antibody kappa light chain comprising the use of this primer set.
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