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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTI-CD20 ANTIBODIES AND FUSION PROTEINS THEREOF AND METHODS OF USE

(57) Abstract: The present invention provides humanized, chimeric and human anti-CD20 antibodies and CD 20 antibody fusion proteins that bind to a human B cell marker, referred to as CD20, which is useful for the treatment and diagnosis of B-cell disorders, such as B-cell malignancies and autoimmune diseases, and methods of treatment and diagnosis.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/28 A61K39/395 C12N15/13 C12N5/10 G01N33/53

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 7 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, CHEM ABS Data, WPI Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 776 456 A (RASTETTER WILLIAM H ET AL) 7 July 1998 (1998-07-07) column 4 - column 5 column 21 - column 24	1,2,6, 32-124
Y		10, 17-24, 27,28

X	US 2002/009444 A1 (GRILLO-LOPEZ ANTONIO J) 24 January 2002 (2002-01-24) paragraphs '0007!, '0031!, '0069!, '0070!, '0106!	1,2, 32-124
Y		6,10, 17-24, 27,28

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

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2004	22.10.04

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	Surdej, P

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/009427 A1 (ROSENBLATT JOSEPH D ET AL) 24 January 2002 (2002-01-24) paragraphs '0002!, '0011!, '0053!, '0055!, '0056!, '0060!	1,2, 32-124
Y		6,10, 17-24, 27,28
X	MALONEY D G ET AL: "NEWER TREATMENTS FOR NON-HODGKIN'S LYMPHOMA: MONOCLONAL ANTIBODIES" ONCOLOGY, S. KARGER AG, BASEL, CH, no. SUPPL 8, October 1998 (1998-10), pages 63-76, XP002935647 ISSN: 0030-2414 abstract page 65, column CENTER	1,2, 32-124
Y		6,10, 17-24, 27,28
A	GOPAL A K ET AL: "CLINICAQL APPLICATIONS OF ANTI-CD20 ANTIBODIES" JOURNAL OF LABORATORY AND CLINICAL MEDICINE, ST. LOUIS, MO, US, vol. 134, no. 5, 1999, pages 445-450, XP002935646 ISSN: 0022-2143 the whole document	1,2,6, 10, 17-24, 27,28, 32-124
X	SHAN D ET AL: "Characterization of scFv-Ig constructs generated from the anti-CD20 mAb 1F5 using linker peptides of varying lengths." JOURNAL OF IMMUNOLOGY (BALTIMORE, MD. : 1950) 1 JUN 1999, vol. 162, no. 11, 1 June 1999 (1999-06-01), pages 6589-6595, XP002296468 ISSN: 0022-1767	1,2,6, 32-124
Y	page 6589 page 6593 figure 3	10, 17-24, 27,28

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PCT/GB 03/00665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/44788 A (HARIHARAN KANDASAMY ; LABARRE MICHAEL J (US); HANNA NABIL (US); HUYNH) 3 August 2000 (2000-08-03)	1,2,6, 32-124
Y	page 3, line 21 figure 1 figures 13-17 examples 6-12	10, 17-24, 27,28
P,X	WO 03/002607 A (LEUNG SHAWN SHUI-ON) 9 January 2003 (2003-01-09)	1,2,6, 32-124
P,Y	page 31, column 32 figure 7	10, 17-24, 27,28
P,X	WO 02/056910 A (HAYDEN-LEDBETTER MARTHA ; LEDBETTER JEFFREY A (US); GENECRAFT INC (US)) 25 July 2002 (2002-07-25)	1,2, 32-124
P,Y	page 11 - page 12 figure 1 figure 10	6,10, 17-24, 27,28

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 03/00665

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

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.:

1,2,10,17-24,27-28,32-124 (inventions 1-10)

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.:

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

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

Invention 1: 1-2,6,32-124 (all partially)

A humanized anti-CD20 (hCD20) monoclonal antibody or antigen-binding fragment thereof comprising the complementary determining regions (CDRs) of a murine anti-CD20 MAb light chain variable region comprising CDR1 comprising the amino acid sequence RASSSVSYIH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQWTSNPPT and the framework regions (FRs) of at least one human MAb variable region, wherein said humanized anti-CD20 MAb or fragment thereof retains substantially the B-cell and B-cell lymphoma and leukemia cell targeting of said murine anti-CD20 MAb. Nucleic acid corresponding to said monoclonal antibody. Uses of said molecules.

Invention 2: 10, 32-124 (all partially), 17-24, 27-28 (completely)

A humanized (or chimeric) anti CD20 (hCD20) monoclonal antibody or antigen binding fragment thereof comprising the complementary determining regions (CDRs) of at least one murine anti-CD20 Mab variable region and the framework regions (FRs) of at least one human Mab variable region, wherein said variable region comprises light and heavy chain regions, wherein said light chain variable region comprises CDR1 comprising the amino acid sequence RASSSVSYIH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQWTSNPPT, and said heavy chain variable region comprises CDR1 comprising an amino acid sequence of SYNMH; CDR2 comprising an amino acid sequence of AIYPGNGDTSYNQKFKG and CDR3 comprising an amino acid sequence selected from the group consisting of STYYGGDWYFDV, SHYGSNYVDYFDV and VVYYSNSYWYFDV, wherein said humanized anti-CD20 MAb or fragment thereof retains substantially the B-cell and B-cell lymphoma and leukemia cell targeting of said murine anti-CD20 MAb. Nucleic acid corresponding to said monoclonal antibody. Uses of said molecules.

Invention 3: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSVSYIH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence HQWSSNPLT

Invention 4: 10, 32-124 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSVSYIH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQSFSNPPT

Invention 5: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSLSFMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQWTSNPPT

Invention 6: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSLSFMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence HQWSSNPLT

Invention 7: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSLSFMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQSFSNPPT

Invention 8: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSVSYMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQWTSNPPT

Invention 9: 10, 32-124 (all partially)

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSVSYMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence HQWSSNPLT

Invention 10: 10, 32-124 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

same as group 2 of invention with the exception that the light chain variable region comprises instead CDR1 comprising the amino acid sequence RASSSVSYMH, CDR2 comprising the amino acid sequence ATSNLAS and CDR3 comprising the amino acid sequence QQSFSNPPT

Inventions 11-99: 1-124 (all partially)

A (humanized or chimeric) anti-CD20 monoclonal antibody (not included in group 1-10 of inventions) or fragment thereof comprising the complementary determining regions (CDRs) of a murine anti-CD20 MAb and having one motif of each CDR1-3 (RASSSVSYIH, RASSSLSFMH, RASSSVSYMH; ATSNLAS; QQWTSNPPT, HQWSSNPLT, QQSFSNPPT) light chain variable region, one motif of each CDR1-3 (SYNMH; AIYPGNGDTSYNQKFKG; STYYGGDWYFDV, STYYGGDWYFNV, SHYGSNYVDYFDV, VVYYSNSYWYFDV) heavy chain variable region or one motif of each said CDR1-3 of both light or heavy chain variable region, wherein said anti-CD20 MAb or fragment thereof retains substantially the B-cell and B-cell lymphoma and leukemia cell targeting of said murine anti-CD20 MAb. Nucleic acid corresponding to said monoclonal antibody. Uses of said molecules.

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