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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: B-CELL REDUCTION USING CD37-SPECIFIC AND CD20-SPECIFIC BINDING MOLECULES

(57) Abstract: The present application generally provides methods for B-cell reduction in an individual using CD37-specific bind-
ing molecules. In particular, the invention provides methods for B-cell reduction using CD37-specific binding molecules alone, or
a combination of CD37-specific binding molecules and CD20-specific binding molecules, in some instances a synergistic combina-
tion. The application further provides materials and methods for application treatment of diseases involving aberrant B-cell activity.
In addition, the application provides humanized CD37-specific binding molecules.



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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/395 C07K16/28 A61P35/00 A61P37/00 A61P21/04
C12N15/13 C12N15/85 C12N5/10 C07K16/46

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)

C07K A61K A61P C12N

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, WPI Data, 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	KIESEL S ET AL: "REMOVAL OF CELLS FROM A MALIGNANT B-CELL LINE FROM BONE MARROW WITH IMMUNOMAGNETIC BEADS AND WITH COMPLEMENT AND IMMUNOGLOBULIN SWITCH VARIANT MEDIATED CYTOLYSIS" LEUKEMIA RESEARCH, NEW YORK, NY, US, vol. 11, no. 12, 1987, pages 1119-1125, XP000570474 ISSN: 0145-2126	1,2,6, 10,25-27
Y	page 1123, left-hand column, paragraphs 1,2 page 1123, right-hand column, paragraph 3 ----- -/--	3-5,7-9, 12,13, 15-24

☒ Further documents are listed in the continuation of Box C.

☒ 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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029038

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAYDEN-LEDBETTER MARTHA ET AL: "Induction of apoptosis in B lymphoma cell lines by Cytox B37G, a small modular immunopharmaceutical (SMIP) that binds CD37." BLOOD, vol. 102, no. 11, 16 November 2003 (2003-11-16), page 432a, XP002420825 & 45TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY; SAN DIEGO, CA, USA; DECEMBER 06-09, 2003 ISSN: 0006-4971	1,6,10, 11,14, 25-27
Y		3-5,7-9, 12,13, 15-24
Y	----- "Trubion Pharmaceuticals Inc. Presents Positive Data On First Pre-Clinical Product Candidates At American Society of Hematology (ASH)" BIOSPACE, [Online] 8 December 2003 (2003-12-08), pages 1-3, XP002420826 San Diego Retrieved from the Internet: URL: http://www.biospace.com/news_story.asp?StoryID=14573420&full=1 [retrieved on 2007-02-15] page 1, paragraph 5-7	3-5,7-9, 12,13, 15-24
Y	& LEANDRO M J ET AL: "Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion" ANNALS OF THE RHEUMATIC DISEASES, BRITISH MEDICAL ASSOCIATION, LONDON, GB, vol. 61, no. 10, October 2002 (2002-10), pages 883-888, XP002348932 ISSN: 0003-4967	3-5,7-9, 15-24
X	----- DAVIES JAMIE: "American society of hematology-45th annual meeting and exposition: hematological malignancies." IDRUGS : THE INVESTIGATIONAL DRUGS JOURNAL JAN 2004, vol. 7, no. 1, January 2004 (2004-01), pages 1-3, XP002420827 ISSN: 1369-7056 page 1, left-hand column, paragraphs 2,3 ----- -/--	1,2,6, 11,14, 25-27

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029038

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEANDRO M J ET AL: "Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion" ANNALS OF THE RHEUMATIC DISEASES, BRITISH MEDICAL ASSOCIATION, LONDON, GB, vol. 61, no. 10, October 2002 (2002-10), pages 883-888, XP002348932 ISSN: 0003-4967 page 884, left-hand column, paragraph 3 - page 885, left-hand column, paragraph 1 page 887, right-hand column, paragraph 1-4	3-5,7-9, 12,13, 15-24
Y	PRESS O W ET AL: "TREATMENT OF REFRACTORY NON-HODGKIN'S LYMPHOMA WITH RADIOLABELED MB-1 (ANTI-CD37) ANTIBODY" JOURNAL OF CLINICAL ONCOLOGY, GRUNE AND STRATTON, NEW YORK, NY, US, vol. 7, no. 8, August 1989 (1989-08), pages 1027-1038, XP002936241 ISSN: 0732-183X page 1028, left-hand column, paragraph 2 page 1029, left-hand column, paragraphs THERAPEUTIC, INFUSIONS	3-5,7-9, 12,13, 15-24
Y	PRESS O W ET AL: "RADIOLABELED-ANTIBODY THERAPY OF B-CELL LYMPHOMA WITH AUTOLOGOUS BONE MARROW SUPPORT" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 329, no. 17, 21 October 1993 (1993-10-21), pages 1219-1224, XP008075157 ISSN: 0028-4793 the whole document	3-5,7-9, 12,13, 15-24
Y	BARONE D ET AL: "Prolonged depletion of circulating B cells in cynomolgus monkeys after a single dose of TRU-015, a novel CD20 directed therapeutic" ANNALS OF THE RHEUMATIC DISEASES, vol. 64, no. Suppl. 3, July 2005 (2005-07), pages 159-160, XP008075207 & ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY; VIENNA, AUSTRIA; JUNE 08 11, 2005 ISSN: 0003-4967 abstract	3-5,7-9, 12,13, 15-24
A	US 2005/136049 A1 (LEDBETTER JEFFREY A [US] ET AL) 23 June 2005 (2005-06-23) cited in the application figure 19; examples 64,65,96-102	
	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029038

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHAO XIAOBIN B ET AL: "Novel anti-CD37 small modular immunopharmaceutical (SMIP) induces B-cell-specific, caspase-independent apoptosis in human CLL cells." BLOOD, vol. 104, no. 11, Part 1, November 2004 (2004-11), page 689A, XP002420828 & 46TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; SAN DIEGO, CA, USA; DECEMBER 04 -07, 2004 ISSN: 0006-4971 abstract	
P,X	----- D. S. BARONE, C. NILSSON, J. LEDBETTER, M. HAYDEN-LEDBETTER AND K. MOHLER: "Efficacy of SMIP-016, a novel CD37-directed biologic therapy, in human NHL tumor xenograft models" JOURNAL OF CLINICAL ONCOLOGY, [Online] vol. 24, no. 18s, 20 June 2006 (2006-06-20), page 1, XP002420829 USA Retrieved from the Internet: URL:http://meeting.jco.org/cgi/gca?sendit=Get+All+Checked+Abstract%28s%29&SEARCHID=1&FULLTEXT=smip&VOLUME=24&ISSUE=18_suppl&FIRSTINDEX=0&hits=10&RESULTFORMAT=&gca=ascomtg%3B24%2F18_suppl%2F2565> [retrieved on 2007-02-16] abstract	1-27
Y	----- REFF M E ET AL: "Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20" BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, vol. 83, no. 2, 15 January 1994 (1994-01-15), pages 435-445, XP002112549 ISSN: 0006-4971 page 438, right-hand column, paragraph 3 - page 441, right-hand column, paragraph 2 page 444, left-hand column, paragraph 2 ----- -/--	3-5,7-9, 12,13, 15-24

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/029038

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BUCHSBAUM D J ET AL: "Therapy with unlabeled and 131I-labeled pan-B-cell monoclonal antibodies in nude mice bearing Raji Burkitt's lymphoma xenografts." CANCER RESEARCH 1 DEC 1992, vol. 52, no. 23, 1 December 1992 (1992-12-01), pages 6476-6481, XP008075262 ISSN: 0008-5472 the whole document	3-5,7-9, 12,13, 15-24

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.: 28-117
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:
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.:
Invention 1: claims 1-27

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.1

Although claims 1-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.:

The present claims 1,2,6,10,11,14-16,25 relate to an extremely large number of possible compounds/methods. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds/methods claimed, [examples and 54-57]. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims (PCT Guidelines 9.19 and 9.23).

The search of claims 1,2,6,10,11,14-16,25 was restricted to those claimed compounds/methods which appear to be supported and a generalisation thereof [anti CD37 and anti CD20 antibodies or antibody derivatives].

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: claims 1-27

methods of reducing B-cell number using a combination of CD37 and CD20 specific binding molecules

Invention 2: claims 28-49

methods of reducing B-cell number using CD37 specific binding molecules

Invention 3: claims 50, 53-69, 71-88, 94, 99-117 (all completely)
52, 70, 90-93, 96-98 (all partially).

humanized CD37 SMIP polypeptides exhibiting at least 80% identity to SEQ ID NO: 2

Inventions 4-36: claims 51, 52, 70, 89-93, 95 96-98 (all partially).

humanized CD37-specific SMIP polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 80, 82, 84, 86, and 88

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/029038

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005136049 A1	23-06-2005	US 2005202023 A1	15-09-2005
		US 2005186216 A1	25-08-2005
		US 2005202028 A1	15-09-2005
		US 2005202012 A1	15-09-2005
		US 2005180970 A1	18-08-2005
		US 2005202534 A1	15-09-2005
		US 2005238646 A1	27-10-2005
		US 2005175614 A1	11-08-2005
