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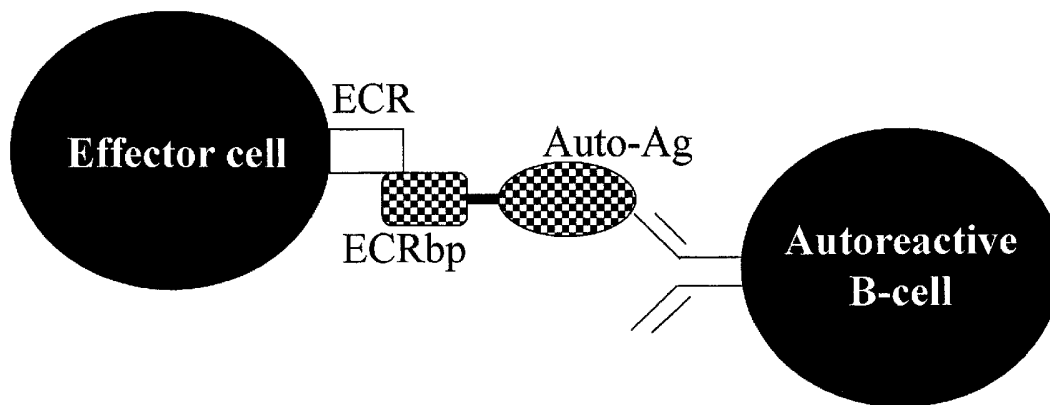
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00117354.1 22 August 2000 (22.08.2000) EP
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- (74) Agent: **VOSSIUS & PARTNER**; Sieberstr. 4, 81675 München (DE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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- (88) Date of publication of the international search report:
7 November 2002
- 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: COMPOSITION FOR THE ELIMINATION OF AUTOREACTIVE B-CELLS



(57) Abstract: The present invention relates to a composition for the selective elimination of autoreactive B-cells comprising at least one (poly)peptide construct consisting of at least two domains wherein one of said domains comprises an autoreactive antigen or (a) fragments(s) thereof specifically recognized by the Ig receptors of said autoreactive B-cells and wherein one of said domains comprises an effector molecule capable of interacting with and/or of activating NK-cells, T-cells, macrophages, monocytes and/or granulocytes and/or capable of activating the complement system.

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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K19/00 C07K14/47 C12N15/62

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 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, BIOSIS, WPI Data, PAJ, MEDLINE, SEQUENCE SEARCH, CHEM ABS Data, EMBASE, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9722 Derwent Publications Ltd., London, GB; AN 1997-241758 XP002196726 "Phemphigus foliaceus antigen-IgG constant region fusion protein - linked through the hinge region used to treat pemphigus" & JP 09 077800 A (NISHIKAWA T), 25 March 1997 (1997-03-25)	1-4, 16, 18, 23-26, 28, 29, 31-38
Y	abstract	5, 6, 13, 15, 17, 19-22, 27, 30

 Further documents are listed in the continuation of box C. 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
- "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

15 July 2002

Date of mailing of the international search report

12.08.02

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09714

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 23867 A (BIOGEN INC ; BROWNING JEFFREY (US)); 20 May 1999 (1999-05-20) cited in the application</p> <p>abstract page 1, line 11-24 page 3, line 6-9 page 4, line 24-26 page 7, line 9-17 page 11, line 3-7 page 22, line 6-14 page 24, line 21-23 page 27, line 14-26</p>	<p>1,2,4, 11,16, 18, 20-29, 31-38</p>
Y	<p>PROBY C M ET AL: "Development of chimeric molecules for recognition and targeting of antigen-specific B cells in pemphigus vulgaris." BRITISH JOURNAL OF DERMATOLOGY., vol. 142, no. 2, February 2000 (2000-02), pages 321-330, XP002196725 ISSN: 0007-0963 cited in the application</p> <p>abstract page 321, column 2, paragraph 2 page 322, column 1, paragraph 2; figure 1 page 326, column 2, paragraph 1 -page 328, column 2, paragraph 2</p>	<p>1-6,11, 13,15-38</p>
X	<p>WO 99 11667 A (RAYMACKERS JOSEPH ; UNION ANN (BE); INNOGENETICS NV (BE); MEHEUS LY) 11 March 1999 (1999-03-11)</p> <p>abstract page 2, line 3 -page 3, line 18 page 4, line 23-25 page 6, line 5-24 page 9, line 7-23 page 19, line 2 -page 20, line 14 page 33, line 8 -page 34, line 26</p>	<p>1-4,15, 16,23-38</p>
Y	<p>WO 95 24220 A (MEDAREX INC) 14 September 1995 (1995-09-14)</p> <p>abstract page 1, line 4 -page 2, line 37 page 4, line 16-23</p>	<p>1-6,11, 13,15-38</p>
Y	<p>US 5 932 448 A (TSO J YUN ET AL) 3 August 1999 (1999-08-03)</p> <p>abstract column 8, line 44 -column 10, line 48</p>	<p>1-6,11, 13,15-38</p>
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INTERNATIONAL SEARCH REPORT

International Application No
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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	<p>SCHROEDER ET AL: "A recombinant bispecific single chain antibody CD19XCD3, induces rapid B cell lymphoma-directed cytotoxicity of unstimulated human T cells" BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, vol. 92, no. 10, 15 November 1998 (1998-11-15), page 511A XP002115457 ISSN: 0006-4971 abstract</p>	1-6,11, 13,15-38
A	<p>WO 00 01732 A (UNIV TENNESSEE RES, CORP ;ZAGHOUANI HABIB (US)) 13 January 2000 (2000-01-13) abstract page 10, line 15-19 page 15, line 27-33 page 28, line 4-26</p>	1-4,11, 16,18, 20,33-38
P,Y	<p>STEFFERL A ET AL: "Butyrophilin, a milk protein, modulates the encephalitogenic T cell response to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis." JOURNAL OF IMMUNOLOGY (BALTIMORE, MD.: 1950) UNITED STATES 1 SEP 2000, vol. 165, no. 5, 1 September 2000 (2000-09-01), pages 2859-2865, XP002206101 ISSN: 0022-1767 cited in the application abstract page 2859, column 1, paragraph 2 -column 2, paragraph 3 page 2862, column 2, paragraph 2 -page 2863, column 1, paragraph 3</p>	1-4,13, 15-20, 23-38
Y	<p>KHANNA A K ET AL: "Antibodies in the sera of acute rheumatic fever patients bind to human cardiac tropomyosin." JOURNAL OF AUTOIMMUNITY. ENGLAND FEB 1997, vol. 10, no. 1, February 1997 (1997-02), pages 99-106, XP002206102 ISSN: 0896-8411 cited in the application abstract page 99, column 1, paragraph 1 -column 2, paragraph 1 page 100, column 1, paragraph 1</p>	1-4,13, 15-20, 23-38
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INTERNATIONAL SEARCH REPORT

International Application No
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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	<p>LAKE D F ET AL: "Autoantibodies to the alpha/beta T-cell receptors in human immunodeficiency virus infection: dysregulation and mimicry." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 8 NOV 1994, vol. 91, no. 23, 8 November 1994 (1994-11-08), pages 10849-10853, XP002206103 ISSN: 0027-8424 abstract page 10849, column 1, paragraph 1 -column 2, paragraph 1</p>	1-4,13, 15-20, 23-38
Y	<p>MATSUKURA H ET AL: "The Goodpasture antigen: common epitopes in the globular domains of collagen IV." NEPHRON. SWITZERLAND 1993, vol. 64, no. 4, 1993, pages 532-539, XP001088498 ISSN: 0028-2766 abstract page 532, column 1, paragraph 1 -page 533, column 1, paragraph 2</p>	1-4,6, 15-20, 23-38
Y	<p>BALDING S D ET AL: "Cicatricial pemphigoid autoantibodies react with multiple sites on the BP180 extracellular domain." THE JOURNAL OF INVESTIGATIVE DERMATOLOGY. UNITED STATES JAN 1996, vol. 106, no. 1, January 1996 (1996-01), pages 141-146, XP001087971 ISSN: 0022-202X abstract page 141, column 1, paragraph 1 -page 142, column 1, paragraph 3</p>	1-4,6, 15-20, 23-38
Y	<p>DÖPP R ET AL: "IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in Bullous pemphigoid: serum levels of these immunoglobulins reflect disease activity." JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY. UNITED STATES APR 2000, vol. 42, no. 4, April 2000 (2000-04), pages 577-583, XP001087911 ISSN: 0190-9622 abstract page 577, column 1, paragraph 1 -column 2, paragraph 1 page 578, column 1, paragraph 3 -column 2, paragraph 1; figure 1 page 579, column 2, paragraph 3</p>	1-4,6, 15-20, 23-38

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International Application No
PCT/EP 01/09714

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DOMINGUEZ-LOPEZ MARIA LILI ET AL: "Cellular immune response to Klebsiella pneumoniae antigens in patients with HLA-B27+ ankylosing spondylitis." JOURNAL OF RHEUMATOLOGY, vol. 27, no. 6, June 2000 (2000-06), pages 1453-1460, XP001088217 ISSN: 0315-162X cited in the application abstract page 1453, column 1, paragraph 1 -column 2, paragraph 2 page 1459, column 1, paragraph 3</p>	1-4, 13, 15-20, 23-38
Y	<p>OBERMAYER-STRAUB P ET AL: "Target proteins in human autoimmunity: cytochromes P450 and UDP-glucuronosyltransferases." CANADIAN JOURNAL OF GASTROENTEROLOGY = JOURNAL CANADIEN DE GASTROENTEROLOGIE. CANADA MAY 2000, vol. 14, no. 5, May 2000 (2000-05), pages 429-439, XP001088216 ISSN: 0835-7900 cited in the application abstract page 430, column 1, paragraph 1 -page 431, column 2, paragraph 3 page 437, column 1, paragraph 2 -column 2, paragraph 1</p>	1-4, 11, 15-20, 23-38
Y	<p>EYSTATHIOY THEOPHANY ET AL: "Human autoantibodies to a novel Golgi protein golgin-67: High similarity with golgin-95/gm 130 autoantigen." JOURNAL OF AUTOIMMUNITY, vol. 14, no. 2, March 2000 (2000-03), pages 179-187, XP001088204 ISSN: 0896-8411 cited in the application abstract page 179, column 1, paragraph 1 -page 180, column 1, paragraph 1 page 183, column 1, paragraph 2 page 185, column 1, paragraph 2</p> <p style="text-align: center;">-/--</p>	1-4, 11, 15-20, 23-38

INTERNATIONAL SEARCH REPORT

 Internati Application No
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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	LOCK R J ET AL: "IgA anti-tissue transglutaminase as a diagnostic marker of gluten sensitive enteropathy." JOURNAL OF CLINICAL PATHOLOGY, (LONDON), vol. 52, no. 4, April 1999 (1999-04), pages 274-277, XP001087690 ISSN: 0021-9746 cited in the application abstract page 274, column 2, paragraph 1 ---	1-4,13, 15-20, 23-38
Y	EBRINGER A ET AL: "HLA molecules, bacteria and autoimmunity." JOURNAL OF MEDICAL MICROBIOLOGY. ENGLAND APR 2000, vol. 49, no. 4, April 2000 (2000-04), pages 305-311, XP001087834 ISSN: 0022-2615 cited in the application abstract page 305, column 1, paragraph 2 page 306, column 2, paragraph 3 -page 307, column 1, paragraph 2 page 308, column 2, paragraph 1 ---	1-4,13, 15-20, 23-38
Y	LINK B K ET AL: "Production and Characterization of a Bispecific IgG Capable of Inducing T-Cell-Mediated Lysis of Malignant B Cells" BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, vol. 81, no. 12, 15 June 1993 (1993-06-15), pages 3343-3349, XP002900864 ISSN: 0006-4971 abstract page 3343, column 2, paragraph 2 page 3348, column 1, paragraph 3 ---	1-6,11, 13,15-38

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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:

Although claims 37 and 38 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 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:
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

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.:

1-4(all partially),5,6,11,13(all completely),15-20(all partially),21,22(all complete),23-38(all partially)
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:

1. Claims: 1-4 (all partially), 5, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of an intracellular autoreactive matrix protein antigen and a domain which allows interaction with an effector cell.

2. Claims: 1-4 (all partially), 6, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of an extracellular autoreactive matrix protein antigen and a domain which allows interaction with an effector cell.

3. Claims: 1-4 (all partially), 7, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of a complement autoreactive protein antigen and a domain which allows interaction with an effector cell.

4. Claims: 1-4 (all partially), 8, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of nuclear autoreactive antigens and a domain which allows interaction with an effector cell.

5. Claims: 1-4 (all partially), 9, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of cell surface receptor autoreactive antigens and a domain which allows interaction with an effector cell.

6. Claims: 1-4 (all partially), 15-20 (all partially),
23-38 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition for the selective elimination of autoreactive B cells consisting of nuclear receptor autoreactive antigens and a domain which allows interaction with an effector cell.

7. Claims: 1-4 (all partially), 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of lipid autoreactive antigens and a domain which allows interaction with an effector cell.

8. Claims: 1-4 (all partially), 10, 15-20 (all partially),
23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of soluble factor autoreactive antigens and a domain which allows interaction with an effector cell.

9. Claims: 1-4 (all partially), 11 (complete),
15-20 (all partially), 21 (complete),
22 (complete), 23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of membrane protein autoreactive antigens and a domain which allows interaction with an effector cell.

10. Claims: 1-4 (all partially), 12 (complete),
15-20 (all partially), 23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of heat shock protein autoreactive antigens and a domain which allows interaction with an effector cell.

11. Claims: 1-4 (all partially), 13 (partially),
15-20 (all partially), 23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of autoreactive antigens derived from proteins with sequence similarity to microbial antigens and a domain which allows interaction with an effector cell.

12. Claims: 1-4 (all partially), 13 (partially),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

15-20 (all partially), 23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of autoreactive antigens derived from proteins with sequence similarity to dietary components and a domain which allows interaction with an effector cell.

13. Claims: 1-4 (all partially), 14 (complete),
15-20 (all partially), 23-38 (all partially)

A composition for the selective elimination of autoreactive B cells consisting of autoreactive antigens derived from proteins with sequence similarity to proteins of intercellular structures and a domain which allows interaction with an effector cell.

INTERNATIONAL SEARCH REPORT
annex on patent family members

International Application No
PCT/EP 01/09714

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 0001732	A	13-01-2000	AU 5090899 A EP 1093464 A2 WO 0001732 A2	24-01-2000 25-04-2001 13-01-2000