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(US). **FORMAN, Stephen** [US/US]; 2580 Oak Knoll Avenue, San Marino, CA 91108 (US). **RAUBITSCHKEK, Andrew** [US/US]; 1691 El Molino, San Marino, CA 91108 (US).

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(74) Agents: **FIGG, E., Anthony** et al.; Rothwell, Figg, Ernst & Manbeck, P.C., 1425 K Street, N.W., Suite 800, Washington, DC 20005 (US).

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(71) Applicant: **CITY OF HOPE** [US/US]; 1500 East Duarte Road, Duarte, CA 91010-3000 (US).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **JENSEN, Michael, C.** [US/US]; 2305 Woodlyn Road, Pasadena, CA 91104

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: CD19-SPECIFIC REDIRECTED IMMUNE CELLS

(57) **Abstract:** Genetically engineered, CD19-specific redirected immune cells expressing a cell surface protein having an extracellular domain comprising a receptor which is specific for CD19, an intracellular signaling domain, and a transmembrane domain. Use of such cells for cellular immunotherapy of CD19⁺ malignancies and for abrogating any untoward B cell function. In one embodiment, the immune cell is a T cell and the cell surface protein is a single chain svFvFc:ζ receptor where scFc designates the V_H and V_L chains of a single chain monoclonal antibody to CD19, Fc represents at least part of a constant region of an IgG₁, and ζ represents the intracellular signaling domain of the zeta chain of human CD3. The extracellular domain scFvFc and the intracellular domain ζ are linked by a transmembrane domain such as the transmembrane domain of CD4. A method of making a redirected T cell expressing a chimeric T cell receptor by electroporation using naked DNA encoding the receptor.



WO 02/077029 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/42997

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/725 C12N5/10 A61P35/02 A61P37/06
A61K35/14

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 C12N C07K A61K

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, SEQUENCE SEARCH, PAJ, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 23573 A (HOPE CITY) 27 April 2000 (2000-04-27) the whole document ---	1-39
Y	JENSEN M ET AL: "CD20 is a molecular target for scFvFc:zeta receptor redirected T cells: implications for cellular immunotherapy of CD20+ malignancy" BIOLOGY OF BLOOD AND MARROW TRANSPLANTATION, KLUGE CARDEN JENNINGS PUBLISHING, CHARLOTTESVILLE, VA, US, vol. 4, no. 2, 1998, pages 75-83, XP000910525 ISSN: 1083-8791 cited in the application the whole document --- -/--	1-39

☒ 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

21 November 2002

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Name and mailing address of the ISA

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

Authorized officer

Madruga, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/42997

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KIPRIYANOV S M ET AL: "Bispecific CD3 x CD19 diabody for T cell-mediated lysis of malignant human B cells" INTERNATIONAL JOURNAL OF CANCER, NEW YORK, NY, US, vol. 77, no. 5, 31 August 1998 (1998-08-31), pages 763-771, XP002115487 ISSN: 0020-7136 the whole document ---	1-39
Y	WO 99 54440 A (RIETHMUELLER GERT ;BARGOU RALF (DE); DOERKEN BERND (DE); KUFER PET) 28 October 1999 (1999-10-28) claims; examples ---	1-39
P,X	JENSEN MICHAEL C ET AL: "Targeting pre-B acute lymphoblastic leukemia with T cell clones engineered to express a CD19-specific chimeric immunoreceptor." BLOOD, vol. 96, no. 11 Part 1, 16 November 2000 (2000-11-16), page 26a XP002220977 42nd Annual Meeting of the American Society of Hematology; San Francisco, California, USA; December 01-05, 2000 ISSN: 0006-4971 the whole document ---	1-39
A	ABKEN H ET AL: "Chimeric T-cell receptors: Highly specific tools to target cytotoxic T-lymphocytes to tumour cells." CANCER TREATMENT REVIEWS, vol. 23, no. 2, 1997, pages 97-112, XP008010631 ISSN: 0305-7372 the whole document ---	1-39
A	WO 00 31239 A (ESHAR ZELIG ;YEDA RES & DEV (IL); BOLHUIS REINDER L H (NL); WILLE) 2 June 2000 (2000-06-02) the whole document ---	1-39

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/42997

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NICHOLSON IAN C ET AL: "Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma." MOLECULAR IMMUNOLOGY, vol. 34, no. 16-17, November 1997 (1997-11), pages 1157-1165, XP002220979 ISSN: 0161-5890 cited in the application the whole document -----	1-39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/42997

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 19-39 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.: 19-22, 35
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 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:

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.:

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 I.2

Claims Nos.: 19-22,35

Present claims 19-22 relate to an extremely large number of possible malignancies. In fact, the claims contain so many options and the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods thus, a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, supported and disclosed, namely relating to the following malignancies: lymphoblastic leukemia, chronic lymphoblastic leukemia, CD19+ lymphoma and chronic lymphocytic leukemia.

Present claim 35 relates to a method of abrogating an untoward B cell function. The claim covers all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claim which appear to be clear, supported and disclosed, namely those parts relating to methods concerning an autoimmune disease.

The applicant's attention is drawn to the fact that claims, or parts of 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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/US 01/42997

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