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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: *IN SITU* IMMUNIZATION

(57) Abstract: The arming of activated T cells (ATC) with BiAbs can overcome major barriers for successful adoptive immunotherapy. The BiAb approach takes the advantage of the targeting specificity of monoclonal antibodies and the cytotoxic capacity of T cells to lyse tumors. Arming of ATC with BiAb makes every T cell an antigen-specific CTL and infusions of such cells will markedly increase the effective precursor frequency of CTL in the cancer patient. Furthermore, the ability of such armed ATC to kill multiple times without rearming with BiAb, secrete tumoricidal cytokines, secrete chemokines, and survive in patients for up to 8 days after the last infusion or in Beige/SCID mice for over 13 weeks after cessation of treatment. The persistence of cells in the Beige/SCID after infusion show long term survival capability in the host. Re-stimulation of armed ATC after 3 Cycles of cytotoxicity with tumor cells resulted in the secretion of interferon gamma indicating the development of tumor specific immune response in the population of cells that have been exposed multiple times to antigen. In summary, armed ATC can act as a cytotoxic "drug", kill multiple times (direct killing), divide after killing (increasing the effector : target ratio *in vivo*), secrete tumoricidal cytokines (indirectly killing), secrete chemokines at the tumor site (recruit naïve T cells and antigen-presenting cells to immunize the patient to tumor lysate) and persist in patients and animal models for weeks to months (long-term survival).



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26258

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 35/14, 39/395; C12N 5/08

US CL : 424/93.71, 136.1, 138.1, 141.1, 534; 435/372, 372.1, 372.3;

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)

U.S. : 424/93.71, 136.1, 138.1, 141.1, 534; 435/372, 372.1, 372.3;

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 practicable, search terms used)

Medline, Biosis, Scisearch, CAnceRlit, Lifesci, Biotechds, Caplus, PCTfull, USpatfull, Europatfull

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 00/78348 A1 (NEWELL et al) 28 December 2000, page 3, lines 15-29, page 3, line 33 to page 4, line 21, page 4 lines 29-32, page 4, line 33 to page 5, line 8, page 5, line 18 to page 6, line 5; page 22 line 29 to page 23, line 3, page 23, lines 10 and 29-33, page 24, lines 1-32.	21, 48-50, 52-59, 61-72, 74-77, 80-84, 88-89, 96, 97 ----- 1-17, 20, 22-37, 39, 47, 86, 90-95
Y	WO 96/37208 A1 (SLAVIN) 28 November 1996, page 4, lines 23-33.	85-87 -
Y	WO 88/03565 CLARK et al) 19 May 1988, claims 1, 2, 13 and 14.	21, 48-50, 52-59, 61-72, 74-77, 80-84, 88, 89, 96, 97
Y	WO 97/29183 A2 (HWU et al) 14 August 1997, page 31, lines 17-20, page 33, line 31 to page 32, line 5, page 37, lines 13-18.	2-17, 20, 22-24, 27-30, 32-37, 39, 47-50, 52-59, 61-72, 74-77, 80-84

☒ 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

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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

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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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/26258

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim 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. ☒ Claim Nos.: 18, 19, 38, 40-46, 60, 73, 78, 79
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.

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FANGER et al. Bispecific Antibodies. Critical Reviews in Immunology. 1992, Vol. 12, No. 3-4, pages 101-124, especially page 105-106, section b. "T Cells", pages 106-107, section 3, "Cytokine Activation", pages 108-109, section 2 "BsAb-Mediated Killing by T Cells", pages 109-110, section C "Studies in animal Models" and pages 110-112, section D "Clinical Trails of BsAb in Redirected Cell-Mediated Cytotoxicity".	1-17, 20-37, 39, 47-50, 51-59, 61-67, 72, 74-77, 80-84, 88-97
Y	DONG et al. 'Cytokines as Vaccine Adjuvants.' In: Vaccine Design: The Subunit and Adjuvant Approach. Edited by Powell et al. New York: Plenum Press. 1995, pages 625-643, especially page 627, section 1.2 and page 628, section 2.1.	1-17, 20, 22-24, 28-37, 39, 47-50, 52-59, 61-72, 74-76, 90-95
Y	SHALABY et al. Development of Humanized Bispecific Antibodies Reactive with cytotoxic Lymphocytes and Tumor Cells Overexpressing the HER2 Protooncogene. Journal of Experimental Medicine. January 1992, Vol. 175, pages 217-225, especially page 220, second column, line 10 to page 221, second column, line 21.	47, 56, 59, 63, 68
X --- Y	KOELEMIJ et al. Administration of BiMAb-Retargeted T Cells in a Rat Hepatic Metastases Colon Tumor Model REsults in T-Cell Tumor Infiltration Independent of the Route of Administration. Scandanavian Journal of Immunology, March 2001, Vol. 53, pages 277-281, especially page 278, first column, lines 13-31 and page 280, first column, line 16 to page 281, first column, line 25.	21, 47-50, 52-58, 61, 62, 64-67, 69, 74-77, 80-84, 88, 89 ----- 1-9, 12-15, 22-30, 95-97
X --- Y	BOHLEN et al. Lysis of Malignant B CELLS From Patients With B-Chronic Lymphocytic Leukemia by Autologous T Cells Activated With CD3 X CD19 Bispecific Antibodies in Combination With Bivalent CD28 Antibodies. Blood. 15 September 1993, Vol. 82, No. 6, pages 1803-1812, especially page 1807, second column, line 4 to page 1810, second column, line 16.	21, 47-50, 52-58, 61, 62, 64-67, 69, 74-77, 80-84, 88, 89 ----- 1-9, 12-15, 22-30, 95-97
X --- Y	BRANDL et al. Bispecific antibody fragments with CD20 X CD28 specificity allow effective autologous and allogenic T-cell activation against malignant cells in peripheral blood and bone marrow cultures from patients with B-cell lineage leukemia and lymphoma. Experimental Hematology. August 1999, Vol. 27, pages 1264-1270, especially page 1268, first column, line 28 to page 1269, second column, last line.	21, 47-50, 52-58, 61, 62, 64-67, 69, 74-77, 80-84, 88, 89 ----- 1-9, 12-15, 22-30, 95-97