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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: AN ANTIBODY SELECTIVE FOR A TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND  
RECEPTOR AND USES THEREOF

(57) Abstract: An antibody of the invention interacts with human DR5 or with human DR4 to produce agonistic or antagonistic effects downstream of the receptor including inhibition of cell proliferation and apoptosis. Nucleic acid sequences and amino acid sequences of DR5 and DR4 antibodies have been elucidated and vectors and cells containing and expressing these sequences have been generated. Methods and uses for the antibodies are detailed including treatment of apoptosis-related disease and treatment of dysregulated cell growth.



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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35333

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/395; C07K 16/28; C07H 21/04; C12P 21/06

US CL : 424/138.1, 141.1, 143.1, 153.1, 154.1, 155.1, 156.1, 173.1, 174.1; 530/387.3, 388.22; 536/23.5; 435/69.1.

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. : 424/138.1, 141.1, 143.1, 153.1, 154.1, 155.1, 156.1, 173.1, 174.1; 530/387.3, 388.22; 536/23.5; 435/69.1.

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)

Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,252,050 A (ASHKENAZI et al) 26 June 2001 (26.06.2001), column 29, line 48- column 31, line 48.	1-7, 10, 58, 59, 85, 88- 91, 94-97, 100, 101, 104
P, X	US 6,461,823 A (NI et al) 08 October 2002 (08.10.2002), column 4, Lines 1-7, column 26, Lines 29-49.	1-10, 58, 59, 85, 89- 91, 95-97, 101
Y	SONG et al. Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL) Is an Inhibitor of Autoimmune Inflammation and Cell cycle Progression. 03 April 2000, Vol. 191, No. 7, pages 1095-1103, especially pages 1095 and 1100.	11-57 and 60-84
Y	PAN et al. The Receptor of the Cytotoxic Ligand TRAIL. Science. 04 April 1997, Vol. 276, Issue 5309, pages 111-113, see entire document.	1

☐ 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 application or patent 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

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35333

## 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.:  
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:  
Please See Continuation 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.:

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

PCT/US02/35333

### **BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-10, 58, 59 and 97-104, drawn to an antibody that bind DR4 and has in vivo and in vitro apoptosis-inducing activity.

Group II, claim(s) 11-57 and 60-84, drawn to drawn to methods of treatment using an antibody that binds DR4.

Group III, claim(s) 85-96, drawn to nucleic acids encoding heavy chains or light chains of antibodies that bind to DR4 and capable of inducing apoptosis.

The inventions listed as Groups I, II, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups I, II and III are not linked by a special technical feature that provides a contribution over the prior art, because antibodies that bind to DR4 and that are agonist antibodies (i.e. induce apoptosis) are known in the art as evidenced by the teachings of Ashkenazi (U.S. Patent 6,252,050; issued June 26, 2001; see col. 22, line 63 - col. 24, line 65 and col. 30, lines 9-21 and col. 31, lines 33-43, Table 3).

### **Continuation of B. FIELDS SEARCHED Item 3:**

Medline, Embase, Biosis, Caplus, US Patents Database (EAST)  
search terms: dr4, apo-2l, apoptosis, trail, 2e12