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*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

**(88) Date of publication of the international search report:**
4 May 2000 (04.05.00)

**(54) Title:** T CELL RECEPTOR PROTEINS, NUCLEIC ACID MOLECULES, AND USES THEREOF

**(57) Abstract**

The present invention relates to TCR V$\beta$ proteins; to TCR V$\beta$ nucleic acid molecules, including those that encode such TCR V$\beta$ proteins; to antibodies raised against such TCR V$\beta$ proteins; and to therapeutic compounds that regulate TCR V$\beta$ function. The present invention also includes methods to identify and obtain such proteins, nucleic acid molecules, antibodies, and inhibitory compounds. Also included in the present invention are therapeutic compositions comprising such proteins, nucleic acid molecules, antibodies and/or inhibitory compounds as well as the use of such therapeutic compositions to regulate an immune response in an animal. Also included in the present invention are methods to detect T cell expansion in an animal using reagents including, or derived from such proteins, nucleic acid molecules or antibodies.

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/17309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N5/10 C07K14/705 C07K16/28
C12Q1/68 A61K38/17 A61K31/70 A61K48/00

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 C12Q 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | DATABASE GENBANK [Online]<br>Accession No. AF082505,<br>6 January 1999 (1999-01-06)<br>DREITZ M.J. & SIM G.K.: "T cell receptor beta chain hcvb3 (Canis familiaris)"<br>XP002122470<br>the whole document<br>--- | 1-48 |
| X | WO 92 12996 A (IMMUNE RESPONSE CORP INC)<br>6 August 1992 (1992-08-06)<br>abstract<br>figure 1<br>examples 1-13<br>claims 1-113<br>---<br>-/-- | 1-48 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 November 1999 | 06.03.00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Galli, I |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter- ·ional Application No
PCT/US 99/17309

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WEDDERBURN L.R. ET AL.: "In vivo clonal dominance and limited T-cell receptor usage in human CD4+ T-cell recognition of house dust mite allergens" PROC. NATL. ACAD. SCI. USA, vol. 90, September 1993 (1993-09), pages 8214-8218, XP002122467 the whole document -& DATABASE GENBANK [Online] Accession No. Z23040, 17 January 1995 (1995-01-17) WEDDERBURN: "T-cell antigen receptor beta chain" XP002122471 compare seq. IDs 1 and 50 with nt 31-381 and 173-191, respectively --- | 1-48 |
| A | TAKANO M. ET AL.: "Identification of dog T-cell receptor beta chain genes" IMMUNOGENETICS, vol. 40, 1994, page 246 XP002122468 cited in the application the whole document --- | 1-48 |
| A | ITO K. ET AL.: "Isolation and sequence analysis of cDNA for the dog T-cell receptor Tcr-alpha and Tcr-beta chains" IMMUNOGENETICS, vol. 38, 1993, pages 60-63, XP002122469 cited in the application the whole document --- | 1-48 |
| A | US 5 635 354 A (KOURILSKY PHILIPPE ET AL) 3 June 1997 (1997-06-03) abstract ----- | 1-48 |

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 99/ 17309

**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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 44,45 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. [X] 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 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.:

4. [X] 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.:

1-48 partially

**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**

1. Claims: (1-48) - partially

   Isolated nCaV-beta3 polypeptide (seq. IDs 2,29,60,61,62) and homologs.

   Corresponding nucleic acids (seq. IDs 1,28) and their allelic variants, complementary DNAs (Seq. ID 3,30), and a unique primer (Seq. ID 50).

   Methods to detect expansion of T cells, therapeutic compositions, antibodies,kits.. Uses of said materials in therapeutic, diagnostic and detection applications.

2. Claims: (1-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta4 (Seq. IDs 5,32,63,64,65; 4,31,7; 6,33,8; 51)

3. Claims: (1-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta12 (Seq. IDs 10,35,66,67,68; 9,34,12; 11,36,13; 52)

4. Claims: (1-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta72 (seq. IDs 15,38,69,70,71,99; 37,98,17; 39,100,18; 53)

5. Claims: (3,6-9,20-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta21 (seq. IDs 20,72,73,74; 19; 54)

6. Claims: (3,6-9,20-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta54 (seq. IDs 23,75,76,77; 22; 24; 55)

7. Claims: (3,6-9,20-48) - partially

   Idem as subject matter 1, but limited to mCaV-beta182 (seq. IDs 26,78,79,80; 25; 27; 56).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 9 (points i and vi) refer to mimetopes and inhibitors of the polypeptides without giving a true technical characterization. Moreover, no such compounds are defined in the characterization. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

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

rmation on patent family members

International Application No
PCT/US 99/17309

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9212996 A | 06-08-1992 | AU 1271692 A | 27-08-1992 |
| | | AU 694062 B | 09-07-1998 |
| | | AU 7032796 A | 16-01-1997 |
| | | CA 2101065 A | 23-07-1992 |
| | | EP 0568623 A | 10-11-1993 |
| | | EP 0722738 A | 24-07-1996 |
| | | JP 6507384 T | 25-08-1994 |
| | | NO 932631 A | 21-09-1993 |
| | | US 5985552 A | 16-11-1999 |
| US 5635354 A | 03-06-1997 | FR 2671356 A | 10-07-1992 |
| | | CA 2100167 A | 10-07-1992 |
| | | DE 69204823 D | 19-10-1995 |
| | | DE 69204823 T | 02-05-1996 |
| | | EP 0566685 A | 27-10-1993 |
| | | ES 2079181 T | 01-01-1996 |
| | | WO 9212260 A | 23-07-1992 |
| | | JP 6508262 T | 22-09-1994 |