

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 September 2000 (28.09.2000)

PCT

(10) International Publication Number
WO 00/56856 A3

(51) International Patent Classification⁷: C07H 21/04,
C12Q 1/70, C12P 19/34

(21) International Application Number: PCT/US00/07938

(22) International Filing Date: 24 March 2000 (24.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/126,215 25 March 1999 (25.03.1999) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, 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, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

(88) Date of publication of the international search report:
4 January 2001

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.



WO 00/56856 A3

(54) Title: POLYMORPHIC MICROSATELLITE REPEATS IN THE COSTIMULATORY RECEPTOR LOCUS AND USES THEREOF

(57) Abstract: The invention relates to polymorphic markers within the costimulatory receptor gene locus. These markers are characterized by sets of oligonucleotide primers according to the invention useful in PCR amplification and DNA segment resolution.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/07938

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; C12Q 1/70; C12P 19/34
 US CL : 435/6, 91.2; 536/23.1, 24.31

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. : 435/6, 91.2; 536/23.1, 24.31

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 5,851,795 A (LINSLEY et al) 22 December 1998 (22.12.1998), columns 21-22.	16
A	YANAGAWA et al. CTLA-4 Gene Polymorphism Associated with Graves' Disease in a Caucasian Population. Journal of Clinical Endocrinology and Metabolism. January 1995, Vol. 80, No. 1, pages 41-45, see entire document.	1, 3-6

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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 30 August 2000 (30.08.2000)	Date of mailing of the international search report 17 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer <i>Juliet C. Einsmann</i> Juliet C. Einsmann Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/07938

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.: 1, 3-6, 16, 18, and 19 as they pertain to ICOS

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

International application No.

PCT/US00/07938

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: Claims 1, 3-5, and 16 drawn to methods for detecting a predisposition for developing an autoimmune disease by detecting polymorphic microsatellite repeat sequences in the CD28 gene, and nucleic acids related to such detection. The generic claims in this group will be examined as they pertain to the CD28 gene.

Group II: Claims 1, 3-6, 16, 18, and 19 drawn to methods for detecting a predisposition for developing an autoimmune disease by detecting polymorphic microsatellite repeat sequences in the ICOS gene, and nucleic acids related to such detection. The generic claims in this group will be examined as they pertain to the ICOS gene. Furthermore, claims 6, and 18-19 will be examined in so much as SEQ ID NO: 33-36 and 53-54 amplify repeats in the ICOS gene.

Group III: Claims 2, 3-6, 7-10, 17, and 18-19 drawn to methods for detecting a predisposition for developing an autoimmune disease by detecting polymorphic microsatellite repeat sequences in the CTLA4 gene, and nucleic acids related to such detection. The generic claims in this group will be examined as they pertain to the CTLA4 gene. Furthermore, claims 6, and 18-19 will be examined in so much as the recited primers amplify repeats in the CTLA4 gene.

Claim 2 recites multiple repeats and in the case of these multiple sequences applicant is entitled to examination of 10 of these sequences. Applicant may pay for search of additional sequences in groups of four. (See Federal Register Publication 10/17/96). (four additional groups)

As noted, Claims 6 and 18-19 will be examined in this group in so much as the recited primers amplify portions of the CTLA4 gene. Applicant is entitled to the examination of ten of these sequences. Applicant may pay for search of additional sequences in groups of four. (8 additional groups)

Group IV: Claims 11 and 13-14 drawn to methods for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject using the CD28 gene. The generic claims in this group will be examined as they pertain to the CD28 gene.

Group V: Claims 11, 13-14, and 15 drawn to methods for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject using the ICOS gene. The generic claims in this group will be examined as they pertain to the ICOS gene. Furthermore, claim 15 will be examined in so much as SEQ ID NO: 33-36 and 53-54 amplify repeats in the ICOS gene.

Group VI: Claims 12, 13-14, and 15 drawn to methods for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject using the CTLA4 gene. The generic claims in this group will be examined as they pertain to the CTLA4 gene. Furthermore, claim 15 will be examined in so much as the recited primers amplify repeats in the CTLA4 gene.

Claim 12 recites multiple repeats and in the case of these multiple sequences applicant is entitled to examination of 10 of these sequences. Applicant may pay for search of additional sequences in groups of four. (See Federal Register Publication 10/17/96). (four additional groups)

As noted, claim 15 will be examined in this group in so much as the recited primers amplify portions of the CTLA4 gene. Applicant is entitled to the examination of ten of these sequences. Applicant may pay for search of additional sequences in groups of four. (8 additional groups)

The inventions listed as Groups I-VI 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: The special technical feature of claim 1 is either the ability to detect a predisposition to autoimmune disease using the CD28 gene or the ability to detect a predisposition to an autoimmune disease using the ICOS gene. These two genes are distinct entities, and methods using them comprise different inventions. Furthermore, claimed within this application are methods for detecting a predisposition to autoimmune disease using a third gene, the CTLA4 gene, also considered to be a separate invention with a separate special technical feature. The methods for typing the costimulatory receptor locus similarly comprise three additional inventions with three additional special technical features.

Furthermore, claims 2, 6, 12, 15, 18, and 19 recite multiple sequences or primers which are considered to lack unity among one another because they are either separate polymorphic repeats or they amplify different repeats. These are considered to lack unity with one another since they are different chemical entities as indicated by their different sequences. As such, and as noted above, applicant is entitled to the examination of ten of these sequences and then may pay for the examination of additional sequences in groups of four.