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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 January 2010 (21.01.2010)

PCT

(10) International Publication Number
WO 2010/009377 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2009/050959

(22) International Filing Date:
17 July 2009 (17.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/081,937 18 July 2008 (18.07.2008) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 61/081,937 (CIP)
Filed on 18 July 2008 (18.07.2008)

(71) Applicant *(for all designated States except US)*: **INTERLEUKIN GENETICS, INC.** [US/US]; 135 Beaver Street, Waltham, MA 02452 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KORNMAN, Kenneth, S.** [US/US]; 920 Centre Street, Newton, MA 02459 (US). **HUTTNER, Kenneth** [US/US]; 840 Newton Street, Chestnut Hill, MA 02467 (US). **ROGUS, John** [US/US]; 458 Foster Street, North Andover, MA 01845 (US). **KONDRAGUNTA, Venkateswarlu** [IN/US]; 10008 Inwood Drive, Woburn, MA 01801 (US). **WU, Xaiodong** [CN/US]; 36 Enslin Road, Needham, MA 02492 (US).

(74) Agents: **ELRIFI, Ivor, R.** et al.; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo PC, One Financial Center, Boston, MA 02111 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

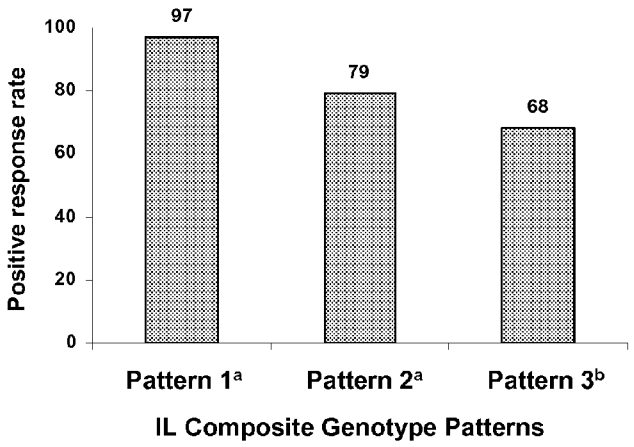
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR PHARMACOGENETIC ANALYSIS OF ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY DISEASES

(57) Abstract: The invention provides methods and compositions for the pharmacogenetic analysis of anti-inflammatory compounds, especially for the pharmacogenetic association of responsiveness to rheumatoid arthritis medications that target TNFα.

Figure 1



a - definition of response #1
b - definition of response #4

WO 2010/009377 A3

TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
27 May 2010

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050959

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68

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)
C12Q

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, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PADYUKOV L ET AL: "Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis" ANNALS OF THE RHEUMATIC DISEASES, BRITISH MEDICAL ASSOCIATION, LONDON, GB, vol. 62, no. 6, 1 June 2003 (2003-06-01), pages 526-529, XP002443558 ISSN: 0003-4967	1,7-8
A	abstract; tables 3,4	2-4

-/--

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

[X] 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 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	Date of mailing of the international search report
7 December 2009	08/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Nurmi, Jussi

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050959

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WESOLY JOANNA ET AL: "Genetic markers of treatment response in rheumatoid arthritis" CURRENT RHEUMATOLOGY REPORTS, CURRENT SCIENCE, PHILADELPHIA, PA, US, vol. 8, no. 5, 1 September 2006 (2006-09-01), pages 369-377, XP008115787 ISSN: 1523-3774	1,7-8
A	page 371 - page 374; tables 1,2	2-4
X	RANGANATHAN PRABHA: "Pharmacogenetics of therapies in rheumatoid arthritis" DRUGS OF TODAY, vol. 41, no. 12, December 2005 (2005-12), pages 799-814, XP002559025 ISSN: 1699-3993	1,7-8
A	page 807 - page 810	2-4
X	KANG C P ET AL: "The influence of a polymorphism at position -857 of the tumour necrosis factor alpha gene on clinical response to etanercept therapy in rheumatoid arthritis" RHEUMATOLOGY, OXFORD UNIVERSITY PRESS, LONDON, GB, vol. 44, no. 4, 1 April 2005 (2005-04-01), pages 547-552, XP002443557 ISSN: 1462-0324	1,7-8
A	abstract	2-4
X	WO 2008/056198 A1 (INST NAT SANTE RECH MED [FR]; MICELI CORINNE [FR]; MARIETTE XAVIER [FR]) 15 May 2008 (2008-05-15)	1,7-8
A	claim 1	2-4
X	EP 1 172 444 A1 (CONARIS RES INST GMBH [DE]) 16 January 2002 (2002-01-16)	1,7-8
A	claims 1-6	2-4
A	CAMP N J ET AL: "Evidence of a pharmacogenomic response to interleukin-I receptor antagonist in rheumatoid arthritis" GENES AND IMMUNITY, vol. 6, no. 6, September 2005 (2005-09), pages 467-471, XP002559026 ISSN: 1466-4879 abstract	1-4,7-8

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050959

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KOCZAN DIRK ET AL: "Molecular discrimination of responders and nonresponders to anti-TNF alpha therapy in rheumatoid arthritis by etanercept" ARTHRITIS RESEARCH & THERAPY 2008,, vol. 10, no. 3, 1 January 2008 (2008-01-01), page R50, XP002554192 abstract	1-4,7-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/050959

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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:

2. ☐ 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:

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 fees, this Authority did not invite payment of additional fees.

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.:

4(completely); 1-3, 7-8(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4(completely); 1-3, 7-8(partially)

Methods for determining the predisposition of a subject for a response to drugs that block TNF-alpha by detecting a genetic pattern from IL1A, wherein the genetic pattern is based on the polymorphism IL1A (4845) or on the combination of polymorphisms of claim 2(a), consisting of IL1A (4845), IL1B (-511) and IL1RN (2018)

---

2. claims: 1-3, 5-13(partially)

Methods for determining the predisposition of a subject for a response to drugs that block TNF-alpha by detecting a genetic pattern from IL1B, wherein the genetic pattern is based on the polymorphism IL1B (-511) or IL1B(-3737); or on a combination of polymorphisms selected from the combinations of claims 2(b),(c), 5, 6, 9-11 and 13, i.e. IL1B(-511) and IL1RN(2018)]; IL1B(-511), IL1B(-3737) and IL1RN(2018); IL1B (-511), IL1B(-3737) and TNFA(-308); IL1B(-511), IL1B(-3737) and IL10(-1082); IL1B(-511), IL1B(-3737), IL1RN(2018) and TNFA(-308); IL1B(-511) and IL1B(-3737).

---

3. claims: 1-3, 5-13(partially)

Methods for determining the predisposition of a subject for a response to drugs that block TNF-alpha by detecting a genetic pattern from IL1RN, wherein the pattern is based on the polymorphism IL1RN(2018).

---

4. claims: 1-3, 5-13(partially)

Methods for determining the predisposition of a subject for a response to drugs that block TNF-alpha by detecting a genetic pattern from IL10, wherein the pattern is based on the polymorphism IL10 (-1082).

---

5. claims: 1-3, 5-13(partially)

Methods for determining the predisposition of a subject for a response to drugs that block TNF-alpha by detecting a genetic pattern from TNFA, wherein the pattern is based on the polymorphism TNFA(-308).

---

6. claims: 14-17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods for determining the predisposition of a subject to differential response to anti-TNF-alpha and anti-IL1 *therapies by detecting a genetic pattern from IL1A and IL1B*, wherein the pattern is based on the polymorphisms of claim 17, i.e. IL1A (4845) and IL1B (-3737).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/050959

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008056198 A1	15-05-2008	CA 2668955 A1	15-05-2008
		EP 2084298 A1	05-08-2009
EP 1172444 A1	16-01-2002	US 2003099943 A1	29-05-2003