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(71) Applicant: INTERLEUKIN GENETICS, INC. [US/US]; 135 Beaver Street, Waltham, MA 02452 (US).

(72) Inventors: DUFF, Gordon, W.; 18 Ashgate Road, Sheffield, S10 3BZ, South Yorkshire (GB). KORNMAN, Kenneth, S.; 920 Centre Street, Newton, MA 02459 (US).

(74) Agents: QUISEL, John, D. et al.; Patent Group, Foley Hoag LLP, 155 Seaport Boulevard, Boston, MA 02210-2698 (US).

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WO 02/000933 A3

(54) Title: SCREENING ASSAYS FOR IDENTIFYING MODULATORS OF THE INFLAMMATORY OR IMMUNE RESPONSES

(57) Abstract: The present invention relates to methods for identifying substances that modulate the immune response in a genotype specific manner. In general, methods of the invention involve genotyping subjects to identify those having a genotype associated with one or more inflammatory disorder. These subjects, or cells derived therefrom, are monitored for a biomarker for activation of the inflammatory system. The subjects or cells are then contacted with a test substance and the biomarker is re-measured. If the biomarker changes to indicate a decreased activation of the inflammatory system, the test substance may have an anti-inflammatory effect on subjects with that genotype.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N5/10 G01N33/50

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 C12Q G01N C07K

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

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X	CAMP N J ET AL: "The relationship between IL-1 genotype and clinical response to recombinant IL-1 receptor antagonist therapy in rheumatoid arthritis." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 4, October 1999 (1999-10), page A198 XP001135186 49th Annual Meeting of the American Society of Human Genetics;San Francisco, California, USA; October 19-23, 1999 ISSN: 0002-9297 cited in the application	1-15
Y	the whole document	16-37

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

[X] Patent family members are listed in 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
20 February 2003	08. 07. 03

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Madlener, M

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 5, line 1 -page 9, line 12 page 42, line 1 -page 42, line 18 example 3	1-27, 32-37
Y	KORNMAN K S ET AL: "Interleukin-1 genotypes and the association between periodontitis and cardiovascular disease." JOURNAL OF PERIODONTAL RESEARCH. DENMARK OCT 1999, vol. 34, no. 7, October 1999 (1999-10), pages 353-357, XP009004778 ISSN: 0022-3484 abstract page 354 -page 357	1-37
Y	WO 99 24615 A (DUFF GORDON W ;GIOVINE MARCO (GB); LIM SIMON (GB); BARNES PETER J) 20 May 1999 (1999-05-20) abstract page 2, line 23 -page 3, line 25 page 13, line 35 -page 14, line 26	1-37
Y	WO 00 22166 A (EURONA MEDICAL AB ;NORBERG LEIF TORBJORN (SE); JONSSON LENA (SE);) 20 April 2000 (2000-04-20) abstract page 23, line 30 -page 28, line 15 page 45, line 29 -page 46, line 26 claims 1-16	1-37
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Y	WO 00 29614 A (EURONA MEDICAL AB) 25 May 2000 (2000-05-25) page 13, line 27 -page 18, line 19 page 35, line 17 -page 37, line 12	1-37

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	WO 00 47619 A (INTERLEUKIN GENETICS INC) 17 August 2000 (2000-08-17) page 4, line 15 -page 4, line 23 table 3	1-15
Y	page 1, line 1 -page 4, line 14 page 11, line 25 -page 12, line 18 page 23, line 18 -page 24, line 29 claims 1-42 figures 1-4	16-37
P,Y	WO 01 00880 A (INTERLEUKIN GENETICS INC) 4 January 2001 (2001-01-04) abstract page 1, line 1 -page 7, line 4 page 6, last paragraph page 18, paragraph 5 -page 24, paragraph 2 page 33, paragraph 2 -page 34, paragraph 2 claims 1-57	1-37
P,Y	WO 00 72015 A (DUFF GORDON W ;CROSSMAN DAVID C (GB); FRANCIS SHEILA E (GB); KORNM) 30 November 2000 (2000-11-30) abstract page 11, line 20 -page 15, line 20 claims 1-40	1-37
A	WO 98 47004 A (CEDARS SINAI MEDICAL CENTER ;PROMETHEUS LAB INC (US)) 22 October 1998 (1998-10-22) abstract page 3, line 6 -page 5, line 28 claims 1-50	1-37
A	US 4 980 281 A (HOUSEY GERARD M) 25 December 1990 (1990-12-25) the whole document	1-37
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	STOKKERS P C F ET AL: "TUMOR NECROSIS FACTOR (TNF) IN INFLAMMATORY BOWEL DISEASE: GENE POLYMORPHISMS, ANIMAL MODELS, AND POTENTIAL FOR ANTI-TNF THERAPY" JOURNAL OF INFLAMMATION, WILEY-LISS INC., NEW YORK, NY, US, vol. 47, no. 1/2, 8 May 1996 (1996-05-08), pages 97-103, XP000197771 ISSN: 1078-7852 abstract	1-37
A	POUW KRAAN VAN DER T C T M ET AL: "AN IL-13 PROMOTER POLYMORPHISM ASSOCIATED WITH INCREASED RISK OF ALLERGIC ASTHMA" GENES AND IMMUNITY, NATURE PUBLISHING GROUP, GB, vol. 1, 1999, pages 61-65, XP001023916 ISSN: 1466-4879 abstract	1-37
A	COX A ET AL: "An analysis of linkage disequilibrium in the interleukin-1 gene cluster, using a novel grouping method for multiallelic markers" AMERICAN JOURNAL OF HUMAN GENETICS, UNIVERSITY OF CHICAGO PRESS, CHICAGO,, US, no. 62, pages 1180-1188, XP002077316 ISSN: 0002-9297 the whole document	1-37
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A	ROSES A D: "Pharmacogenetics and future drug development and delivery" LANCET, XX, XX, vol. 355, no. 9212, 15 April 2000 (2000-04-15), pages 1358-1361, XP004263436 ISSN: 0140-6736 the whole document	1-37

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ROSES ALLEN D: "Pharmacogenetics and the practice of medicine." NATURE (LONDON), vol. 405, no. 6788, 2000, pages 857-865, XP002228520 ISSN: 0028-0836 the whole document ---	1-37
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INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 01/20079

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. ☐ 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 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.:

1-37 (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: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1A (+4845); cells comprising a heterologous IL-1A (+4845)-allele; kits comprising primers for identification of the IL-1A (+4845) polymorphism.

2. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1A (222/223); cells comprising a heterologous IL-1A (222/223)-allele; kits comprising primers for identification of the IL-1A (222/223) polymorphism.

3. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1A (gz5/gz6); cells comprising a heterologous IL-1A (gz5/gz6)-allele; kits comprising primers for identification of the IL-1A (gz5/gz6) polymorphism.

4. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1A (-889); cells comprising a heterologous IL-1A (-889)-allele; kits comprising primers for identification of the IL-1A (-889) polymorphism.

5. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1B (-511); cells comprising a heterologous IL-1B (-511)-allele; kits comprising primers for identification of the IL-1B (-511) polymorphism.

6. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype

involving genotyping at gaat.p33330; cells comprising a heterologous gaat.p33330-allele; kits comprising primers for identification of the gaat.p33330 polymorphism.

7. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at Y31; cells comprising a heterologous Y31-allele; kits comprising primers for identification of the Y31 polymorphism.

8. Claims: 1-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (+2018); cells comprising a heterologous IL-1RN (+2018)-allele; kits comprising primers for identification of the IL-1RN (+2018) polymorphism.

9. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (1731); cells comprising a heterologous IL-1RN (1731)-allele; kits comprising primers for identification of the IL-1RN (1731) polymorphism.

10. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (1812); cells comprising a heterologous IL-1RN (1812)-allele; kits comprising primers for identification of the IL-1RN (1812) polymorphism.

11. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (1868); cells comprising a heterologous IL-1RN (1868)-allele; kits comprising primers for identification of the IL-1RN (1868) polymorphism.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

12. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (1887); cells comprising a heterologous IL-1RN (1887)-allele; kits comprising primers for identification of the IL-1RN (1887) polymorphism.

13. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (8006); cells comprising a heterologous IL-1RN (8006)-allele; kits comprising primers for identification of the IL-1RN (8006) polymorphism.

14. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (8061); cells comprising a heterologous IL-1RN (8061)-allele; kits comprising primers for identification of the IL-1RN (8061) polymorphism.

15. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1RN (9589); cells comprising a heterologous IL-1RN (9589)-allele; kits comprising primers for identification of the IL-1RN (9589) polymorphism.

16. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-1B (+6912); cells comprising a heterologous IL-1B (+6912)-allele; kits comprising primers for identification of the IL-1B (+6912) polymorphism.

17. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype

involving genotyping at TNFA (-308); cells comprising a heterologous TNFA (-308)-allele; kits comprising primers for identification of the TNFA (-308) polymorphism.

18. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at TNFA (-238); cells comprising a heterologous TNFA (-238)-allele; kits comprising primers for identification of the TNFA (-238) polymorphism.

19. Claims: 1-2, 4-17, 19-37 (partially)

Methods for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype involving genotyping at IL-13 (+2581); cells comprising a heterologous IL-13 (+2581)-allele; kits comprising primers for identification of the IL-13 (+2581) polymorphism.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/20079

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