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(54) Title: METHODS UTILIZING NOVEL TARGET GENES RELATED TO IMMUNE-MEDIATED DISEASES

(57) Abstract: The present invention provides methods utilizing novel target genes related to immune-mediated diseases, such as asthma, allergy and autoimmune diseases. The invention is based on a molecular level description of the polarization of CD4+ precursor cells (Thp) from which T helper cells are known to originate. Particularly, the present invention provides a method of identifying a compound capable of modulating the polarization of CD4+ lymphocytes. The invention is also related to a method for assessing the presence of, or a predisposition to, an immune-related disorder in a subject.

WO 2004/083366 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2004/000155

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12Q 1/68
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)

IPC7: C12Q, A61P, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI-DATA, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Salvi H. et al: Gene expression analysis of 1,25(OH)2D3-dependent differentiation of HL-60 cells: a cDNA array study, British journal of haematology, 2002, 118, 1065-1070: See abstract.	5-6
X	WO 0228999 A2 (GENE LOGIC, INC.), 11 April 2002 (11.04.2002), See page 1, lines 12-26, page 2, line 31 - page 3, line 8, page 4, line 20 - page 7, line 2 and Table 7, SEQ ID NO: 208	5-6,27

[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 application or patent 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
24 August 2004	07 -09- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer SARA NILSSON/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2004/000155

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Bellucci R. et al: Identification of target antigens associated with graft-vs-myeloma response after allogeneic bone marrow transplantation and donor lymphocyte infusion, Blood, vol. 98, nr. 11 part 1, November 2001, p. 405a. See entire abstract.	5-6
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A	WO 0188199 A2 (GENETICS INSTITUTE, INC.), 22 November 2001 (22.11.2001), See abstract, page 4, line 10 - page 8, line 20, page 10, lines 20-36, page 11, lines 25-37, page 55, lines 15-24, pages 78-80, examples E-F, and the claims	1-4,12-31
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A	US 6414117 B1 (LEVINSON), 2 June 2002 (02.06.2002), See abstract, column 1, lines 16-49, column 3, line 63 - column 4, line 1, column 4, lines 12-34 and column 76, lines 49-62	1-4,12-31
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A	Hamalainen H et al: Distinct gene expression profiles of human type 1 and type 2 T helper cells, Genome Biol. 2001;2(7): See abstract, p. 5 right col. last paragraph and p. 9 left col. paragraph 2.	1-4,12-31
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A	WO 9957130 A1 (GENE LOGIC, INC.), 11 November 1999 (11.11.1999), See page 32, example 1, page 39, example 5 and pages 42-43, examples 8-9	1-4,12-31
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A	Chen Z et al: Identification of IL-4 inducible genes in T lymphocytes, Journal of interferon and cytokine research, vol. 22 supplement 1, 2002. page S-172: See the entire abstract.	1-4,12-31
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2004/000155

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.: 7-9
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 7-9 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)).

2. ☒ Claims Nos.: 10-11 and 7-9
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 next sheet

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 next 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.: 1-31 all partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

<Box II.2>

Present claims 10-11 and 7-9 relate to a product defined by reference to a desirable characteristic or property, namely that the composition "alters the expression or activity of at least one gene listed in Table 2 or Table 6". The claims cover all compounds having this characteristic or property, whereas the application lacks support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for such products. No examples of compounds are given in the description. In claim 11 it is stated that the compound is an antibody, but no specific examples of such antibodies are provided in the description. Additionally, previously known compounds may be included in the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search for claims 7-11 impossible.

<Box III>

1: Claims: 1-31 (all partially) directed to a method of identifying a compound capable of modulating the polarization of CD4+ lymphocytes comprising comparing the expression of KIAA0053 in lymphocytes contacted with the compound and induced to polarize, methods of identifying a compound that modulates the expression or activity of KIAA0053, methods for classifying lymphocytes or diagnosing immune related disorders by measuring expression of KIAA0053 and further methods comprising the step of determining the expression level of KIAA0053

2: Claims: 1-31 (all partially) directed to a method of identifying a compound capable of modulating the polarization of CD4+ lymphocytes comprising comparing the expression of LRRN3 in lymphocytes contacted with the compound and induced to polarize, methods of identifying a compound that modulates the expression or activity of LRRN3, methods for classifying lymphocytes or diagnosing immune related disorders by measuring expression of LRRN3 and further methods
comprising the step of determining the expression level of LRRN3

3-11: Claims: 1-31 (all partially) directed to a method of identifying a compound capable of modulating the polarization of CD4+ lymphocytes comprising comparing the expression of each of the other nine genes mentioned in claims 14-15 in lymphocytes contacted with the compound and induced to polarize, methods of identifying a compound that modulates the expression or activity of each of the other nine genes mentioned in claims 14-15, methods for classifying lymphocytes or diagnosing immune related disorders by measuring expression of each of the other nine genes mentioned in claims 14-15 and further methods comprising the step of determining the expression level of each of the other nine genes mentioned in claims 14-15

.../...

The searching authority could not find any same or corresponding technical feature in terms of a common property or activity, and a shared structural element essential to such a common property or activity, among the genes listed in the application. No grouping of the genes has therefore been made, and each gene is so far considered to constitute one invention (see also the motivation below).

The present application has been considered to contain 11 inventions which are not linked such that they form a single general inventive concept, as required by Rules 13.1, 13.2 and 13.3 PCT for the following reasons:

The prior art has been identified as: WO0188199 (D1).

The marker genes disclosed in D1 are identified by analyzing the changes in gene expression in response to Thl-inducing or Th2-inducing conditions. Naïve CD4+ cells are activated by contact with CD3/CD28 and either IL-12 (Th1-inducing conditions) or IL-4 (Th2-inducing conditions). RNA was isolated from samples taken at different times and RNA probes were used to probe the Affymetrix human 6800 DNA microarray set. Genes with significant differences between expression in Th1 and/or Th2 cells as compared to naïve undifferentiated CD4+ T cells are shown. Naïve CD4+ T cells are cultured in the presence of anti-CD3 and anti-CD28.
D1 discloses a method for assessing whether Th1 or Th2 cells are present in a subject comprising comparing the expression level of a marker gene in a sample from a subject and in a control sample, methods for monitoring the differentiation of naïve T cells into Th1 or Th2 cells, methods for assessing the efficacy of a test compound or therapy for modulating differentiation of Th1 or Th2 cells in a subject, methods of selecting a composition for modulating differentiation, growth or maturation of Th1 or Th2 cells and methods for assessing the potential of a test compound to trigger the differentiation of Th1 or Th2 cells from naïve T cells, all methods involving measuring the expression of genes differentially expressed in Th1 and/or Th2 cells in a sample and a control. The marker genes can be used to diagnosing conditions associated to Th-cells (e.g. asthma) by measuring the activity or expression of the marker gene in a sample. D1 also provides methods for identifying compounds which have a modulatory effect on the activity of the marker gene. See abstract, p. 4 line 10- p. 8 line 20, p. 10 line 20-36, p. 11 lines 25-37, p. 55 lines 15-24 p. 78-80, examples E-F, and the claims.

Thus, D1 shows genes being differentially expressed in CD4+ cells polarized under conditions corresponding to conditions used in the present application for identifying genes included in Tables 1-3 and 6.
The genes mentioned in claims 14-15 are differentially expressed in Th1-induced vs. Th2-induced cells (see Table 1), genes with such characteristics are shown in D1. Genes with an increased expression in Th2 cells as compared to Th1 cells are shown in D1.

.../...

Genes differentially expressed within and/or Th-cell subpopulations are also disclosed in US6414117 (D2). Murine as well as human genes are identified. The genes identified can be used diagnostically or as targets for therapeutic intervention relating to immune disorders. The genes are identified essentially as in D1. D2 provides methods for the identification of compounds which modulate the expression of genes or the activity of gene products involved in TH cell subpopulation-related disorders. See the abstract, col. 1 lines 16-49, col. 3 line 63-col. 4 line 1, col. 4 lines 12-34 and col. 76 lines 49-62.
Hamalainen H et al Genome Biol. 2001;2(7): (D3) also shows genes differentially expressed by polarized Th1 and Th2 cells. The genes are identified by polarization conditions as the ones used in the present application. See abstract, p. 5 right col. last paragraph and p. 9 left col. paragraph 2.

Invention I:

The special technical features which make a contribution over this prior art (Rule 13.2 PCT) are the following: the gene KIAA0053 is identified as being differentially expressed in CD4+ cells polarized under certain conditions.
From these special technical features the objective problem to be solved by the first invention can be construed as: providing the gene marker KIAA0053, which is differentially expressed in CD4+ cells polarized under certain conditions.

Invention II-XI:
The special technical features of claims 1-31 (all partially) are the following: each of the other nine marker genes mentioned in claims 14-15 is identified as being differentially expressed in CD4+ cells polarized under certain conditions.
From these special technical features the objective problem to be solved by the first invention can be construed as: providing each of the other nine marker genes mentioned in claims 14-15, which is differentially expressed in CD4+ cells polarized under certain conditions.

The above analysis shows that the special technical features of invention I (claim(s) 1-31 all partially) are neither the same as nor corresponding to those of inventions II-XI.

Consequently, neither the objective problem underlying the subjects of the claimed inventions, nor their solutions defined by the special technical features allow for a relationship to be established between the said inventions, which involves a single general inventive concept.

In conclusion, therefore, the XI groups of claims are not linked by common or corresponding special technical features and define different inventions not linked by a single general inventive concept.
The application, hence does not meet the requirements of unity of invention as defined in Rule 13.1 and 13.2 PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/FI 2004/000155

WO	0228999	A2	11/04/2002	AU	2126502 A	15/04/2002
WO	0188199	A2	22/11/2001	AU	5978801 A	26/11/2001
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