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Published:

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

(88) Date of publication of the international search report:
24 April 2014

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(54) Title: CXCR4 AS A SUSCEPTIBILITY LOCUS IN JUVENILE IDIOPATHIC ARTHRITIS (JIA) AND METHODS OF USE THEREOF FOR THE TREATMENT AND DIAGNOSIS OF THE SAME

(57) Abstract: Compositions and methods useful for the diagnosis and treatment of juvenile idiopathic arthritis are disclosed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/60430

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2012.01)
USPC - 435/6.11
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(8) - C12Q 1/68 (2012.01)
USPC - 435/6.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6.12 435/6.13

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar; ScienceDirect; Thomson Innovation
Search terms: juvenile idiopathic arthritis, juvenile rheumatoid arthritis, CXCR4, CXCR-4, C-X-C chemokine receptor type 4, fusin, CD184, SNP, polymorphism, vector, host, host cell, screen, test agent, test compound

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCDOWELL et al., A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. Arthritis Rheum. February 1995, Vol 38, No 2, pages 221-228. Especially abstract; p 222, right col, para 1-2; p 223, left col, para 1-2	1-18
Y	NCBI publication "Cluster Report: rs953387", 6 September 2000 [online]. [Retrieved on 10 May 2012]. Retrieved from the internet: <URL: http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=953387>	1-18
Y	NCBI publication "IL1A interleukin 1, alpha [Homo sapiens]", July 2008 [online]. [Retrieved on 23 February 2012]. Retrieved from the internet: <URL: http://www.ncbi.nlm.nih.gov/gene/3552>	1-18
Y	US 2007/0134690 A1 (PASCUAL et al.) 14 June 2007 (14.06.2007) para [0011], [0013]-[0015], [0017], [0056], [0066]	1-12-18
Y	US 2009/0298063 A1 (KORNMAN et al.) 3 December 2009 (03.12.2009) para [0037], [0048], [0114]-[0115], [0125], [0127],-[0128], [0134], [0136], [0154]	6-11, 13-14

☐ Further documents are listed in the continuation of Box C. ☐

* 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
10 May 2010 (10.05.2012)	25 MAY 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/60430

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:
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 1-18, drawn to a method for detecting an increased risk for developing juvenile idiopathic arthritis (JIA) in a test subject, comprising,
a) obtaining a nucleic acid sample from said subject and determining whether said sample contains at least one SNP identified in the CXCR4 locus wherein if said SNP is detected, said patient has an increased risk for developing JIA, wherein said SNP containing nucleic acid is selected from the group of SNPs consisting of those provided in Table 4 or any SNP in LD [Linkage Disequillibrium] with those listed. The first invention is restricted to rs953387. Should an additional fee(s) be paid, Applicant is invited to elect an additional SNP(s) to be searched.

---please see continuation on extra 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 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.:
1-18, restricted to rs953387

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/60430

Continuaiton of Box No. III Observations where unity of invention is lacking

The inventions listed as Groups I+ 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 inventions of Group I+ share the technical feature of a method of claim 1. However, this shared technical feature does not represent a contribution over prior art as being anticipated by an article titled "A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism" by McDowell, et al. (Arthritis Rheum. 1995, 38(2):221-228) hereinafter ("McDowel") that discloses a method for detecting an increased risk for developing JIA [JIA is synonumous with JRA [juvenile rheumatoid arthritis], as evidenced by a publication titled "Juvenile idiopathic arthritis" (12 November 2010) [Retrieved from the Internet 23 February 2012: <http://en.wikipedia.org/w/index.php?title=Juvenile_idiopathic_arthritis&oldid=396305337>] ("JIA replaces the term juvenile rheumatoid arthritis (JRA)")] in a test subject, comprising,
a) obtaining a nucleic acid sample from said subject and determining whether said sample contains at least one SNP identified in the CXCR4 locus wherein if said SNP is detected, said patient has an increased risk for developing JIA (Abstract, a C (IL-1A1) to T (IL-1A2) transition polymorphism at position -889 in the IL-1a gene) in a human IL-1a gene (Abstract, "OBJECTIVE: ... This study was performed to test whether polymorphisms of the human IL-1 alpha gene might be associated with JRA. METHODS: We sequenced the 5' regulatory region (containing the promoter) of the human IL-1 alpha gene in 18 normal subjects. This revealed a C (IL-1A1) to T (IL-1A2) transition polymorphism at position -889. We studied the frequencies of both alleles in patients with JRA (n = 269) and controls (n = 99). RESULTS: An increased gene carriage of IL-1A2 was found in patients with early-onset, pauciarticular JRA (EOPA-JRA; n = 103) compared with controls (0.66 versus 0.49; P = 0.01, odds ratio [OR] = 2.1)"; pg 227, col 1, "we have indentified a polymorphism in the 5' regulatory region of the IL-1a gene that, in a case-controled study, was associated with the presence of chronic iridocyclitis and increased ESR in patients with EOPA-JRA... Further functional studies are required to define whether this polymorphism is ... a marker for a more improtant linked gene").
McDowell does not expressly disclose that said polymorphism is in CXCR4 locus. However, this limitation is inherently present in McDowell, because McDowell's polymorphism is in LD with the rs6430612 SNP, the 5th SNP provided in Table 4 as follows:

1) the claimed rs6430612 is located on chromosome 2, locus 2q14.3 at 137,006,198 base, as evidenced by NCBI publication titled "Cluster Report: rs6430612" [Retrieved from the Internet 23 February 2012: <http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6430612>];

2) the IL1a gene is located on chromosome 2, locus 2q14 at 113,531,492-113,542,971, as evidenced by NCBI publication titled "IL1A interleukin 1, alpha [Homo sapiens]" (19 February 2012) [Retrieved from the Internet 23 February 2012: <http://www.ncbi.nlm.nih.gov/gene/3552>].

3) Thus, the two SNPs at issue are located in the same locus of chromosome 2, specifically, the 2q14 locus, and are only about 500K apart. As such, they are indeed in linkage disequilibrium, and therefore, the polymorphism of McDowell is in CXCR4 locus, as claimed. As said method was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is the specific SNP recited therein. The inventions do not share a special technical feature, because no significant structural similarities can readily be ascertained among the SNPs. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.