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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 February 2010 (04.02.2010)

PCT

(10) International Publication Number
WO 2010/014905 A3

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

(21) International Application Number:
PCT/US2009/052412

(22) International Filing Date:
31 July 2009 (31.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/137,492 31 July 2008 (31.07.2008) US

(71) Applicant *(for all designated States except US)*: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GLIMCHER, Laurie, H.** [US/US]; 51 Hampshire Street, West Newton, MA 02165 (US). **BLUMBERG, Richard, S.** [US/US]; 195 Fox Road, #101, Waltham, MA 02451 (US).

(74) Agents: **WILLIAMS, Megan, E.** et al.; Lahive & Cockfield, LLP, One Post Office Square, Boston, MA 02109-2127 (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, 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:
8 July 2010

(54) Title: POLYMORPHISMS IN THE XBP-1 GENE ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

(57) Abstract: The present invention is based, at least in part, on the discovery that certain known and novel SNPs located in the XBP-I genomic region at human chromosome 22q are significantly associated with IBD. Such SNPs are useful for determining the predisposition of a human subject to develop inflammatory bowel disease. Accordingly, the present invention provides methods for detecting at least one SNP in the human XBP-I genomic region, as well as methods to determine the predisposition of a human subject to develop inflammatory bowel disease.

WO 2010/014905 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/052412

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, WPI Data, Sequence Search, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/039445 A2 (HARVARD COLLEGE [US]; BRIGHAM & WOMENS HOSPITAL [US]; BLUMBERG RICHARD) 3 April 2008 (2008-04-03) the whole document	1-3,5-11
X,P	KASER ARTHUR ET AL: "XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease" CELL, vol. 134, no. 5, September 2008 (2008-09), pages 743-756, XP002559654 ISSN: 0092-8674 the whole document	1-3,5-11

-/--

[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
6 May 2010	20/05/2010

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	Schmitt, Anja

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/052412

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KASER A ET AL: "Endoplasmic reticulum stress in the intestinal epithelium and inflammatory bowel disease" SEMINARS IN IMMUNOLOGY, W.B. SAUNDERS COMPANY, PA, US, vol. 21, no. 3, 1 June 2009 (2009-06-01), pages 156-163, XP026140246 ISSN: 1044-5323 the whole document	1-3,5-11
X,P	VAN LIMBERGEN JOHAN ET AL: "The genetics of Crohn's disease." ANNUAL REVIEW OF GENOMICS AND HUMAN GENETICS 2009, vol. 10, 19 May 2009 (2009-05-19), pages 89-116, XP0026140246 ISSN: 1545-293X the whole document	1-3,5-11
A	KASER ET AL: "001 TRANSCRIPTION FACTOR XBP1 REGULATES PANETH CELL FUNCTION AND INFLAMMATION IN THE INTESTINE" 20070301, vol. 1, no. 1, 1 March 2007 (2007-03-01), pages 1-2, XP022365957 abstract	1-3,5-11
A	US 2004/077020 A1 (MANNICK ELIZABETH E [US] ET AL) 22 April 2004 (2004-04-22) table 2	1-3,5-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/052412

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.:

1-3, 5-8(completely); 9-11(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:

Invention: 1; Claims: 1-3, 5-8(completely); 9-11(partially)

Invention 1 (claims 1-3 completely, 6-11 partially):
A method for determining the predisposition of a human subject to develop inflammatory bowel disease comprising detecting in a nucleic acid sample from the subject at least one single nucleotide polymorphism (SNP) in intron 4 of XBP-1, especially wherein said SNP is at position 31 of SEQ ID NO:170 or SEQ ID NO:169.

1.1. claims: 5-11(partially)

Inventions 2-3 (claims 5-11 partially):
A method for determining the predisposition of a human subject to develop inflammatory bowel disease comprising detecting in a nucleic acid sample from the subject at least one SNP in the XBP-1 gene, wherein said SNP is at position 31 of the nucleic acid molecule of SEQ ID NO:166 (168).

1.2. claims: 5, 9-11(all partially)

Inventions 4-5 (claims 5, 9-11 partially):
A method for determining the predisposition of a human subject to develop inflammatory bowel disease comprising detecting in a nucleic acid sample from the subject at least one SNP in the XBP-1 gene, wherein said SNP is at position 31 of the nucleic acid molecule of SEQ ID NO:167 (171).

1.3. claims: 6-11(partially)

Inventions 6-9 (claims 6-11 partially):
A method for determining the predisposition of a human subject to develop inflammatory bowel disease comprising detecting in a nucleic acid sample from the subject at least one SNP in the XBP-1 gene, wherein said SNP is at position 31 of the nucleic acid molecule of SEQ ID NO:172 (173, 174, 175).

Inventions: 2-53; Claims: 4, 9-13(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Inventions 10-61:

A method for determining the predisposition of a human subject to develop inflammatory bowel disease comprising detecting in a nucleic acid sample from the subject at least one SNP in the XBP-1 gene, wherein said SNP is at position 48 of SEQ ID NO:114 (15, 116, 117, ...165).

An insolated probe of about 5-50 nucleotides that specifically detects a SNP at position 48 of SEQ ID NO:114 (15, 116, 117, ...165).

A diagnostic kit comprising an oligonucleotide that specifically detects a SNP at position 48 of SEQ ID NO:114 (15, 116, 117, ...165).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/052412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008039445 A2	03-04-2008	NONE	
US 2004077020 A1	22-04-2004	NONE	