

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 12993-WO-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2018/048240	International filing date (<i>day/month/year</i>) 28 August 2018 (28-08-2018)	(Earliest) Priority Date (<i>day/month/year</i>) 30 August 2017 (30-08-2017)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- the international application in the language in which it was filed
- a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. **Certain claims were found unsearchable** (See Box No. II)

3. **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- the text is approved as submitted by the applicant
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant
- the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

- as suggested by the applicant
- as selected by this Authority, because the applicant failed to suggest a figure
- as selected by this Authority, because this figure better characterizes the invention

b. none of the figures is to be published with the abstract

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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.:

1-4, 10, 11(completely); 6-9(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.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6883
ADD.
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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HU YANHUA SARAH ET AL: "Gene Signature for Glucocorticoid, from in Vitro to In Vivo (Abstract n°: 759)", ARTHRITIS & RHEUMATOLOGY, vol. 68, no. Suppl. 10, October 2016 (2016-10), XP002786366, & ANNUAL MEETING OF THE AMERICAN-COLLEGE-OF-RHEUMATOLOGY/ASSOCIATION-OF-RHEUMATOLOGY-HEALTH-PROFESSIONALS (ACR/ARHP); WASHINGTON, DC, USA; NOVEMBER 11 -16, 2016 the whole document ----- -/--	1-4,6-11

Further documents are listed in the continuation of Box C.

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 9 November 2018	Date of mailing of the international search report 29/01/2019
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Costa Roldán, Nuria
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/048240

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TOONEN ERIK J M ET AL: "Prednisolone-induced changes in gene-expression profiles in healthy volunteers.", PHARMACOGENOMICS JUL 2011, vol. 12, no. 7, July 2011 (2011-07), pages 985-998, XP009509199, ISSN: 1744-8042 the whole document</p> <p style="text-align: center;">-----</p>	1-4,6-11
A	<p>GALON J ET AL: "Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells", THE FASEB JOURNAL, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, US, vol. 16, no. 1, 1 January 2002 (2002-01-01), pages 61-71, XP002240642, ISSN: 0892-6638, DOI: 10.1096/FJ.01-0245COM the whole document</p> <p style="text-align: center;">-----</p>	1-4,6-11
A	<p>HAKONARSON HAKON ET AL: "Profiling of genes expressed in peripheral blood mononuclear cells predicts glucocorticoid sensitivity in asthma patients.", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 11 OCT 2005, vol. 102, no. 41, 11 October 2005 (2005-10-11), pages 14789-14794, XP002786367, ISSN: 0027-8424 abstract</p> <p style="text-align: center;">-----</p>	1-4,6-11
A	<p>TOONEN E J M ET AL: "Gene expression profiling in rheumatoid arthritis: Current concepts and future directions", ANNALS OF THE RHEUMATIC DISE, BRITISH MEDICAL ASSOCIATION, GB, vol. 67, no. 12, 1 December 2008 (2008-12-01), pages 1663-1669, XP009183610, ISSN: 0003-4967, DOI: 10.1136/ARD.2007.076588 [retrieved on 2008-02-04] abstract</p> <p style="text-align: center;">-----</p>	1-4,6-11
T	<p>HU YANHUA ET AL: "Development of a Molecular Signature to Monitor Pharmacodynamic Responses Mediated by In Vivo Administration of Glucocorticoids", ARTHRITIS & RHEUMATOLOGY, vol. 70, no. 8, 13 March 2018 (2018-03-13), pages 1331-1342, XP002786368, the whole document</p> <p style="text-align: center;">-----</p>	1-4,6-11

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-4, 10, 11(completely); 6-9(partially)

Methods to determine a person's response to glucocorticoids comprising:

- a) administering the glucocorticoid of interest to said person,
- b) drawing blood from the person of step (a) 4 hours post-administration,
- c) isolating the RNA from the blood collected in step (b),
- d) profiling the gene expression of the RNA isolated in step (c), and
- e) comparing the gene signature score post-administration with a control gene signature score, wherein an increase in the gene signature score for FKBP5, ECHDC3, IL1R2, ZBTB16, IRS2, IRAK3, ACSL1, DUSP1 indicates a response to the glucocorticoid; or wherein step e) of the method reads as follows:

- comparing the gene signature score post-administration with a control gene signature score, wherein an increase in the gene signature score for FKBP5, ECHDC3, IL1R2, ZBTB16, IRS2, IRAK3, ACSL1, DUSP1, PHC2, TLR2, TSC22D3, SLA, CRISPLD2, MAN2A2, FAR2, CEBPD, SPTLC2, HSPA6 indicates a response to the glucocorticoid;
- comparing the gene signature score post-administration with a control gene signature score, wherein an increase in the gene signature score for FKBP5, ECHDC3, IL1R2 indicates a response to the glucocorticoid;
- comparing the gene signature score post-administration with a control gene signature score, wherein an increase in the gene signature score for FKBP5, ECHDC3, IL1R2, ZBTB16, IRS2, IRAK3 indicates a response to the glucocorticoid.

2. claims: 5(completely); 6-9(partially)

A method to determine a person's response to glucocorticoids comprising: a) administering the glucocorticoid of interest to said person, b) drawing blood from the person of step (a) 4 hours post-administration, c) isolating the RNA from the blood collected in step (b), d) profiling the gene expression of the RNA isolated in step (c), and e) comparing the gene signature score post-administration with a control gene signature score, wherein a decrease in the gene signature score for KMO, CCR5, CXCL8, FPR3, PLA2G7, PEA15, TRAF1, CSF2RB, TRDC, OLR1, KIAA0226L, FCGR2B, ATF5, CX3CR1, MYOF, SLAMF7, CD9, IL1RN indicates a response to the glucocorticoid.
