PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2018/048240	28.08.2018	30.08.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/6883

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Telephone No. +49 89 2399-0

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established 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)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 5(completely); 6-9(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 5(completely); 6-9(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4, 10, 11(completely); 6-9(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 10, 11(completely); 6-9(partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1, 2, 10, 11
	No:	Claims	3, 4(completely); 6-9(partially)
Industrial applicability (IA)	Yes:	Claims	1-4, 10, 11(completely); 6-9(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

Claims 1 to 4, 6 to 11 (according to Invention 1).

Re Item IV

Lack of unity of invention

This Authority considers that there are 2 inventions (2 groups of inventions) not linked as to form a single general inventive concept, as required by Rule 13.1 PCT.

Invention 1 (claims 1 to 4, 10 and 11 in full, claims 6 to 9 partial) relates to a method to determine glucocorticoid response comprising the determination of an increase in a gene signature score for a set of genes.

Invention 2 (claim 5 in full, claims 6 to 9 partial) relates to a method to determine glucocorticoid response comprising the determination of a decrease in a gene signature score for a set of genes.

The only identifiable technical feature that all inventions have in common is a signature score for glucocorticoids. However, said feature cannot represent special technical feature in the sense of Rule 13.2 PCT as it is known in the art. See e.g. any of the following documents:

D1 (see whole document) describes a gene-signature score for glucocorticoid comprising 64 genes.

D2 describes Prednisolone-induced gene expression in healthy volunteers.

D3 describes the effect of glucocorticoid on gene expression profile of blood cells from healthy donors.

D4 describes gene expression profiles in blood from two cohorts glucocorticoid resistant and sensitive asthma patients predict responders.

In view of the prior art represented by any of D1 to D4, the problem of the underlying application may be defined as the provision of a further gene signature/s for glucocorticoids. Thus:

The special technical feature of invention 1, representing the contribution over the prior art, is the provision of a further list of genes according to claims 1, 2, 3 and 4 for the signature score. This solves the technical problem of providing an alternative signature score wherein an increased of said score is indicative of glucocorticoid response.

The special technical feature of invention 2, representing the contribution over the prior art, is the provision of a further a further list of genes according to claim 5. This solves the technical problem of providing an alternative signature score wherein an decrease of said score is indicative of glucocorticoid response.

The different inventions are grouped as follows:

Invention 1 (claims 1 to 4, 10 and 11 in full, claims 6 to 9 partial).

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.

Invention 2 (claim 5 in full, claims 6 to 9 partial).

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.

The special technical features of invention 1 and 2 are neither the same nor corresponding since each solve different problems. Hence, the technical relationship between the subject-matter of (I) claims 1 to 4, 10 and 11 in full, claims 6 to 9 partial (invention 1) and; (ii) of claims 5 in full, claims 6 to 9 partial (invention 2) is lacking.

Therefore, the ISA is of the opinion that there is no single inventive concept in the sense of Rule 13.1 PCT. Consequently, there is a lack of unity, and different inventions have been formulated as different subjects on the communication pursuant Article 17 (a) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 HU YANHUA SARAH ET AL: "Gene Signature for Glucocorticoid, from in Vitro to In Vivo",ARTHRITIS & RHEUMATOLOGY, vol. 68, no. Suppl. 10, October 2016 (2016-10), pages 759-760,& ANNUAL MEETING OF THE AMERICAN-COLLEGE-OF-RHEUMATOLOGY/ASSOCIATION-OF-RHEUMATOLOGY-HEALTH-PROFESSIONALS (ACR/ARHP); WASHINGTON, DC, USA; NOVEMBER 11 -16, 2016

D2 TOONEN ERIK J M ET AL: "Prednisolone-induced changes in gene-expression profiles in healthy volunteers.",PHARMACOGENOMICS JUL 2011, vol. 12, no. 7, (2011-07), pages 985-998,ISSN: 1744-8042

D3 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, (2002-01-01), pages 61-71, ISSN: 0892-6638, DOI: 10.1096/FJ.01-0245COM

D4 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, pages 14789-14794,ISSN: 0027-8424

D5 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

V.1. NOVELTY (Article 33(2) PCT)

Methods as described according to any of the independent claims have not been described in the prior art. Therefore, the set of claims is considered novel.

V.2. INVENTIVE STEP (Article 33(3)PCT)

1 With respect to claim 1:

D1 could be considered the closest prior art. D1 is an Abstract publication of the inventors of present application wherein 64 genes were identified as potential prednisolone gene signature. This document does not provide the identity of said 64 genes of the signature.

The problem to be solved could be regarded as the provision of a simplified score signature for determining response to glucocorticoids. The solution provided is a 8-gene signature score as disclosed in claim 1.

The available prior art provides the technical information that glucocorticoids (i.e. prednisolone) induce changes in gene expression in healthy subjects, see for example Abstracts of D2 (this document mentions FKBP5 and ZBTB16) or D3.

However, a signature score comprising the 8 marker genes as disclosed in independent claim 1 has neither been suggested nor it is obvious in view of the prior art. It seems that the application provides data showing that high expression of the gene signature was detected in healthy subjects dosed with glucocorticoids and that expression of the signature in blood from patients with Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) correlated with glucocorticoid-mediated pharmacodynamic effects. Figures 6A and 6B shows the validation results of the 8-gene glucocorticoid signature. Therefore, independent claim 1 seems to solve the problem. Mutatis mutandis applies to independent claims 10 and 11 relating to RA and SLE respectively.

Inventive step for independent claim 2 comprising said 8-gene signature and additionally 10 further genes as disclosed in said claim, can be also acknowledged since it is plausible that said enlarged signature generates the technical effect of monitoring response to glucocorticoid. Inventive step for the dependent claims cannot be acknowledged due to to the dependency wording.

With respect to independent claims 3 and 4, the application does not provide any technical data and/or information which supports that narrowing down the signature score to 6 specific genes or to 3 specific genes would enable the monitoring of response to glucocorticoids. Therefore, the problem has not shown to have been solved and thus no inventive step for claims 3 and 4 can be acknowledged.

Re Item VIII

Support, Article 6 PCT.

2 Article 6 PCT requires that the matter for which protection is south must be defined in the claims in a clear an concise manner and that the claims must be supported in the description. This is the case for claims 3 and 4 (see above). Therefore, the present application does not fulfill the requirements of Article 6 PCT.

3 Remarks:

3.1 Claims comprising the expressions: "drawing blood from the person..." and "administering a treatment (glucocorticoid) to the individual...", relate to subject-matter considered by the present Authority to be covered by the provisions of Rule 39.1(iv) and Rule 67.1 (iv) PCT. The patentability depend upon the formulation of the claims, thus the EPO does not recognize as patentable claims directed to surgical and therapeutic treatment of individuals, this shall be taken into consideration when entering the Regional Phase. This applies to all independent claims.

3.2 D5 corresponds to the scientific publication of the inventors of present application. This document was published on-line on the 13-03-2018. The priority of the application was not available at the time of issuing the present opinion. If the priority of the application enters the Regional Phase and the priority would not be valid, D5 would be considered novelty destroying for the set of claims.