PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant’s or agent’s file reference
PP-B1767

FOR FURTHER ACTION
International application No. PCT/KR2015/007627
International filing date (day/month/year) 22 July 2015 (22.07.2015)
Priority date (day/month/year) 22 July 2014 (22.07.2014)

International Patent Classification (8th edition unless older edition indicated)
See relevant information in Form PCT/ISA/237

Applicant
ORUM THERAPEUTICS INC.

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.
   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:
   - [x] Box No. I  Basis of the report
   - □ Box No. II  Priority
   - [x] Box No. III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - □ Box No. IV  Lack of unity of invention
   - [x] Box No. V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - □ Box No. VI  Certain documents cited
   - [x] Box No. VII  Certain defects in the international application
   - □ Box No. VIII  Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

Date of issuance of this report
24 January 2017 (24.01.2017)

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Form PCT/IB/373 (January 2004)
PATENT COOPERATION TREATY

INTERNATIONAL SEARCHING AUTHORITY

To:

PP-B1767

PCT/W2015/007627

International filing date (day/month/year) 22.07.2015
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Date of mailing (day/month/year) 30.09.2015

FOR FURTHER ACTION

See paragraph 2 below

International Patent Classification (IPC) or both national classification and IPC
A61K 39/395 (2006.01)i, C07K 16/32 (2006.01)i, C07K 16/46 (2006.01)i, A61K 47/48 (2006.01)i, C12N 15/13 (2006.01)i, G01N 33/53(2006.01)i, A61P 35/00(2006.01)i

Applicant

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 43bis.1(a)(i) with regard to novelty, inventive step or 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 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 notified the International Bureau under Rule 66.1b(a)(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/KR

Date of completion of this opinion
Authorized officer

Facsimile No.
Telephone No.

Form PCT/ISA/237 (cover sheet) (January 2015)
Box No. 1  Basis of this 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 43bis.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/S:25 text file.
      - ☐ on paper or in the form of an image file.
   b. ☐ furnished together with the international application under PCT Rule 13rer.1(a) for the purposes of international search only in the form of an Annex C/S: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/S:25 text file (Rule 13rer.1(a)).
      - ☐ on paper or in the form of an image file (Rule 13rer.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:
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. ____________________________________________

because:

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

Claims 1–16 and 31–32 pertain to a method for treatment of the human body by therapy (PCT Article 43bis.1(b), 67.1(iv)).

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

Claim 36 refers to a multiple dependent claim, which does not meet the requirement of PCT Rule 6.4(a), and thus claim 36 is not clear.

☐ 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 said claims Nos. 1–16, 31–32, 35–39

☐ 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 13ter.1(a) or (b).

☐ See Supplemental Box for further details.
**Reference is made to the following documents:**


1. **Novelty and Inventive Step**

1.1. Claims 17-19

Document D1, which is considered the closest prior art document to the present international application, discloses an antibody which can specifically bind to (GTP-bound) RAS activated in the intracellular environment and includes heavy chain and light chain...
variable domains (see paragraphs [0233]-[0237] and [0240]-[0244]; and claims 1-16).

Claim 17 differs from document D1 in that claim 17 pertains to a heavy chain variable region inducing an antibody in an intact immunoglobulin form to penetrate into cytoplasm to thereby bind to activated RAS in cytoplasm. Moreover, said different feature would not be obvious to a person skilled in the art. In addition, said different feature is distinct from features in any other documents, and would not be obvious to a person skilled in the art. Thus, claim 17 is novel and involves an inventive step (PCT Article 33(2) and (3)).

Claims 18-19 are dependent on claim 17, and are thus novel and involve an inventive step (PCT Article 33(2) and (3)).

1.2. Claims 20-30
Claim 20 pertains to an antibody including the heavy chain variable region of any one of claims 17 to 19.

Since claim 17 is considered novel and involves an inventive step, claim 20 pertaining to the antibody including the heavy chain variable region is subjected to the same logic. Thus, claim 20 is novel and involves an inventive step (PCT Article 33(2) and (3)).

Claims 21-30 are substantially dependent on claim 20, and are thus novel and involve an inventive step (PCT Article 33(2) and (3)).
1.3. Claims 33-34

Document D1, which is considered the closest prior art document to the present international application, discloses a method for screening an antibody which can specifically bind to (GTP-bound) RAS activated in the intracellular environment and includes a heavy chain variable domain, the method comprising the steps of: (a) screening an antibody which can specifically bind to (GTP-bound) RAS activated in the intracellular environment and includes a heavy chain variable domain; (b) binding the screened antibody to activated (GTP-bound) RAS immobilized on a chip; and (c) measuring and analyzing binding affinity of the antibody to the activated (GTP-bound) RAS (see paragraphs [0233]-[0237] and [0240]-[0244]; and claims 1-16).

Claim 33 differs from document D1 in that claim 33 pertains to screening of a heavy chain variable region after expressing a library of heavy chain variable regions. However, said different feature could be easily conceived of by considering that the antibody which binds to GTP-bound RAS is screened after expressing the antibody library disclosed in document D1 and the screened antibody only includes heavy chain variable domain type (see paragraphs [0234]-[0237] and [0242]-[0244]; and claims 1-2). Moreover, the effect obtained therefrom is considered sufficiently predictable and obvious. Thus, claim 33 is novel, but does not involve an inventive step (PCT Article 33(2) and (3)).

Claim 34, which refers to claim 3, delimits a particular heavy chain variable region to have a mutation. This
<table>
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<th>Box No. V</th>
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<td>feature is not disclosed in documents D1 to D5. In addition, said different feature would not be obvious to a person skilled in the art from documents D1 to D5 individually or in combination thereof. Thus, claim 34 is novel and involves an inventive step (PCT Article 33(2) and (3)).</td>
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2. **Industrial Applicability**

The invention as set forth in claims 17-30 and 33-34 is industrially applicable (PCT Article 33(4)).
Since a multiple dependent claim cannot serve as a basis for any other multiple dependent claims, claims 35, and 37-39 do not satisfy the requirements of PCT Rule 6.4(a).