

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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.
PCT/US2019/049748

International filing date (day/month/year)
05.09.2019

Priority date (day/month/year)
07.09.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61P35/00

Applicant
PFIZER INC.

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 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 notified the International Bureau under Rule 66.1bis(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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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 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/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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:

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-12, 14-17, 19-47</u>
	No: Claims	<u>13, 18</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-47</u>
Industrial applicability (IA)	Yes: Claims	<u>1-47</u>
	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

Summary

The application relates to antibodies (also humanized) to $\alpha\beta 8$ integrin.

Cited documents

Reference is made to the following documents:

- D1 EP 2 744 823 A2 (UNIV CALIFORNIA [US]) 25 June 2014 (2014-06-25)
- D2 WO 2014/165524 A2 (UNIV CALIFORNIA [US]) 9 October 2014
(2014-10-09)
- D3 WO 2018/064478 A1 (UNIV CALIFORNIA [US]) 5 April 2018 (2018-04-05)
- D4 WO 2015/195835 A2 (UNIV CALIFORNIA [US]; MEDIMMUNE LLC [US];
MEDIMMUNE LTD [GB]) 23 December 2015 (2015-12-23)
- D5 Julie Stockis ET AL: "Blocking immunosuppression by human Tregs in vivo
with antibodies targeting integrin $[\alpha]V[\beta]8$ ", Proceedings of the
National Academy of Sciences, vol. 114, no. 47, 6 November 2017
(2017-11-06), pages E10161-E10168, XP055481957, ISSN: 0027-8424,
DOI: 10.1073/pnas.1710680114
- D6 WO 2011/020529 A2 (MERCK PATENT GMBH [DE]; GOODMAN SIMON
[DE] ET AL.) 24 February 2011 (2011-02-24)
- D7 Olivier Leger: "Humanization of Antibodies", 12 July 2012 (2012-07-12),
XP055032589, Retrieved from the Internet: URL:[http://www.icpress.co.uk/
etextbook/p743/p743_chap01.pdf](http://www.icpress.co.uk/etextbook/p743/p743_chap01.pdf) [retrieved on 2012-07-12]
- D8 Yaghoub Safdari ET AL: "Antibody humanization methods - a review and
update", BIOTECHNOLOGY AND GENETIC ENGINEERING REVIEWS,
vol. 29, no. 2, 1 October 2013 (2013-10-01), pages 175-186,
XP055250530, GB ISSN: 0264-8725, DOI:
10.1080/02648725.2013.801235

- D9 XINHUA WANG ET AL: "IgG Fc engineering to modulate antibody effector functions", PROTEIN & CELL, vol. 9, no. 1, 6 October 2017 (2017-10-06), pages 63-73, XP055457296, Beijing, CN ISSN: 1674-800X, DOI: 10.1007/s13238-017-0473-8
- D10 Kristian M. Hargadon ET AL: "Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors", INTERNATIONAL IMMUNOPHARMACOLOGY, vol. 62, 1 September 2018 (2018-09-01), pages 29-39, XP055637409, NL : 1567-5769, DOI: 10.1016/j.intimp.2018.06.001

Re Item V

Novelty, inventive step and industrial applicability

- 1 D1 discloses a humanized antibody specific for $\alpha\beta 8$ integrin which shows increased affinity *in vitro* and stronger efficacy in inhibiting $\alpha\beta 8$ -mediated activation of TGF- β in cultured cells, and which has an effective dose *in vitro* in the picomolar range (see for instance pages 12-13). Also disclosed are pharmaceutical compositions comprising said antibodies (pages 20-21), along with their use in the treatment of cancer (page 23).

D2 discloses murine antibodies specific for human $\alpha\beta 8$ integrin (pages 18-22), which block adhesion to TGF β 1 LAP, cross react with murine $\alpha\beta 8$, and block TGF β activation (page 26). Antibody ADWA11 is identified as the most potent antibody, with an apparent IC₅₀ for inhibiting TGF β activation of less than 5 nM (page 26). Pharmaceutical compositions comprising these antibodies are also provided (page 25).

D3 discloses antibodies that specifically bind $\alpha\beta 8$ and block binding of TGF β peptide to $\alpha\beta 8$ (pages 46-53), which can be humanized (pages 66-67). Use of the antibodies (alone or combined with other pharmacological agents) to treat cancer, such as adenocarcinoma, squamous carcinomas and breast carcinoma (page 69) and in diagnostics (pages 73-77) is also shown.

D4 discloses antibodies (also humanized, page 21) that specifically bind $\alpha\beta 8$ such that the binding inhibits the release of active mature TGF β peptide but does not significantly inhibit adhesion of latent TGF β to $\alpha\beta 8$ on a $\alpha\beta 8$ -expressing cell (pages 17-18).

D5 discloses antibodies directed to the extracellular domain of $\alpha\beta 8$ (pages 8 and 15-16) and their use in detection (example 7).

D6 discloses antibodies to the $\beta 8$ subunit of $\alpha \nu \beta 8$ that are able to block active TGF $\beta 1$ production (page E10163 and figure 3A).

None of these documents discloses antibodies comprising the sequences recited in claims 1-12. These claims can therefore be considered novel (**Article 33(2) PCT**).

This consideration, however, does not apply to claims 13 and 18. The antibody of claim 4 is a humanized versions of antibody ADWA11, which was disclosed in D2 (page 29). It is certainly expected that ADWA11 will compete with its humanized variants for the same epitope, and for this reason, this antibody falls within the scope of claims 13 and 18.

2 The present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of claims 1-12, 14-17 and 19-47 does not involve an inventive step in the sense of **Article 33(3) PCT**.

2.1 D1 is regarded as being the closest prior art to the subject-matter of claims 1-12, 14-17 and 19-47, and discloses a humanized antibody specific for $\alpha \nu \beta 8$ integrin (see above).

The subject-matter of claims 1-12 therefore differs from this known D1 in that the claimed antibodies comprise certain sequences. There is no apparent technical effect linked to said differences, however.

The problem to be solved by the present invention may therefore be regarded as the provision of alternative anti- $\alpha \nu \beta 8$ integrin antibodies.

The solution proposed in claims 1-12 of the present application cannot be considered as involving an inventive step (**Article 33(3) PCT**) for the following reasons. Given the fact that methods to obtain monoclonal antibodies, directed against every well known and defined antigen (such as $\alpha \nu \beta 8$) and to screen said antibodies in order to select those presenting specific characteristics (such as high binding affinity or high neutralizing activity) are considered routine in the art, the subject-matter of claims 1-12 cannot be considered inventive. In the present case, the skilled person would consider obvious producing further anti- $\alpha \nu \beta 8$ monoclonal antibodies to solve the problem posed and to do so, said skilled person would apply any of the standard methods. An inventive step could only be acknowledged if the antibodies would show unexpected properties or if it was unexpected that such antibodies could be produced at all, which does not seem to be the case for the antibodies claimed.

Regarding the humanized antibodies present in said claims, the following is noted. Given the fact that there are numerous techniques in the art to obtain humanized antibodies (see D7 and D8), the provision of humanized antibodies to $\alpha\text{v}\beta 8$, devoid of any unexpected properties, cannot be considered inventive either.

- 2.2 The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding independent claims 19, 21, 27, 28, 30-32, 37-40 and 42-44, directed to pharmaceutical compositions comprising the non-inventive antibodies of previous claims, to nucleic acids encoding said antibodies, to vectors comprising said nucleic acids and host cells comprising said vectors, to methods of producing said antibodies using said host cells and to the use of said non-inventive antibodies in therapy and diagnosis, which therefore are also considered not inventive (**Article 33(3) PCT**).
- 2.3 Dependent claims 14-17, 20, 22-26, 29, 33-36, 41 and 45-47 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the **PCT** in respect of inventive step, see documents D1-D9 and the corresponding passages cited in the search report. In particular, regarding claim 14, the mutations to IgG1 Fc region were widely known to affect antibody effector functions, see D9, for instance table 1; see D1, §111, for claims 15-17; see point 2.1 above for claims 20 and 22-26; D1, §115 for claim 29; D3, page 72 for claim 33, 34 and 41; D1, §11 and §65, for claims 36, 45 and 46; finally, regarding claims 35 and 47, the skilled person would consider obvious combining the non-inventive antibodies with well known anti-cancer treatments such as checkpoint inhibitors (see D10, table 1).
- 3 Claims 31-37 and 39-47 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 39.1(iv)/67.1(iv) PCT**.

The patentability can be dependent upon the formulation of the claims. The **EPO**, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 31-37 and 39-47 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VIII

The application does not meet the requirements of **Article 6 PCT**, because claims 13 and 29 are not clear.

Claim 13 refers to the murine antibody ADWA11. The term "ADWA11" is an arbitrary denomination which has no precise meaning, thereby rendering the definition of the subject-matter of this claim unclear (**Article 6 PCT**).

Furthermore, claim 13 does not meet the requirements of **Article 6 PCT** because the matter for which protection is sought is not clearly defined. This claim attempts to define the subject-matter in terms of the result to be achieved (i.e.: having at least one of a certain list of properties), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

Claim 29 refers to the host cell of claim 27. Claim 27, however, is directed to a vector. This inconsistency leads to a lack of clarity.

Additionally, although claims 1, 6-9, 11-13 and 18 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of **Article 6 PCT**.