

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2020/060663

International filing date (day/month/year)
16.11.2020

Priority date (day/month/year)
22.11.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61P25/28

Applicant
ELI LILLY AND 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 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

Authorized Officer

Pérez-Mato, Isabel

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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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2020/060663

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	<u>1-20</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-20</u>
Industrial applicability (IA)	Yes: Claims	<u>1-20</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Summary

The application relates to anti-TREM2 antibodies and their use to treat neurodegenerative disorders.

Cited documents

Reference is made to the following documents:

- D1 WO 2018/015573 A2 (DEUTSCHES ZENTRUM FÜR NEURODEGENERATIVE ERKRANKUNGEN E V (DZNE) [DE] E) 25 January 2018 (2018-01-25)
- D2 WO 2017/062672 A2 (ALECTOR LLC [US]) 13 April 2017 (2017-04-13)
- D3 WO 2019/055841 A1 (DENALI THERAPEUTICS INC [US]) 21 March 2019 (2019-03-21)
- D4 WO 2019/118513 A1 (PIONYR IMMUNOTHERAPEUTICS INC [US]) 20 June 2019 (2019-06-20)
- D5 GRATUZE MAUD ET AL: "New insights into the role of TREM2 in Alzheimer's disease", MOLECULAR NEURODEGENERATION, vol. 13, no. 1, 1 December 2018 (2018-12-01), XP055775843, DOI: 10.1186/s13024-018-0298-9 Retrieved from the Internet: URL:<http://link.springer.com/content/pdf/10.1186/s13024-018-0298-9.pdf>
- D6 SABER MAHA ET AL: "Triggering Receptor Expressed on Myeloid Cells 2 Deficiency Alters Acute Macrophage Distribution and Improves Recovery after Traumatic Brain Injury", JOURNAL OF NEUROTRAUMA., vol. 34, no. 2, 15 January 2017 (2017-01-15), pages 423-435, XP055775826, US ISSN: 0897-7151, DOI: 10.1089/neu.2016.4401 Retrieved from the Internet: URL:<https://www.liebertpub.com/doi/pdf/10.1089/neu.2016.4401> cited in the application

Re Item V

Novelty, inventive step and industrial applicability

- 1 D1 discloses antibodies that bind TREM2 and inhibit its cleavage (pages 51-54). By inhibiting TREM2 cleavage, the antibody preserves and/or stimulates activity of microglia cells, and/or the activity of other TREM2 expressing cells, wherein said activity may be phagocytosis activity, migration, calcium signaling, Syk activation, and/or proliferation. TREM2 is also regulating the inflammatory cytokine production and survival of microglia cells (page 10).

D2 discloses anti-TREM2 antibodies, some of which are antagonistic antibodies: 10A9 and 10C1 (see page 270) and 8F8, which is shown to be a blocking antibody in vivo (page 278). Use of these antibodies to treat neurodegenerative disorders is also disclosed (pages 7-8).

D3 discloses anti-TREM2 antibodies and their use in treating neurodegenerative disorders (pages 21-23). Antibody 21D11 is antagonistic (page 165) and has a K_d of 5.25×10^{-10} M (page 144).

D4 discloses anti-TREM2 antibodies and their use in methods and compositions for enhancing an immune response and/or for the treatment of an immune-related condition in an individual, e.g., cancer, comprising killing, disabling, or depleting non-stimulatory myeloid cells (see pages 34-39 and 66-67).

None of these documents disclose an antibody comprising the sequences recited in claim 1. This claim, along with claims 2-20, can therefore be considered novel in the sense of **Article 33(2) PCT**.

- 2 The present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of claims 1-20 does not involve an inventive step in the sense of **Article 33(3) PCT**.

- 2.1 Any of D1-D4, for instance D1, can be regarded as being the closest prior art to the subject-matter of claims 1-20, and discloses antibodies that bind to TREM2 and their use to treat neurodegenerative disorders (see above).

The subject-matter of claims 1-3 therefore differs from this known D1 in that the antibody comprises different sequences. There is no apparent technical effect derived from said difference, however, due to the fact that

The problem to be solved by the present invention may therefore be regarded as the provision of alternative anti-TREM2 inhibiting antibodies for treating neurodegenerative disorders.

The solution proposed in claims 1-3 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 TREM2) and to screen said antibodies in order to select those presenting specific characteristics (such as antagonistic activity) are considered routine in the art, the subject-matter of claims 1-3 cannot be considered inventive. In the present case, the skilled person would consider obvious producing further anti-TREM2 monoclonal antibodies to solve the problem posed and to do so, said skilled person would apply any of the standard methods (see D1, pages 34-36, D2, pages 165-175, D3, pages 103-106 and D4, pages 49-52). 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.

- 2.2 The same reasoning applies, *mutatis mutandis*, to the subject-matter of the corresponding independent claims 4, 5, 7, 8, 12, 13, 16 and 17, directed to a pharmaceutical composition comprising said not inventive antibodies and to the use of said pharmaceutical compositions or antibodies in therapy, which therefore are also considered not inventive.
- 2.3 Dependent claims 6, 9-11, 14, 15 and 18-20 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-D4 and the corresponding passages cited in the search report. In particular, see D1 page and D2, page 43 and D3, pages 21-22, relevant for claims 6, 9-11, 14, 15 and 18-20.
- 3 Claims 5-20 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 5-20 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority (ISA) will establish an international search report (ISR) accompanied by a written opinion of the International Searching Authority (WO/ISA). The WO/ISA may be responded to by

- filing informal comments with the International Bureau of WIPO (IB) (where no demand for international preliminary examination (demand) is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a demand is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the WO/ISA (where a demand is actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the ISR and WO/ISA, the applicant may file informal comments on the WO/ISA, directly with the IB (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability (IPRP) at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file amended claims under Art. 19 PCT, directly with the IB by the later of the following dates:

- 2 months from the date of mailing of the ISR and the WO/ISA
- 16 months from the priority date

However, any such amendment received by the IB after the expiration of the applicable time limit shall be considered to have been received on time by the IB, if it reaches it before the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be accompanied by a letter identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a demand is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report (IPER), see Rule 70.2(c-bis) PCT.

**Filing a demand
for international
preliminary
examination**

In principle, the **WO/ISA** will be considered to be the written opinion of the International Preliminary Examining Authority (IPEA). Where the **WO/ISA** issued by the EPO as ISA gives a positive opinion on the international application and the invention to which it relates, filing a **demand** with the EPO as IPEA would normally be unnecessary, since a positive IPRP would anyway be established by the IB based on the **WO/ISA** (see also further below).

If the applicant wishes to file a **demand** (for example, to allow him to argue his case in international preliminary examination with regard to objections raised in a negative **WO/ISA** before the IPEA issues an IPER), this must be done before expiration of **3 months after the date of mailing of the ISR and WO/ISA or 22 months after priority date**, whichever expires later (Rule 54*bis* PCT). Amendments under Art. 34 PCT can be filed with the IPEA, normally at the same time as filing the demand (Rule 66.1(b) PCT) or within the time limit set for reply to any written opinion issued during international preliminary examination by the IPEA.

If a **demand** is filed at the EPO as IPEA and no comments/amendments have been received by the time the EPO starts drawing up the IPER (Rule 66.4*bis* PCT), the **WO/ISA** will be transformed by the IPEA into an IPER (also called the IPRP (Chapter II) which would merely reflect the content of the **WO/ISA** (OJ 10/2011, 532). The **demand** can still be withdrawn (Art. 37 PCT).

Please also note that, when filing amendments under Art. 34 PCT, such amendments shall be accompanied by a letter which identifies the amendments made and also the basis for the amendments in the application as originally filed (Rule 66.8(a) PCT). Failure to comply with this requirement may result in the amendments being ignored in the IPER (IPRP (Chapter II)), see Rule 70.2(c-*bis*) PCT.

**Filing a request
for supplementary
international
search**

The applicant may, with the IB, file a request for **supplementary international search** under Rule 45*bis*.1 PCT. The present **ISR** and **WO/ISA** may also be taken into account in the execution of that supplementary international search, provided that these are available to the Authority charged with this task before it starts the supplementary search (Rule 45*bis*.5 PCT).

This kind of request **cannot be filed specifying the ISA who did the international search**.

More information on this topic can be found in the **PCT Applicant's Guide**, Chapter 8 (<http://www.wipo.int/pct/en/guide/ip08.html>).

**End of the
international
phase**

Where no **demand** is filed, at the end of the international phase, the IB will transform the **WO/ISA** into the IPRP (PCT Chapter I) (Rule 44*bis* PCT), which will then be transmitted together with possible informal comments to the designated Offices. Where a **demand** is filed, the **WO/ISA** is not transformed into an IPRP (Chapter I) by the IB, but rather the IPEA will establish an IPER, (the IPER is the same as the IPRP (PCT Chapter II), see Rule 70.15 PCT).

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