

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

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/US2020/044462

International filing date (day/month/year)
31.07.2020

Priority date (day/month/year)
31.07.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/64 C07K16/00

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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Surdej, Patrick

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 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>1-47</u>
	No: Claims	
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

Reference is made to the following documents:

- D1 WO 2017/100540 A2 (CALIFORNIA INST BIOMEDICAL RES [US]) 15 June 2017 (2017-06-15)
- D2 WO 2018/138170 A1 (MEDIMMUNE LLC [US]; MEDIMMUNE LTD [GB]) 2 August 2018 (2018-08-02)

Introduction

The application discloses a compound comprising a structure of: VHH-L1-A-L2-B, VHH-L1-B-L2-A, A-L2-B-L1-VHH, or B-L2-A-L1-VHH, wherein A is a relaxin A chain, wherein B is a relaxin B chain, wherein L1 is a first linker, wherein L2 is a second linker, VHH is a single-domain heavy chain variable region antibody and uses thereof.

Item V

Reasoned statement Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty and inventive step (Art. 33(1)-(3) PCT)

- 1 The subject-matter of claims 1-47 is new but not inventive in view of D1.

D1 discloses a compound comprising a structure of: VHH-L1-A-L2-B, VHH-L1-B-L2-A, A-L2-B-L1-VHH, or B-L2-A-L1-VHH, wherein A is a relaxin A chain, wherein B is a relaxin B chain, wherein L1 is a first linker, wherein L2 is a second linker, VHH is a single-domain heavy chain variable region antibody (e.g. paragraphs [0005] - [0007], [0013] - [0025], [0028], [0037] - [0038], [0049], [0188] - [0211]; examples 1-12; claims 1-17).

The difference between the application and the prior art document is the nature of the VHH.

The effect of the invention of the present application and the invention of the document is an improved stability of relaxin analog.

In view of the prior art document D1, considered to be the closest prior art, the technical problem can be defined as an alternative way to improve stability of a relaxin analog.

The solution of the application is the compound of claim 1 with sequences having 90% sequence similarity with sequence SEQ ID NOS: 10, 11, 12 and 13.

The sequences SEQ ID NOS: 10, 11, 12 and 13 in a relaxin analog do not appear to confer any unexpected effect over the prior art. The molecules disclosed in the present application appear therefore to be only mere variants of the molecules of the prior art. Likewise, the sequences SEQ ID NOS: 10, 11, 12 and 13 as such and sequences SEQ ID NOS: 45-66 are mere variants of the VHH of the prior art.

A compound comprising a structure of: VHH-L1-A-L2-B, VHH-L1-B-L2-A, A-L2-B-L1-VHH, or B-L2-A-L1-VHH, wherein A is a relaxin A chain, wherein B is a relaxin B chain, wherein L1 is a first linker, wherein L2 is a second linker, VHH is a single-domain heavy chain variable region antibody is known in the prior art. The variations disclosed in the present application are well within the reach of the skilled person without the exercise of an inventive step.

Therefore an inventive step cannot be acknowledged for the subject-matter of claims 1-47.

- 2 For the assessment of the present claims 18 and 21 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VIII

Certain observations on the international application

- 3 With the term "similarity", the subject-matter of claims 1, 14-16, 22-47 lacks clarity in the sense of Article 6 PCT since the percentage of identity of the sequence is not known. This deficiency is not overcome by the definition of similarity in the description.
- 4 With "essentially" which is a relative term, the subject-matter of claim 15 lacks clarity in the sense of Article 6 PCT.