

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

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| To:                  |
| see form PCT/ISA/220 |

## PCT

### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

|                                                                         |
|-------------------------------------------------------------------------|
| Date of mailing<br>(day/month/year) see form PCT/ISA/210 (second sheet) |
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| Applicant's or agent's file reference<br>see form PCT/ISA/220 |
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| <b>FOR FURTHER ACTION</b><br>See paragraph 2 below |
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|                                                                                                                                   |                                                          |                                              |
|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------|
| International application No.<br>PCT/EP2019/068570                                                                                | International filing date (day/month/year)<br>10.07.2019 | Priority date (day/month/year)<br>11.07.2018 |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. C07K16/00 C07K16/18 C07K19/00 A61K39/00 |                                                          |                                              |
| Applicant<br>UCB BIOPHARMA SPRL                                                                                                   |                                                          |                                              |

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:<br><br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Date of completion of<br>this opinion<br><br>see form<br>PCT/ISA/210 | Authorized Officer<br><br>Saame, Tina<br><br>Telephone No. +49 89 2399-0 |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------|

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**Box No. I Basis of the opinion**

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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:

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

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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. 7-11(completely); 1, 12-47(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. 7-11(completely); 1, 12-47(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 13ter.1(a) or (b).
- ☐ See Supplemental Box for further details

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**Box No. IV Lack of unity of invention**

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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. 2-6(completely); 1, 12-47(partially)

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**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**

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1. Statement
- |                               |             |                                             |
|-------------------------------|-------------|---------------------------------------------|
| Novelty (N)                   | Yes: Claims | <u>6(completely); 12-47(partially)</u>      |
|                               | No: Claims  | <u>2-5(completely); 1(partially)</u>        |
| Inventive step (IS)           | Yes: Claims |                                             |
|                               | No: Claims  | <u>2-6(completely); 1, 12-47(partially)</u> |
| Industrial applicability (IA) | Yes: Claims | <u>2-6(completely); 1, 12-47(partially)</u> |
|                               | No: Claims  |                                             |
2. Citations and explanations
- see separate sheet**

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**Box No. VIII    Certain observations on the international application**

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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 IV**

**Lack of unity of invention**

- 1 The claimed subject-matter comprises the following two inventions:
  1. claims: 2-6(completely); 1, 12-47(partially)  
An antibody comprising a variable (V) domain and an insert polypeptide, wherein the insert polypeptide is within the framework 3 region of the V domain, wherein the V domain is a VH domain.
  2. claims: 7-11(completely); 1, 12-47(partially)  
An antibody comprising a variable (V) domain and an insert polypeptide, wherein the insert polypeptide is within the framework 3 region of the V domain, wherein the V domain is a VL domain.
- 2 The reasons, for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Article 3(4)(iii) in combination with Rule 13.1 PCT stipulates that the international application shall relate to one invention only or to a group so linked as to form a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed in one and the same international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding 'special technical features', i.e. technical features that define a novel and inventive contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

For assessment of unity, the feature 'polypeptide' is interpreted as a molecule containing two or more amino acids in the molecule joined together by peptide bonds.

Both inventions as set out above solve the technical problem of providing antibodies and antigen binding fragments thereof with inserts in the non-antigen binding sequences of the molecule.

The common matter linking the alternatives within inventions 1 and 2 is the following:

  - an antibody comprising a variable (V) domain and an insert polypeptide, wherein the insert polypeptide is within the framework 3 region of the V domain (same technical feature);

This common matter does not comprise a single general inventive concept, based on same or corresponding special technical features in view of the relevant prior art.

Simon and Rajewsky, 1992 (D1, see below) had already disclosed a functional antibody mutant with an insertion in the framework 3 loop of the VH domain. In particular, a mutant with duplication of amino acids 73-76 in framework 3 of the VH region of the anti-NP antibody B1-8 was disclosed (figure 1), leading to a mutant with an unaltered affinity (table 1). As a conclusion, the FR3 loop is proposed as a target site for antibody engineering, with the FR3 loop being a candidate for several possible insertions (page 233, left to right column).

The technical features of inventions 1 and 2 representing the difference over the non-inventive common matter are the different domains whose framework regions are engineered, i.e. framework 3 of VH (invention 1) versus framework 3 of VL (invention 2).

Each of said domains solves the problem of providing a different location for the framework 3 insertion site. However, frameworks 3 of VH and VL do not share a significant common structural element leading to a common technical effect. Furthermore, VH framework 3 insertions had explicitly been disclosed in D1 (see above) and VL framework 3 insertions had been theoretically discussed therein (page 231, right column). Hence, these differences can not confer a common inventive concept.

As the claims comprise neither the same, nor corresponding special technical features, the technical relationship between the subject matter of the claims required by Rule 13.2 PCT is lacking and the claims are not so linked as to form a single general inventive concept. The application does not fulfil the requirement for unity of invention in the sense of Article 3(4)(iii) in combination with Rule 13.1 PCT.

- 3 The following opinion relates to the invention first mentioned in the claims, i.e. invention 1 as set out above.

### **Re Item V**

#### **Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

##### **1 Subject-matter of application**

The application relates to antibodies having an insert polypeptide in the framework 3 region of the V domain.

## 2 Documents

Reference is made to the following documents:

- D1 SIMON T ET AL: "A FUNCTIONAL ANTIBODY MUTANT WITH AN INSERTION IN THE FRAMEWORK REGION 3 LOOP OF THE V-H DOMAIN IMPLICATIONS FOR ANTIBODY ENGINEERING", PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB,  
vol. 5, no. 3, 1 January 1992 (1992-01-01), pages 229-234,  
XP008083103,  
ISSN: 0269-2139
- D2 DIMITRIS NIKOLOUDIS ET AL: "A complete, multi-level conformational clustering of antibody complementarity-determining regions",  
PEERJ,  
vol. 2, 1 July 2014 (2014-07-01), page e456, XP055622131,  
DOI: 10.7717/peerj.456
- D3 US 2005/266000 A1 (BOND CHRISTOPHER J [US] ET AL) 1  
December 2005 (2005-12-01)

## 3 Novelty (Article 33(2) PCT)

- 3.1 D1 disclosed a functional antibody mutant with an insertion in the framework 3 loop of the VH domain. In particular, a mutant with duplication of amino acids 73-76 in framework 3 of the VH region of the anti-NP antibody B1-8 was disclosed (figure 1), leading to a mutant with an unaltered affinity (table 1). As a conclusion, the FR3 loop is proposed as a target site for antibody engineering, with the FR3 loop being a candidate for several possible insertions (page 233, left to right column).

Since the feature 'polypeptide' is interpreted as a molecule containing two or more amino acids in the molecule joined together by peptide bonds, at least the subject-matter of claims 1-3 lacks novelty over D1.

- 3.2 D2 disclosed two anti-HIV antibodies showing insertions of 3 and 7 residues at heavy chain framework 3 position H74 (page 5). Hence, at least the subject-matter of claims 1-5 lacks novelty over D2.

## 4 Inventive step (Article 33(3) PCT)

- 4.1 The dependent claims do not disclose additional features which are on their own sufficient to establish an inventive step of the claimed subject-matter in view of D1. In particular with respect to claims 4-6, it is noted that D1 already disclosed the region between amino acids 73 and 78 as target site for insertion of additional amino acids (see figure 1).
- 4.2 Concerning claims 21-26 and 31, specifying sequences of acceptor antibodies, it is noted that no particular technical effect is associated to the use of these specific acceptor antibodies, which could not be foreseen. Hence, no inventive contribution can be recognized.
- 4.3 The entire claimed subject-matter furthermore lacks inventive step over document D3, which disclosed that antibody FRH3 (amino acids 71-78) can accommodate diversities comparable to those observed in the CDRs. In the natural human/mouse antibody database, FRH3 exhibited Shannon entropies comparable to that of CDRH1 (paragraph [0319]. Hence, the skilled person looking for a suitable insertion site for heterologous (poly)peptides in antibodies would have considered the FRH3 region based on D3.

**5 Method of treatment**

Claims 45-47 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 45-47 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**

**Certain observations on the international application**

- 1 Reference to specific amino acid positions (claims 4-6) has no meaning in the absence of a definition of a reference sequence or a numbering scheme (Article 6 PCT).
- 2 Claims 38 and 39 define the subject-matter in terms of the result to be achieved, i.e. in terms of the underlying technical problem instead of the solution thereof, thus contravening the requirements of Article 6 PCT.