

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

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(day/month/year) **02 SEP 2020**

Applicant's or agent's file reference
792702000240

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 20/25469

International filing date (day/month/year)

27 March 2020 (27.03.2020)

Priority date (day/month/year)

28 March 2019 (28.03.2019)

International Patent Classification (IPC) or both national classification and IPC

IPC - C07K 16/46; C07K 16/00 (2020.01)

CPC - C07K 16/46; C07K 16/468; C07K 2317/52; C07K 2317/526

Applicant AB STUDIO 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 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/US
Mail Stop PCT, Attn: ISA/US
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P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

30 June 2020

Authorized officer

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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 43*bis*.1(b)).
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 13*ter*.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 13*ter*.1(a)).
- on paper or in the form of an image file (Rule 13*ter*.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

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. 4-43

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. 4-43 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-43 are multiple dependent claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a)

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. 4-43

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

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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-3, drawn to a heteromultimeric protein composition.

Group II: Claim 44, drawn to a method of generating a heteromultimeric protein that specifically binds to a first target and a second target.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I has the special technical feature of a heteromultimeric protein comprising one or more amino acid substitutions relative to wild type, not required by Group II.

Group II has the special technical feature of a method of generating a heteromultimeric protein with specific steps involving amino acid substitutions in one or more amino acid positions in a first or second CH3 domain, not required by Group I.

Group II has the special technical feature of providing a first polypeptide comprising a first binding domain that specifically binds to a first target, and a second polypeptide comprising a second binding domain that specifically binds to a second target, not required by Group I.

Common Technical Features:

Groups I and II share the common technical features of:

1. A heteromultimeric protein comprising a first polypeptide comprising a first heavy chain constant domain 3 (CH3) domain and a second polypeptide comprising a second CH3 domain.
2. the first CH3 domain comprises a substitution relative to a wildtype CH3 domain at amino acid position 354 with a bulky hydrophobic amino acid.

However, said common technical features do not represent a contribution over the prior art and is disclosed by WO 2018/016881 A1 to Ibtentrus Co., Ltd. (hereinafter "Ibtentrus") [Google Korean to English translation provided].

-----continued in Supplemental Box-----

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- all parts.
- the parts relating to claims Nos. 1-3

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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

1. Statement

Novelty (N)	Claims	<u>NONE</u>	YES
	Claims	<u>1-3</u>	NO
Inventive step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-3</u>	NO
Industrial applicability (IA)	Claims	<u>1-3</u>	YES
	Claims	<u>NONE</u>	NO

2. Citations and explanations:

Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by CA 3031082 A1 to Ibenetrus Inc. (hereinafter "Ibenetrus").

As to claim 1, Ibenetrus discloses a heteromultimeric protein comprising a first polypeptide comprising a first heavy chain constant domain 3 (CH3) domain and a second polypeptide comprising a second CH3 domain (abstract; "a bispecific protein with a purity of heterodimers which is prepared by introducing a mutation into a heavy chain and/or a light chain to thus increase a heterodimer formation rate between a heavy chain (CH3 domain or Fc) and a heavy chain (CH3 domain or Fc)"; claim 1: "A bispecific protein for targeting two different kinds of targets, the bispecific protein comprising a first CH3 domain or a first Fc region comprising the first CH3 domain and a second CH3 domain or a second Fc region comprising the second CH3 domain, wherein the first CH3 domain and the second CH3 domain are mutated such that at least one selected from among amino acid pairs forming respective amino acid-amino acid bonds between the first CH3 domain and the second CH3 domain is modified by at least one of the following mutations: ... (3) a mutation in which, of at least one amino acid pair between the CH3 domains, one amino acid is substituted with a large hydrophobic amino acid while the other is substituted with a small hydrophobic amino acid (size mutation), wherein the large amino acid is selected from the group consisting of tryptophan and phenylalanine and the small amino acid is selected from the group consisting of alanine, glycine, and valine"), wherein the first CH3 domain comprises a substitution relative to a wildtype CH3 domain at amino acid position 354 with a bulky hydrophobic amino acid (pg 44 ln 15-24; "selected positions in CH3 domains and mutated amino acids thereat are summarized in Table 3. Each of the mutation pairs was applied two Fc regions (respectively represented by A chain and B chain) derived from different antibodies ... Swapping-associated mutation was carried out to exchange the corresponding amino acids on A chain and B chain with each other. For size-associated mutation, the corresponding amino acids were substituted with W (tryptophan) on A chain and with the small size amino acid A (alanine) on B chain"; pg 44 Table 3: Amino Acid Pair No: 7; Swap: Chain 1: S354Y Chain 2: Y349S or Size: Chain 1: S354W Y349A"), and wherein the amino acid residue numbering is based on EU numbering (pg 33 ln 13-14; "Numbering of amino acid residues within a region is performed according to the EU index described in Kabat et al.").

As to claim 2, Ibenetrus further discloses that the bulky hydrophobic amino acid at amino acid position 354 forms a hydrophobic interaction with an amino acid residue in the second CH3 domain (pg 44 Table 3 Amino Acid Pair No: 7: "Y349").

As to claim 3, Ibenetrus further discloses the second CH3 domain comprises a tyrosine (Y) at amino acid position 349 (pg 44 Table 3 Amino Acid Pair No: 7: "Y349").

Claims 1-3 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box IV-3: Lack of Unity of Invention

As to common technical feature #1, Ibenrus discloses a heteromultimeric protein comprising a first polypeptide comprising a first heavy chain constant domain 3 (CH3) domain and a second polypeptide comprising a second CH3 domain (abstract; "a bispecific protein with a purity of heterodimers which is prepared by introducing a mutation into a heavy chain and/or a light chain to thus increase a heterodimer formation rate between a heavy chain (CH3 domain or Fc) and a heavy chain (CH3 domain or Fc)").

As to common technical feature #2, Ibenrus discloses the first CH3 domain comprises a substitution relative to a wildtype CH3 domain at amino acid position 354 with a bulky hydrophobic amino acid (PDF pg 27 Example 1; "For the associated i mutation by swapping the A chain and the amino acid of the B chain was changed to each other. In the case of associated mutations by size, the A chain is the W (tryptophan), B chain is the size Replaced with a small A (alanine)"; PDF pg 27 Table 3: Amino Acid Pair No: 7; Swap: Chain 1: S354Y Chain 2: Y349S or Size: Chain 1: S354W Y349A).

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I and II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (cont.): Claims 4-43 are multiple dependent claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a).

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