PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2016/078898	25.11.2016	30.11.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61L27/36

Applicant
BIOCOMPATIBILITY INNOVATION SRL

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Cadamuro, Sergio Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2016/078898

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 43*bis*.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 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:

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	7, 9, 10, 12
	No:	Claims	1-6, 8, 11, 13-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

Re Item V

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

Reference is made to the following documents:

D1 WO 2004/047620 A2 (UNIV CLEMSON [US]) 10 June 2004 (2004-06-10)

D2 WO 2007/133479 A2 (COOK INC [US]; MED INST INC [US]; RAGHEB ANTHONY O [US]; RUANE PATRICK) 22 November 2007 (2007-11-22)

1 Article 33(2) PCT

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-6, 8, 11, 13-15 is not new.

D1 discloses (paragraphs 40-45, claim 1)

A method for inactivating xenoantigens in biological tissues that can be used to manufacture bioprosthetic substitutes intended for human clinical use,characterized in that it provides for the following steps:

- providing a solution based on the polyphenolic compounds tannic acid, gallotannins, catechins, flavonoids, for the inactivation of at least part of the xenogeneic epitopes from said tissues;

- incubating the samples to be treated in the solution based on polyphenols in controlled conditions, including a temperature in the range of 20 to 40 °C;

- subjecting the treated tissues to a series of washes.

The subject matter of claims 1-6, 8, 11, 13-15 is therefore not novel over D1.

2 Article 33(3) PCT

The subject matter of claims 1-6, 8, 11, 13-15 is not novel, therefore it does not involve an inventive step in the meaning of Article 33(3) PCT.

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 7, 9-10, 12 does not involve an inventive step.

D1 is regarded as being the prior art closest to the subject-matter of claims 7, 9-10, 12, and discloses a method for inactivating xenoantigens in biological tissues comprising treating the tissue with a compound selected from the polyphenolic compounds tannic acid, gallotannins, catechins, flavonoids (see point 1 above).

The subject-matter of claims 7, 9-10, 12 therefore differs from this known method in that the compound is caffeic acid or hydroxytyrosol and is therefore new.

There is no apparent technical effect linked to the type of phenolic compound used.

The problem to be solved by the present invention may therefore be regarded as providing a method comprising treatment with an alternative phenolic compound.

The solution proposed in claims 7, 9-10, 12 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D1 (paragraphs 40-45, claim 1) and D2 (p.14, tables A-S) disclose that various phenolic compounds can be used to stabilize and reduce antigenicity of collagenous tissues.

The specific compounds of claims 7, 9-10, 12 are regarded as just few of several alternatives that the person skilled in the art could have considered in order to solve the problem posed by the present application. It is noted that each alternative could be regarded as a separate non unitary subject matter.

3 Article 33(4) PCT

The subject matter of claims 1-15 is industrially applicable and therefore meets the criteria of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

The term "derivatives" in claims 1, 6-12 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this terms (Article 6 PCT).

Terms like analogues/derivatives include compounds obtained from another compound by a chemical reaction (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds, wherein hetero-atoms are exchanged by alternative atoms), compounds with numerous different types of side groups etc.

Furthermore, due to the wording "derivatives... are constituted by" in claims 6-12 it is unclear if the derivatives are the specific compounds mentioned in the claims, or compounds obtained by modifying the compounds mentioned in the claim.