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/US2018/050211	10.09.2018	08.09.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/02 A61K35/66

Applicant
EVELO BIOSCIENCES, 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 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 D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Stoyanov, Borislav 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 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. 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:

   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.

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	18, 21-39, 41-75, 80, 82, 86-88, 102, 112, 119, 120, 123, 125, 126, 128-131, 133, 134, 136, 137, 139-146, 148-160
	No:	Claims	1-17, 19, 20, 40, 76-79, 81, 83-85, 89-101, 103-111, 113-118, 121, 122, 124, 127, 132, 135, 138, 147, 161
Inventive step (IS)	Yes:	Claims	119, 120, 123, 125, 126, 128-131, 133, 134, 136, 137, 139-146, 148-160
	No:	Claims	1-118, 121, 122, 124, 127, 132, 135, 138, 147, 161
Industrial applicability (IA)	Yes:	Claims	1-161
	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 EP 2 494 865 A2 (AEON MEDIX INC [KR]) 5 September 2012 (2012-09-05)

D2 WO 03/051379 A1 (HEALTH PROT AGENCY [GB]; FOSTER KEITH ALAN [GB]; GORRINGE ANDREW RICHA) 26 June 2003 (2003-06-26)

D3 GUNNSTEIN NORHEIM ET AL: "An OMV Vaccine Derived from a Capsular Group B Meningococcus with Constitutive FetA Expression: Preclinical Evaluation of Immunogenicity and Toxicity", PLOS ONE, vol. 10, no. 9, 21 September 2015 (2015-09-21), page e0134353, XP055524302, DOI: 10.1371/journal.pone.0134353

D4 MARIA P. CABRAL ET AL: "Design of live attenuated bacterial vaccines based on D-glutamate auxotrophy", NATURE COMMUNICATIONS, vol. 8, 26 May 2017 (2017-05-26), page 15480, XP055524585, DOI: 10.1038/ncomms15480

D5 IAN A. MACDONALDA AND META J. KUEHN: "Stress-Induced Outer Membrane Vesicle Production by Pseudomonas aeruginosa", JOURNAL OF BACTERIOLOGY, vol. 195, no. 13, 1 July 2013 (2013-07-01), pages 2971-2981,

D6 WO 2014/152484 A1 (UNIV MINNESOTA [US]) 25 September 2014 (2014-09-25)

Although claim3 76-115 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Re Item IV

The present application does not comply with the requirements of unity of invention. Rule 13(2) PCT states that "the requirement of unity of the invention is fulfilled only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression

'special technical features' means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art."

Furthermore, "If the common matter of the independent claims is well known and the remaining subject matter of each claim differs from that of the others without there being any unifying novel inventive concept common to all, then clearly there is lack of unity of invention." [PCT International Search and Preliminary Examination Guidelines 10.04].

The presently claimed subject-matter does not fulfil the necessary requirements for unity of invention as outlined above for the following reason:

Having regard to the present application taken as a whole, two underlying technical problems to be solved could be identified:

(I) the provision of a composition for use in medicine ("a pharmaceutical composition");

(II) the provision of modified bacteria having improved ability to secrete EV.

The proposed solution (I) is the use of bacterial material.

In the present claims 1-161 there is no common special technical feature shared by all claims because on one side a composition is claimed that comprises extracellular vesicles (EVs) (claims 1-2, special technical feature (i)), on another side a composition is claimed that comprises bacteria isolated from EVs (claim 9, special technical feature (ii)).

The use of EVs (claim 1), EVs and bacteria (claim 2) or bacteria isolated from EVs (claim 9) to prepare a composition suitable for the use in medicine are well documented in the prior art.

Thus for instance, D1 discloses the use of gut flora-derived EVs for the treatment of a cancer disease.

D2 and D3 disclose the use of OMVs (that is, EVs) as vaccines.

Mixed bacteria and EVs in a composition suitable for the use in medicine is known as yogurt or, if one wishes, as fecal transplant.

Any bacterial culture that has been centrifuged and washed with suitable buffer is novelty destroying for the pharmaceutical composition of claim 9 (see e.g. D4).

The proposed solution (II) is seen in the provision of modified bacteria. However, the subject matter of claims 116-161 is not novel over D5 (e.g. see Abstract).

Therefore, the proposed solutions in their general form which can be seen as two different general inventive concepts solving the two underlying technical problems are not novel. Thus, the present international application no more relates to one single invention, but to at least three groups of inventions (non-unity a priory and a posteriori) formulated bellow on the basis of the material comprised in the pharmaceutical composition, and bacterial modifications,namely:

Invention Group I: A pharmaceutical composition comprising isolated bacterial extracellular vesicles (EVs), methods of producing same and the uses thereof. (claims: 1-8, 10-115(completely); 116-161(partially);

Invention Group II: A pharmaceutical composition comprising bacteria isolated from EVs. (claims: 9(completely); 10-115(partially);

Invention Group III: A method of generating an engineered bacterium comprising introducing into the bacterium a modification that results in the increased production of EVs, or that results the production of EVs with an improved therapeutic property by the bacterium. (claims: 116, 127(completely); 117-126, 128-161(partially);

Re Item V

Novelty

The use of EVs (claim 1), EVs and bacteria (claim 2) or bacteria isolated from EVs (claim 9) to prepare a composition suitable for the use in medicine are well documented in the prior art.

Thus for instance, D1 discloses the use of gut flora-derived EVs for the treatment of a cancer disease (see e.g. pages 2-13, examples 1-11 and 18-22). Therefore, claims 1, 11-17, 19-20, 40, 76-78, 94-101, 106-110, 113-115, 147 and 161 are not novel (Article 33(2) PCT).

D2 and D3 disclose the use of OMVs (that is, EVs) as vaccines (see e.g. D2, page 6, line 3 - page 15, line4 and examples 5-8; D3, page 5/23 - page 9/23, page 11/23 - page 12/23). Therefore, claims 1, 11, 13-15, 76-78,106, 110, 113-115, 147 and 161 are not novel over D2, claims 1, 11, 76-78, 106, 107, and 110 are not novel over D3 (Article 33(2) PCT).

Mixed bacteria and EVs in a composition suitable for the use as medicine is known as yogurt or, if one wishes, as fecal transplant (see e.g. D6, claims 1-44). Therefore, claims 2-8, 10, 11, 13-15, 76, 77, 79, 81, 83-85, 89, 91-94, 103, 108, 111, 113, 161 are not novel (Article 33(2) PCT).

Any bacterial culture that has been centrifuged and washed with suitable buffer is novelty destroying for the pharmaceutical composition of claim 9 (see e.g. D4, page 14, right-hand column, the fourth full paragraph). Therefore, claims 9- 10, 14, 15, 76-77, 90, 92, 95, 98, 106, 107, 109, 110, 113-115 are not novel (Article 33(2) PCT).

The proposed solution (II) is seen in the provision of modified bacteria. However, the subject matter of claims 116-161 is not novel over D5 (see e.g. Abstract) (Article 33(2) PCT).

Inventive step

Claim 12 and claim 9 are contradictory as regards the presence of EVs. Consequently, all claims dependant on claim 11 are unclear too. Claims relating to unclear subject matter cannot be acknowledged to be inventive. Therefore, claims 11-115 do not fulfil the requirement of Article 33(3) PCT.

Re Item VIII

The term "bacteria protein" in claims 5 and 6 is unclear (Article 6 PCT).

The term "bacteria lipids" in claim 8 is unclear (Article 6 PCT).

Therefore, claims 5, 6 and 8 are unclear.

Claim 12 and claim 9 are contradictory as regards the presence of EVs (Article 6 PCCT). Consequently, all claims dependant on claim 11 are unclear (Article 6 PCT).

The subject matter of the present claim 147 is defined as a product-by-process. Such type of claims is unclear because the claimed product has no technical features and cannot be evaluated for novelty. Consequently, claim 161 is unclear and may not be novel too.

Claim 116 lacks clarity (Article 6 PCT) because the claimed method is defined solely by the result to be achieved and no other technically meaningful steps are defined in the claim.