PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference ETB-04225	**FOR FURTHER ACTION** See item 4 below	
International application No. PCT/US2020/037210	International filing date *(day/month/year)* 11 June 2020 (11.06.2020)	Priority date *(day/month/year)* 11 June 2019 (11.06.2019)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant EVELO BIOSCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) with regard to novelty, inventive step or 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 14 December 2021 (14.12.2021)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Xin Wang e-mail pct.team2@wipo.int

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/US2020/037210	11.06.2020	11.06.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K35/74 A61K35/745 A61K35/744 A61P37/00 A61P35/00

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 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	Nurmi, Jussi Telephone No. +31 70 340-0

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. 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	18-22, 66, 67, 74, 75
	No:	Claims	1-17, 23-65, 68-73, 76
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-76
Industrial applicability (IA)	Yes:	Claims	1-76
	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

1 Reference is made to the following documents:

D1 EP 3 403 670 A1 (MD HEALTHCARE INC [KR]) 21 November 2018 (2018-11-21)

D2 WO 2019/051380 A1 (EVELO BIOSCIENCES INC [US]) 14 March 2019 (2019-03-14)

D3 WO 2019/051381 A1 (EVELO BIOSCIENCES INC [US]) 14 March 2019 (2019-03-14)

D4 WO 2019/099482 A1 (EVELO BIOSCIENCES INC [US]) 23 May 2019 (2019-05-23)

D5 WO 2019/099682 A1 (EVELO BIOSCIENCES INC [US]) 23 May 2019 (2019-05-23)

D6 WO 2019/010255 A1 (EVELO BIOSCIENCES INC [US]) 10 January 2019 (2019-01-10)

D7 CHIL-SUNG KANG ET AL: "Extracellular Vesicles Derived from Gut Microbiota, Especially Akkermansia muciniphila, Protect the Progression of Dextran Sulfate Sodium-Induced Colitis", PLOS ONE, vol. 8, no. 10, 1 January 2013 (2013-01-01), pages e76520-e76520, XP055106720, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0076520

2 NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT)

2.1 Concerning claim interpretation it is noted that the expression "*processed microbial extracellular vesicle*" (pmEV), which does not have any specific, established meaning in the art, would normally be interpreted as referring to microbial extracellular vesicles that have been "processed" (such as isolated, purified, mixed with other components etc.) in whichever manner. However, according to the description of the present application at par. 154, in particular on page 25, l. 18-25 the pmEVs are actually not necessarily even microbial extracellular vesicles but are in fact obtained by disrupting whole microbial cells and by separating the microbial membrane components from the intracellular

components at least to some undefined extent. This opinion is therefore established so that in addition to actual extracellular vesicles, basically any preparation of microbial cells that contains an excess of membrane components is regarded as containing "processed microbial extracellular vesicles".

2.2 Document D1 (paragraphs [0011], [0017], [0042]; claims 1-11) discloses:

2.2.1 A pharmaceutical composition comprising isolated processed microbial extracellular vesicles (pmEVs) (see par. 11, claims 1 and 7); and

2.2.2 Use of a pharmaceutical composition of any one of claims 1 to 39 for the preparation of a medicament for the treatment of a disease (par. 42, claim 10); and

2.2.3 A method of treating a subject comprising administering to the subject a pharmaceutical composition of any one of claims 1 to 41 (see claim 10).

2.2.4 A method for preparing a pharmaceutical composition comprising pmEVs in a suspension, the method comprising: combining pmEVs with a pharmaceutically acceptable buffer, thereby preparing the pharmaceutical composition (par. 42); and

2.2.5 A pharmaceutical composition prepared by the method of any one of claims 62 to 67 (par. 42); and

2.2.6 A method for preparing a solid dose form of pharmaceutical composition comprising pmEVs (e.g., a therapeutically effective amount thereof) in a solid dose form, the method comprising:
a) combining pmEVs with a pharmaceutically acceptable excipient; and
b) compressing the combined pmEVs and pharmaceutically acceptable excipient; thereby preparing a solid dose form of a pharmaceutical composition (par. 42); and

2.2.7 A pharmaceutical composition prepared by the method of any one of claims 69 to 75 (see par. 42).

2.3 In view of the above, none of the independent claims 1, 40, 42, 63, 68, 69 or 76 is novel over document D1.

2.4 Documents D2-D6 (see the passages cited in the search report) are all by the same applicant as the present application and in a similar manner to the present application disclose pharmaceutical compositions comprising bacterial membrane components from virtually any bacterium for the treatment of virtually any imaginable disease. To the extent that the present application provides an

enabling disclosure of the subject-matter of independent claims 1, 40, 42, 63, 68, 69 and 76, these claims are therefore also not novel over each of the documents D2-D6.

2.5 Finally, D7 (Abstract; Introduction and Discussion) discloses the use of processed extracellular vesicles from *Akkermansia muciniphila* for the treatment of inflammatory bowel disease. At least claims 1, 40, 42, 63 and 68 are therefore not novel over D7.

2.6 Dependent claims 2-39, 41, 43-62, 64-67, and 70-75 do not appear to contain any additional features which could render these claims novel and/or inventive because the additional features are already known from the prior art or relate to minor modifications that, in the absence of any unexpected technical effects, the skilled person would carry out in order to solve the problem of providing alternative compositions, uses and methods to those known from the documents D1-D7. For example:

claim 2: e.g. D2, claim 3

claims 3-6, 45-48: e.g. D2, par. 81

claims 7, 41, 51-54: e.g. D2, par. 2

claim 8: implicit to all cited documents

claim 9: D2, par. 300

claims 10,11: D2, example 16, par. 332

claims 12, 56, 72: each of D1-D7 comprises pmEVs from at least one strain of bacteria

claims 13, 57, 73: D2, example 24

claims 14-17, 43: e.g. D4, par. 66

claims 18-22, 66, 67, 74, 75: in the absence of an unexpected technical effect obvious alternatives in view of each of the documents D1-D7 when taken alone

claims 23-25: see e.g. D1, par. 42

claims 26-29, 58, 70, 71: see e.g. D4, pars. 97-100, D1 par. 42

claim 30,32, 64, 65: D4, pars. 60,61

claim 31, 59-62: e.g. D4 par. 243

claim 33: D1, par. 42

claim 34: e.g. D2, table 1

claim 35: e.g. D1, claim 2

claims 36-38: D2, table 1

claim 39, 55: D2, claim 15

claim 44: see each of D1-D7; all bacteria are live at some point before the vesicles can be processed

claims 49-50: the result-to-be-achieved formulation of claims 49 and 50 does not allow a distinction to be made with the prior art, hence each of the documents D1-D7 takes away the novelty of this claim

3 REMARKS

3.1 Therapeutic methods

3.1.1 Claims 42 to 62 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.

3.2 Unity of invention

3.2.1 Although no objection to lack of unity (Rule 13.1, 13.2 PCT) is raised at this stage, such an objection may arise later during the prosecution of the application, because the common concept shared by all embodiments of all claims is well known in the art.

Re Item VII

Certain defects in the international application

4 Documents D1-D7 are not cited in the description (Rule 5.1(a)(ii) PCT).

5 The application contains statements of incorporation by reference that violate the requirements of sufficiency of disclosure (Art. 5 PCT).

6 The application contains statements that suggest the scope of protection could extend beyond what is claimed, contrary to the requirements of Art. 6 PCT (see e.g. par. 835).

Re Item VIII

Certain observations on the international application

7 There are a total of 76 claims, many with overlapping scope (see e.g. claims 1, 68 and 76; 40, 63 and 69), and a total of 7 independent claims. The requirements of conciseness (Art. 6 PCT) are not met.

8 The claims contain a multitude of result-to-be-achieved and product-by-process formulations and functional features. These render the claims unclear (Art. 6 PCT).

9 The claims contain features in parentheses. These render the claims unclear (Art. 6 PCT).

10 The scope of the claims covers any pmEVs from any microbial species for the treatment of any disease. There are serious doubts supported by verifiable facts (see e.g. D7, 2nd last par. of the Introduction and the last par. of the Discussion and D1, par. 6) that not all extracellular vesicles from all bacteria are beneficial and there is absolutely no reason to expect that any disease for which experimental support is not provided could be treated with pmEVs. Since the claims are not restricted to a single, specific embodiment for which there is experimental support, it is not plausible that the subject matter of the present claims could be carried out over the whole scope of the claims and the application lacks disclosure (Art. 5 PCT). In this context it is noted that the examples of the application are drafted using "may" language, for which reason it remains unclear whether any of the examples were actually carried out or if they could even be carried out in practice. As it stands, the application seems to describe wishful thinking rather than an actual invention.