

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.
PCT/US2018/050212

International filing date (day/month/year)
10.09.2018

Priority date (day/month/year)
08.09.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/195 C12R1/01 A61K35/74 C12N1/20

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 notified 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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 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:

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 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-8, 17, 18, 22-81, 84-104, 106, 107, 109-115, 117-122, 132-158, 161-171, 179-181</u>
	No: Claims	<u>9-16, 19-21, 82, 83, 105, 108, 116, 123-131, 159, 160, 172-178</u>
Inventive step (IS)	Yes: Claims	<u>1-8, 17, 18, 22-81, 84-104, 106, 107, 109-115, 117-122, 132-158, 161-171, 179-181</u>
	No: Claims	<u>9-16, 19-21, 82, 83, 105, 108, 116, 123-131, 159, 160, 172-178</u>
Industrial applicability (IA)	Yes: Claims	<u>1-181</u>
	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

The present written opinion refers to the following documents cited in the search report:

- D1 WO 2014 196 913 A1 (BJÖRCK INGER [SE]; NILSSON ANNE [SE]; BÄCKHED FREDRIK [SE]; KOVATCHEVA) 11 December 2014 (2014-12-11)
- D2 WO 2011/053653 A2 (MAYO FOUNDATION [US]; MURRAY JOSEPH A [US]; MARIETTA ERIC V [US]; BART) 5 May 2011 (2011-05-05)
- D3 STUBBS S ET AL: "Effect of environmental haemin upon the physiology and biochemistry of *Prevotella intermedia* R78",
LETTERS IN APPLIED MICROBIOLOGY,
vol. 29, no. 1, July 1999 (1999-07), pages 31-36,
ISSN: 0266-8254
- D4 H. BOUALLAGUI ET AL: "Microbial monitoring by molecular tools of a two-phase anaerobic bioreactor treating fruit and vegetable wastes",
BIOTECHNOLOGY LETTERS,
vol. 26, no. 10, 1 May 2004 (2004-05-01), pages 857-862,
Dordrecht
ISSN: 0141-5492, DOI: 10.1023/B:BILE.0000025892.19733.18
- D5 US 5 674 733 A (SALYERS ABIGAIL A [US] ET AL) 7 October 1997 (1997-10-07)

Subject-matter of the application

The application relates to the isolation of extracellular vesicles (EVs) from *Prevotella* bacteria (=Xylanibacter), the use of EVs or bacteria or a combination thereof in pharmaceutical compositions for the treatment of diseases like cancer and diabetes, methods for generating engineered *Prevotella* bacteria resulting in an increased production of EVs, optionally with an improved therapeutic property, methods for increasing EV production in *Prevotella* by culturing the bacteria under stress-inducing growth conditions, optionally in a bioreactor. EVs are shown to activate dendritic cells, PBMC-mediated and NK-mediated tumor cell killing.

RE Item IV

Lack of unity

1. The presently claimed subject-matter would appear to lack unity of invention. The following individual potential inventions have been identified:

1. claims: 1-181

Pharmaceutical compositions comprising Prevotella extracellular vesicles (EVs), Prevotella bacteria or both, methods of generating engineered Prevotella bacteria resulting in increased or modified EV production, methods of culturing Prevotella for improved EV production under stress-inducing conditions, as well as a bioreactor comprising Prevotella bacteria.

1.1. claims: 1-131

Pharmaceutical compositions comprising Prevotella extracellular vesicles (EVs), Prevotella bacteria or both, as well as related subject-matter.

1.2. claims: 132-159

Methods of generating engineered Prevotella bacteria resulting in increased or modified EV production, as well as related subject-matter.

1.3. claims: 160-174

Methods of culturing Prevotella for improved EV production under stress-inducing conditions, as well as related subject-matter.

1.4. claims: 175-181

A bioreactor comprising Prevotella bacteria.

Rule 13 PCT stipulates that where a group of inventions is claimed the requirement of unity shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. "Special" technical features are those features that define a contribution which each of the inventions makes over the prior art.

The technical feature shared by the presently claimed inventions are Prevotella bacteria in general. The existence of Prevotella bacteria was widely known from the prior art (see e.g. D1-D5). Consequently, in the light of the prior art the present application provides solutions for three different problems. The first problem underlying the present application in the light of the prior art can be formulated as the

provision of pharmaceutical compositions comprising Prevotella bacterial EVs, bacteria or both. The second problem may be formulated as methods of improving EV production in Prevotella. The third problem may be formulated as the provision of means for culturing Prevotella. The solution to problem 1 are the compositions according to present subject 1, the solution to problem 2 are the methods according to subjects 2 and 3, while the solution to problem 3 is the bioreactor according to subject 4. Due to the fact that Prevotella bacteria are known and so are methods for the improvement of EV production in Prevotella (see e.g. D3), and no other technical features could be recognized which could be regarded to make a contribution over the art, i.e. to be special technical features, the present solutions are regarded as individual potential inventions.

2. Since no undue additional search efforts were necessary to carry out a search for inventions 2-4, no search fees were requested. The present opinion consequently relates to all four subjects as listed above.

RE Item V

Novelty, Inventive step, and Industrial applicability

1. The subject-matter of claims 9-16, 19-21, 82, 83, 105, 108, 116, and 123-131 would appear to lack novelty over the teaching of cited documents D1 and D2 (**Article 33(2) PCT**).

D1 discloses the treatment of a variety of diseases by administration of a strain of Prevotella as a prebiotic.

D2 discloses use of pharmaceutical preparations comprising Prevotella bacteria for the treatment of autoimmune diseases in humans.

The subject-matter of the above claims therefore does not go beyond the teaching of D1 or D2.

2. The subject-matter of claims 159, 160, and 172-178 would appear to lack novelty over the teaching of cited document D3 (**Article 33(2) PCT**).

D3 discloses culturing Prevotella under limited concentrations of haemin, for which the bacteria have an obligate requirement (= stress). This leads to an increased production of EVs.

In consequence, the subject-matter of the above claims does not go beyond the teaching of D3.

3. The subject-matter of claims 175-178 would appear to lack novelty over the teaching of cited document D4 (**Article 33(2) PCT**).

D4 discloses a bioreactor comprising Prevotella bacteria.

Consequently, the subject-matter of the above claims does not go beyond the teaching of D4.

4. The prior art, however, would appear to be silent about the pharmaceutical use of Prevotella EVs, optionally in combination with Prevotella bacteria.

5. For the assessment of the present independent claims 82, 91, 95-100, 116 as well as claims dependent thereon, and furthermore claims 152-158 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

RE Item VIII

Clarity (Article 6 PCT)

1. The term "about" as used in several of the present claims would appear to be vague and consequently renders the scope of said claims unclear.

2. Claim 6 relates to "some embodiments", a formulation which would appear to render the claimed subject-matter unclear.

3. The formulation of claim 9 "Prevotella bacteria isolated from EVs" would appear to lack clarity. It does not become apparent if the claim is directed to bacteria free of EVs or if the bacteria were isolated from the EVs, the latter option probably not making any sense.

4. The subject-matter of claim 132 and 142 would appear to lack clarity due to the fact that the claimed methods are characterized by unclear desirable features ("a modification") and a result to be achieved ("that results in the (increased) production of EVs (with an improved therapeutic property)").