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A61K 35/745 (2015.01) A61P 35/00 (2006.01)
A61P 1/00 (2006.01) A61P 37/02 (2006.01)
A61P 3/04 (2006.01)

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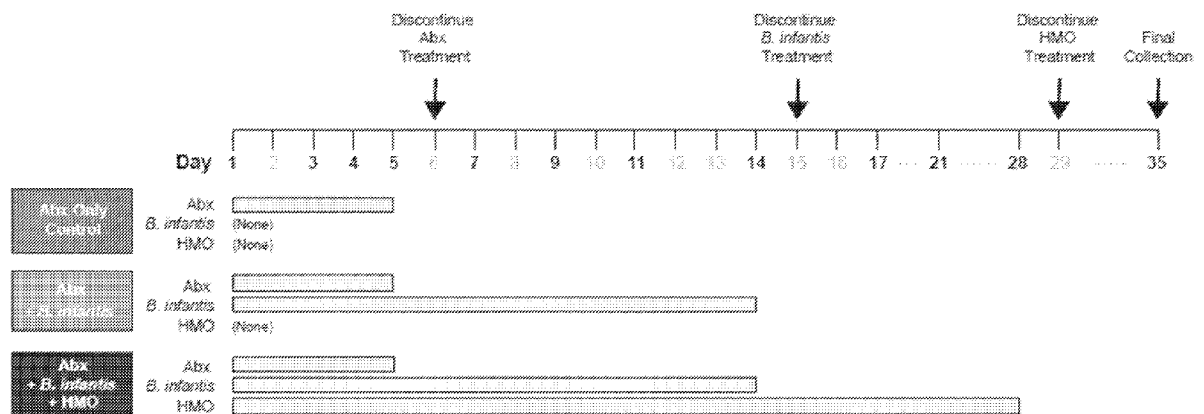
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(54) Title: SYNBIOTIC COMPOSITIONS FOR SHORT CHAIN FATTY ACID PRODUCTION

FIG. 1



(57) Abstract: Provided herein are compositions, methods, strategies, kits, and articles of manufacture that are useful, *inter alia*, in the treatment or prevention of diseases, disorders, or conditions that may be associated with inflammation, infection, allergy, immune dysfunction, or dysbiosis of the intestinal microbiome. In some aspects, the invention provides a synergistic combination of a prebiotic, *e.g.*, a mixture of human milk oligosaccharides, and probiotic strains of bacteria, such as one or more strains capable of internalizing and consuming the prebiotic, *e.g.*, *Bifidobacterium longum* subsp. *infantis*, and one or more strains capable of producing short chain fatty acids such as propionate, *e.g.*, *Veillonella sp.*



TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:

18 July 2024 (18.07.2024)

INTERNATIONAL SEARCH REPORT

International application No PCT/US2023/084290

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K35/742 A61K31/702 A61K35/745 A61P1/00 A61P3/04
 A61P3/10 A61P29/00 A61P35/00 A61P37/02

ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2022/036225 A1 (PROLACTA BIOSCIENCE INC [US]) 17 February 2022 (2022-02-17) cited in the application par. 15, 16, 19, 45, 64, 67, 75, 131, 140, 149, 151, 188, 198 <p style="text-align: center;">----- - / - -</p>	1 - 16, 36 - 52, 72 - 92, 99 17 - 23, 35, 53 - 59, 71

<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
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<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 16 April 2024	Date of mailing of the international search report 12/06/2024
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Seregélyes, Csaba
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/084290

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. forming part of the international application as filed.
 - b. furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)).
 accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/084290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SCHEIMAN JONATHAN ET AL: "Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism", NATURE MEDICINE, NATURE PUBLISHING GROUP US, NEW YORK, vol. 25, no. 7, 24 June 2019 (2019-06-24), pages 1104-1109, XP036928348, ISSN: 1078-8956, DOI: 10.1038/S41591-019-0485-4 [retrieved on 2019-06-24] Abstract</p> <p style="text-align: center;">-----</p>	<p>17-23, 35, 53-59,71</p>
Y	<p>LOUIS PETRA ET AL: "The gut microbiota, bacterial metabolites and colorectal cancer", NATURE REVIEWS MICROBIOLOGY, vol. 12, no. 10, 8 September 2014 (2014-09-08), pages 661-672, XP093040336, GB ISSN: 1740-1526, DOI: 10.1038/nrmicro3344 Retrieved from the Internet: URL:http://www.nature.com/articles/nrmicro3344> p. 4, col. 2, par. 4, 5; p.5 col. 2, par. 2,3; Fig. 1</p> <p style="text-align: center;">-----</p>	<p>17-23, 35, 53-59,71</p>
Y	<p>Liu Yafei ET AL: "Substrate Use Prioritization by a Coculture of Five Species of Gut Bacteria Fed Mixtures of Arabinoxylan, Xyloglucan, [beta]-Glucan, and Pectin", Applied and environmental microbiology, 1 November 2019 (2019-11-01), pages e01905-e01919, XP093142662, United States DOI: 10.1128/AEM.01905-19 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6952225/pdf/AEM.01905-19.pdf [retrieved on 2024-03-19] Abstract; p. 9, par. 5; p. 10, par. 1,2</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/-</p>	<p>17-23, 35, 53-59,71</p>

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/084290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MASHIMA IZUMI ET AL: "Comparative Pan-Genome Analysis of Oral Veillonella Species", MICROORGANISMS, vol. 9, no. 8, 20 August 2021 (2021-08-20), page 1775, XP093142826, ISSN: 2076-2607, DOI: 10.3390/microorganisms9081775 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8400620/pdf/microorganisms-09-01775.pdf> Abstract; p. 8, par. 2</p> <p>-----</p>	<p>17-23, 35, 53-59,71</p>
Y	<p>Anonymous: "Veillonella dispar strain NCTC11831 genome assembly, chromosome: 1 - Nucleotide - NCBI", Veillonella dispar strain NCTC11831 genome assembly, chromosome: 1, 19 December 2018 (2018-12-19), pages 1-5, XP093143061, Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/nucleotide/R134375.1 [retrieved on 2024-03-19] Nucleotides 1684880-1685546</p> <p>-----</p>	<p>35,71</p>
Y	<p>WO 2016/049932 A1 (BGI SHENZHEN CO LTD [CN]; BGI SHENZHEN [CN]) 7 April 2016 (2016-04-07) SEQ ID NO: 23947</p> <p>-----</p>	<p>35,71</p>
Y	<p>WO 2021/108728 A1 (SERES THERAPEUTICS INC [US]) 3 June 2021 (2021-06-03) SEQ ID NO: 84-86, 90, 96</p> <p>-----</p>	<p>35,71</p>
Y	<p>WO 2010/057022 A1 (GENOMATICA INC [US]; BURK MARK J [US] ET AL.) 20 May 2010 (2010-05-20) V. parvula decarboxylases CAA80872 and CAA80876 of Table 20</p> <p>-----</p>	<p>35,71</p>
A	<p>P DELIA ET AL: "Use of probiotics for prevention of radiation-induced diarrhea", WORLD J GASTROENTEROL, vol. 14, no. 6, 14 February 2007 (2007-02-14), pages 912-915, XP055592130, DOI: 10.3748/wjg.v13.i6.912 Abstract</p> <p>-----</p> <p style="text-align: center;">-/-</p>	<p>1-23, 35-59, 71-92,99</p>

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/084290

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SULIGOJ TANJA ET AL: "Effects of Human Milk Oligosaccharides on the Adult Gut Microbiota and Barrier Function", NUTRIENTS, vol. 12, no. 9, 13 September 2020 (2020-09-13), page 2808, XP093142605, CH ISSN: 2072-6643, DOI: 10.3390/nu12092808 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7551690/pdf/nutrients-12-02808.pdf> p. 8, par. 2</p> <p style="text-align: center;">-----</p>	1-23, 35-59, 71-92,99

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/084290

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
17-23, 53-59 (completely); 1-16, 35-52, 71-92, 99 (partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 17-23, 53-59 (completely); 1-16, 35-52, 71-92, 99 (partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one Bifidobacterium capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above, wherein the at least one propionate producing bacterium comprises one or more strains of the genus Veillonella (including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to any of SEQ ID NO: 40-49 and/or an amino acid sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 50 or 51)

2. claims: 24-26, 60-62 (completely); 1-16, 35-52, 71-92, 99 (partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one Bifidobacterium capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above, wherein the at least one propionate producing bacterium comprises one or more strains of the genus Megasphaera

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

(including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 52 or 53)

3. claims: 27, 28, 63, 64(completely); 1-16, 35-52, 71-92, 99(partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one Bifidobacterium capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above, wherein the at least one propionate producing bacterium comprises one or more strains of the genus Anaerotignum (including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 54)

4. claims: 29, 30, 65, 66(completely); 1-16, 35-52, 71-92, 99(partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one Bifidobacterium capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above, wherein the at least one propionate producing bacterium

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

comprises one or more strains of the genus *Bacteroides* (including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 55 or 57)

5. claims: 31, 32, 67, 68(completely); 1-16, 35-52, 71-92, 99(partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one *Bifidobacterium* capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above, wherein the at least one propionate producing bacterium comprises one or more strains of the genus *Coprococcus* (including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 56)

6. claims: 33, 34, 69, 70(completely); 1-16, 35-52, 71-92, 99(partially)

A method of treating or preventing a disease, disorder, or condition associated with one or more of inflammation, immune dysfunction, cancer, allergy, or dysbiosis of the intestinal microbiome in a subject in need thereof, comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
 - ii) at least one *Bifidobacterium* capable of consuming the one or more human milk oligosaccharides; and
 - iii) at least one propionate producing bacterium,
- a method of ameliorating the symptoms of the same disease, disorder, or condition as above, comprising administering to the subject the same prebiotic mixture as above,
 - a method for increasing propionate concentration and/or propionate production in the gut of a subject, comprising administering the same prebiotic mixture as above,
 - a kit, a pharmaceutical composition or an article of manufacture comprising the same prebiotic mixture as above,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

wherein the at least one propionate producing bacterium comprises one or more strains of the genus Merdimmobilis (including the strains comprising a nucleotide sequence with at least 97%, 98%, or 99% sequence identity to SEQ ID NO: 58)

7. claims: 93-98 (completely); 99 (partially)

A method for treating one or more symptoms of acute radiation syndrome in a subject in need thereof, the method comprising administering to the subject a prebiotic mixture, comprising

- i) one or more human milk oligosaccharides,
- ii) at least one Bifidobacterium capable of consuming the one or more human milk oligosaccharides,
- an article of manufacture

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2023/084290

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022036225 A1	17-02-2022	AU 2021325955 A1	02-03-2023
		BR 112023002758 A2	02-05-2023
		CA 3188645 A1	17-02-2022
		CN 116322371 A	23-06-2023
		EP 4195953 A1	21-06-2023
		IL 300573 A	01-04-2023
		JP 2023537608 A	04-09-2023
		KR 20230088680 A	20-06-2023
		US 2024139222 A1	02-05-2024
		WO 2022036225 A1	17-02-2022
WO 2016049932 A1	07-04-2016	CN 107075446 A	18-08-2017
		WO 2016049932 A1	07-04-2016
WO 2021108728 A1	03-06-2021	AU 2020394211 A1	14-07-2022
		BR 112022010411 A2	23-08-2022
		CA 3159711 A1	03-06-2021
		CN 115175575 A	11-10-2022
		EP 4064862 A1	05-10-2022
		JP 2023505098 A	08-02-2023
		KR 20220120573 A	30-08-2022
		US 2023125810 A1	27-04-2023
		WO 2021108728 A1	03-06-2021
		WO 2010057022 A1	20-05-2010
WO 2010057022 A1	20-05-2010		