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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	07/26/2022	11395838	MDAC.P1149US/1001074761	2735

32425 7590 07/02/2022

NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 175 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Jennifer WARGO, Houston, TX;
Vancheswaran GOPALAKRISHNAN, Houston, TX;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, Austin, TX

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

32425 7590 03/18/2022
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Laurie Stellman	(Typed or printed name)
/Laurie Stellman/	(Signature)
June 17, 2022	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	MDAC.PI 149US/1001074761	2735

TITLE OF INVENTION: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	06/20/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARIANI, KADE	1651	424-093300

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Norton Rose Fulbright US LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
Board of Regents, The University of Texas System	Austin, TX

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☒ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-1212/1001074761

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

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NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Laurie Stellman/ Date June 17, 2022

Typed or printed name Laurie Stellman Registration No. 66,817

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000002

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	28-Mar-2019
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Attorney Docket Number:	MDAC.P1149US/1001074761

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	600	600

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt

EFS ID:	45985816
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	MDAC.P1149US/1001074761
Receipt Date:	17-JUN-2022
Filing Date:	28-MAR-2019
Time Stamp:	13:24:18
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$600
RAM confirmation Number	E20226GD24343433
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	MDACP1149US_ISSUE1.pdf	1166823 fef78202b658d546e177d7550c6a296285b00442	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38546 6a27a0d123cfabc18bbd8a36689f9823b9b1673c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1205369		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/337,820	03/28/2019	1651	2070	MDAC.P1149US/1001074761	28	3

CONFIRMATION NO. 2735

CORRECTED FILING RECEIPT

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

OC000000132889972

Date Mailed: 03/25/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jennifer WARGO, Houston, TX;
Vancheswaran GOPALAKRISHNAN, Houston, TX;

Applicant(s)

BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, Austin, TX

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US17/53717 09/27/2017
which claims benefit of 62/400,372 09/27/2016
and claims benefit of 62/508,885 05/19/2017
and claims benefit of 62/557,566 09/12/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/23/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/337,820**
Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000010

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

32425 7590 03/18/2022

NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/18/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	MDAC.P1149US/1001074761	2735

TITLE OF INVENTION: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	06/20/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

32425 7590 03/18/2022
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

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(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TITLE OF INVENTION: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

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EXAMINER	ART UNIT	CLASS-SUBCLASS
ARIANI, KADE	1651	424-093300

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(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

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❑ Applicant asserting small entity status. See 37 CFR 1.27

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Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000012

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	MDAC.P1149US/1001074761	2735

32425 7590 03/18/2022

NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

EXAMINER	
ARIANI, KADE	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/18/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/337,820	Applicant(s) WARGO et al.	
	Examiner KADE ARIANI	Art Unit 1651	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to See Continuation Sheet.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 44,46,49,66,162-164 and 167-178 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/01/2021.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/KADE ARIANI/
Primary Examiner, Art Unit 1651

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Continuation of 1. This communication is responsive to: Request for continued examination (filed on 02/28/2022), and telephonic interview with applicant's representative Laurie Stellman on 03/03/2022.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/28/2022 has been entered.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Examiner-initiated Interview Summary:

Authorization for this examiner's amendment was given in an interview with applicant's reresentative Laurie Stellman on March 03, 2022.

Amendments to the Claims:

The application has been amended as follows:

In claim 44, line 1, delete "treating cancer or", and line 1, replace "tumor growth" with –growth of a skin cancer tumor--.

In claim 46, line 1, replace "cancer is a skin cancer" with –skin cancer is--.

Cancel claim 165.

In claims 167 and 171-173, line 1, replace "165" with –44--.

Rejoinder:

Claims 44, 46, 49, 66, 162-164 and 167-177 are allowable. Claim 178, previously withdrawn from consideration as a result of election by original presentation (see Office cation mailed on 09/27/2021), requires all the limitations of an allowable claim, therefore claim 178 is hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KADE ARIANI whose telephone number is (571)272-6083. The examiner can normally be reached IFP, Monday - Friday, 8:00 AM -4:00 PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Renee Claytor can be reached on (571)272-8394. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KADE ARIANI/
Primary Examiner, Art Unit 1651

Examiner-Initiated Interview Summary	**Application No.** 16/337,820	**Applicant(s)** WARGO et al.		
	Examiner KADE ARIANI	**Art Unit** 1651	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
KADE ARIANI	Primary Examiner	Telephonic
Laurie Stellman	Attorney of Record	

Date of Interview: 03 March 2022

Issues Discussed:

Proposed Amendment(s)

Examiner contacted Applicant's representative Laurie Stellman on 03/02/2022 and discussed proposed claim amendments to claims 44, 46, 167 and 170-173, canceling claim 165, and rejoining claim 178 (see Examiner amendment Communication for details). Applicant's representative Laurie Stellman authorized said Examiner's amendment during a telephonic interview on 03/03/2022.

	/KADE ARIANI/ Primary Examiner, Art Unit 1651

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	**Art Unit**
	KADE ARIANI	1651

CPC							
Symbol						**Type**	**Version**
A61K	/	35	/	741		F	2013-01-01
A61P	/	35	/	02		I	2018-01-01
A61P	/	35	/	00		I	2018-01-01
A61K	/	9	/	0053		I	2013-01-01
A61K	/	45	/	06		I	2013-01-01
C12N	/	1	/	20		I	2013-01-01
C12Q	/	1	/	04		I	2013-01-01
A61K	/	2035	/	115		A	2013-01-01

CPC Combination Sets								
Symbol						**Type**	**Set**	**Ranking**	**Version**
	/		/						

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	19	
/KADE ARIANI/ Primary Examiner, Art Unit 1651	04 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	---

U.S. Patent and Trademark Office — Part of Paper No.: 20220302

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	**Art Unit**
	KADE ARIANI	1651

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K35/741	/	35	/	741
A61P35/00	/	35	/	00
A61K9/00	/	9	/	00
A61K45/06	/	45	/	06
C12N1/20	/	1	/	20
A61K35/00	/	35	/	00
NON-CLAIMED				
A61P35/02	/	35	/	02

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 19	
/KADE ARIANI/ Primary Examiner, Art Unit 1651 (Primary Examiner)	04 March 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure ---

U.S. Patent and Trademark Office

Part of Paper No.: 20220302

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	KADE ARIANI	1651

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	44	10	169	19	178										
2	46	11	170												
3	49	12	171												
4	66	13	172												
5	162	14	173												
6	163	15	174												
7	164	16	175												
8	167	17	176												
9	168	18	177												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/KADE ARIANI/ Primary Examiner, Art Unit 1651	04 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	---

U.S. Patent and Trademark Office — Part of Paper No.: 20220302

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	04/02/2021	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	04/02/2021	KA
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	09/21/2021	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	09/21/2021	KA
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	03/02/2022	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	03/02/2022	KA

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	Art Unit
	KADE ARIANI	1651

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	04/02/2021	KA
EAST (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	04/02/2021	KA
NPL (google and google scholar) (see attached text search results)	04/02/2021	KA
Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	09/21/2021	KA
EAST (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	09/21/2021	KA
STN (BIOSIS, CAPLUS, MEDLINE) (see attached search results)	09/22/2021	KA
Updated Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	03/02/2022	KA
Updated EAST search (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	03/02/2022	KA

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115		03/02/2022	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115		03/02/2022	KA
Updated EAST search (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)		03/02/2022	KA

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S254	3,863	((("THE") near3 ("BOARD") near3 ("OF") near3 ("REGENTS") near3 ("THE") near3 ("UNIVERSITY") near3 ("OF") near3 ("TEXAS") near3 ("SYSTEM"))).AS,AANM.	USPAT	OR	OFF	2022/03/02 10:56
S255	5	((("WARGO") near3 ("Jennifer")) OR (("GOPALAKRISHNAN") near3 ("Vancheswaran"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2022/03/02 10:56
S256	386,264	(A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115).cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S257	2	(A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115).cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S258	30,672	Clostridia and cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S259	13	Clostridia adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S260	82,883	skin adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S261	5,072	S258 and S260	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S262	79,830	Clostridia	US-PGPUB; USPAT;	OR	ON	2022/03/02 10:56

			USOCR; EPO; JPO; DERWENT			
S263	80,918	Clostridia or Mollicutes or Clostridiales or Ruminococcaceae or Faecalibacterium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S264	119,313	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S265	7,287	S263 and S264	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S266	2,498	S260 and S265	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S267	1,487	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S268	42	S266 and S267	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S269	210,312	melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S270	80,918	Clostridia or Mollicutes or Clostridiales or Ruminococcaceae or Faecalibacterium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S271	13,484	S269 and S270	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56

S272	119,313	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S273	5,610	S271 and S272	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S274	0	Clostridia adj melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S275	1,487	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S276	511	melanoma adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S277	0	S275 and S276	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S278	210,312	melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S279	165	S275 and S278	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S280	0	S275 adj S278	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S281	119	S272 and S279	US-PGPUB; USPAT; USOCR; EPO;	OR	ON	2022/03/02 10:56

			JPO; DERWENT			
S282	119,313	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S283	766,123	tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S284	1,047	Ruminococcaceae	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S285	780,024	S282 or S283	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S286	348	S284 and S285	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S287	1,487	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S288	178	S286 and S287	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S289	176	S283 and S288	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S290	128,641	tumor adj growth	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56

S291	74	S284 and S290	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S292	51	S287 and S291	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S293	59	S282 and S290 and S284	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 10:56
S294	1,047	Ruminococcaceae	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:03
S295	0	Ruminococcaceae near cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:21
S296	0	Ruminococcaceae near tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:21
S297	82,883	skin adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:32
S298	86,516	skin near cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:32
S299	86,516	S297 or S298	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:33
S300	69	S294 and S299	US-PGPUB; USPAT; USOCR; EPO;	OR	ON	2022/03/02 11:33

			JPO; DERWENT			
S301	1,379	Ruminococc$5 and tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:36
S302	82,883	skin adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:36
S303	0	Ruminococc$5 adj tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:36
S304	0	Ruminococc$5 near tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:36
S305	211	S301 and S302	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:36
S306	210,312	melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:37
S307	189	S305 and S306	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:37
S308	448	S301 and S306	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:37
S309	113	S294 and S308	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2022/03/02 11:38

3/4/2022 9:43:59 AM
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Examiner: Kade Ariani
Art Unit: 1651 /K.A/

Form PTO-1449 (modified)	Atty. Docket No.: MDAC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name
	A1	2018/0243351	08/30/18	Hlavka
	A2	2020/0129569	04/30/20	Wargo et al.

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B1	WO 2011/008369	01/20/11	WIPO	English
	B2	WO 2015/095241	06/25/15	WIPO	English
	B3	WO 2015/153639	10/08/15	WIPO	English

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	Borody et al. "Fecal microbiota transplantation and emerging applications" *Nat. Rev. Gastroenterol. & Hepatol.* 2011, 9, 88–96.
	C2	Dubin et al., "Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis." *Nat Commun.* 2016, 7:10391, 8 pages.
	C3	Extended European Search Report Issued in Corresponding European Patent Application No. 17857329.1, dated August 7, 2020. (Attorney Docket No. MDAC..P1149EP).
	C4	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2020/013808, mailed June 2, 2020. (Attorney Docket No. MDAC.P1154WO)

103060504.1

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A/

Form PTO-1449 (modified)	Atty. Docket No.: MDAC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C5	Jenq et al., "Intestinal Blautia Is Associated with Reduced Death from Graft-versus-Host Disease" *Biol. Blood Marrow Transplant.* 2015, 21, 1373-1383.
	C6	Litvak et al., "Dysbiotic Proteobacteria expansion: a microbial signature of epithelial dysfunction" *J. Curr. Opin. Microbiol.* 2017, 39, 1-6.
	C7	Moco, et al., "Metabolomics View on Gut Microbiome Modulation by Polyphenol-Rich Foods," Journal of Proteome Research, 11(10): 4781-4790, 2012. . (Attorney Docket No. MDAC.P1149EP).
	C8	Png et al., "Mucolytic Bacteria With Increased Prevalence in IBD Mucosa AugmentIn VitroUtilization of Mucin by Other Bacteria" Am. J. Gastroenterol. 2010, 105, 2420-2428.
	C9	Roh et al., "Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance." *Sci Transl Med.* 2017, 9(379), 24 pages.
	C10	Segata et al., "Metagenomic biomarker discovery and explanation." *Genome Biol.* 2011, 12:R60, 18 pages.
	C11	Wang et al., "Bifidobacterium can mitigate intestinal immunopathology in the context of CTLA-4 blockade." *PNAS* 2018, 115(1), 157-161.
	C12	Wang et al., "P038 Fecal Microbiota Transplant (FMT) For Immuno-checkpoint Inhibitor-Induced Colitis (ICI-C) In A 50 Year Old Female With Bladder Cancer" Gastroenterology 2018, 154(1S), S19-S20.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.A/

103060504.1

EXAMINER: /KADE ARIANI/	DATE CONSIDERED: 03/02/2022

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16/337,820	Filing Date	2019-03-28	Docket Number (if applicable)	MDAC.P1149US/1001074761	Art Unit	1651
First Named Inventor	Jennifer Wargo			Examiner Name	Ariani, KADE		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other Request for Two Months Extension of Time

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 501212

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

X Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Signature of Registered U.S. Patent Practitioner			
Signature	/Laurie Stellman/	Date (YYYY-MM-DD)	2022-02-28
Name	Laurie Stellman	Registration Number	66817

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: 1651 Examiner: Ariani. KADE
Serial No.: 16/337,820	Atty. Dkt. No.: MDAC.P1149US/1001074761
Filed: March 28, 2019	
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

February 28, 2022 /Laurie Stellman/
Date Laurie Stellman

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION DATED SEPTEMBER 27, 2021

Applicant submits this paper in response to the Final Office Action dated September 27, 2021. Since February 27, 2022 fell on a Sunday, the date for response is February 28, 2022, in view of the attached Request for Two Months Extension of Time.

The required fees are being charged to a credit card through the EFS-Web. Should any additional fees be required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper, the Commissioner is authorized to deduct said fees from Norton Rose Fulbright US LLP Account No.: 50-1212/MDAC.P1149US/1001074761.

Amendments to the Claims begin on page 2.

Remarks begin on page 5.

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AMENDMENT TO THE CLAIMS

The listing of claims will replace all prior versions, and listing of claims in the application.

1-43. (Canceled)

44. (Currently Amended) A method of treating cancer or reducing or delaying tumor growth in a subject in need thereof, comprising administering to the subject a composition comprising ~~one or more~~ an isolated or purified population of bacteria belonging to the family Ruminococcaceae.

45. (Canceled)

46. (Previously Presented) The method of claim 44, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47-48. (Canceled)

49. (Previously presented) The method of claim 44, wherein the method further comprises administering an additional anticancer treatment.

50-65. (Canceled)

66. (Previously presented) The method of claim 44, wherein the population of bacteria comprises the bacteria *Faecalibacterium prausnitzii*.

67-161. (Canceled)

162. (Previously presented) The method of claim 49, wherein the anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

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163. (Previously Presented) The method of claim 162, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

164. (Previously presented) The method of claim 49, wherein the anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

165. (Currently Amended) The method of claim 44, wherein the subject has a tumor.

166. (Canceled)

167. (Previously presented) The method of claim 165, wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor.

168. (Previously presented) The method of claim 167, wherein the T lymphocytes are cytotoxic T lymphocytes.

169. (Previously presented) The method of claim 44, wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cells in the systemic circulation or the peripheral blood of the subject.

170. (Previously Presented) The method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

171. (Previously presented) The method of claim 165, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

172. (Previously presented) The method of claim 165, wherein administration of the composition to the subject results in a decrease in RORγT expression in a tumor immune infiltrate.

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173. (Previously presented) The method of claim 165, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or $HLA\text{-}DR^+$ cells in the tumor.

174. (Previously Presented) The method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

175. (Previously Presented) The method of claim 174, wherein the innate effector cells are $CD45^+CD11b^+Ly6G^+$ cells.

176. (Previously Presented) The method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

177. (Previously Presented) The method of claim 176, wherein suppressive myeloid cells are $CD45^+CD11b^+CD11c^+$ cells.

178. (Withdrawn) The method of claim 44, wherein the method further comprises administering an immune checkpoint inhibitor.

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REMARKS

A. Status of the Claims

Upon entry of the foregoing amendment, claims 44, 46, 49, 66, 162-165, 167-178 are pending in the Application. Claim 44 is amended. Support for the amendment to claim 44 can be found throughout the specification and at, inter alia, ¶ [0006] of the Application. No claims are canceled. Claim 178 is withdrawn, but as explained below, Applicant traverses the election of species in the present Office Action. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

B. Election by Original Presentation

Claim 178 was withdrawn in the pending Office Action as a "newly presented *species* of anticancer treatment (see previously presented claims 162 and 163)"). Office Action at page 2 (emphasis added). The Office Action states: "[i]n this case, the newly presented species of anticancer treatment recited in claim 178, has distinct function or effect, has mutually exclusive characteristics, and is not an obvious variant of the previously presented anticancer treatments, and would have been restricted had it been presented previously." *Id.* Applicant respectfully disagrees and ***traverses*** this election.

Applicant respectfully notes that claim 164, which was introduced at the same time as claims 162 and 163, recited "The method of claim 49, wherein the at least one *immune checkpoint inhibitor* and/or at least one additional anticancer treatment…." *See* February 10, 2021 Response to Restriction Requirement Dated November 10, 2020, page 3 (emphasis added). Thus, the subject matter of present claim 178, i.e., an immune checkpoint inhibitor, was earlier presented and was

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not restricted from the species of claims 162 and 163 in the April 9, 2021 Office Action. However, because claim 49 (which depends from claim 44) did not recite an immune checkpoint inhibitor, Applicant removed reference to immune checkpoint inhibitor from claim 164 and moved it to new claim 178 in its July 8, 2021 Amendment and Response to Office Action Dated April 9, 2021, to avoid any antecedent basis issues.

Thus, Applicant traverses the restriction of claim 178 on the basis that it was not "newly presented," as the subject matter was present in claim 164 when the first action on the merits was issued. Because the subject matter of an immune checkpoint inhibitor was not at that time restricted from the subject matter of claims 162 and 163, Applicant understood that no further election of species would be required beyond those identified in the November 10, 2020 Requirement for Unity of Invention and Election of Species. Applicant respectfully requests that the species election be reconsidered and withdrawn. However, out of an abundance of caution, Applicant has marked claim 178 as withdrawn while the Examiner considers Applicant's traversal.

C. Rejections under 35 U.S.C. § 112

Claims 44, 46, 49, 66, 162-165, and 167-177 are rejected as allegedly failing to comply with the written description requirement. The Office alleges the specification does not provide support for "'administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae' for treating cancer or reducing or delaying tumor growth in a subject in need thereof," and requests Applicant to "specifically point out the support for any amendments." Office Action at p. 4. Applicant disagrees.

Solely to advance examination, Applicant has amended claim 44 to recite "…administering to the subject a composition comprising an isolated or purified population of bacteria belonging to

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the family Ruminococcaceae." Applicant's disclosure is not limited to "direct injection of a fecal microbiota sample (FMT) to said tumor," which is an overly-narrow reading of the Application. Office Action at p. 4. Applicant has discovered, *inter alia*, that a population of bacteria belonging to the family Ruminococcaceae is capable of treating cancer or reducing or delaying tumor growth in a subject in need thereof. And the specification amply describes the presently claimed invention in sufficient detail such that one skilled in the art would reasonably conclude that Applicant had possession of the claimed invention as of the effective filing date. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

For example, the specification discloses analysis of the presence of bacteria of the family Ruminococcaceae in responder samples by measuring genes of co-abundance group CAG00327. CAG00327 is shown in the specification at Table 2A (Application, ¶ [00115]) as corresponding to 50 particular SEQ ID NOs corresponding to genes detected, **ensuring broad coverage of detected Ruminococcaceae**. Figure 2F indicates "Ruminococcaceae CAG00327" tested from 25 different fecal samples with two asterisks, indicating strong statistical significance ($p<0.01$). *See* Application ¶ [0043]. Figure 2C shows a taxonomic analysis with numerous Ruminococcaceae (grouped as "m" in the figure) designated as "Responder."

Example 1 further demonstrates not only statistically significant enrichment of the family Ruminococcaceae in responder ("R") samples relative to non-responder ("NR") samples (adjusted and unadjusted p-values < 0.001 in Table 4), but also a **large effect size** (-19.5579), indicating **a strong relationship** between the presence of bacteria of the family Ruminococcaceae and response to immune checkpoint inhibition therapy. *See id.* at ¶¶ [00185], [00186], and Table 4; *see also* ¶ [00207] ("The primary advantage…over traditional statistical tests is that an effect size is produced in addition to a p-value. This allows sorting of results of multiple tests by the magnitude

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of the difference between groups."). In fact, at least four bacteria species from the family Ruminococcaceae showed consistent transfer results and were found to be *only* present in R fecal microbial transplant ("FMT") mice, but *not* present in NR FMT mice, when analyzing administration of two R FMTs (FMT1 and FMT2) in Example 4: "This analysis revealed that OTUs classified as … *Faecalibacterium prausnitzii*,… *Ruminococcus gauvreauii*, *Ruminococcus gnavus*, *Ruminococcus torques*,…were found only in R-FMT mice in both experiments." *Id.* at ¶ [00237].

Moreover, the **abundance** of bacteria of the family Ruminococcaceae is shown to directly correlate with cytotoxic T-cell infiltrate, establishing dosage effect (i.e., that an increase in the **abundance** of bacteria of the family Ruminococcaceae is a driver of tumor killing):

> Pairwise comparisons using Spearman rank correlation were then performed between specific bacterial taxa enriched in the gut microbiome of R and NR and immune markers in the tumor microenvironment, demonstrating **a strong positive correlation between the abundance of Ruminococcaceae**/*Faecalibacterium* **in the gut and cytotoxic T-cell infiltrate in the tumor**, and a strong negative correlation with Bacteroidales (FIG. 4B-C and 19-20). Analysis of systemic immune responses via flow cytometry and cytokine assays revealed that **patients with a high abundance of Ruminococcaceae in the gut had higher levels of effector CD4+ and CD8+ T cells in the systemic circulation with a preserved cytokine response to PD- 1 blockade**, whereas patients with a higher abundance of Bacteroidales in the gut microbiome had higher levels of regulatory T cells (Treg) and myeloid derived suppressor cells (MDSC) in the systemic circulation, with a blunted cytokine response (FIG. 4D and 21-22).

Id. at ¶ [00189] (emphasis added).

And while the data demonstrate that compositions of bacteria of the family Ruminococcaceae in combination with immune checkpoint inhibition therapy treat cancer, the data also demonstrate that compositions of bacteria of the family Ruminococcaceae alone treat cancer.

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For example, as described in Example 4, stool samples from R or NR patients were administered orally to germ-free mice. *Id.* at ¶ [00225]. FMT1 was an FMT sample derived from an R patient. Administration of **FMT1 significantly delayed tumor growth relative to NR** FMT administration, **without co-administration with an immune checkpoint inhibitor**. *Id.* at ¶ [00226]. Relative to NR stool administration, FMT1 resulted in stable transplantation (*id.* at ¶ [00229]) and "a higher percentage of innate effector cells (expressing $CD45^+CD11b^+Ly6G^+$) and lower frequency of suppressive myeloid cells (expressing $CD11b^+CD11c^+$) in the spleen compared to mice in the NR-FMT group" which suggested "that specific subpopulations in the innate immune compartment play a role in the anti-tumoral response elicited by transplantation of a favorable gut microbiota in GF recipient mice." *Id.* at ¶ [00227]. "Indeed, tumors of mice receiving R-FMT had a higher density of $CD45^+$ and $CD8^+$ T cells…." *Id.* at ¶ [00228]. To validate the experiment and control for FMT source, the tumor growth experiment was repeated with a different donor source (FMT3), and the result was the same. *Id.* at ¶¶ [00238]-[00239]. Accordingly, the administered FMTs, which comprise bacteria species from the family Ruminococcaceae, have an anti-cancer effect which is independent of administration with an immune checkpoint inhibitor.

Further, the specification shows that bacteria of the administered FMT compositions are shown to persist and engraft:

> Stability of the microbiome in germ-free mice post engraftment with FMT. 16S sequencing was performed on longitudinal fecal pellets collected from germ-free mice that received stool from a patient who responded to PD- 1 blockade to versus a patient who did not. Examination of phylogenetic taxa at the order level and comparison of baseline pellets with those collected two weeks after FMT completion revealed **successful engraftment**. Moreover, **persistence of the most**

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abundant orders over time suggested that the engrafted microbiome was stable during the whole experiment.

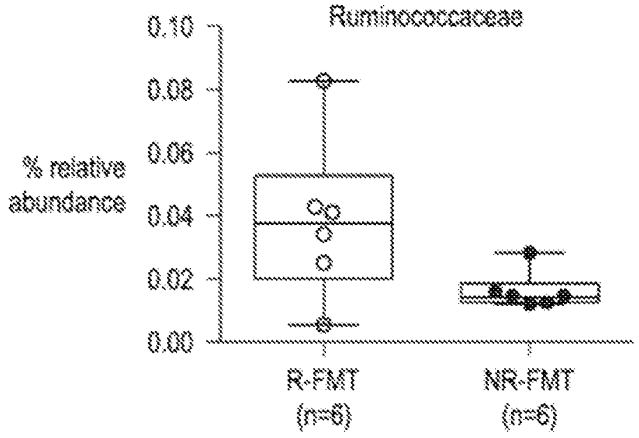
Id. at ¶ [00236] (emphasis added).

Bacteria of the family Ruminococcaceae in particular are shown to persist in the gut microbiome:

> FIGs. 34A-C: 16S analysis of fecal samples from R and NR donors and germ-free recipient mice. Relative abundance comparisons of (A) Faecalibacterium, (B) **Ruminococcaceae** and (C) Bacteroidales on **day 14 post tumor injection**. Data from 2 independent experiments are presented. ** $p<0.01$.

Id. at ¶ [0076] (emphasis added). Figure 34B is reproduced herein:

FIG. 34B



Finally, the specification describes species of the family Ruminococcaceae (at least 19 identified with particularity), identified in the samples described in the Application or as members of the family, useful in compositions for treating cancer or reducing or delaying tumor growth. See, for example, *id.* at ¶ [00125] (emphasis added):

> In some embodiments, the compositions of the embodiments comprise one or more of the species of bacteria that produce short chain fatty acids. ... **In particular**

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> **aspects, the bacterial species is from the family Ruminococcaceae**, Christensenellaceae, Clostridiaceae or Coriobacteriacease. ... **Examples of bacterial species include, but are not limited to, Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti, Ruminococcus obeum, Ruminococcus palustris, Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques**, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum, and Eubacterium oxidoreducens. In particular aspects, the bacterial species is Faecalibacterium prausnitzii.

Thus, as described in detail in the Application, compositions comprising isolated or purified populations of bacteria belonging to the family Ruminococcaceae treat cancer or reduce or delay tumor growth.

According to the M.P.E.P., "[a] description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." § 2163 (citing *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). The burden is on the Examiner to rebut the presumption by "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." M.P.E.P. § 2163 (citing *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)). Here, in view of the numerous experiments, statistical analysis, data validation, and demonstrated effects of compositions comprising bacteria of the family Ruminococcaceae on, for example, T cell infiltrate, which drives tumor killing, disclosed in the Application, there should be no doubt regarding adequacy of the written description for claim 44.

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For at least the reasons discussed above, Applicant requests that the written description rejection of claim 44, and claims 46, 49, 66, 162-165, and 167-177 which depend therefrom, be reconsidered and withdrawn.

CONCLUSION

In light of the presented remarks, Applicant respectfully asserts that the pending claims are patentable for at least the reasons set forth above. Should additional information be required, Examiner is respectfully asked to notify Applicant of such need. If any impediments to the prompt allowance of the claims can be resolved by a telephone interview, Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

/Laurie Stellman/

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Agent for Applicants

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Date: February 28, 2022

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Page 000049

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	28-Mar-2019
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Attorney Docket Number:	UTSC.P1149US/1001074761

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	2252	1	320	320
Miscellaneous:				
RCE- 1ST REQUEST	2801	1	680	680
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt

EFS ID:	45101966
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	28-FEB-2022
Filing Date:	28-MAR-2019
Time Stamp:	14:00:08
Application Type:	U.S. National Stage under 35 USC 371

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Information:					
2	Request for Continued Examination (RCE)	MDACP1149US_RCE.pdf	1667143 c45f1f481f00bb2d038423a5060628b5f98e8ac6	no	3
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3		MDACP1149US_RFOA.pdf	317531 3ce52ed50f635a8571372a27c4922bd5b85b1314	yes	12

Multipart Description/PDF files in .zip description		
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Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	12

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/22 (10-20)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): MDAC.P1149US/1001074761

Application Number: 16/337,820

Filed: March 28, 2019

For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Art Unit: 1651

Examiner: Ariani, KADE

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$220	$110	$55	$
☑	Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$ 320
☐	Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$
☐	Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐	Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☑ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1212/1001074761.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 66,817.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Laurie Stellman/ — Signature

February 28, 2022 — Date

Laurie Stellman — Typed or printed name

512-536-3072 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/337,820	Filing Date 03/28/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/28/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 28	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LINDA HUMES/
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Form PTO-1449 (modified)	Atty. Docket No.: MDAC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name
	A1	2018/0243351	08/30/18	Hlavka
	A2	2020/0129569	04/30/20	Wargo et al.

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B1	WO 2011/008369	01/20/11	WIPO	English
	B2	WO 2015/095241	06/25/15	WIPO	English
	B3	WO 2015/153639	10/08/15	WIPO	English

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	Borody et al. "Fecal microbiota transplantation and emerging applications" *Nat. Rev. Gastroenterol. & Hepatol.* 2011, 9, 88–96.
	C2	Dubin et al., "Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis." *Nat Commun.* 2016, 7:10391, 8 pages.
	C3	Extended European Search Report Issued in Corresponding European Patent Application No. 17857329.1, dated August 7, 2020. (Attorney Docket No. MDAC..P1149EP).
	C4	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2020/013808, mailed June 2, 2020. (Attorney Docket No. MDAC.P1154WO)

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EXAMINER:	DATE CONSIDERED:

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Form PTO-1449 (modified)	Atty. Docket No.: MDAC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C5	Jenq et al., "Intestinal Blautia Is Associated with Reduced Death from Graft-versus-Host Disease" *Biol. Blood Marrow Transplant.* 2015, 21, 1373-1383.
	C6	Litvak et al., "Dysbiotic Proteobacteria expansion: a microbial signature of epithelial dysfunction" *J. Curr. Opin. Microbiol.* 2017, 39, 1-6.
	C7	Moco, et al., "Metabolomics View on Gut Microbiome Modulation by Polyphenol-Rich Foods," Journal of Proteome Research, 11(10): 4781-4790, 2012. . (Attorney Docket No. MDAC.P1149EP).
	C8	Png et al., "Mucolytic Bacteria With Increased Prevalence in IBD Mucosa AugmentIn VitroUtilization of Mucin by Other Bacteria" Am. J. Gastroenterol. 2010, 105, 2420-2428.
	C9	Roh et al., "Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance." *Sci Transl Med.* 2017, 9(379), 24 pages.
	C10	Segata et al., "Metagenomic biomarker discovery and explanation." *Genome Biol.* 2011, 12:R60, 18 pages.
	C11	Wang et al., "Bifidobacterium can mitigate intestinal immunopathology in the context of CTLA-4 blockade." *PNAS* 2018, 115(1), 157-161.
	C12	Wang et al., "P038 Fecal Microbiota Transplant (FMT) For Immuno-checkpoint Inhibitor-Induced Colitis (ICI-C) In A 50 Year Old Female With Bladder Cancer" Gastroenterology 2018, 154(1S), S19-S20.

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EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION
UTSC-P1154WO-1001107435	see Form PCT/ISA/220 as well as, where applicable, item 5 below.

International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 20/13808	16 January 2020 (16.01.2020)	16 January 2019 (16.01.2019)

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/13808

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.: 6-31, 36-67, 71-82
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:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-5, directed to a treatment method comprising administering fecal matter from a healthy donor.

Group II, claims 32-35 directed to a treatment method comprising administering a composition comprising at least one isolated or purified population of bacteria.

Group III, claims 68-70, directed to a composition comprising at least one isolated or purified population of bacteria.

The inventions listed as Groups I-III do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
*****Continued in Supplemental Box*****

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 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.:
1-5

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.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/13606

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A01N 65/00, A23L 33/135, A61K 35/37 (2020.01)
CPC - A61K 35/74, A61K 35/742, C12N 1/20

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/0243351 A1 (REBIOTIX, INC.) 30 August 2018 (30.08.2018); abstract; para [0011]-[0012], [0158]	1-5
Y	WO 2016/063263 A2 (INSTITUT GUSTAVE ROUSSY) 28 April 2016 (28.04.2016); pg 2, ln 20-37; pg 10, ln 28-29; pg 18, ln 25-28; pg 42, ln 30-37	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2020	02 JUN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US 20/13808

Continuation of Box No. III (Observations where unity of invention is lacking):

Special technical features:

Group I has the special technical feature of administering fecal matter from a healthy donor, that is not required by Groups II, III.

Group II has the special technical feature of administering a composition comprising at least one isolated or purified population of bacteria, that is not required by Groups I, III.

Group III has the special technical feature of a composition comprising at least one isolated or purified population of bacteria, that is not required by Groups I, II.

Common technical features:

Groups I-III share the common technical feature of a composition comprising bacteria.

Groups I and II further share the common technical feature of a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject comprising administering a composition comprising bacteria to the subject.

Groups II and III further share the common technical feature of a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the genera Escherichia, Akkermansia, Bacteroides, Lachnospiraceae, Blautia, Tyzzerella, Bifidobacterium, Streptococcus, Colinsella, and Fusicatenibacter.

However, these shared technical feature does not represent a contribution over prior art, because these shared technical features are previously made obvious over WO 2016/063263 A2 to Institut Gustave Roussy (hereinafter "IGR") in view of US 2018/0243351 A1 to Rebiotix, Inc (hereinafter "Rebiotix").

Rebiotix teaches a method of treating colitis in a subject comprising administering fecal samples from healthy donor subjects that contain bacteria to the subject (Abstract "the donor fecal sample can be screened and processed for subsequent use in fecal bacteriotherapy to displace pathogenic or undesired organisms in the digestive track of a patient with healthy or desirable gut microbiota."; para [0011] "Each individual has a personalized gut microbiota including an estimated 500 to 5000 or more species of bacteria...an improperly balanced or functioning gut microbiota may play a role in certain diseases or afflictions, such as pseudomembranous colitis, clostridium difficile colitis, antibiotic-associated diarrhea (AAD), ulcerative colitis (UC)"; [0012] "methods for providing bacteriotherapy to treat afflictions associated with the gut microbiota, including clostridium difficile colitis, by displacing pathogenic organisms in the digestive track of a patient with healthy bacterial flora, or bacterial flora intended to benefit a specific individual with an affliction associated with the gut microbiota."; [0158] "providing a fecal dose to the clinician to be administered to a patient"). Rebiotix fails to teach the method of treating ICI-associated colitis, or a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the genera Escherichia, Akkermansia, Bacteroides, Lachnospiraceae, Blautia, Tyzzerella, Bifidobacterium, Streptococcus, Colinsella, and Fusicatenibacter.
IGR teaches a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject (pg 2, ln 20-37 "ipilimumab is a fully human monoclonal antibody (mAh) directed against CTLA4, a key negative regulator of T cell activation...The enterocolitis associated with ipilimumab has features similar to both graftversus-host disease and inflammatory bowel disease, the a ute phase being characterized by neutrophilic infiltrates while the chronic phase involves granulomata and lymphocytes."; pg 10, ln 28-29 "Figure 1.3. Co -blockade of CTLA4 provokes colitis in tumor escape."; pg 42, ln 30-37 "Patients treated with ipilimumab develop antibodies tc components of the enteric flora (8), suggesting that such immune reactions ma contribute to colitis. Despite these potentially live-threatening eolitogenic effects, clinicians have combined CTLA blockade with that of another immune checkpoint, relying on the interraction between PD-1 and PD-L1, further increasing objective responses as well as the side effects. Therefore addressing the role of gut mierobiota in the immunomodulatory effects of CTL4 blockade is crucial for the future development of immune checkpoint blockers as antineoplastic agents."). Given that Rebiotix teaches wherein fecal matter from healthy donors can restore healthy bacteria levels and treat colitis, and because Escherichia coli species was well known to be present in human feces and could easily be isolated for use in a composition, it would have been obvious to an artisan of ordinary skill in the art to experiment with feces or bacteria isolated therefrom, in order to treat colitis in patients being treated with immune checkpoint inhibitors, such as those taught by IGR.

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I-III inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, continuation of item 4 above: claims 6-31, 36-67, 71-82 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: LAURIE FRIESENHAHN STELLMAN
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BLVD., SUITE 1100
AUSTIN, TX 78701

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 02 JUN 2020

Applicant's or agent's file reference	FOR FURTHER ACTION
UTSC-P1154WO-1001107435	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 20/13808	16 January 2020 (16.01.2020)	16 January 2019 (16.01.2019)

International Patent Classification (IPC) or both national classification and IPC

IPC - A01N 65/00, A23L 33/135, A61K 35/37 (2020.01)

CPC - A61K 35/74, A61K 35/742, C12N 1/20

Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

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 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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	4 May 2020	Lee Young PCT Help Desk Telephone No. 571-272-4300

Form PCT/ISA/237 (cover sheet) (revised January 2019)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/13808

Box No. I Basis of this 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(b)).

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:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/13808

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-31, 36-67, 71-82

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 6-31, 36-67, 71-82 are so unclear that no meaningful opinion could be formed *(specify)*:

because they are depencent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 6-31, 36-67, 71-82

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/13808

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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-5, directed to a treatment method comprising administering fecal matter from a healthy donor.

Group II, claims 32-35 directed to a treatment method comprising administering a composition comprising at least one isolated or purified population of bacteria.

Group III, claims 68-70, directed to a composition comprising at least one isolated or purified population of bacteria.

The inventions listed as Groups I-III do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features:

Group I has the special technical feature of administering fecal matter from a healthy donor, that is not required by Groups II, III.

Group II has the special technical feature of administering a composition comprising at least one isolated or purified population of bacteria, that is not required by Groups I, III.

Group III has the special technical feature of a composition comprising at least one isolated or purified population of bacteria, that is not required by Groups I, II.

Common technical features:

Groups I-III share the common technical feature of a composition comprising bacteria.

Groups I and II further share the common technical feature of a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject comprising administering a composition comprising bacteria to the subject.

Groups II and III further share the common technical feature of a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the genera Escherichia, Akkermansia, Bacteroides, Lachnospiraceae, Blautia, Tyzzerella, Bifidobacterium, Streptococcus, Colinsella, and Fusicatenibacter.

*****Continued in Supplemental Box*****

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-5

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/13808

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**

1. Statement

Novelty (N)	Claims	1-5	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5 lack an inventive step under PCT Article 33(3) as being obvious over US 2018/0243351 A1 to Rebiotix, Inc (hereinafter "Rebiotix") in view of WO 2016/063263 A2 to Institut Gustave Roussy (hereinafter "IGR").

Regarding claim 1, Rebiotix teaches a method for treating colitis in a subject comprising administering fecal matter from a healthy donor to the subject (Abstract "the donor fecal sample can be screened and processed for subsequent use in fecal bacteriotherapy to displace pathogenic or undesired organisms in the digestive track of a patient with healthy or desirable gut microbiota."; para [0011] "Each individual has a personalized gut microbiota including an estimated 500 to 5000 or more species of bacteria...an improperly balanced or functioning gut microbiota may play a role in certain diseases or afflictions, such as pseudomembranous colitis, clostridium difficile colitis, antiobiotic-associated diarrhea (AAD), ulcerative colitis (UC)"; [0012] "methods for providing bacteriotherapy to treat afflictions associated with the gut microbiota, including clostridium difficile colitis, by displacing pathogenic organisms in the digestive track of a patient with healthy bacterial flora, or bacterial flora intended to benefit a specific individual with an affliction associated with the gut microbiota."; [0158] "providing a fecal dose to the clinician to be administered to a patient"). Rebiotix does not specify that the colitis is immune checkpoint inhibitor (ICI)-associated.
IGR teaches a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject (pg 2, ln 20-37 "Ipilimumab is a fully human monoclonal antibody (mAh) directed against CTLA4, a key negative regulator of T cell activation...The enterocolitis associated with ipilimumab has features similar to both graft versus-host disease and inflammatory bowel disease, the acute phase being characterized by neutrophilic infiltrates while the chronic phase involves granulomata and lymphocytes."; pg 10, ln 28-29 "Figure 1.3. Co-blockade of CTLA4 provokes colitis in tumor escape."; pg 42, ln 30-37 "Patients treated with ipilimumab develop antibodies to components of the enteric flora (8), suggesting that such immune reactions ma contribute to colitis. Despite these potentially live-threatening eolitogenic effects, clinicians have combined CTLA blockade with that of another immune checkpoint, relying on the interaction between PD-1 and PD-L1, further increasing objective responses as well as the side effects. Therefore addressing the role of gut mierobiota in the immunomodulatory effects of CTL4 blockade is crucial for the future development of immune checkpoint blockers as antineoplastic agents."). Given that Rebiotix teaches wherein fecal matter from healthy donors can restore healthy bacteria levels and treat colitis, and because Escherichia coli species was well known to be present in human feces and could easily be isolated for use in a composition, it would have been obvious to an artisan of ordinary skill in the art to experiment with feces or bacteria isolated therefrom, in order to treat colitis in patients being treated with immune checkpoint inhibitors, such as those taught by IGR.

Regarding claim 2, the combination of Rebiotix and IGR makes obvious the method of claim 1, however fail to teach wherein the ICI-associated colitis comprises refractory ICI associated colitis.
IGR teaches a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject (pg 2, ln 20-37 "Ipilimumab is a fully human monoclonal antibody (mAh) directed against CTLA4, a key negative regulator of T cell activation...The enterocolitis associated with ipilimumab has features similar to both graft versus-host disease and inflammatory bowel disease, the acute phase being characterized by neutrophilic infiltrates while the chronic phase involves granulomata and lymphocytes."; pg 10, ln 28-29 "Figure 1.3. Co-blockade of CTLA4 provokes colitis in tumor escape."; pg 42, ln 30-37 "Patients treated with ipilimumab develop antibodies to components of the enteric flora (8), suggesting that such immune reactions ma contribute to colitis. Despite these potentially live-threatening eolitogenic effects, clinicians have combined CTLA blockade with that of another immune checkpoint, relying on the interaction between PD-1 and PD-L1, further increasing objective responses as well as the side effects. Therefore addressing the role of gut mierobiota in the immunomodulatory effects of CTL4 blockade is crucial for the future development of immune checkpoint blockers as antineoplastic agents."). Given that Rebiotix teaches wherein fecal matter from healthy donors can restore healthy bacteria levels and treat colitis, and because Escherichia coli species was well known to be present in human feces and could easily be isolated for use in a composition, it would have been obvious to an artisan of ordinary skill in the art to experiment with feces or bacteria isolated therefrom, in order to treat colitis in patients, being treated with immune checkpoint inhibitors, such as those taught by IGR. Furthermore it would have been obvious to an artisan of ordinary skill in the art to experiment with treating various forms of colitis, including refractory ICI associated colitis, in order to treat patients that could not be effectively treated with conventional therapies.

*****Continued in Supplemental Box*****

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box IV(3) Lack of unity of invention:

However, these shared technical feature does not represent a contribution over prior art, because these shared technical features are previously made obvious over WO 2016/063263 A2 to Institut Gustave Roussy (hereinafter "IGR") in view of US 2018/0243351 A1 to Rebiotix, Inc (hereinafter "Rebiotix").

Rebiotix teaches a method of treating colitis in a subject comprising administering fecal samples from healthy donor subjects that contain bacteria to the subject (Abstract "the donor fecal sample can be screened and processed for subsequent use in fecal bacteriotherapy to displace pathogenic or undesired organisms in the digestive track of a patient with healthy or desirable gut microbiota."; para [0011] "Each individual has a personalized gut microbiota including an estimated 500 to 5000 or more species of bacteria...an improperly balanced or functioning gut microbiota may play a role in certain diseases or afflictions, such as pseudomembranous colitis, clostridium difficile colitis, antiobiotic-associated diarrhea (AAD), ulcerative colitis (UC)"; [0012] "methods for providing bacteriotherapy to treat afflictions associated with the gut microbiota, including clostridium difficile colitis, by displacing pathogenic organisms in the digestive track of a patient with healthy bacterial flora, or bacterial flora intended to benefit a specific individual with an affliction associated with the gut microbiota."; [0158] "providing a fecal dose to the clinician to be administered to a patient"). Rebiotix fails to teach the method of treating ICI-associated colitis, or a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the genera Escherichia, Akkermansia, Bacteroides, Lachnospiraceae, Blautia, Tyzzerella, Bifidobacterium, Streptococcus, Colinsella, and Fusicatenibacter.
IGR teaches a method for treating immune checkpoint inhibitor (ICI)-associated colitis in a subject (pg 2, ln 20-37 "Ipilimumab is a fully human monoclonal antibody (mAh) directed against CTLA4, a key negative regulator of T cell activation...The enterocolitis associated with ipilimumab has features similar to both graftversus-host disease and inflammatory bowel disease, the a ute phase being characterized by neutrophilic infiltrates while the chronic phase involves granulomata and lymphocytes."; pg 10, ln 28-29 "Figure 1.3. Co-blockade of CTLA4 provokes colitis in tumor escape."; pg 42, ln 30-37 "Patients treated with ipilimumab develop antibodies to components of the enteric flora (8), suggesting that such immune reactions ma contribute to colitis. Despite these potentially live-threatening eolitogenic effects, clinicians have combined CTLA blockade with that of another immune checkpoint, relying on the interraction between PD-1 and PD-L1, further increasing objective responses as well as the side effects. Therefore addressing the role of gut mierobiota in the immunomodulatory effects of CTL4 blockade is crucial for the future development of immune checkpoint blockers as antineoplastic agents."). Given that Rebiotix teaches wherein fecal matter from healthy donors can restore healthy bacteria levels and treat colitis, and because Escherichia coli species was well known to be present in human feces and could easily be isolated for use in a composition, it would have been obvious to an artisan of ordinary skill in the art to experiment with feces or bacteria isolated therefrom, in order to treat colitis in patients being treated with immune checkpoint inhibitors, such as those taught by IGR.

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I-III inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, continuation of Item 4 above: claims 6-31, 36-67, 71-82 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000069

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/13808

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V(2) Citations and Explanations:

Regarding claim 3, the combination of Rebiotix and IGR makes obvious the method of claims 1-2, and IGR further teaches wherein the subject has been treated with anti-CTLA-4 monotherapy (pg 1, ln 5-8 "the present invention concerns the role of the microbiota in the efficacy of cancer treatments with a drug blocking an immune checkpoint, and provides methods and probiotics to improve the efficacy of such a treatment in patients in need thereof"; pg 2, ln 20-37 "ipilimumab is a fully human monoclonal antibody (mAh) directed against CTLA4, a key negative regulator of T cell activation...The enterocolitis associated with ipilimumab has features similar to both graft versus-host disease and inflammatory bowel disease, the acute phase being characterized by neutrophilic infiltrates while the chronic phase involves granulomata and lymphocytes."; pg 18, ln 25-28 "In the present text, a "drug blocking an immune checkpoint", or "immune checkpoint blocker" or immune checkpoint blockade drug" designates any drug, molecule or composition which blocks an immune checkpoint. In particular, it encompasses anti-CTLA-4 antibodies and anti-PD-1 antibodies").

Regarding claim 4, the combination of Rebiotix and IGR makes obvious the method of claims 1-2, however fail to teach the method further wherein the subject has been treated with anti-PD-l monotherapy.
IGR teaches wherein immune checkpoint inhibitor therapy can consisted of anti-CTLA-4 OR anti-PD-l (pg 1, ln 5-8 "the present invention concerns the role of the microbiota in the efficacy of cancer treatments with a drug blocking an immune checkpoint, and provides methods and probiotics to improve the efficacy of such a treatment in patients in need thereof"; pg 18, ln 25-28 "In the present text, a "drug blocking an immune checkpoint", or "immune checkpoint blocker" or immune checkpoint blockade drug" designates any drug, molecule or composition which blocks an immune checkpoint. n particular, it encompasses anti-CTLA-4 antibodies, anti-PD-l antibodies and anti-PD-L1 antibodies."). While IGR does not specifically state that therapy is a combination therapy, it would have been obvious to an artisan or ordinary skill in the art that immune checkpoint inhibitor therapy could include a single checkpoint inhibitor, or a combination of checkpoint inhibitors, in order to optimize the therapy for a given patient.

Regarding claim 5, the combination of Rebiotix and IGR makes obvious the method of claims 1-2, however fails to teach wherein the subject has been treated with anti-CTLA-4 and anti-PD-l combination therapy.
IGR teaches wherein immune checkpoint inhibitor therapy can consisted of anti-CTLA-4 OR anti-PD-l (pg 1, ln 5-8 "the present invention concerns the role of the microbiota in the efficacy of cancer treatments with a drug blocking an immune checkpoint, and provides methods and probiotics to improve the efficacy of such a treatment in patients in need thereof"; pg 18, ln 25-28 "In the present text, a "drug blocking an immune checkpoint", or "immune checkpoint blocker" or immune checkpoint blockade drug" designates any drug, molecule or composition which blocks an immune checkpoint. n particular, it encompasses anti-CTLA-4 antibodies, anti-PD-l antibodies and anti-PD-L1 antibodies."). While IGR does not specifically state that therapy is a combination therapy, it would have been obvious to an artisan or ordinary skill in the art that immune checkpoint inhibitor therapy could include a single checkpoint inhibitor, or a combination of checkpoint inhibitors.

Claims 1-5 have industrial applicability under PCT Article 33(4) because the subject matter can be made or used in industry.

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SEARCH HISTORY

Application Number	PCT/US 20/13808
Search Conducted By	MAB
Search Approved By	DEM

CPC/IPC Classifications Searched	IPC(8): A01N 65/00, A23L 33/135, A61K 35/37 (2020.01) CPC: A61K 35/74, A61K 35/742, C12N 1/20
Date Conducted	**12 March 2020, 8 April 2020**

Documentation Searched	IPC(8): A01N 65/00, A23L 33/135, A61K 35/37 (2020.01) CPC: A61K 35/74, A61K 35/742, C12N 1/20
Search Terms Used	Colitis, immune-checkpoint, inhibit*, fecal, bacteria, Escherichia, Akkermansia, Bacteroides, Lachnospiraceae, Blautia, Tyzzerella, fidobacterium, Streptococcus, Colinsella, Fusicatenibacter
Date Conducted	**12 March 2020, 8 April 2020**

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	12 March 2020, 8 April 2020
Search Logic:	

Search history

Search 1:	IC=(A01N65/00 OR A23L33/135 OR A61K35/37) (Results 22202)
Search 2:	CPC=(A61K35/74 OR A61K35/742 OR C12N1/20) (Results 18378)
Search 3:	1 or 2 (Results 39321)
Search 4:	3 and colitis (Results 1080)
Search 5:	4 and (immune-checkpoint w5 inhibit*) (Results 3)
Search 6:	5 and fecal (Results 2)
Search 7:	6 and bacteria* (Results 2)
Search 8:	7 and (Escherichia OR Akkermansia OR Bacteroides OR Lachnospiraceae OR Blautia OR Tyzzerella OR fidobacterium OR Streptococcus OR Colinsella OR Fusicatenibacter) (Results 2)

Search history

Search 1:	colitis (Results 46311)
Search 2:	1 and (immune-checkpoint w5 inhibit*) (Results 57)
Search 3:	2 and (checkpoint w8 colitis) (Results 10)
Search 4:	3 and bacteri* (Results 5)
Search 5:	4 and (Escherichia OR Akkermansia OR Bacteroides OR Lachnospiraceae OR Blautia OR Tyzzerella OR fidobacterium OR Streptococcus OR Colinsella OR Fusicatenibacter) (Res
Search 6:	2 and bacteri* (Results 45)
Search 7:	6 and (Escherichia OR Akkermansia OR Bacteroides OR Lachnospiraceae OR Blautia OR Tyzzerella OR fidobacterium OR Streptococcus OR Colinsella OR Fusicatenibacter) (Res
Search 8:	7 and fecal* (Results 2)

Electronic Database Searched	**Google**
Files Searched	**Scholar**
Date Conducted	**12 March 2020, 8 April 2020**

Search Logic:

4 results (0.05 sec) "ICI-colitis" and fecal matter

About 7,960 results (0.12 sec) Immune checkpoint inhibitor associated colitis and fecal matter bacteria

About 10,600 results (0.17 sec) Immune checkpoint inhibitor associated colitis and fecal matter

About 26,700 results (0.07 sec) "colitis" and fecal matter

About 577 results (0.08 sec) "colitis" and fecal matter and "immune checkpoint inhibitor"

4 results (0.07 sec) "ICI-colitis" and fecal matter

About 92 results (0.08 sec) colitis and immunotoxicity and checkpoint inhibitor therapy and fecal matter

About 130,000 results (0.07 sec) colitis and (Escherichia OR Akkermansia OR Bacteroides OR Lachnospiraceae OR Blautia OR Tyzzerella OR fidobacterium OR Streptococcus OR Colinsella" OR "Fusicatenibacter")

About 198,000 results (0.08 sec) colitis and ("Escherichia" OR "Akkermansia" OR "Bacteroides" OR "Lachnospiraceae" OR "Blautia" OR "Tyzzerella" OR "fidobacterium" OR "Streptococcus" OR "Colinsella" OR "Fusicatenibacter")

About 60,300 results (0.10 sec) colitis and ("Escherichia" OR "Akkermansia" OR "Bacteroides" OR "Lachnospiraceae" OR "Blautia" OR "Tyzzerella" OR "fidobacterium" OR "Streptococcus" OR "Colinsella" OR "Fusicatenibacter") and fecal

About 6,210 results (0.06 sec) fecal matter donor and colitis

About 21,300 results (0.10 sec) immune checkpoint inhibitors and colitis

Electronic Database Searched	**Google**
Files Searched	**Patents**
Date Conducted	**12 March 2020, 8 April 2020**

Search Logic:

About 3,460 results (0.44 seconds) Immune checkpoint inhibitor associated colitis and fecal matter bacteria

About 3,510 results (0.36 seconds) Immune checkpoint inhibitor associated colitis and fecal matter

1 result (0.35 seconds) "Immune checkpoint inhibitor associated colitis" and fecal matter

About 5,380 results (0.37 seconds) "colitis" and fecal matter

About 268 results (0.32 seconds) "colitis" and fecal matter and "immune checkpoint inhibitor"

About 0 results (0.30 seconds) "ICI-colitis" and fecal matter

About 25 results (0.33 seconds) colitis and immunotoxicity and checkpoint inhibitor therapy and fecal matter

About 38,900 results (0.53 seconds) colitis and (Escherichia OR Akkermansia OR Bacteroides OR Lachnospiraceae OR Blautia OR Tyzzerella OR fidobacterium OR Streptococcus OR Colinsella" OR "Fusicatenibacter")

About 42,100 results (0.54 seconds) colitis and ("Escherichia" OR "Akkermansia" OR "Bacteroides" OR "Lachnospiraceae" OR "Blautia" OR "Tyzzerella" OR "fidobacterium" OR "Streptococcus" OR "Colinsella" OR "Fusicatenibacter")

About 7,490 results (1.01 seconds) colitis and ("Escherichia" OR "Akkermansia" OR "Bacteroides" OR "Lachnospiraceae" OR "Blautia" OR "Tyzzerella" OR "fidobacterium" OR "Streptococcus" OR "Colinsella" OR "Fusicatenibacter") and fecal

About 4,770 results (0.49 seconds) colitis and ("Escherichia" OR "Akkermansia" OR "Bacteroides" OR

"Lachnospiraceae" OR "Blautia" OR "Tyzzerella" OR "fidobacterium" OR "Streptococcus" OR "Colinsella" OR "Fusicatenibacter") and "fecal"

About 1,710 results (0.32 seconds) fecal matter donor and colitis

About 810 results (0.33 seconds) "checkpoint inhibitors" and "colitis"

1 result (0.26 seconds) "Immune checkpoint inhibitor associated colitis"

About 4,300 results (0.33 seconds) immune checkpoint inhibitors and colitis

About 4,380 results (0.40 seconds) immune checkpoint inhibitors induced colitis

About 9,720 results (0.50 seconds) Cancer Immunotherapy with Anti-CTLA-4 Monoclonal Antibodies Induces an Inflammatory Bowel Disease and "colitis"

SAO SUPPLEMENTAL SEARCH HISTORY

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	07 May 2020

Search Logic:

Search 25: ft=((fecal or feces) W4 "healthy donor") (Results 47)

Search 26: 25 and ft=(Escherichia or Akkermansia or Bacteroides) (Results 35)

Search 27: 26 and tac=(fecal or feces) (Results 23)

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	28-Mar-2019
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Ashley Overton
Attorney Docket Number:	UTSC.P1149US/1001074761

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	130	130
		Total in USD ($)		**130**

Electronic Acknowledgement Receipt

EFS ID:	43929655
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Ashley Overton
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	01-OCT-2021
Filing Date:	28-MAR-2019
Time Stamp:	16:13:31
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$130
RAM confirmation Number	E202101G13553661
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MDACP1149US_SIDS1.pdf	61463 c64f1d22f572c93d76c8d9a73cace9c8c6b1cec2	yes	5
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	5	
Warnings:					
Information:					
2	Foreign Reference	WO2011008369A1.pdf	2263172 e119f34c859388b2d4178bdba28af869ed394f47	no	21
Warnings:					
Information:					
3	Foreign Reference	WO2015095241A2.pdf	8682017 23ca11585099739067bbcc3a4f3237f2ba4f16a9	no	69
Warnings:					
Information:					
4	Foreign Reference	WO2015153639A1.pdf	13886281 6eb39aa4dda60fe90b8df0e88939d0f0719f324e	no	93
Warnings:					
Information:					
5	Non Patent Literature	Borody.pdf	3418506 cc7f2936d7be483616a5dc1c2b1bf3c52ad91575	no	9
Warnings:					
Information:					

6	Non Patent Literature	Dubin.pdf	554589 db7a8d1b88ebbe6e26e3be1a12d9f98e8d32c03d	no	8
Warnings:					
Information:					
7	Non Patent Literature	EESR_1149EP_AUG2020.pdf	1220291 893fa9cdb091f9b58cdf570651f3db69937ae862	no	13
Warnings:					
Information:					
8	Non Patent Literature	1154WO_ISRWO.pdf	2346209 89c23d184a19cc1c323f748b9dc4fd011267622c	no	15
Warnings:					
Information:					
9	Non Patent Literature	Jenq.pdf	1793374 95fc972e85b6e88167e92b1b18c61738c178724d	no	11
Warnings:					
Information:					
10	Non Patent Literature	Litvak.pdf	1056345 551b162e2f6fcce50f6154c898cdd8ad332af1dc	no	6
Warnings:					
Information:					
11	Non Patent Literature	MOCO.pdf	2440516 509b1d39a2519a235fde34123c59b573d9f3cda1	no	10
Warnings:					
Information:					
12	Non Patent Literature	PNG.pdf	472441 de1a429ac50bbafe1f80d08b0ef7504d0e0605ae	no	9
Warnings:					
Information:					

13	Non Patent Literature	Roh.pdf	1814047 affb530daf2c0d7046ec46d2a80f9d0abc2d8ffb	no	24
Warnings:					
Information:					
14	Non Patent Literature	Segata.pdf	2901688 a0061c32805cc45f681d83833f925d2629e2a0ea	no	18
Warnings:					
Information:					
15	Non Patent Literature	Wang.pdf	1210007 de5f10f5133c2f6e4bc0f0b05751679f8cd43752	no	5
Warnings:					
Information:					
16	Non Patent Literature	Wang_2018.pdf	1092126 5305b5afc7aa1d802edeb13ef75fe533e8f814f4	no	2
Warnings:					
Information:					
17	Fee Worksheet (SB06)	fee-info.pdf	38077 178328001c4f7c3687fec4f0e3c75fba6f670334	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	45251149		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Jennifer WARGO	Group Art Unit: 1651
Serial No.: 16/337,820	Examiner: ARIANI, KADE
Filed: March 28, 2019	Atty. Dkt. No.: MDAC.P1149US/1001074761
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION (37 C.F.R. § 1.8)
I, Ashley Overton, hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on October 1, 2021. Signed: /Ashley Overton/

INFORMATION DISCLOSURE STATEMENT

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record.

In accordance with 37 C.F.R §§ 1.97(g), (h), this Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

Timing and Fees

☐ Under 37 C.F.R. § 1.97(b), **no fee or statement is required** for filing this Information Disclosure Statement because it is filed:

- ☐ within three months of the filing date of a national application other than a CPA under § 1.53(d); **OR**
- ☐ within three months of the actual filing date of the national phase of a PCT application; **OR**
- ☐ before the mailing of a first substantive office action (including after filing of an RCE).

☐ Under 37 C.F.R. § 1.97(c), this Information Disclosure Statement is filed after the periods specified in 37 C.F.R. § 1.97(b), but **before** the mailing date of:

- ☐ a final rejection under 37 C.F.R. § 1.113; **OR**
- ☐ termination of prosecution, e.g. Ex Parte Quayle, M.P.E.P. § 609(B)(2); **OR**

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☐ a notice of allowance under 37 C.F.R. § 1.311;

AND is accompanied by:

☐ the statement as specified in 37 C.F.R. § 1.97(e) set out below; **OR**

☐ payment covering the fee of $130.00 (small entity) under 37 C.F.R. § 1.17(p).

☒ Under 37 C.F.R. § 1.97(d), this Information Disclosure Statement is filed **after** the mailing date of the following actions which have not been withdrawn:

☒ a final action under 37 C.F.R. § 1.113; **OR**

☐ termination of prosecution; e.g. Ex Parte Quayle, M.P.E.P. § 609(B)(2); **OR**

☐ a notice of allowance under 37 C.F.R. § 1.311 and is filed on or before payment of the issue fee;

AND is accompanied by:

the statement as specified in 37 C.F.R. § 1.97(e) as set forth below, **AND** payment covering the fee of $130.00 (small entity) under 37 C.F.R. § 1.17(p).

Statements Under 37 C.F.R. § 1.97(e) (if applicable)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the present Information Disclosure Statement; **OR**

☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and to the knowledge of the undersigned attorney after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing date of the Information Disclosure Statement.

Statement Under 37 C.F.R. § 1.704(d) (if applicable)

☐ Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application and that this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this Information Disclosure Statement.

Copies of Cited Materials (if applicable)

☐ Copies of materials listed but not attached were cited in benefit (35 U.S.C. § 120) ancestor application Serial No. _____ on Form 892 by the Examiner and/or Form 1449 by the applicant; see 37 C.F.R. § 1.98(d).

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☒ This application may be related by inventorship and/or subject matter to co-pending U.S. application Serial No. 15/733,682, filed September 28, 2020, Serial No. 17/296,072, filed May 21, 2021, and Serial No. 17/422,719, filed July 13, 2021.

Payment of Fees Due (if applicable)

☒ Payment is made by credit card via EFS-Web for $130.00 (small entity) covering the fee identified above.

☐ Please charge Deposit Account No. 50-1212/_____ $_____ for the fee identified above.

☒ The Commissioner is hereby authorized to charge or credit any overpayment to Deposit Account 50-1212/MDAC.P1149US/1001074761.

Respectfully submitted,

/Laurie Stellman/

Laurie B.F. Stellman
Reg. No. 66,817
Patent Agent for Applicant

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd., Suite 1100
Austin, TX 78701
(512) 474-5201

Date: October 1, 2021

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000084

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001074761	2735

32425 7590 09/27/2021

NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
09/27/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

aoipdocket@nortonrosefulbright.com

Office Action Summary	Application No. 16/337,820	Applicant(s) WARGO et al.	
	Examiner KADE ARIANI	Art Unit 1651	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 08 July 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 44,46,49,66,162-165 and 167-178 is/are pending in the application.

5a) Of the above claim(s) 178 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 44,46,49,66,162-165 and 167-177 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The amendments filed on July 08, 2021 has been received.

Claim 166 is canceled by applicant.

New claim 178 is added.

Claims 44, 46, 49, 66, 162-165 and 167-178 are pending in this application, claim 178 is withdrawn from further consideration (see Election by Original Presentation below), and claims 44, 46, 49, 66, 162-165 and 167-177 were examined on the merits.

Election by Original Presentation:

Newly submitted claim 178 is directed to a species that is independent or distinct from originally claimed for the following reasons:

Newly submitted claim 178, i.e., further ... administering an immune checkpoint inhibitor, is drawn to a newly presented species of anticancer treatment (see previously presented claims 162 and 163).

In this case, the newly presented species of anticancer treatment recited in claim 178, has distinct function or effect, has mutually exclusive characteristics, and is not an obvious variant of the previously presented anticancer treatments, and would have been restricted had it been presented previously.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claim 178 is withdrawn from consideration as being directed to a non-elected invention/species. See 37 CFR 1.142(b) and MPEP § 821.03.

Answer to Arguments:

Withdrawn Rejection(s):

The rejection of claim 44 and its dependent claims 46, 49, 66 and 162-177 on the basis that they contain an improper Markush grouping of alternatives, is withdrawn due to the amendments to the claims filed on 07/08/2021.

The rejection of claims 167 and 173 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite, is withdrawn due to the amendments to the claims filed on 07/08/2021.

The rejection of claims 44, 66, 166 and 171 under 35 U.S.C. 102 (a)(1) as being anticipated by Miquel et al., is withdrawn due to the amendments to the claims filed on 07/08/2021.

The rejection of claims 44, 49 and 162-177 under 35 U.S.C. 102 (a)(1) as being anticipated by Patyar et al., is withdrawn due to the amendments to the claims filed on 07/08/2021.

The rejection of claims 44, 46, 49 and 162-177 under 35 U.S.C. 103 as being unpatentable over Patyar et al., as applied to claims 44, 49, and 162-177 above, and further in view of Wei et al., is withdrawn due to the amendments to the claims filed on 07/08/2021.

Applicant arguments with respect to the above-mentioned rejections are mot because the rejections are withdrawn.

Applicant's amendment to claim 44, necessitated the new ground(s) of rejection presented in this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44, 46, 49, 66, 162-165 and 167-177 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had possession of the claimed invention.

The added material which is not supported by the original disclosure is as follows:

In amended claim 44:

"administering to the subject [in need] a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae".

Because, the specification while provides support for reduce implanted melanoma tumor growth in germ-free mice by direct injection of a fecal microbiota sample (FMT) to said tumor (see for example paragraph [0103]), it does not necessarily provides support for "administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae" for treating cancer or reducing or delaying tumor growth in a subject in need thereof, as required by amended claim 44.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP § 2163.06.

Conclusions:

No claim(s) is allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KADE ARIANI whose telephone number is (571)272-6083. The examiner can normally be reached on IFP, Monday - Friday, 8:00 AM -4:00 PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Renee Claytor can be reached on (571)272-8394. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KADE ARIANI/
Primary Examiner, Art Unit 1651

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	04/02/2021	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	04/02/2021	KA
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	09/21/2021	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	09/21/2021	KA

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000092

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	04/02/2021	KA
EAST (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	04/02/2021	KA
NPL (google and google scholar) (see attached text search results)	04/02/2021	KA
Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	09/21/2021	KA
EAST (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	09/21/2021	KA
STN (BIOSIS, CAPLUS, MEDLINE) (see attached search results)	09/22/2021	KA

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000093

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S110	3,762	((("THE") near3 ("BOARD") near3 ("OF") near3 ("REGENTS") near3 ("THE") near3 ("UNIVERSITY") near3 ("OF") near3 ("TEXAS") near3 ("SYSTEM"))).AS,AANM.	USPAT	OR	OFF	2021/09/21 15:31
S111	3	((("WARGO") near3 ("Jennifer")) OR (("GOPALAKRISHNAN") near3 ("Vancheswaran"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2021/09/21 15:31
S112	370,484	(A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115).cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S113	2	(A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115).cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S114	29,564	Clostridia and cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S115	13	Clostridia adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S116	79,413	skin adj cancer	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S117	4,799	S114 and S116	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S118	77,612	Clostridia	US-PGPUB; USPAT;	OR	ON	2021/09/21 15:31

			USOCR; EPO; JPO; DERWENT			
S119	78,643	Clostridia or Mollicutes or Clostridiales or Ruminococcaceae or Faecalibacterium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S120	115,700	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S121	7,021	S119 and S120	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S122	2,382	S116 and S121	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S123	1,366	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S124	35	S122 and S123	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S125	203,559	melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S126	78,643	Clostridia or Mollicutes or Clostridiales or Ruminococcaceae or Faecalibacterium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S127	12,953	S125 and S126	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31

S128	115,700	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S129	5,396	S127 and S128	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S130	0	Clostridia adj melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S131	1,366	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S132	491	melanoma adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S133	0	S131 and S132	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S134	203,559	melanoma	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S135	148	S131 and S134	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S136	0	S131 adj S134	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S137	106	S128 and S135	US-PGPUB; USPAT; USOCR; EPO;	OR	ON	2021/09/21 15:31

			JPO; DERWENT			
S139	115,700	cancer adj therapy	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S140	744,160	tumor	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S141	979	Ruminococcaceae	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S142	757,777	S139 or S140	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S143	315	S141 and S142	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S144	1,366	Faecalibacterium adj prausnitzii	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S145	162	S143 and S144	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S146	160	S140 and S145	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S147	124,564	tumor adj growth	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31

S148	65	S141 and S147	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S149	45	S144 and S148	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31
S150	52	S139 and S147 and S141	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2021/09/21 15:31

9/22/2021 12:31:02 PM
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                D SET

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CHARGED TO COST=S RUMINOCOCCACEAE MICROBIOTA CANCER

     FILE 'BIOSIS, MEDLINE' ENTERED AT 12:41:57 ON 22 SEP 2021
CHARGED TO COST=S RUMINOCOCCACEAE MICROBIOTA CANCER
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L2             0 SEA ABB=ON  PLU=ON  RUMINOCOCCACEAE CANCER TUMOR
L3             0 SEA ABB=ON  PLU=ON  RUMINOCOCCACEAE TUMOR
L4             0 SEA ABB=ON  PLU=ON  RUMINOCOCCACEAE CANCER
```

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: 1651 Examiner: Ariani. KADE
Serial No.: 16/337,820	Atty. Dkt. No.: MDAC.P1149US/1001074761
Filed: March 28, 2019	
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

July 8, 2021	/Laurie Stellman/
Date	Laurie Stellman

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED APRIL 9, 2021

Applicant submits this paper in response to the Office Action dated April 9, 2021, for which the date for response is July 9, 2021. It is believed that no fees are due; however, should any fees be required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper, the Commissioner is authorized to deduct said fees from Norton Rose Fulbright US LLP Account No.: 50-1212/ MDAC.P1149US/1001074761.

Amendments to the Claims begin on page 2.

Remarks begin on page 5.

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Page 000100

Electronic Acknowledgement Receipt

EFS ID:	43199696
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	08-JUL-2021
Filing Date:	28-MAR-2019
Time Stamp:	14:30:03
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MDACP1149US_ROA.pdf	163641 861f8990de1eec2268c4459054e0939ebdffbde0	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	5	8
	Claims	2	4
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	163641	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

A. Status of the Claims

Upon entry of the foregoing amendment, claims 44, 46, 49, 66, and 162-165, and 167-178 are pending in the application, with claim 44 being the independent claim. Claim 166 canceled without prejudice to or disclaimer of the subject matter therein. Claims 44, 49, 66, 162, 164, 165, 167, 169, 171, 172, and 173 are amended. Claim 178 is new. Support for the amendments to the claims is found throughout the specification and claims originally filed. For example, support for the amendments to claims 44, 49, and 66 can be found throughout the specification and claims as originally filed, *inter alia*, at page 2, lines 23-27; page 28, lines 1-6; page 28, line 24 to page 29, line 2; page 37, line 29 to page 38, line 11; page 161, lines 16-26; page 202, line 19 to page 203, line 5; page 203, line 25 to page 204, line 10; and page 206, lines 3-16. Support for new claim 178 can be found, *inter alia*, at page 4, lines 19-22; page 15, lines 13-21; page 16, lines 20-23; page 153, lines 18-29; and page 161, lines 16-26. Claim 44 has been amended to recite "the family Ruminococcaceae," which is within the class of Clostridia. Claims 162, 164, 165, 167, 169, and 171-173 have been amended to adjust antecedent basis or claim form. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

B. Improper Markush Grouping

Claim 44 and its dependent claims 46, 49, 66, and 162-177 are rejected on the basis that they contain an improper Markush grouping of alternatives. (Office Action at page 2.) Applicant respectfully disagrees. Solely to advance prosecution, and not in acquiescence to any rejection, claim 44 has been amended to recite a composition comprising one or more isolated or purified

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population of bacteria belonging to the family Ruminococcaceae. The claim as amended is in proper form. Applicant respectfully requests withdrawal of this rejection.

C. Rejections under 35 U.S.C. § 112

Claims 167 and 173 are rejected under 35 U.S.C. § 112(b) for alleged indefiniteness. The Office Action states that claims 167 and 173 recite the limitation "the tumor" for which there is insufficient antecedent basis because claim 44 does not recite a tumor. (Office Action at page 4.)

Claims 167 and 173 have been amended herewith to depend from claim 165 that recites that the subject has a tumor. Therefore, proper antecedent basis for claims 167 and 173 is provided. Applicant respectfully requests withdrawal of this rejection.

D. Rejections under 35 U.S.C. § 102

1. The Claims Are Novel In View Of Miquel.

Claims 44, 66, 166, and 171 are rejected under 35 U.S.C. § 102(a)(1) for allegedly lacking novelty in view of Miquel et al. (Current Opinion in Microbiology, 2013, Vol. 16, p. 255-261.). The Office asserts:

> Claim Interpretation:
> Giving the claims the broadest reasonable interpretation of "a subject at risk of developing a cancer" is being interpreted as a population which are susceptible to development of cancer (see for example, p. 41 right-hand column 3rd paragraph of Maronpot et al., Toxicologic Pathology, 2004, Vol. 32, Suppl. 1, p. 40-48).

(Office Action at page 4.)

Applicant respectfully disagrees with this interpretation. The Office appears to rely on an extraneous source for claim interpretation without considering the claim language "in light of the specification as it would be interpreted by one of ordinary skill in the art." MPEP § 2111. However, solely to advance prosecution, Applicant has canceled claim 166, which recited "the subject is identified as at risk of developing a cancer." Applicant reserves the right to address the interpretation of this phrase in continuing applications.

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The Examiner appears to assert that Miquel teaches a method of preventing cancer. Solely to advance prosecution, and not in acquiescence to any rejection, Applicant has amended claim 44 to recite a method of treating cancer or reducing or delaying tumor growth in a subject in need thereof, comprising administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae. Applicant believes the amendment renders the rejection of claim 44, and its dependent claims 66 and 171, over Miquel moot. Applicant respectfully requests withdrawal of this rejection.

2. The Claims Are Novel In View Of Patyar.

Claims 44, 49, and 162-177 are rejected under 35 U.S.C. § 102(a)(1) for allegedly lacking novelty in view of Patyar et al. (Journal of Biomedical Science, 2010, Vol. 17, Nol. 21, p. 1-9.) Applicant respectfully disagrees.

The Office appears to assert that Patyar teaches the claimed method of treating cancer by administering *C. novyi*-NT. Solely to advance prosecution, and not in acquiescence to any rejection, Applicant has amended claim 44 to recite a method of treating cancer or reducing or delaying tumor growth in a subject in need thereof, comprising administering to the subject a composition comprising one or more isolated or purified population of bacteria belonging to the family Ruminococcaceae. Applicant believes the amendment renders the rejection of claim 44, and its dependent claims 49 and 162-177, over Patyar moot as *C. novyi*-NT is not in the family Ruminococcaceae. Applicant respectfully requests withdrawal of this rejection.

E. Rejections under 35 U.S.C. § 103

Claims 44, 46, 49, and 162-177 are rejected under 35 U.S.C. § 103 for alleged obviousness in view of Patyar and Wei et al. (Cancer Letters, 2008, Vol. 259, p. 16-27.). Applicant respectfully disagrees.

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Patyar has been discussed above with respect to claims 44, 49, and 162-177. The Office Action appears to rely on Wei to reject claim 46. However, Wei fails to bridge the gap between the teachings of Patyar and claim 44, from which claim 46 depends, as it also does not teach administration of a bacteria in the family of Ruminococcaceae. Therefore, the references fail to render claim 46 obvious. Applicant respectfully requests withdrawal of this rejection.

CONCLUSION

In light of the presented remarks, Applicant respectfully asserts that the pending claims are patentable for at least the reasons set forth above. Should additional information be required, Examiner is respectfully asked to notify Applicant of such need. If any impediments to the prompt allowance of the claims can be resolved by a telephone interview, Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

/Laurie Stellman/

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Date: July 8, 2021

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AMENDMENT TO THE CLAIMS

The listing of claims will replace all prior versions, and listing of claims in the application.

1-43. (Canceled)

44. (Currently Amended) A method of treating ~~or preventing~~ cancer or reducing or delaying tumor growth in a subject in need thereof, comprising administering to the subject a composition comprising ~~at least~~ one or more isolated or purified population of bacteria belonging to ~~one or more of the class Clostridia, class Mollicutes, order Clostridiales,~~ the family Ruminococcaceae ~~and/or genus Faecalibacterium~~.

45. (Canceled)

46. (Previously Presented) The method of claim 44, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47-48. (Canceled)

49. (Currently Amended) The method of claim 44, wherein the method further comprises administering ~~at least one~~ an additional anticancer treatment.

50-65. (Canceled)

66. (Currently Amended) The method of claim 44, wherein the population of bacteria ~~composition~~ comprises the bacteria *Faecalibacterium prausnitzii*.

67-161. (Canceled)

162. (Currently Amended) The method of claim 49, wherein the ~~at least one additional~~ anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

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163. (Previously Presented) The method of claim 162, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

164. (Currently Amended) The method of claim 49, wherein the ~~at least one immune checkpoint inhibitor and/or at least one additional~~ anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

165. (Currently Amended) The method of claim 44, ~~defined as method of treating a cancer~~ wherein the subject has a tumor.

166. (Canceled)

167. (Currently Amended) The method of claim [[44]]165, wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor.

168. (Previously Presented) The method of claim 167, wherein the T lymphocytes are cytotoxic T lymphocytes.

169. (Currently Amended) The method of claim 44, wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic ~~cell~~cells in the systemic circulation or the peripheral blood of the subject.

170. (Previously Presented) The method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

171. (Currently Amended) The method of claim [[44]]165, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

172. (Currently Amended) The method of claim [[44]]165, wherein administration of the composition to the subject results in ~~an~~ a decrease in RORγT expression in a tumor immune infiltrate.

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173. (Currently Amended) The method of claim [[44]]165, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or $HLA\text{-}DR^+$ cells in the tumor.

174. (Previously Presented) The method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

175. (Previously Presented) The method of claim 174, wherein the innate effector cells are $CD45^+CD11b^+Ly6G^+$ cells.

176. (Previously Presented) The method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

177. (Previously Presented) The method of claim 176, wherein suppressive myeloid cells are $CD45^+CD11b^+CD11c^+$ cells.

178. (New) The method of claim 44, wherein the method further comprises administering an immune checkpoint inhibitor.

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/337,820	Filing Date 03/28/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	07/08/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 28	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001074761	2735

32425 7590 04/09/2021

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EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
04/09/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

aoipdocket@nortonrosefulbright.com

Office Action Summary	Application No. 16/337,820	Applicant(s) WARGO et al.	
	Examiner KADE ARIANI	Art Unit 1651	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10 February 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 44,46,49,66 and 162-177 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 44,46,49,66 and 162-177 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 6/5/2020.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The response filed on February 10, 2021 has been received.

Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43, 73, 75, 79, 129, 131, 136, 139, 140 and 143, were canceled by applicant.

New claims 162-177 are added.

Claims 44, 46, 49, 66 and 162-177 are pending in this application and were examined on the merits (Also, see Restriction/Election below).

Restriction/Election:

Applicant's election without traverse of Group III claims 44, 46, 49 and 66, in the reply filed on 02/10/2021 is acknowledged.

Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43, 73, 75, 79, 129, 131, 136, 139, 140 and 143, were canceled by applicant in the same reply.

Election was made **without** traverse in the reply filed on 02/10/2021.

Improper Markush Grouping

Claim 44 and its dependent claims 46, 49, 66 and 162-177 are rejected on the basis that they contain an improper Markush grouping of alternatives. See *In re Harnisch*, 631 F.2d 716, 721-22 (CCPA 1980) and *Ex parte Hozumi*, 3 USPQ2d 1059, 1060 (Bd. Pat. App. & Int. 1984).

A Markush grouping is proper if the alternatives defined by the Markush group (i.e., alternatives from which a selection is to be made in the context of a combination or process, or alternative chemical compounds as a whole) share a "single structural similarity" and a common use. A Markush grouping meets these requirements in two situations. First, a Markush grouping is proper if the alternatives are all members of the same recognized physical or chemical class or the same art-recognized class, and are

disclosed in the specification or known in the art to be functionally equivalent and have a common use. Second, where a Markush grouping describes alternative chemical compounds, whether by words or chemical formulas, and the alternatives do not belong to a recognized class as set forth above, the members of the Markush grouping may be considered to share a "single structural similarity" and common use where the alternatives share both a substantial structural feature and a common use that flows from the substantial structural feature. See MPEP § 706.03(y).

The Markush grouping "class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus Faecalibacterium" recited in claim 44 is improper because the alternatives defined by the Markush grouping do not share both a single structural similarity and a common use for the following reasons:

In this case, the members of the Markush grouping "class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus Faecalibacterium" recited in claim 44, do not known in the art to be structurally or functionally equivalent and they do not share a common use.

In this case, for example, class Clostridia consists of a large and heterogeneous species of bacteria reside in soil, vegetation, and mammalian GI flora including many animal and human pathogens, while Mollicutes is a class of bacteria that lack cell wall, as such the members are not functionally or structurally equivalent, and share a common feature or use.

To overcome this rejection, Applicant may set forth each alternative (or grouping of patentably indistinct alternatives) within an improper Markush grouping in a series of independent or dependent claims and/or present convincing arguments that the group members recited in the alternative within a single claim in fact share a single structural similarity as well as a common use.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 167 and 173 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 167 recites the limitation "the tumor" in claims 44. There is insufficient antecedent basis for this limitation in the claim. Because claim 44 does not recite a tumor.

Claim173 recites the limitation "the tumor" in claims 44. There is insufficient antecedent basis for this limitation in the claim. Because claim 44 does not recite a tumor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claims 44, 66, 166 and 171 are rejected under 35 U.S.C. 102 (a)(1) as being anticipated by Miquel et al. (Current Opinion in Microbiology, 2013, Vol. 16, p. 255-261).

Claim Interpretation:

Giving the claims the broadest reasonable interpretation of "a subject at risk of developing a cancer" is being interpreted as a population which are susceptible to development of cancer (see for example, p. 41 right-hand column 3rd paragraph of Maronpot et al., Toxicologic Pathology, 2004, Vol. 32, Suppl. 1, p. 40–48).

Regarding claims 44, 66, and 166, Miquel et al. disclose a method of preventing cancer in a subject at risk of developing a cancer comprising administering to the subject at risk of developing a cancer composition comprising at least one isolated or purified population of bacteria *Faecalibacterium prausnitzii* (administering *Faecalibacterium prausnitzii* to mice, *Faecalibacterium prausnitzii* A2-165 deposit number DSM 17677, *Faecalibacterium prausnitzii* is the most abundant bacteria in the intestinal microbiota and further teach beneficial effects of butyrate-producing *Faecalibacterium prausnitzii* for health and reduction of cancer progression) (see for example, p. 255 left-hand column last paragraph, right-hand column 2nd paragraph, p. 256 left-hand column last 3rd paragraph, and Abstract).

Regarding claim 171, Miquel et al. further disclose wherein administration of the composition to the subject results in an increase FoxP3, … (anti-inflammatory mechanism of *F. prausnitzii*, by enhance the suppressive activity of Foxp3+ Tregs) (see for example, p. 258 Figure 2. legend and p. 259 left-hand column 1st paragraph lines 22-28).

Regarding the limitations of claims 167-170 and 172-177 not explicitly disclosed by Miquel et al., i.e., wherein administration of the composition results in an increase of CD8+ T lymphocytes in the tumor (claim 167), wherein the T lymphocytes are cytotoxic T lymphocytes (claim 168), wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject (claim 169), wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject (claim 170), wherein administration of the composition to the subject results in an decrease in RORγT expression in a tumor immune infiltrate (claim 172), wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20/CD56+, CD68+ and/or HLA-DR+ cells in the tumor (claim 173), wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject (claim 174), wherein the innate effector cells are CD45 CD1 1b+Ly6G+ cells (claim 175), wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject (claim 176), and wherein suppressive myeloid cells are CD45-

CD11b+CD11c' cells (claim177), the above-mentioned "wherein" clauses in claims 167-170 and 172-177 are not given weight because they simply express the intended results of the method step positively recited by Miquel et al.

Miquel et al. therefore anticipates the claimed method.

Claims 44, 49 and 162-177 are rejected under 35 U.S.C. 102 (a)(1) as being anticipated by Patyar et al. (Journal of Biomedical Science, 2010, Vol. 17, Nol. 21, p. 1-9).

Regarding claim 44, Patyar et al. disclose a method of treating cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia (administration of clostridia to animals having tumor, and significant anti-tumor effects of *C. novyi*-NT) (see for example, p. 2 right-hand column 1st paragraph).

Regarding claim 49, Patyar et al. disclose administering at least one additional anticancer treatment (*C. novyi*-NT used in combination with radiotherapy, chemotherapy, radioimmunotherapy, and anti-microtuble agents) (see for example, p. 2 right-hand column 2nd paragraph).

Regarding claim 162, Patyar et al. disclose wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy (*C. novyi*-NT used in combination with radiotherapy, chemotherapy, radio-immunotherapy, and anti-microtuble agents) (see for example, p. 2 right-hand column 2nd paragraph).

Regarding claim 163, Patyar et al. disclose wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy (monoclonal antibody or Mab B3) (see for example, p. 5 left-hand column 2nd paragraph).

Regarding claim 164, Patyar et al. disclose wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion (intravenously administration of clostridia) (see for example, p. 2 right-hand column 1st paragraph).

Regarding claim 165, Patyar et al. disclose defined as method of treating a cancer wherein the subject has a tumor (administration of clostridia to animals having tumor, and significant anti-tumor effects of *C. novyi*-NT) (see for example, p. 2 right-hand column 1st paragraph).

Regarding the limitations of claims 167-177 not explicitly disclosed by Patyar et al., i.e., wherein administration of the composition results in an increase of CD8+ T lymphocytes in the tumor (claim 167), wherein the T lymphocytes are cytotoxic T lymphocytes (claim 168), wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject (claim 169), wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject (claim 170), wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate (claim 171), wherein administration of the composition to the subject results in an decrease in RORγT expression in a tumor immune infiltrate (claim 172), wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20/CD56+, CD68+ and/or HLA-DR+ cells in the tumor (claim 173), wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject (claim 174), wherein the innate effector cells are CD45 CD1 1b+Ly6G+ cells (claim 175), wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject (claim 176), and wherein suppressive myeloid cells are CD45-CD11b+CD11c' cells (claim177), the

above-mentioned "wherein" clauses in claims 167-170 and 172-177 are not given weight because they simply express the intended results of the method step positively recited by Patyar et al.

Patyar et al. therefore anticipates the claimed method of treating cancer in a subject.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 44, 46, 49 and 162-177 are rejected under 35 U.S.C. 103 as being unpatentable over Patyar et al. (Journal of Biomedical Science, 2010, Vol. 17, Nol. 21, p. 1-9), as applied to claims 44, 49, and 162-177 above, and further in view of Wei et al. (Cancer Letters, 2008, Vol. 259, p. 16–27).

The teachings of Patyar et al. with respect to the limitations of claims 44, 49, and 162-177 were discussed above in detail.

Regarding claim 46, Wei et al. teach treating melanoma in a subject using bacteria belonging to one or more of the class Clostridia (spores of *C. oncolyticum* M-55 to treat mice bearing Harding-Passey melanoma) (see for example p. 20 right-hand column 2nd column), and (treating B16 melanoma with *C. novyi-NT* combination therapy) (see p. 21, Table 2 last strain).

Therefore, a person of ordinary skill in the art before the effective filing date of the invention knowing that bacteria belonging to one or more of the class Clostridia can be used to treat melanoma (as taught by Wei et al.) would have been motivated to modify the method taught by Patyar et al. and administer to a subject having melanoma (skin cancer) a composition comprising at least one isolated or purified population of the class Clostridia according to the teachings of Patyar et al. and Wei et al. with a reasonable expectation of success in providing the claimed method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia. Because Patyar et al. teach a method of treating cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, and further because Wei et al. teach treating melanoma in a subject using bacteria belonging to one or more of the class Clostridia.

Conclusions:

No claim(s) is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KADE ARIANI whose telephone number is (571)272-6083. The examiner can normally be reached on IFP, Monday - Friday, 8:00 AM -4:00 PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Renee Claytor can be reached on (571)272-8394. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KADE ARIANI/
Primary Examiner, Art Unit 1651

Notice of References Cited	Application/Control No. 16/337,820	Applicant(s)/Patent Under Reexamination WARGO et al.	
	Examiner KADE ARIANI	Art Unit 1651	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Patyar et al. Journal of Biomedical Science, 2010, Vol. 17, Nol. 21, p. 1-9.
	V	Miquel et al., Current Opinion in Microbiology, 2013, Vol. 16, p. 255-261.
	W	Maronpot et al., Toxicologic Pathology, 2004, Vol. 32, Suppl. 1, p. 40–48
	X	Wei et al. Cancer Letters, 2008, Vol. 259, p. 16–27.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K35/741 or A61P35/02 or A61P35/00 or A61K9/0053 or A61K45/06 or C12N1/20 or C12Q1/04 or A61K2035/115	04/02/2021	KA
A61K35/741 and A61P35/02 and A61P35/00 and A61K9/0053 and A61K45/06 and C12N1/20 and C12Q1/04 and A61K2035/115	04/02/2021	KA

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor/Applicant/Assignee names searched in PALM and EAST (Jennifer WARGO, Vancheswaran GOPALAKRISHNAN, THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM)	04/02/2021	KA
EAST (US-PGPUB, USPAT, USOCR, EPO, JPO, DERWENT) (see attached EAST text and Class./CPC search results)	04/02/2021	KA
NPL (google and google scholar) (see attached text search results)	04/02/2021	KA

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000123

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/337,820	WARGO et al.
	Examiner	Art Unit
	KADE ARIANI	1651

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000124

Examiner: Kade Ariani
Art Unit: 1651

/K.A/

Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: The Board of Regents, The University of Texas System	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name
	A1	2016/0193257	07/07/16	Honda, et al.
	A2	2018/0303934	10/25/18	Clube, et al.

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Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B1	CN 105296590	02/03/16	China	Chinese (English Abstract)
	B2	WO 2011/008369	01/20/11	PCT	English
	B3	WO 1995/001994	01/19/95	PCT	English
	B4	WO 1998/042752	10/01/98	PCT	English
	B5	WO 2000/037504	06/29/00	PCT	English
	B6	WO 2001/014424	03/01/01	PCT	English
	B7	WO 2005/003168	01/13/05	PCT	English
	B8	WO 2005/009465	02/03/05	PCT	English
	B9	WO 2006/00317	01/05/06	PCT	German (English Abstract)
	B10	WO 2006/072625	07/13/06	PCT	English
	B11	WO 2006/072626	07/13/06	PCT	English
	B12	WO 2006/121168	11/16/06	PCT	English
	B13	WO 2007/042573	04/19/07	PCT	English
	B14	WO 2008/084106	07/17/08	PCT	English
	B15	WO 2008/132601	11/06/08	PCT	English
	B16	WO 2009/044273	04/09/09	PCT	English

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Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: The Board of Regents, The University of Texas System	
	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
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	B18	WO 2009/114335	09/17/09	PCT	English
	B19	WO 2010/027827	03/11/10	PCT	English
	B20	WO 2010/065939	06/10/10	PCT	English
	B21	WO 2011/014438	02/03/11	PCT	English
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	B31	WO 2015/075688	05/28/15	PCT	English
	B32	WO 2016/063263	04/28/16	PCT	English
	B33	WO 2016/196605	12/08/16	PCT	English
	B34	WO 2017/172894	10/05/17	PCT	English
	B35	WO 2018/115519	06/28/18	PCT	English
	B36	WO 2019/191390	10/03/19	PCT	English
	B37	WO 96/15660	05/30/96	PCT	German (Corresponding U.S. Patent No. 5,873,196)

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U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

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	C2	Chaput, et al., "Baseline Gut Microbiota Predicts Clinical Response and Colitis in Metastatic Melanoma Patients Treated with Ipilimumab," *Annals of Oncolology*, 28(6): 1368-1379, 2017.
	C3	Chen, et al., "Analysis of Immune Signatures in Longitudinal Tumor Samples Yields Insight Into Biomarkers of Response and Mechanisms of Resistance to Immune Checkpoint Blockade," *Cancer Discovery*, 6: 827-837, 2016.
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	C6	Gopalkrishnan, et al. "Gut Microbiome Modulates Response to Anti-PD-1 Immunotherapy in Melanoma Patients," *Science*, 359(6371): 97-103, 2018.
	C7	Gueimonde, et al., Antibiotic Resistance in Probiotic Bacteria," Frontiers in Microbiology, 4(202): 1-6, 2013.
	C8	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2017/053717, mailed February 2, 2018. (Attorney Docket No. UTSC.P1149WO)
	C9	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2019/024519, dated October 24, 2019. (Attorney Docket No. UTSC.P1148WO).
	C10	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2019/62659, mailed March 30, 2020. (Attorney Docket No. UTSC.P1150WO).

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	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

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EXAMINER: /KADE ARIANI/	DATE CONSIDERED: 04/01/2021

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BIB DATA SHEET

CONFIRMATION NO. 2735

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/337,820	03/28/2019 RULE	424	1651	UTSC.P1149US/1001074761

APPLICANTS

THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, Austin, TX

INVENTORS

Jennifer WARGO, Houston, TX;
Vancheswaran GOPALAKRISHNAN, Houston, TX;

**** CONTINUING DATA ************************

This application is a 371 of PCT/US17/53717 09/27/2017
which claims benefit of 62/400,372 09/27/2016
and claims benefit of 62/508,885 05/19/2017
and claims benefit of 62/557,566 09/12/2017

**** FOREIGN APPLICATIONS ************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
01/23/2020

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ❑ No	/KADE ARIANI/ Examiner's Signature	❑ Initials	TX	78	28	3

ADDRESS

NORTON ROSE FULBRIGHT US LLP
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AUSTIN, TX 78701-4255
UNITED STATES

TITLE

METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

FILING FEE RECEIVED		
2070	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

BIB (Rev. 05/07).

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/337,820	Filing Date 03/28/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/10/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 28	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/JULIET MCMILLAN/
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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PATENT

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In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: 1651 Examiner: Ariani. KADE
Serial No.: 16/337,820 Filed: March 28, 2019	Atty. Dkt. No.: UTSC.P1149US/1001074761
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

February 10, 2021	/Laurie Stellman/
Date	Laurie Stellman

RESPONSE TO RESTRICTION REQUIREMENT DATED NOVEMBER 10, 2020

Applicant's submit this paper in response to the Restriction Requirement dated November 10, 2020, for which the date for response is February 10, 2021 in view of the Request for One Month Extension of Time submitted herewith.

The required fees are being charged to a credit card through the EFS-Web. Should any additional fees be required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper, the Commissioner is authorized to deduct said fees from Norton Rose Fulbright US LLP Account No.: 50-1212/UTSC.P1149US/1001074761

Amendments to the Claims beginning on page 2.

Remarks begin on page 5.

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AMENDMENT TO THE CLAIMS

The listing of claims will replace all prior versions, and listing of claims in the application.

1-43. (Canceled)

44. (Original) A method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*.

45. (Canceled)

46. (Previously Presented) The method of claim 44, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47-48. (Canceled)

49. (Original) The method of claim 44, wherein the method further comprises administering at least one additional anticancer treatment.

50-65. (Canceled)

66. (Original) The method of claim 44, wherein the composition comprises the bacteria *Faecalibacterium prausnitzii*.

67-161. (Canceled)

162. (New) The method of claim 49, wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy.

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163. (New) The method of claim 162, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

164. (New) The method of claim 49, wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

165. (New) The method of claim 44, defined as method of treating a cancer wherein the subject has a tumor.

166. (New) The method of claim 44, defined as method of preventing cancer wherein the subject is identified as at risk of developing a cancer.

167. (New) The method of claim 44, wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor.

168. (New) The method of claim 167, wherein the T lymphocytes are cytotoxic T lymphocytes.

169. (New) The method of claim 44, wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

170. (New) The method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

171. (New) The method of claim 44, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

172. (New) The method of claim 44, wherein administration of the composition to the subject results in an decrease in RORγT expression in a tumor immune infiltrate.

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173. (New) The method of claim 44, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or $HLA\text{-}DR^+$ cells in the tumor.

174. (New) The method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

175. (New) The method of claim 174, wherein the innate effector cells are $CD45^+CD11b^+Ly6G^+$ cells.

176. (New) The method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

177. (New) The method of claim 176, wherein suppressive myeloid cells are $CD45^+CD11b^+CD11c^+$ cells.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000134

REMARKS

A. Claim Amendments

Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43, 44, 46, 49, 66, 73, 75, 79, 129, 131, 136, 139, 140, and 143 were pending at the time of the Action. Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43, 73, 75, 79, 129, 131, 136, 139, 140, and 143 are canceled. Claims 162-177 are new and supported by at least original claims 50-65. No new matter has been added. Claims 44, 46, 49, 66, and 162-177 are pending.

B. Restriction Requirement Election

In response to the restriction requirement, Applicants elect, without traverse, to prosecute Group III. In response to the species election, Applicants elect a bacteria species of class Clostridia. Claims 44, 46, 49, 66, and 162-177 relate to the election.

The Examiner is invited to contact the undersigned patent agent with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Laurie Stellman/

Laurie Stellman
Reg. No. 66,817
Agent for Applicants

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd., Suite 1100
Austin, Texas 78701
(512) 536-3072

Date: February 10, 2021

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000135

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	28-Mar-2019
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Attorney Docket Number:	UTSC.P1149US/1001074761

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	110	110
Miscellaneous:				
		Total in USD ($)		**110**

Electronic Acknowledgement Receipt

EFS ID:	41888580
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Deborah Roszkowski
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	10-FEB-2021
Filing Date:	28-MAR-2019
Time Stamp:	13:29:27
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$110
RAM confirmation Number	E202120D29573875
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	UTSCP1149US_EOT.pdf	173475 46f1f80d1476a00267ff2aa5dee24ee0e347f84f	no	2
Warnings:					
Information:					
2		UTSCP1149US_RRR1.pdf	147315 8e5136971cacd172e8f6f8b6dfdb2ae8885f118d	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31299 085970de07b3c02c269aa342e699d9900c24cf59	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	352089		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/22 (10-20)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): UTSC.P1149US/1001074761

Application Number: 16/337,820

Filed: March 28, 2019

For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Art Unit: 1651

Examiner: Ariani Kade

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$220	$110	$55	$ 110
☐	Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☐	Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$
☐	Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐	Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1212/1001074761.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 66,817.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Laurie Stellman/ — Signature

February 10, 2021 — Date

Laurie Stellman — Typed or printed name

512-536-3072 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: R46C.REQ
Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
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REQUEST TO CORRECT OR UPDATE THE NAME OF THE APPLICANT UNDER 37 CFR 1.46(c)(1), OR CHANGE THE APPLICANT UNDER 37 CFR 1.46(c)(2)

(FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER SEPTEMBER 16, 2012)

Application Number	16/337,820
Filing Date	March 28, 2018
First Named Inventor	Jennifer Wargo
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Practitioner Docket Number	UTSC.P1149US-1001074761

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant hereby **requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2),** in the above-identified application. **Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.**

Please check the applicable box(es) below.

■ 1. This request is to **correct or update the name of the applicant** (**under 37 CFR 1.46(c)(1)**) and includes:

■ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (*e.g.*, underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (*i.e.*, where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

☐ 2. This request is to **change the applicant** (**under 37 CFR 1.46(c)(2)**) and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

☐ A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

☐ applicant* ■ attorney or agent of record Registration number 45104 ■ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature / Gina N. Shishima/

Typed or printed name Gina H. SHISHIMA

Date November 12, 2020

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

■ ** Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.36. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/~~1001065871~~ 1001074761
	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jennifer		WARGO	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Houston	State/Province	TX	Country of Residence	US

Mailing Address of Inventor:

Address 1	1814 Bissonnet St.		
Address 2			
City	Houston	State/Province	TX
Postal Code	77005	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Vancheswaran		GOPALAKRISHNAN	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Houston	State/Province	TX	Country of Residence	US

Mailing Address of Inventor:

Address 1	7900 Cambridge, Apt. 10-1b		
Address 2			
City	Houston	State/Province	TX
Postal Code	77054	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/~~1001065871~~ 1001074761
	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

☐ An Address is being provided for the correspondence Information of this application.			
Customer Number	32425		
Email Address	aoipdocket@nortonrosefulbright.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME		
Attorney Docket Number	UTSC.P1149US/1~~001065871~~ 1001074761	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	78	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	32425		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/~~1001065871~~ 1001074761
	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	a 371 of international	PCT/US2017/053717	2017-09-27
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2017/053717	Claims benefit of provisional	62/557566	2017-09-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2017/053717	Claims benefit of provisional	62/508885	2017-05-19
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2017/053717	Claims benefit of provisional	62/400372	2016-09-27

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/~~1001065871~~ 1001074761
	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/~~1001065871~~ 1001074761
	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◯ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	~~THE~~ BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

Mailing Address Information For Applicant:

Address 1	210 West 7th St.		
Address 2			
City	Austin	**State/Province**	TX
Country	US	Postal Code	78701
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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	Application Number	16/337,820
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Gina Shishima/			Date (YYYY-MM-DD)	~~2018-03-28~~ 2020-11-12
First Name	Gina	Last Name	Shishima	Registration Number	45,104

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	41105571
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Gina N. Shishima/Sherry Stowers
Filer Authorized By:	Gina N. Shishima
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	12-NOV-2020
Filing Date:	28-MAR-2019
Time Stamp:	13:29:16
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Req to correct/update/change appl name until pay issue fee	UCLA_P1149US_CorrectApplicantRequest.pdf	194285 88f2daaa45799ce8be52a871a18cad3aec0948d9	no	2
Warnings:					

Information:					
2	Application Data Sheet	UTSC_P1149US_Corrected_ADS.pdf	133554 320a645402adea7fdba9de7e1af2c209870fadda	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
			Total Files Size (in bytes):	327839	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001074761	2735

32425 7590 11/10/2020

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EXAMINER	
ARIANI, KADE	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
11/10/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

aoipdocket@nortonrosefulbright.com

Office Action Summary	Application No. 16/337,820	Applicant(s) WARGO et al.	
	Examiner KADE ARIANI	Art Unit 1651	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,3,5,7-9,18,20,25-27,35,37,40,43-44,46,49,66,73,75,79,129,131,136,139-140 and 143 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 1,3,5,7-9,18,20,25-27,35,37,40,43-44,46,49,66,73,75,79,129,131,136,139-140 and 143 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

When Claims Are Directed to Multiple Categories of Inventions:

As provided in 37 CFR 1.475 (b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475 (c).

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1, 3, 5, 7-9, 18, 20 and 25-27 are drawn to a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

Group II, claims 35, 37, 40 and 43 are drawn to a method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

Group III, claims 44, 46, 49 and 66 are drawn to a method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus Faecalibacterium.

Group IV, claims 73, 75 and 79 are drawn to a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition of claim 1, the response to the immune checkpoint inhibitor is favorable.

Group V, claims 129, 131, 136, 139, 140 and 143 are drawn to a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of butyrate-producing bacteria; (c) one or more bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R), then the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

Part A)

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I and II of invention fall within category (2) a product and a process of use of said product.

The inventions of Groups I and III of invention do not belong to any of the above-mentioned specific categories of invention.

The inventions of Groups I and IV of invention do not belong to any of the above-mentioned specific categories of invention.

The inventions of Groups I and V of invention do not belong to any of the above-mentioned specific categories of invention.

In addition, to the requirement that a group of inventions must belong to only one of the specific categories provided by PCT Rule 13.2, the inventions must have a special technical feature that unites them. See Patent Rules 1.475, where a special technical feature is a contribution OVER THE PRIOR ART.

In this case, the inventions of Groups I and II lack unity of invention because even though the inventions of these groups require the technical feature of a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of WO 2015/066625 A1 (also cited in IDS filed on 06/05/2020) who disclose/teach a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae (see for example, paragraphs [0077], [0084], [0086], [0093], [0095], [0098], [0100], [0155] and Figures 9G, 17F).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35

U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Part B)

Election of species:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Each type of bacteria (as recited in claims 1 or 35), the corresponding 16S rRNA gene SEQ ID NO (as recited in claim 18), the corresponding "response status of responder" or "R" (in Table 2) (as recited in claims 20 or 129), and the corresponding "enrichment index" or "ei" (in Table 1) (as recited in claim 129).

In addition, each type of bacteria (as recited in claim 44).

The unity of invention is lacking between the above-mentioned species of bacteria, in view of WO 2015/066625 A1 (also cited in IDS filed on 06/05/2020) who disclose/teach at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae (see for example, paragraphs [0077], [0084], [0086], [0093], [0095], [0098], [0100], [0155] and Figures 9G, 17F).

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an

allowed generic claim. Currently, the following claim(s) are generic: at least claims 1, 35 and 44 are generic.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

*If applicant elects Group I as the elected invention, then:

One species of bacteria (as recited in claim 1), for example, bacteria of the family of Ruminococcaceae,

One corresponding 16S rRNA gene SEQ ID number (from 1 to 876) (as recited in claim 18),

and

One corresponding "response status of responder" or "R" (in Table 2)(as recited in claim 20).

OR

*If applicant elects Group II as the elected invention, then:

One species of bacteria (as recited in claim 1), for example, bacteria of the family of Ruminococcaceae,

One corresponding 16S rRNA gene SEQ ID number (from 1 to 876) (as recited in claim 18),

and

One corresponding "response status of responder" or "R" (in Table 2) (as recited in claim 20).

OR

*If applicant elects Group III as the elected invention, then:

One species of bacteria (as recited in claim 44), for example, bacteria of family Ruminococcaceae.

OR

*If applicant elects Group V as the elected invention, then:

One "response status of responder" or "R" (in Table 2) (as recited in claim 129), and

One "enrichment index" or "ei" (in Table 1) (as recited in claim 129).

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KADE ARIANI whose telephone number is (571)272-6083. The examiner can normally be reached on IFP, in general, Monday - Friday, 8:00 AM -5:00 PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Renee Claytor can be reached on (571)272-8394. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KADE ARIANI/
Primary Examiner, Art Unit 1651

Electronic Acknowledgement Receipt

EFS ID:	39638954
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Monica Wozniak
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	05-JUN-2020
Filing Date:	28-MAR-2019
Time Stamp:	13:20:56
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Poutahidis.pdf	682073 f94cf099210eaaf9e337cd7bd3ad8f74741d0e49	no	5

Warnings:

Information:					
2	Non Patent Literature	Routy.pdf	600578 a14d6af91fa35ed4a8c86b78bdd288c696fa6375	no	9
Warnings:					
Information:					
3	Non Patent Literature	Sivan_2015.pdf	949351 63f4e3dded1c06f1d556acf1ff87620d02d9dd37	no	7
Warnings:					
Information:					
4	Non Patent Literature	Smelt_2013.pdf	2992548 00f96d408d45ff7c24c8b20435dbeb6362f7252e	no	12
Warnings:					
Information:					
5	Non Patent Literature	Taur_2014.pdf	963713 94bfdbae9f888bf1088708b5048feada229b7283	no	9
Warnings:					
Information:					
6	Non Patent Literature	Viaud_2014.pdf	1245643 834f4ab8594bf1b7596bdff348c27190bfe165cd	no	16
Warnings:					
Information:					
7	Non Patent Literature	Tumeh_2014.pdf	2382871 876c265c9532250466c6bc7da8ee1c56003bc842	no	24
Warnings:					
Information:					
8	Non Patent Literature	Vetizou_2015.pdf	1230641 4357737182b2ac0d7f8e9185ebc0c66ac9f1f8e1	no	13
Warnings:					
Information:					
		Total Files Size (in bytes):	11047418		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: The Board of Regents, The University of Texas System	
	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name
	A1	2016/0193257	07/07/16	Honda, et al.
	A2	2018/0303934	10/25/18	Clube, et al.

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B1	CN 105296590	02/03/16	China	Chinese (English Abstract)
	B2	WO 2011/008369	01/20/11	PCT	English
	B3	WO 1995/001994	01/19/95	PCT	English
	B4	WO 1998/042752	10/01/98	PCT	English
	B5	WO 2000/037504	06/29/00	PCT	English
	B6	WO 2001/014424	03/01/01	PCT	English
	B7	WO 2005/003168	01/13/05	PCT	English
	B8	WO 2005/009465	02/03/05	PCT	English
	B9	WO 2006/00317	01/05/06	PCT	German (English Abstract)
	B10	WO 2006/072625	07/13/06	PCT	English
	B11	WO 2006/072626	07/13/06	PCT	English
	B12	WO 2006/121168	11/16/06	PCT	English
	B13	WO 2007/042573	04/19/07	PCT	English
	B14	WO 2008/084106	07/17/08	PCT	English
	B15	WO 2008/132601	11/06/08	PCT	English
	B16	WO 2009/044273	04/09/09	PCT	English

99916921.1

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: The Board of Regents, The University of Texas System	
	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B17	WO 2009/101611	08/20/09	PCT	English
	B18	WO 2009/114335	09/17/09	PCT	English
	B19	WO 2010/027827	03/11/10	PCT	English
	B20	WO 2010/065939	06/10/10	PCT	English
	B21	WO 2011/014438	02/03/11	PCT	English
	B22	WO 2011/066342	06/03/11	PCT	English
	B23	WO 2012/071411	05/31/12	PCT	English
	B24	WO 2012/160448	11/29/12	PCT	English
	B25	WO 2013/006490	01/10/13	PCT	English
	B26	WO 2013/025779	02/21/13	PCT	English
	B27	WO 2013/067492	05/10/13	PCT	English
	B28	WO 2014/022021	02/06/14	PCT	English
	B29	WO 2015/016718	02/05/15	PCT	English
	B30	WO 2015/066625	05/07/15	PCT	English
	B31	WO 2015/075688	05/28/15	PCT	English
	B32	WO 2016/063263	04/28/16	PCT	English
	B33	WO 2016/196605	12/08/16	PCT	English
	B34	WO 2017/172894	10/05/17	PCT	English
	B35	WO 2018/115519	06/28/18	PCT	English
	B36	WO 2019/191390	10/03/19	PCT	English
	B37	WO 96/15660	05/30/96	PCT	German (Corresponding U.S. Patent No. 5,873,196)

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Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: The Board of Regents, The University of Texas System	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	Bultman, et al., "Microbial-Derived Butyrate: Oncometabolite or Tumor-Suppressive Metabolite?" Cell Host & Microbe, 16: 143-145, 2014.
	C2	Chaput, et al., "Baseline Gut Microbiota Predicts Clinical Response and Colitis in Metastatic Melanoma Patients Treated with Ipilimumab," *Annals of Oncolology*, 28(6): 1368-1379, 2017.
	C3	Chen, et al., "Analysis of Immune Signatures in Longitudinal Tumor Samples Yields Insight Into Biomarkers of Response and Mechanisms of Resistance to Immune Checkpoint Blockade," *Cancer Discovery*, 6: 827-837, 2016.
	C4	Frankel, et al., "Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients," *Neoplasia*, 19(10): 848-855, 2017.
	C5	Garrett, "Cancer and the Microbiota," *Science*, 348(6230): 80-86, 2015.
	C6	Gopalkrishnan, et al. "Gut Microbiome Modulates Response to Anti-PD-1 Immunotherapy in Melanoma Patients," *Science*, 359(6371): 97-103, 2018.
	C7	Gueimonde, et al., Antibiotic Resistance in Probiotic Bacteria," Frontiers in Microbiology, 4(202): 1-6, 2013.
	C8	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2017/053717, mailed February 2, 2018. (Attorney Docket No. UTSC.P1149WO)
	C9	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2019/024519, dated October 24, 2019. (Attorney Docket No. UTSC.P1148WO).
	C10	International Search Report and Written Opinion Issued in Corresponding PCT Patent Application No. PCT/US2019/62659, mailed March 30, 2020. (Attorney Docket No. UTSC.P1150WO).

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Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: The Board of Regents, The University of Texas System	
	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C11	Klieve, et al., "Ruminococcus Bromii, Identification and Isolation as a Dominant Community Member in the Rumen of Cattle Fed A Barley Diet," Journal of Applied Microbiology, 103: 2065-2073, 2007.
	C12	Matson, et al., "The Commensal Microbiome is Associated with Anti-PD-1 Efficacy in Metastatic Melanoma Patients," Science, 359(6371): 104-108, 2018.
	C13	Pitt, et al., "Fine-Tuning Cancer Immunotherapy: Optimizing the Gut Microbiome," *Cancer Research*, 76(16): 4602-4607, 2016.
	C14	Pitt, et al., "Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors," Immunity, 44(6), 1255-1269, 2016.
	C15	Poutahidis Theofilis, et al., "Gut Microbiota and the Paradox of Cancer Immunotherapy," *Frontiers in Immunology*, 5(Article 157): 1-5, 2014.
	C16	Routy, et al. "Gut Microbiome Influences Efficacy of PD-1-Based Immunotherapy Against Epithelial Tumors," *Science*, 359(6371), 91-97, 2018.
	C17	Sivan, et al., "Commensal Bifidobacterium Promotes Antitumor Immunity and Facilitates Ant-PD-L1 Efficacy," *Science,* 350: 1084-1089, 2015.
	C18	Smelt, et al., "Probiotics Can Generate FoxP23 T-Cell Responses in the Small Intestine an Simultaneously CD4 and CD8 T Cell Activation in the Large Intestine," PLOS One, 8(7):e68952, 1-12, 2013.
	C19	Taur, et al., "The Effects of Intestinal Tract Bacterial Diversity on Mortality Following Allogenic Hematopoietic Stem Cell Transplantation," *Blood*, 124: 1174-1182, 2014.
	C20	Tumeh, et al., "PD-1 Blockade Induces Responses by Inhibiting Adaptive Immune Resistance," *Nature,* 515: 568-571, 2014.
	C21	Vetizou, et al., "Anticancer Immunotherapy by CTLA-4 Blockade Relies on the Gut Microbiota," *Science*, 350(6264), 1079-1084, 2015.
	C22	Viaud, et al., "Gut Microbiome and Anticancer Immune Response: Really Hot Sh*t!" Cell Death and Differentiation, 22(2): 199-214, 2014.

99916921.1

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)	Atty. Docket No.: UTSC.P1149US/1001074761	Serial No.: 16/337,820
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: The Board of Regents, The University of Texas System	
(Use several sheets if necessary)	Filing Date: March 28, 2019	Group: 1651

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1-2*	*See Page 3-4*

99916921.1

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000173

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference UTFC.P1305WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US17/53717	International filing date *(day/month/year)* 27 September 2017 (27.09.2017)	(Earliest) Priority Date *(day/month/year)* 27 September 2016 (27.09.2016)
Applicant Board of Regents, The University of Texas System		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1A

☐ as suggested by the applicant.

☒ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

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:

      ☒ 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).

2. ☐ 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.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

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.: 35-43, 151, 152, 157
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:

-***-Please see supplemental page-***-

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 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.:
Groups I+, Claims 1-34, 44-66; Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518) (bacterial species)

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 9/19, 31/7105, 35/742, 9/00; C12R 1/145 (2017.01)
CPC - A61K 9/19, 31/7105, 35/742, 9/0053; C12R 1/145

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

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 2015/066625 A1 (WASHINGTON UNIVERSITY) 7 May 2015; title; paragraphs [0077], [0084], [0086], [0093], [0095], [0098], [0100], [0155]; Figures 9G, 17F	1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2 -- 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 32/1-2
Y	(BULTMAN, SJ et al.) Microbial-derived butyrate: An oncometabolite or tumor-suppressive metabolite? 13 August 2014, Vol. 16, No. 2; pages 143-145; Figure 1; DOI: 10.1016/j.chom.2014.07.011	33/1-2, 34/1-2
X -- Y	(KLIEVE, AV et al.) Ruminococcus bromii, identification and isolation as a dominant community member in the rumen of cattle fed a barley diet. Journal of Applied Microbiology. 2 August 2007, Vol. 103, Issue 6; pages 2065-2073; abstract; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph; DOI: 10.1111/j.1365-2672.2007.03492.x	1, 15/1, 16/1, 17/1, 19/1 -- 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2
X -- Y	US 2016/193257 A1 (THE UNIVERSITY OF TOKYO, et al.) 7 July 2016; paragraphs [0028], [0067], [0097], [0101], [0205], [0265]; Figure 12	44 -- 45-54
Y	(GUEIMONDE, M et al.) Antibiotic resistance in probiotic bacteria. Frontiers in Microbiology. 18 July 2013, Vol. 4, Article 202; pages 1-6; abstract; page 5, 2nd column, 2nd paragraph; DOI: 10.3389/fmicb.2013.00202	32/1-2

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2018 (10.01.2018)	02 FEB 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/075688 A1 (INSTITUT GUSTAVE ROUSSY) 28 May 2015; page 3, lines 10-11; page 20, lines 20-23; page 21, line 37 – page 22, line 9; page 22, line 9; page 22, lines 30-32; page 22, line 35 – page 23, line 1; page 23, lines 16-19; page 23, lines 25-30; page 32, lines 5-7; page 41, lines 19-27; page 44, lines 3-6; page 46, lines 13-16; Figure 20	45-54
A	(VIAUD, S et al.) Gut microbiome and anticancer immune response: really hot Sh*t! Cell Death and Differentiation. February 2015, Epub 16 May 2014, Vol 22, No. 2; pages 199-214; page 204, 2nd column, 1st paragraph; page 205, 1st column, 1st paragraph; DOI: 10.1038/cdd.2014.56	55-65
A	(SMELT, MJ et al.) Probiotics Can Generate FoxP3 T-Cell Responses in the Small Intestine and Simultaneously Inducing CD4 and CD8 T Cell Activation in the Large Intestine. Plos One. 4 July 2013, Vol. 8, Issue 7; e68952; pages 1-12; abstract; page 8, 1st column, 1st paragraph; page 8, 2nd column, 1st paragraph; Table 3; DOI: 10.1371/journal.pone.0068952	55-65
A	(PITT, JM et al.) Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors. Immunity. 21 June 2016, Vol. 44, No. 6; pages 1255-1269; DOI: 10.1016/j.immuni.2016.06.001	1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44-65
P, X	WO 2016/196605 A1 (THE UNIVERSITY OF CHICAGO) 8 December 2016; entire document	1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44-65
P, X	WO 2017/172894 A2 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 5 October 2017; entire document	1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44-65

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/53717

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-34, 44-66 and Ruminococcaceae Ruminococcus bromii are directed toward compositions and a method for treating cancer, comprising at least one isolated or purified population of bacteria.

The compositions and method will be searched to the extent they encompass the bacterial species Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518) (bacterial species). Applicant is invited to elect additional bacterial specie(s), with, where applicable, specified associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s), for each, to be searched. Additional bacterial specie(s) with associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 8 (in-part), 9 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 19 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 27 (in-part), 28 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 33 (in-part), 34 (in-part), 44 (in-part), 45 (in-part), 46 (in-part), 47 (in-part), 48 (in-part), 49 (in-part), 50 (in-part), 51 (in-part), 52 (in-part), 53 (in-part), 54 (in-part), 55 (in-part), 56 (in-part), 57 (in-part), 58 (in-part), 59 (in-part), 60 (in-part), 61 (in-part), 62 (in-part), 63 (in-part), 64 (in-part) and 65 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518) (bacterial species). Applicants must specify the claims that encompass any additionally elected bacterial specie(s), with, where applicable, specified associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a bacterial species encompassing Ruminococcaceae Sporobacter termitidis (NCBI taxonomy 44749)(bacterial species).

Groups II+, Claims 67-79, 115 -150, 153-156, 158-161 and Ruminococcaceae Acutalibacter muris are directed toward methods of predicting a response to an immune checkpoint inhibitor, and methods of treating cancer in a subject associated therewith.

The methods can be searched to the extent they encompass the bacterial species Ruminococcaceae Acutalibacter muris (bacterial species). Applicant is invited to elect additional bacterial specie(s) to be searched. Additional bacterial specie(s) can be searched upon the payment of additional fees. It is believed that claims 67 (in-part), 68 (in-part), 69 (in-part), 70 (in-part), 71 (in-part), 72 (in-part), 73 (in-part), 74 (in-part), 75 (in-part), 76 (In-part), 77 (In-part), 78 (in-part), 79 (in-part), 115 (in-part), 116 (in-part), 117 (in-part), 118 (in-part), 119 (in-part), 120 (in-part), 121 (in-part), 122 (in-part), 123 (in-part), 124 (in-part), 125 (in-part), 126 (in-part), 127 (in-part), 128 (in-part), 129 (in-part), 130 (in-part), 131 (in-part), 132 (in-part), 133 (in-part), 134 (in-part), 135 (in-part), 136 (in-part), 137 (in-part), 138 (in-part), 139 (in-part), 140 (in-part), 141 (in-part), 144 (in-part), 145 (in-part), 146 (in-part), 147 (in-part), 148 (in-part), 149 (in-part), 150 (in-part), 153 (in-part), 154 (in-part), 155 (in-part), 156 (in-part), 158 (in-part), 159 (in-part), 160 (in-part) and 161 (in-part) encompass this first named invention of Groups II+ and thus these claims can be searched with payment of a fee for the search of Groups II+, to the extent that they encompass Ruminococcaceae Acutalibacter muris (bacterial species). Applicants must specify the claims that encompass any additionally elected bacterial specie(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups x+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups x+ to be searched/examined. An exemplary election would be Ruminococcaceae Anaerotruncans colihominis (bacterial species).

Groups III+, Claims 80-114 and butyrate are directed toward a method of treating cancer in a subject comprising administering a therapeutically effective amount of butyrate, an isolated or purified butyrate-producing bacterial population.

The method can be searched to the extent that it comprises an agent encompassing butyrate (agent). Applicant is invited to elect additional agent(s), including specified butyrate-producing bacterial population(s), to be searched. Additional agent(s), including specified butyrate-producing bacterial population(s) can be searched upon the payment of additional fees. It is believed that claims 80 (in-part), 81 (in-part), 82 (in-part), 92 (in-part), 93 (in-part), 94 (in-part), 95 (in-part), 96 (in-part), 97 (in-part), 98 (in-part), 99 (in-part), 100 (in-part), 101 (in-part), 102 (in-part), 103 (in-part), 104 (in-part), 105 (in-part), 106 (in-part), 107 (in-part), 108 (in-part), 109 (in-part), 110 (in-part), 111 (in-part) 112 (in-part), 113 (in-part) and 114 (in-part) encompass this first named invention of Groups III+ and thus these claims can be searched with payment of a fee for the search of Groups III+, to the extent that they encompass butyrate (agent). Applicants must specify the claims that encompass any additionally elected agent(s), including specified butyrate-producing bacterial population(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups III+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups x+ to be searched/examined. An exemplary election would be a butyrate-producing bacterial population encompassing Faecalibacterium prausnitzii (butyrate-producing agent).

The inventions listed as Groups I+, II+ and III+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include SEQ ID NO: 1, not present in either of Groups II+ or III+; the special technical features of Groups II+ include a microbial profile of the gut microbiome, not present in either of Groups I+ or III+; the special technical features of Groups III+ include administering butyrate, not present in either of Groups I+ or II+.

Groups I+, II+ and III+ share the technical features including: a method of treating cancer in a subject comprising administering. Groups I + and II+ share the technical features including: a composition comprising at least one isolated or purified population of bacteria; Groups II+ and III+ share the technical features including administering an immune checkpoint inhibitor.

However, these shared technical features are previously disclosed by the article 'Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors' by Pitt, J.M. et al. (hereinafter 'Pitt').

-***-Continued Within the Next Supplemental Box-***-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

-***-Continued from Previous Supplemental Box-***-

Pitt discloses a method of treating cancer in a subject comprising administering (a method of treating cancer comprising administering: page 1256, second column, second paragraph); a composition comprising at least one isolated or purified population of bacteria (oral feeding with Bifidobacterium (a composition comprising at least one isolated or purified population of bacteria); page 1262, second column, first paragraph); administering an immune checkpoint inhibitor (administering an immune checkpoint inhibitor; page 1256, first column, first paragraph; second column, second paragraph).

No technical features are shared between the bacteria of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a composition comprising at least one, or at least two isolated or purified population of bacteria; and a method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria; these shared technical features are previously disclosed by WO 2016/110585 A1 to Wageningen Universiteit (hereinafter 'Wageningen').

Wageningen discloses a composition comprising at least one (a composition comprising at least one; page 4, lines 10-13; page 6, lines 1-2), or at least two isolated or purified population of bacteria (or at least two isolated or purified population of bacteria; page 20, lines 1-2); and a method of treating or preventing cancer in a subject (and a method of treating or preventing cancer in a subject; abstract, page 6, lines 21-24) comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria (comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria; page 4, lines 10-13; page 7, lines 7-10).

No technical features are shared between the bacteria of Groups II+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups II+ were considered to share the technical features including: a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial profile in the gut microbiome having one or more of bacterial populations; and a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition, the response to the immune checkpoint inhibitor is favorable; and wherein if the microbial profile comprises: a low abundance of butyrate-producing bacteria; or one or more bacteria species designated with a response status of non-responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor; these shared technical features are previously disclosed by Pitt, as above.

Pitt discloses a method of treating cancer in a subject (a method of treating melanoma (cancer) in a subject; page 1262, first column, first paragraph) comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject (comprising administering a therapeutically effective amount of ipilimumab (an immune checkpoint inhibitor) to said subject; page 1262, first column, first paragraph), wherein the subject has been determined to have a favorable microbial profile in the gut microbiome (wherein the subject was determined to have a 'cluster C' (favorable) microbial profile in the gut microbiome; page 1262, first column, first paragraph) having one or more bacterial populations (having a Bacteriodes fragilis population (one or more bacterial populations); page 1262, first column, first paragraph). Pitt further discloses wherein an unfavorable profile (wherein a 'cluster B' (unfavorable') profile; page 1262, first column, first paragraph) was correlated with complete resistance to the immune checkpoint inhibitor (was correlated with complete resistance to the mAb (Immune checkpoint inhibitor); page 1262, first column, first paragraph).

Pitt does not disclose a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition, the response to the immune checkpoint inhibitor is favorable; and wherein if the microbial profile comprises: a low abundance of butyrate-producing bacteria; or one or more bacteria species designated with a response status of non-responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. However, based upon the disclosure of Pitt with regard to microbial profiles correlating with response or a complete lack of response to an immune checkpoint inhibitor, it would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Pitt to have specifically provided a method of predicting a response to Ipilimumab, comprising providing a profile of the gut microbiota of a subject, wherein a profile comprising favorable bacteria indicates that a response to the immune checkpoint inhibitor is favorable; and wherein the presence of one or more bacteria present in an unfavorable profile, as disclosed by Pitt, is indicative of a non-responder, wherein the patient is predicted to not have a favorable response to the immune checkpoint inhibitor; in order to better enable the selection of an appropriate course of therapy, and whether to include immune checkpoint inhibitors, or a specific immune checkpoint inhibitor in the therapy, so as to maximize the potential for response of the patient to therapy while minimizing potential adverse side effects.

No technical features are shared between the agents and bacteria of Groups III+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups III+ were considered to share the technical features including: a method of treating cancer in a subject comprising administering a therapeutically effective amount of butyrate, an isolated or purified butyrate-producing bacterial population, and/or a composition comprising at least one, or at least two isolated or purified population of bacteria to said subject, wherein the subject has been administered an immune checkpoint inhibitor; these shared technical features are previously disclosed by Wageningen, as above, in view of Pitt, as above.

Wageningen discloses a method of treating cancer in a subject (a method of treating or preventing cancer in a subject; abstract, page 6, lines 21-24) comprising administering a therapeutically effective amount an isolated or purified butyrate-producing bacterial population to said subject (comprising administering a therapeutically effective amount an isolated or purified butyrate-producing bacterial population to said subject; page 4, lines 10-13; page 6, lines 21-24; page 7, lines 7-10).

Wageningen does not disclose wherein the subject has been administered an immune checkpoint inhibitor.

-***-Continued Within the Next Supplemental Box-***-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/53717

-***-Continued from Previous Supplemental Box-***-

Pitt discloses administration of immunogenic commensal bacteria in combination with immune checkpoint blockade (administration of immunogenic commensal bacteria in combination with immune checkpoint blockade; page 1264, first column, second paragraph); and wherein Treg cells play a role in immune tolerance (wherein Treg cells play a role in immune tolerance; page 1261, first column, third paragraph) and are affected by commensal bacteria (are affected by commensal bacteria; page 1261, first column, third paragraph) and butyrate (and butyrate; page 1261, first column, third paragraph).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Wageningen to have included combining an immune checkpoint inhibitor, as disclosed by Pitt, with a butyrate-producing commensal strain of bacteria, as disclosed by Wageningen, in order to enable the generation of a microbial profile in the gut of a subject that favors the effectiveness of the immune checkpoint inhibitor, in order to better provide treatment for cancer.

Since none of the special technical features of the Groups I+, II+ and III+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Pitt and Wageningen references, unity of invention is lacking.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Marshall P. Byrd
Parker Highlander PLLC
1120 S. Capital of Texas Highway
Bldg. One, Suite 200
Austin, TX 78746
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	02 FEB 2018
Applicant's or agent's file reference UTFC.P1305WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US17/53717	27 September 2017 (27.09.2017)	27 September 2016 (27.09.2016)

International Patent Classification (IPC) or both national classification and IPC
IPC - A61K 9/19, 31/7105, 35/742, 9/00; C12R 1/145 (2017.01)
CPC - A61K 9/19, 31/7105, 35/742, 9/0053; C12R 1/145

Applicant Board of Regents, The University of Texas System

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 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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	10 January 2018 (10.01.2018)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/53717

Box No. I Basis of this 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:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/53717

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 35-43, 151, 152, 157

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 35-43, 151, 152, 157 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 35-43, 151, 152, and 157 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 35-43, 151, 152, 157

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

Form PCT/ISA/237 (Box No. III) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/53717

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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-34, 44-66 and Ruminococcaceae Ruminococcus bromii are directed toward compositions and a method for treating cancer, comprising at least one isolated or purified population of bacteria.

The compositions and method will be searched to the extent they encompass the bacterial species Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518) (bacterial species). Applicant is invited to elect additional bacterial specie(s), with, where applicable, specified associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s), for each, to be searched. Additional bacterial specie(s) with associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 8 (in-part), 9 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 19 (in-part), 24 (in-part), 25 (in-part), 26 (in-part), 27 (in-part), 28 (in-part), 29 (in-part), 30 (in-part), 31 (in-part), 32 (in-part), 33 (in-part), 34 (in-part), 44 (in-part), 45 (in-part), 46 (in-part), 47 (in-part), 48 (in-part), 49 (in-part), 50 (in-part), 51 (in-part), 52 (in-part), 53 (in-part), 54 (in-part), 55 (in-part), 56 (in-part), 57 (in-part), 58 (in-part), 59 (in-part), 60 (in-part), 61 (in-part), 62 (in-part), 63 (in-part), 64 (in-part) and 65 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518) (bacterial species). Applicants must specify the claims that encompass any additionally elected bacterial specie(s), with, where applicable, specified associated NCBI taxonomy number(s) and/or 16S rRNA SEQ ID NO(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a bacterial species encompassing Ruminococcaceae Sporobacter termitidis (NCBI taxonomy 44749)(bacterial species).

Groups II+, Claims 67-79, 115 -150, 153-156, 158-161 and Ruminococcaceae Acutalibacter muris are directed toward methods of predicting a response to an immune checkpoint inhibitor, and methods of treating cancer in a subject associated therewith.

The methods can be searched to the extent they encompass the bacterial species Ruminococcaceae Acutalibacter muris (bacterial species). Applicant is invited to elect additional bacterial specie(s) to be searched. Additional bacterial specie(s) can be searched upon the payment of additional fees. It is believed that claims 67 (in-part), 68 (in-part), 69 (in-part), 70 (in-part), 71 (in-part), 72 (in-part), 73 (in-part), 74 (in-part), 75 (in-part), 76 (in-part), 77 (in-part), 78 (in-part), 79 (in-part), 115 (in-part), 116 (in-part), 117 (in-part), 118 (in-part), 119 (in-part), 120 (in-part), 121 (in-part), 122 (in-part), 123 (in-part), 124 (in-part), 125 (in-part), 126 (in-part), 127 (in-part), 128 (in-part), 129 (in-part), 130 (in-part), 131 (in-part), 132 (in-part), 133 (in-part), 134 (in-part), 135 (in-part), 136 (in-part), 137 (in-part), 138 (in-part), 139 (in-part), 140 (in-part), 141 (in-part), 144 (in-part), 145 (in-part), 146 (in-part), 147 (in-part), 148 (in-part), 149 (in-part), 150 (in-part), 153 (in-part), 154 (in-part), 155 (in-part), 156 (in-part), 158 (in-part), 159 (in-part), 160 (in-part) and 161 (in-part) encompass this first named invention of Groups II+ and thus these claims can be searched with payment of a fee for the search of Groups II+, to the extent that they encompass Ruminococcaceae Acutalibacter muris (bacterial species). Applicants must specify the claims that encompass any additionally elected bacterial specie(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups x+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups x+ to be searched/examined. An exemplary election would be Ruminococcaceae Anaerotruncans colihominis (bacterial species).

-***-Continued Within Supplemental Box-***-

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-34, 44-66; Ruminococcaceae Ruminococcus bromii (NCBI taxonomy 40518)

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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**

1. Statement

Novelty (N)	Claims	9, 15/2, 16/2, 17/2, 19/2, 32/1-2, 45-65	YES
	Claims	-***-Please See Below-***-	NO
Inventive step (IS)	Claims	55-65	YES
	Claims	-***-Please See Below-***-	NO
Industrial applicability (IA)	Claims	-***-Please See Below-***-	YES
	Claims	NONE	NO

2. Citations and explanations:

-***-Continued from Box No. V: 1. Statement-***-

Novelty (N): NO: Claims 1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 15/1, 16/1, 17/1, 19/1, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44

Inventive step (IS): NO: Claims 1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44-54

Industrial Applicability (IA): YES: Claims 1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, 44-65

-***-Box No. V: 2. Citations and Explanations-***-

Claims 1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, and 31/1-2 lack novelty under PCT Article 33(2) as being anticipated by WO 2015/066625 A1 to WASHINGTON UNIVERSITY (hereinafter 'Washington').

As per claim 1, Washington discloses a composition comprising at least one isolated or purified population of bacteria belonging to the family Ruminococcaceae (A composition comprising Ruminococcus obeum A TCC29714 or a bacterial isolate that is a member of the taxon Ruminococcus obeum OTU ID 178122 may be formulated for oral or rectal administration, and may be administered alone or with an additional therapeutic agent; paragraphs [0077], [0084], [0086]).

As per claim 2, Washington discloses a composition comprising at least two isolated or purified populations of bacteria belonging to the family Ruminococcaceae (R. obeum finds use with one or more additional bacterial taxa of the invention, artificial community that included R. obeum, Ruminococcus torques, and Faecalibacterium prausnitzii (a member of Ruminococcaceae as defined by the instant PCT application; claims 10-11); paragraph [0084], [0155]).

As per claim 3/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein each of the populations of bacteria is present in the composition at a concentration of at least 10^3 CFU (total amount of bacteria per unit dose include from about 10^2 to about 10^12 colony forming units (CFU) of each bacterial strain; paragraph [0093]).

As per claim 4/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition is a live bacterial product or a live biotherapeutic product (bacterial taxon of the invention, or a combination of bacterial taxa of the invention, is formulated to maintain a suitable level of viable cells during the formulation's shelf life and upon administration to a subject; paragraph [0093]).

As per claim 5/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are provided as bacterial spores (Generally, a bacterial strain may be provided as a frozen or freeze-dried culture, or as bacterial spores; paragraph [0093]).

As per claim 7/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the family Ruminococcaceae (A composition comprising Ruminococcus obeum ATCC29714 or a bacterial isolate that is a member of the taxon Ruminococcus obeum OTU ID 178122 may be formulated for oral or rectal administration, and may be administered alone or with an additional therapeutic agent; paragraphs [0077], [0084], [0086]).

As per claim 8/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus Ruminococcus (A composition comprising Ruminococcus obeum ATCC29714 or a bacterial isolate that is a member of the taxon Ruminococcus obeum OTU ID 178122 may be formulated for oral or rectal administration, and may be administered alone or with an additional therapeutic agent; paragraphs [0077], [0084], [0086]).

-***-Continued within the Next Supplemental Box-***-

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Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 2016/196605 A1	8 December 2016 (08.12.2016)	1 June 2016 (01.06.2016)	1 June 2015 (01.06.2015)
WO 2017/172894 A2	5 October 2017 (05.10.2017)	29 March 2017 (29.03.2017)	30 March 2016 (30.03.2016)

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

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Box No. VII Certain defects in the international application

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

Claim 7 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: the claim contains the phrase "the the family Ruminococcaceae" which contains the repeated word 'the'. The claim is interpreted to mean "the family Ruminococcaceae".

Claim 28 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: the claim contains the phrase "two isolated or purified populationss" which contains a typo of a repeated 's'. Thus, the claim is interpreted to mean "two isolated or purified populations".

Claim 60 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: the claim contains the phrase "results in an decrease" which incorrectly uses the Indefinite article 'an' instead of 'a'. The phrase is interpreted to say "results in a decrease".

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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:

Claim 52 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 52 indefinite for the following reason: the claim lacks antecedent basis as it contains the phrase "the at least one immune checkpoint inhibitor" and depends upon claims 44 and 49, neither of which contain the phrase "immune checkpoint inhibitor". Thus, the phrase is interpreted to mean "an immune checkpoint inhibitor".

Claim 55 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 55 indefinite for the following reason: the claim lacks antecedent basis as it contains the phrase "the tumor" and depends upon claims 44, which does not contain the phrase "a tumor". Thus, the phrase is interpreted to mean "a tumor".

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

-***-Continued from Box V: Citations and Explanations-***-

As per claim 8/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus Ruminococcus (A composition comprising Ruminococcus obeum ATCC29714 or a bacterial isolate that is a member of the taxon Ruminococcus obeum OTU ID 178122 may be formulated for oral or rectal administration, and may be administered alone or with an additional therapeutic agent; paragraphs [0077], [0084], [0086]).

As per claim 24/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the bacteria are lyophilized or freeze dried (Generally, a bacterial strain may be provided as a frozen or freeze-dried culture, or as bacterial spores; paragraph [0093]).

As per claim 25/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition is formulated for oral delivery (A composition comprising Ruminococcus obeum A TCC29714 or a bacterial isolate that is a member of the taxon Ruminococcus obeum OTU ID 178122 may be formulated for oral or rectal administration, and may be administered alone or with an additional therapeutic agent; paragraphs [0077], [0084], [0086]).

As per claim 26/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition formulated for oral delivery is a tablet or capsule (The mixture is then processed into granules or pressed into tablets; paragraph [0095]).

As per claim 27/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the tablet or capsule comprises an acid resistant enteric coating (Since the viability of a bacterial strain may be negatively impacted by acidic media, the above-mentioned granules or tablets may be coated with an enteric coating; paragraph [0095]).

As per claim 28/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition comprising the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria is formulated for administration rectally, via colonoscopy, sigmoidoscopy by nasogastric tube, or enema (a bacterial taxon of the invention, or a combination of bacterial taxa of the invention, may be prepared in the form of a ready-made enema; paragraph [0098]).

As per claim 29/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition is lyophilized or is frozen (Generally, a bacterial strain may be provided as a frozen or freeze-dried culture, or as bacterial spores; paragraph [0093]).

As per claim 30/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition is capable of being reformulated for final delivery as comprising a liquid, a suspension, a gel, a geltab, a semisolid, a tablet, a sachet, a lozenge, a capsule, or as an enteral formulation (The mixture is then processed into granules or pressed into tablets; paragraph [0095]).

As per claim 31/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the composition is formulated for multiple administrations (The desired dose may be presented in multiple, e.g. two, three, four, five, six, or more, sub-doses administered at appropriate intervals throughout the day; paragraph [0100]).

Claims 33/1-2 and 34/1-2 lack novelty under PCT Article 33(2) as being anticipated by Washington as evidenced by the publication entitled "Microbial-derived butyrate: An oncometabolite or tumor-suppressive metabolite?" by Bultman, SJ et al. (hereinafter 'Bultman').

As per claim 33/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are butyrate-producing populations of bacteria (A composition comprising a bacterial isolate that is a member of the taxon Ruminococcus obeum, and an artificial community included R. obeum, Ruminococcus torques, and Faecalibacterium prausnitzii (a member of Ruminococcaceae as defined by the instant PCT application; claims 10-11), where Ruminococcaceae biotriansoform carbohydrates into butyrate as evidenced by the Bultman reference (Figure 1); paragraphs [0077], [0084], [0086], [0155]).

As per claim 34/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses comprising butyrate (A composition comprising a bacterial isolate that is a member of the taxon Ruminococcus obeum, and an artificial community included R. obeum, Ruminococcus torques, and Faecalibacterium prausnitzii (a member of Ruminococcaceae as defined by the instant PCT application; claims 10-11), where Ruminococcaceae biotriansoform carbohydrates into butyrate as evidenced by the Bultman reference (Figure 1); paragraphs [0077], [0084], [0086], [0155]).

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Claims 1, 15/1, 16/1, 17/1, and 19/1 lack novelty under PCT Article 33(2) as being anticipated by the publication entitled "Ruminococcus bromii, identification and isolation as a dominant community member in the rumen of cattle fed a barley diet" by Klieve, AV et al. (hereinafter 'Klieve').

As per claim 1, Klieve discloses a composition comprising at least one isolated or purified population of bacteria belonging to the family Ruminococcaceae (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph).

As per claim 15/1, Klieve discloses the composition of claim 1 or claim 2, and Klieve further discloses wherein at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belongs to Ruminococcus bromii with an enrichment index, ei, greater than 0.5 (samples from steers showed Ruminococcus bromii, which was subsequently isolated (enrichment of 100%) using traditional culture-based techniques; abstract).

As per claim 16/1, Klieve discloses the composition of claim 1 or claim 2, and Klieve further discloses wherein at least one isolated or purified population bacteria or the at least two isolated or purified population of bacteria belongs to Ruminococcus bromii with an "ei" equal to 1 (samples from steers showed Ruminococcus bromii, which was subsequently isolated (enrichment of 100%) using traditional culture-based techniques; abstract).

As per claim 17/1, Klieve discloses the composition of claim 1, and Klieve further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria comprise a 16S ribosomal RNA, rRNA, nucleotide sequence that is at least 90% identical to the 16S rRNA nucleotide sequence of bacteria identified by NCBI Taxonomy ID: 40518 (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 (97% identical according to NCBI BLAST multiple allgnment of R. bromii 16S rRNA gene, GenBank: X85099.1, with R. bromii YE282 16S rRNA gene, GenBank: DQ882649.1) were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph).

As per claim 19/1, Klieve discloses the composition of claim 1, and Klieve further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains of Ruminococcus bromii (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph).

Claim 44 lacks novelty under PCT Article 33(2) as being anticipated by US 2016/193257 A1 to THE UNIVERSITY OF TOKYO, et al. (hereinafter 'Tokyo').

As per claim 44, Tokyo discloses a method of treating or preventing cancer (examples of target diseases for which the composition is useful for treatment include colon cancer; paragraph [0097]) in a subject comprising administering to the subject a composition (a pharmaceutical preparation for oral administration comprises an additional component that enables efficient delivery of the bacterial composition of the present invention to the colon; paragraph [0101]) comprising at least one isolated or purified population of bacteria (methods of identifying and culturing intestinal commensal bacteria, isolated from humans; paragraphs [0028]) belonging to class Clostridia, order Clostridiales, family Ruminococcacea (mice inoculated with faecalibacterium prausnitzii (a member of Ruminococcaceae as defined by the instant PCT application; claims 10-11); paragraphs [0067], [0265]; Figure 12).

Claims 9, 15/1-2, 16/1-2, 17/1-2, and 19/1-2 lack an inventive step under PCT Article 33(3) as being obvious over Washington in view of Klieve.

As per claim 9, Washington discloses the composition of claim 8, and Washington further discloses wherein the population of bacteria belonging to the genus Ruminococcus is further defined as a population of bacteria belonging to the species Ruminococcus bromii (within a larger list Recovery-associated Taxa, Ruminococcus bromii; Figures 9G, 17F). Washington does not specifically disclose wherein the population of bacteria belonging to the genus Ruminococcus is further defined as a population of bacteria belonging to the species Ruminococcus bromii. Klieve discloses a population of Ruminococcus bromii (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising an isolated population of bacteria belonging to the family Ruminococcaceae, as disclosed by Washington, to incorporate or instead use an isolated population of Ruminococcus bromii, as disclosed by Klieve, as Washington discloses the administration of a composition comprising Ruminococcus obeum, allows for administration with additional species presented in the disclosure, and contemplates taxa associated with recovery, such as Ruminococcus bromii, Klieve discloses isolated Ruminococcus bromii and evaluation of its role in gut the gut microbiome, and this combination would allow the method of Washington to benefit from the administration of Ruminococcus bromii, affording the ability to restore normal gut microbiota function, as contemplated by Washington (abstract) by restoring or enhancing starch utilization, as taught by Klieve (Ruminococcus bromii YE282 may be useful as a probiotic inoculant to increase the efficiency of starch utilization; abstract).

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As per claim 15/1-2, Washington discloses the composition of claim 1 or claim 2, but Washington does not disclose wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belongs to Ruminococcus bromii with an enrichment index, ei, greater than 0.5. Klieve discloses at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belongs to Ruminococcus bromii with an enrichment index, ei, greater than 0.5 (samples from steers showed Ruminococcus bromii, which was subsequently isolated (enrichment of 100%) using traditional culture-based techniques; abstract). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising Ruminococcus bromii isolates, as disclosed by Washington, to incorporate enrichment of Ruminococcus bromii, as disclosed by Klieve, as Washington discloses using bacterial isolates, requiring prior enrichment, Klieve discloses isolation of Ruminococcus bromii from samples, thereby enriching the sample by 100%, and this combination would allow the methods of Washington to be performed using Ruminococcus bromii isolated from additional sources or to avoid having to purchase previously isolated strains.

As per claim 16/1-2, Washington discloses the composition of claim 1 or claim 2, but Washington does not disclose wherein the at least one isolated or purified population bacteria or the at least two isolated or purified population of bacteria belongs to Ruminococcus bromii with an "ei" equal to 1. Klieve discloses at least one isolated or purified population bacteria or the at least two isolated or purified population of bacteria belongs to Ruminococcus bromii with an "ei" equal to 1 (samples from steers showed Ruminococcus bromii, which was subsequently isolated (enrichment of 100%) using traditional culture-based techniques; abstract). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising Ruminococcus bromii isolates, as disclosed by Washington, to incorporate enrichment of Ruminococcus bromii, as disclosed by Klieve, as Washington discloses using bacterial isolates, requiring prior enrichment, Klieve discloses isolation of Ruminococcus bromii from samples, thereby enriching the sample by 100%, and this combination would allow the methods of Washington to be performed using Ruminococcus bromii isolated from additional sources or to avoid having to purchase previously isolated strains

As per claim 17/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria comprise a 16S ribosomal RNA, rRNA, nucleotide sequence that is at least 90% identical to the 16S rRNA nucleotide sequence of bacteria identified by NCBI Taxonomy ID: 40518 (within a larger list Recovery-associated Taxa, Ruminococcus bromii (which intrinsically comprises the 16S rRNA sequence corresponding to NCBI Taxonomy ID: 40518, correspondent to Ruminococcus bromii); Figures 9G, 17F). Washington does not specifically disclose wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria comprise a 16S ribosomal RNA nucleotide sequence that is at least 90% identical to the 16S rRNA nucleotide sequence of bacteria identified by NCBI Taxonomy ID: 40518. Klieve discloses a population of Ruminococcus bromii (NCBI Taxonomy ID: 40518) (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 (97% identical according to NCBI BLAST multiple alignment of R. bromii 16S rRNA gene, GenBank: X85099.1, with R. bromii YE282 16S rRNA gene, GenBank: DQ882649.1) were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising an isolated population of bacteria belonging to the family Ruminococcaceae, as disclosed by Washington, to incorporate or instead use an isolated population of Ruminococcus bromii, as disclosed by Klieve, as Washington discloses the administration of a composition comprising Ruminococcus obeum, allows for administration with additional species presented in the disclosure, and contemplates taxa associated with recovery, such as Ruminococcus bromii, Klieve discloses isolated Ruminococcus bromii and evaluation of its role in gut the gut microbiome, and this combination would allow the method of Washington to benefit from the administration of Ruminococcus bromii, affording the ability to restore normal gut microbiota function, as contemplated by Washington (title) by restoring or enhancing starch utilization, as taught by Klieve (Ruminococcus bromii YE282 may be useful as a probiotic inoculant to increase the efficiency of starch utilization; abstract).

As per claim 19/1-2, Washington discloses the composition of claim 1 or claim 2, and Washington further discloses wherein the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains of Ruminococcus bromii (within a larger list Recovery-associated Taxa, Ruminococcus bromii; Figures 9G, 17F). Washington does not specifically disclose at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains of Ruminococcus bromii. Klieve discloses wherein one isolated or purified population of bacteria is Ruminococcus bromii (R. bromii is culturable and has been isolated from humans, and quantitative standards containing known numbers of R. bromii YE282 were prepared by directly enumerating a pure culture of YE282; page 2068, 1st column, 2nd paragraph; page 2072, 2nd column, 3rd paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising an isolated population of bacteria belonging to the family Ruminococcaceae, as disclosed by Washington, to incorporate or instead use an isolated population of Ruminococcus bromii, as disclosed by Klieve, as Washington discloses the administration of a composition comprising Ruminococcus obeum, allows for administration with additional species presented in the disclosure, and contemplates taxa associated with recovery, such as Ruminococcus bromii, Klieve discloses isolated Ruminococcus bromii and evaluation of its role in gut the gut microbiome, and this combination would allow the method of Washington to benefit from the administration of Ruminococcus bromii, affording the ability to restore normal gut microbiota function, as contemplated by Washington (title) by restoring or enhancing starch utilization, as taught by Klieve (Ruminococcus bromii YE282 may be useful as a probiotic inoculant to increase the efficiency of starch utilization; abstract).

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In case the space in any of the preceding boxes is not sufficient.
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Claim 31/1-2 lacks an inventive step under PCT Article 33(3) as being obvious over Washington in view of the publication entitled "Antibioticresistanceinprobioticbacteria" by Gueimonde, M et al. (hereinafter 'Gueimonde').

As per claim 32/1-2, Washington discloses the composition of claim 1 or claim 2, but Washington does not disclose wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprise an antibiotic resistance gene. Gueimonde discloses wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprise an antibiotic resistance gene (some probiotic strains with intrinsic antibiotic resistance could be useful for restoring the gut microbiota after antibiotic treatment, and it is worth noting the presence of specific antibiotic resistance mechanisms in certain Bacillusclausii strains, which have been used as probiotics in humans, especially for the prevention of infectious bacterial diarrhea; abstract; page 5, 2nd column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition comprising bacteria, as disclosed by Washington, to incorporate an antibiotic resistance gene, as disclosed by Gueimonde, as Washington discloses bacterial isolates for use as probiotics, Gueimonde discloses administration of bacteria as probiotics which have antibiotic resistance, and further contemplates the value of antibiotics in probiotics (title), and this combination would allow the composition of Washington to benefit from an antibiotic resistance gene, such as to aid in the prevention of infectious bacterial diarrhea, as specifically taught by Gueimonde.

Claims 45-54 lack an inventive step under PCT Article 33(3) as being obvious over Tokyo in view of WO 2015/075688 A1 to INSTITUT GUSTAVE ROUSSY (hereinafter 'Gustave').

As per claim 45, Tokyo discloses the method of claim 44, but Tokyo does not disclose wherein the cancer is a skin cancer. Gustave discloses wherein the cancer is a skin cancer (impact of CTX on microbiotia significantly altered microbial composition of the small intestine in mice bearing subcutaneous cancers, namely metastasizing B16F10 melanomas and non-metastsizing MCA205 sarcomas, where the probiotic composition according to the invention may be administered to a patient in need thereof after the administration of an antineoplastic treatment, for example a chemotherapeutic agent such as cyclophosphamide, CTX, to said patient; page 23, lines 16-19; page 41, lines 19-27). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target skin cancer, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, such as colon cancer, Gustave discloses the administration of a probiotic for the purpose of treating melanoma, and this combination would allow the method of Tokyo to treat skin cancers, such as melanomas.

As per claim 46, Tokyo discloses the method of claim 44, but Tokyo does not disclose wherein the cancer is basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma. Gustave discloses wherein a cancer is melanoma (impact of CTX on microbiotia significantly altered microbial composition of the small intestine in mice bearing subcutaneous cancers, namely metastasizing B16F10 melanomas and non-metastsizing MCA205 sarcomas, where the probiotic composition according to the invention may be administered to a patient in need thereof after the administration of an antineoplastic treatment, for example a chemotherapeutic agent such as cyclophosphamide, CTX, to said patient; page 23, lines 16-19; page 41, lines 19-27). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target skin cancer, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, such as colon cancer, Gustave discloses the administration of a probiotic for the purpose of treating melanoma, and this combination would allow the method of Tokyo to treat skin cancers, such as melanomas.

As per claim 47, Tokyo discloses the method of claim 44, but Tokyo does not disclose wherein the cancer is melanoma. Gustave discloses wherein a cancer is melanoma (impact of CTX on microbiotia significantly altered microbial composition of the small intestine in mice bearing subcutaneous cancers, namely metastasizing B16F10 melanomas and non-metastsizing MCA205 sarcomas, where the probiotic composition according to the invention may be administered to a patient in need thereof after the administration of an antineoplastic treatment, for example a chemotherapeutic agent such as cyclophosphamide, CTX, to said patient; page 23, lines 16-19; page 41, lines 19-27). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target skin cancer, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, such as colon cancer, Gustave discloses the administration of a probiotic for the purpose of treating melanoma, and this combination would allow the method of Tokyo to treat skin cancers, such as melanomas.

As per claim 48, Tokyo and Gustave, in combination, disclose the method of claim 47, but Tokyo does not disclose wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma. Gustave discloses wherein a melanoma is metastatic melanoma (impact of CTX on microbiotia significantly altered microbial composition of the small intestine in mice bearing subcutaneous cancers, namely metastasizing B16F10 melanomas and non-metastsizing MCA205 sarcomas, where the probiotic composition according to the invention may be administered to a patient in need thereof after the administration of an antineoplastic treatment, for example a chemotherapeutic agent such as cyclophosphamide, CTX, to said patient; page 23, lines 16-19; page 41, lines 19-27). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target metastatic melanoma, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, such as colon cancer, Gustave discloses the administration of a probiotic for the purpose of treating melanoma, and this combination would allow the method of Tokyo to treat skin cancers, such as metastatic melanoma.

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As per claim 49, Tokyo discloses the method of claim 44, but Tokyo does not disclose wherein the method further comprises administering at least one additional anticancer treatment. Gustave discloses wherein a method further comprises administering at least one additional anticancer treatment (invention further pertains to cell compositions and their use in adoptive cell transfer in combination with a chemotherapeutic agent, for example a chemotherapeutic agent such as cyclophosphamide; page 3, lines 10-11; page 23, lines 16-19). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate an additional anticancer treatment with the administration of a probiotic, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with a chemotherapeutic, and this combination would allow the method of Tokyo to benefit from combination therapies with well-known anticancer treatments, such as administration of cyclophosphamide, as taught by Gustave.

As per claim 50, Tokyo and Gustave, in combination, disclose the method of claim 49, but Tokyo does not disclose wherein the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy. Gustave discloses wherein the at least one additional anticancer treatment is chemotherapy (invention further pertains to cell compositions and their use in adoptive cell transfer in combination with a chemotherapeutic agent, for example a chemotherapeutic agent such as cyclophosphamide; page 3, lines 10-11; page 23, lines 16-19) or a biological therapy (anticancer biological therapies; page 21, line 37 – page 22, line 9). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate an additional anticancer treatment, such as a chemotherapeutic or biological therapy with the administration of a probiotic, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with a chemotherapeutic agent or biological therapy, and this combination would allow the method of Tokyo to benefit from combination therapies with well-known anticancer treatments, such as administration of cyclophosphamide, as taught by Gustave.

As per claim 51, Tokyo and Gustave, in combination, disclose the method of claim 50, but Tokyo does not disclose wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy. Gustave discloses wherein the biological therapy (a probiotic comprising bacteria as an adjuvant to an antineoplastic treatment administered to a cancer agent, where antineoplastic treatments include biological therapies; page 20, lines 20-23; page 21, line 37 – page 22, line 9; page 22, line 35 – page 23, line 1) is a monoclonal antibody (monoclonal antibodies; page 22, line 2) or gene therapy (gene therapy; page 22, line 9). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate an additional anticancer treatment, such as a biological therapy, such as a monoclonal antibody or gene therapy, with the administration of a probiotic, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with a biological therapy, including monoclonal antibodies and gene therapy, and this combination would allow the method of Tokyo to benefit from combination therapies with well-known anticancer treatments, such as the use of directed monoclonal antibodies.

As per claim 52, Tokyo and Gustave, in combination, disclose the method of claim 49, but Tokyo does not disclose wherein an immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion. Gustave discloses wherein the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intraperitoneally (Chemotherapy was performed by intratumoral injection or intraperitoneal inoculation of CTX; page 32, lines 5-7). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate an additional anticancer treatment administered intraperitoneally, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with an additional therapy and the administration of that therapeutic by intraperitoneal inoculation, and this combination would allow the method of Tokyo to benefit from combination therapies with well-known anticancer treatments, such as administration of cyclophosphamide, as taught by Gustave, via a well-known administration method, such as intraperitoneal injection.

As per claim 53, Tokyo discloses the method of claim 44, but Tokyo does not disclose defined as method of treating a cancer wherein the subject has a tumor. Gustave discloses a method of treating a cancer wherein the subject has a tumor (invention further pertains to cell compositions and their use in adoptive cell transfer in combination with a chemotherapeutic agent, and treatment refers to any reduction or amelioration of the progression, severity, and/or duration of cancer, particularly a solid tumor; page 3, lines 10-11; page 22, lines 30-32). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target a subject having a tumor, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with an additional therapy where the treatment may be directed towards a solid tumor, and this combination would allow the method of Tokyo to treat cancers presenting tumors.

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As per claim 54, Tokyo discloses the method of claim 44, but Tokyo does not disclose defined as method of preventing cancer wherein the subject is identified as at risk of developing a cancer. Gustave discloses a method of preventing cancer wherein the subject is identified as at risk of developing a cancer (a particularly useful application of the probiotic compositions according to the present invention is their use in combination with such a chemotherapeutic agent, for further increasing the efficacy of cancer vaccination; page 23, lines 25-30). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method for treating cancer comprising administering a member of Ruminococcaceae, as disclosed by Tokyo, to incorporate or instead target a subject a risk for developing cancer, so as to vaccinate against the cancer, as disclosed by Gustave, as Tokyo discloses the administration of the gut bacteria to treat or ameliorate cancer, Gustave discloses the administration of a probiotic in combination with an additional therapy where the treatment may be directed towards improving a cancer vaccination, and this combination would allow the method of Tokyo to pre-treat subjects at risk for developing cancer, such as those who might receive a cancer vaccination.

Claims 55-65 meets the criteria set out in PCT Article 33(2)-(3).

Claim 55 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in an increase of CD8+ T lymphocytes in a tumor.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition results in an increase of CD8+ T lymphocytes in a tumor.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTl7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition results in an increase of CD8+ T lymphocytes in a tumor.

The publication entitled "Gut microbiome and anticancer immune response: really hot Sh*t!" by Viaud, S et al. (hereinafter 'Viaud') discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8β T effector/ Foxp3β regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition results in an increase of CD8+ T lymphocytes in a tumor.

The publication entitled "Probiotics Can Generate FoxP3 T-Cell Responses in the Small Intestine and Simultaneously Inducing CD4 and CD8 T Cell Activation in the Large Intestine" by Smelt, MJ et al. (hereinafter 'Smelt') discloses wherein probiotics result in an induction of CD8+ T lymphocytes (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells; abstract). Smelt does not disclose wherein administration of the composition results in an increase of CD8+ T lymphocytes in a tumor.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in an increase of CD8+ T lymphocytes in the tumor, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 55, as no reference teaches the administration of Ruminococcaceae for the treatment of cancer, wherein the specific effect is an increase in CD8+ T lymphocytes in a tumor.

Claim 56 meets the criteria set out in PCT Article 33(2)-(3), because it depends on claim 55.

Claim 57 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition results in an increase of effector CD4 +, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTl7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

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Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

Smelt discloses wherein probiotics result in an induction of CD4+ and CD8+ T lymphocytes (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells; abstract). Smelt does not disclose wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in an increase of effector CD4+, CD8+ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 57.

Claim 58 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTI7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

Smelt discloses wherein probiotics result in an induction of T lymphocytes (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells; abstract). Smelt does not disclose wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 58.

Claim 59 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTI7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

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Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

Smelt discloses wherein probiotics result in an induction of T lymphocytes (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells; abstract). Smelt does not disclose wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 59.

Claim 60 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTl7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate.

Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate.

Smelt discloses wherein probiotics result in an induction of T lymphocytes and considers ROR-gamma-T (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells, and ROR-gamma-T transcripts were not changed in probiotic treatments ; abstract; page 8, 2nd column, 1st paragraph; Table 3). Smelt does not disclose wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in a decrease in ROR-gamma-T expression in a tumor immune infiltrate, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 60.

Claim 61 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTl7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20 +/CD56+, CD68+ and/or HLA-DR+ cells in the tumor.

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Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor.

Smelt discloses wherein probiotics result in an induction of CD4 and CD8+ T lymphocytes (L. salivarius UCC118 induced activation in both CD4 and CD8+ T-cells; abstract). Smelt does not disclose wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 61.

Claim 62 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells (antibiotic-mediated elimination of commensal bacteria causes defects at the level of innate immunity, loss of γδTl7 cells in the tumor microenvironment, that result in modulations of cognate antitumor immune responses, effector memory TILs, with a reduced CD8+/Foxp3 ratio; page 46, lines 13-16; Figure 20). Gustave does not disclose wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

Viaud discloses the effect of loss of gram-positive bacteria and effect of CTX on effector cells (validated the concept that the eradication of Gram-positive bacteria correlated with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio, and CTX facilitates the priming of effector pTh17 and memory Th1 cell responses directed against distinct commensals in distant secondary lymphoid organs; page 204, 2nd column, 1st paragraph; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

Smelt discloses wherein probiotics result in an induction of CD4 and CD8+ T lymphocytes (increased percentage of CD25+ cells after L. salivarius UCC118 treatment as compared with medium treatment, and the balance between effector CD4 T cells and regulatory T cells in the PP was not changed; page 8, 1st column, 1st paragraph). Smelt does not disclose wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in an increase in the level of innate effector cells in the subject, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 62.

Claim 63 meets the criteria set out in PCT Article 33(2)-(3), because it depends on claim 62.

Claim 64 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

Tokyo discloses wherein Clostridium affect CD8+ T lymphocytes in the colon (it has been reported that Clostridium spp. Exert an influence on the accumulation of CD8+ intestinal tract intraepithelial lymphocytes, and exhibits a marked ability to induce and maintain Treg cells; paragraph [0205]). Tokyo does not disclose wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

Gustave discloses wherein the administration of a chemotherapeutic decreases T cells and an effect on myeloid differentiation (the increase in pTh17 cells required expression of myeloid differentiation primary response gene 88, which signals downstream of toll-like receptors and is required for the therapeutic success of anticancer chemotherapies in several tumor models; page 44, lines 3-6). Gustave does not disclose wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

-***-Continued Within the Next Supplemental Box-***-

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Viaud discloses the effect of loss of gram-positive bacteria (preclinical model mimicking human tumorigenesis, we validated the concept that the eradication of Gram-positive bacteria by vancomycin compromised the efficacy of CTX-based chemotherapy, correlating with a reduced intratumoral CD8+ T effector/ Foxp3 regulatory T-cell ratio; page 205, 1st column, 1st paragraph). Viaud does not disclose wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

Smelt discloses wherein probiotics result in an induction of CD4 and CD8+ T lymphocytes (increased percentage of CD25+ cells after L. salivarius UCC118 treatment as compared with medium treatment, and the balance between effector CD4 T cells and regulatory T cells in the PP was not changed; page 8, 1st column, 1st paragraph). Smelt does not disclose wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject.

The prior art does not teach or fairly suggest the method of claim 44, wherein administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject, and sufficient motivation, based upon the previous disclosures of the Tokyo, Gustave, Viaud, and Smelt references, does not exist to have determined and implemented the method as described by Claim 64.

Claim 65 meets the criteria set out in PCT Article 33(2)-(3), because it depends on claim 64.

Claims 1-2, 3/1-2, 4/1-2, 5/1-2, 7/1-2, 8/1-2, 9, 15/1-2, 16/1-2, 17/1-2, 19/1-2, 24/1-2, 25/1-2, 26/1-2, 27/1-2, 28/1-2, 29/1-2, 30/1-2, 31/1-2, 33/1-2, 34/1-2, and 44-65 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Box No. IV: Lack of unity of invention-***-

Groups III+, Claims 80-114 and butyrate are directed toward a method of treating cancer in a subject comprising administering a therapeutically effective amount of butyrate, an isolated or purified butyrate-producing bacterial population.

The method can be searched to the extent that it comprises an agent encompassing butyrate (agent). Applicant is invited to elect additional agent(s), including specified butyrate-producing bacterial population(s), to be searched. Additional agent(s), including specified butyrate-producing bacterial population(s) can be searched upon the payment of additional fees. It is believed that claims 80 (in-part), 81 (in-part), 82 (in-part), 92 (in-part), 93 (in-part), 94 (in-part), 95 (in-part), 96 (in-part), 97 (in-part), 98 (in-part), 99 (in-part), 100 (in-part), 101 (in-part), 102 (in-part), 103 (in-part), 104 (in-part), 105 (in-part), 106 (in-part), 107 (in-part), 108 (in-part), 109 (in-part), 110 (in-part), 111 (in-part) 112 (in-part), 113 (in-part) and 114 (in-part) encompass this first named invention of Groups III+ and thus these claims can be searched with payment of a fee for the search of Groups III+, to the extent that they encompass butyrate (agent). Applicants must specify the claims that encompass any additionally elected agent(s), including specified butyrate-producing bacterial population(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups III+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups x+ to be searched/examined. An exemplary election would be a butyrate-producing bacterial population encompassing Faecalibacterium prausnitzii (butyrate-producing agent).

The inventions listed as Groups I+, II+ and III+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include SEQ ID NO: 1, not present in either of Groups II+ or III+; the special technical features of Groups II+ include a microbial profile of the gut microbiome, not present in either of Groups I+ or III+; the special technical features of Groups III+ include administering butyrate, not present in either of Groups I+ or II+.

Groups I+, II+ and III+ share the technical features including: a method of treating cancer in a subject comprising administering. Groups I + and II+ share the technical features including: a composition comprising at least one isolated or purified population of bacteria; Groups II+ and III+ share the technical features including administering an immune checkpoint inhibitor.

However, these shared technical features are previously disclosed by the article 'Resistance Mechanisms to Immune-Checkpoint Blockade in Cancer: Tumor-Intrinsic and -Extrinsic Factors' by Pitt, J.M. et al. (hereinafter 'Pitt').

Pitt discloses a method of treating cancer in a subject comprising administering (a method of treating cancer comprising administering: page 1256, second column, second paragraph); a composition comprising at least one isolated or purified population of bacteria (oral feeding with Bifidobacterium (a composition comprising at least one isolated or purified population of bacteria); page 1262, second column, first paragraph); administering an immune checkpoint inhibitor (administering an immune checkpoint inhibitor; page 1256, first column, first paragraph; second column, second paragraph).

No technical features are shared between the bacteria of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a composition comprising at least one, or at least two isolated or purified population of bacteria; and a method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria; these shared technical features are previously disclosed by WO 2016/110585 A1 to Wageningen Universiteit (hereinafter 'Wageningen').

Wageningen discloses a composition comprising at least one (a composition comprising at least one; page 4, lines 10-13; page 6, lines 1-2), or at least two isolated or purified population of bacteria (or at least two isolated or purified population of bacteria; page 20, lines 1-2); and a method of treating or preventing cancer in a subject (and a method of treating or preventing cancer in a subject; abstract, page 6, lines 21-24) comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria (comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria; page 4, lines 10-13; page 7, lines 7-10).

No technical features are shared between the bacteria of Groups II+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups II+ were considered to share the technical features including: a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microblal profile in the gut microbiome having one or more of bacterial populations; and a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition, the response to the immune checkpoint inhibitor is favorable; and wherein if the microbial profile comprises: a low abundance of butyrate-producing bactoria; or one or more bacteria species designated with a response status of non-responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor; these shared technical features are previously disclosed by Pitt, as above.

-***-Continued Within the Next Supplemental Box-***-

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

-***-Continued from Previous Supplemental Box-***-

Pitt discloses a method of treating cancer in a subject (a method of treating melanoma (cancer) in a subject; page 1262, first column, first paragraph) comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject (comprising administering a therapeutically effective amount of ipilimumab (an immune checkpoint inhibitor) to said subject; page 1262, first column, first paragraph), wherein the subject has been determined to have a favorable microbial profile in the gut microbiome (wherein the subject was determined to have a 'cluster C' (favorable) microbial profile in the gut microbiome; page 1262, first column, first paragraph) having one or more bacterial populations (having a Bacteriodes fragilis population (one or more bacterial populations); page 1262, first column, first paragraph). Pitt further discloses wherein an unfavorable profile (wherein a 'cluster B' (unfavorable') profile; page 1262, first column, first paragraph) was correlated with complete resistance to the immune checkpoint inhibitor (was correlated with complete resistance to the mAb (immune checkpoint inhibitor); page 1262, first column, first paragraph).

Pitt does not disclose a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition, the response to the immune checkpoint inhibitor is favorable; and wherein if the microbial profile comprises: a low abundance of butyrate-producing bacteria; or one or more bacteria species designated with a response status of non-responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. However, based upon the disclosure of Pitt with regard to microbial profiles correlating with response or a complete lack of response to an immune checkpoint inhibitor, it would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Pitt to have specifically provided a method of predicting a response to Ipilimumab, comprising providing a profile of the gut microbiota of a subject, wherein a profile comprising favorable bacteria indicates that a response to the immune checkpoint inhibitor is favorable; and wherein the presence of one or more bacteria present in an unfavorable profile, as disclosed by Pitt, is indicative of a non-responder, wherein the patient is predicted to not have a favorable response to the immune checkpoint inhibitor; in order to better enable the selection of an appropriate course of therapy, and whether to include immune checkpoint inhibitors, or a specific immune checkpoint inhibitor in the therapy, so as to maximize the potential for response of the patient to therapy while minimizing potential adverse side effects.

No technical features are shared between the agents and bacteria of Groups III+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups III+ were considered to share the technical features including: a method of treating cancer in a subject comprising administering a therapeutically effective amount of butyrate, an isolated or purified butyrate-producing bacterial population, and/or a composition comprising at least one, or at least two isolated or purified population of bacteria to said subject, wherein the subject has been administered an immune checkpoint inhibitor; these shared technical features are previously disclosed by Wageningen, as above, in view of Pitt, as above.

Wageningen discloses a method of treating cancer in a subject (a method of treating or preventing cancer in a subject; abstract, page 6, lines 21-24) comprising administering a therapeutically effective amount an isolated or purified butyrate-producing bacterial population to said subject (comprising administering a therapeutically effective amount an isolated or purified butyrate-producing bacterial population to said subject; page 4, lines 10-13; page 6, lines 21-24; page 7, lines 7-10).

Wageningen does not disclose wherein the subject has been administered an immune checkpoint inhibitor.

Pitt discloses administration of immunogenic commensal bacteria in combination with immune checkpoint blockade (administration of immunogenic commensal bacteria in combination with immune checkpoint blockade; page 1264, first column, second paragraph); and wherein Treg cells play a role in immune tolerance (wherein Treg cells play a role in immune tolerance; page 1261, first column, third paragraph) and are affected by commensal bacteria (are affected by commensal bacteria; page 1261, first column, third paragraph) and butyrate (and butyrate; page 1261, first column, third paragraph).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Wageningen to have included combining an immune checkpoint inhibitor, as disclosed by Pitt, with a butyrate-producing commensal strain of bacteria, as disclosed by Wageningen, in order to enable the generation of a microbial profile in the gut of a subject that favors the effectiveness of the immune checkpoint inhibitor, in order to better provide treatment for cancer.

Since none of the special technical features of the Groups I+, II+ and III+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Pitt and Wageningen references, unity of invention is lacking.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
UTSC-P1148WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2019/024519	28 March 2019 (28-03-2019)	28 March 2018 (28-03-2018)
Applicant		
SERES THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 13 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out 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))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☐ none of the figures is to be published with the abstract

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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:

      ☐ 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).

2. ☐ 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.

3. Additional comments:

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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.:

1-3, 56-58(completely); 4-19, 59-74, 108-115(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.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 A61K35/742 A61K35/745 A61K35/747
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)
A61P A61K

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, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/142605 A1 (SAMARITAN HEALTH SERVICES [US]; CUNNINGHAM GLEN [US]) 18 October 2012 (2012-10-18) claims 1-6	1-19, 56-74, 108-115
X	DATABASE WPI Week 201642 Thomson Scientific, London, GB; AN 2016-098523 XP002793308, & CN 105 296 590 A (SHANGHAI REAL BIOTECHNOLOGY CO LTD) 3 February 2016 (2016-02-03) abstract	1-19, 56-74, 108-115

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2019	24/10/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rodrigo-Simón, Ana

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Form PCT/ISA/210 (second sheet) (April 2005)

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BERTRAND ROUTY ET AL: "Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors", SCIENCE, vol. 359, no. 6371, 5 January 2018 (2018-01-05), pages 91-97, XP055554928, US ISSN: 0036-8075, DOI: 10.1126/science.aan3706 the whole document	1-19, 56-74, 109-115
A	A. SIVAN ET AL: "Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy", SCIENCE, vol. 350, no. 6264, 27 November 2015 (2015-11-27), pages 1084-1089, XP055310361, US ISSN: 0036-8075, DOI: 10.1126/science.aac4255 the whole document	1-19, 56-74, 109-115
A	WO 2016/196605 A1 (UNIV CHICAGO [US]) 8 December 2016 (2016-12-08) claim 23	1-19, 56-74, 109-115
A	WO 2016/063263 A2 (ROUSSY INST GUSTAVE [FR]) 28 April 2016 (2016-04-28) claims 10-13	1-19, 56-74, 109-115
A	J. M. PITT ET AL: "Fine-Tuning Cancer Immunotherapy: Optimizing the Gut Microbiome", CANCER RESEARCH, vol. 76, no. 16, 29 July 2016 (2016-07-29) , pages 4602-4607, XP055522231, US ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-16-0448 page 4605, column 1, paragraph 3	1-19, 56-74, 109-115

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	V. GOPALAKRISHNAN ET AL: "Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients", SCIENCE, vol. 359, no. 6371, 5 January 2018 (2018-01-05), pages 97-103, XP055554925, US ISSN: 0036-8075, DOI: 10.1126/science.aan4236 the whole document	1-19,56, 74, 109-115
A	POUTAHIDIS THEOFILOS ET AL: "Gut microbiota and the paradox of cancer immunotherapy", FRONTIERS IN IMMUNOLOGY, FRONTIERS RESEARCH FOUNDATION, CH , vol. 5, no. Article 157 7 April 2014 (2014-04-07), pages 1-5, XP009512851, ISSN: 1664-3224, DOI: 10.3389/FIMMU.2014.00157 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/doi/10.3389/fimmu.2014.00157 the whole document	1-19, 56-74, 109-115
A	VYARA MATSON ET AL: "The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients", SCIENCE, vol. 359, no. 6371, 5 January 2018 (2018-01-05), pages 104-108, XP055564226, US ISSN: 0036-8075, DOI: 10.1126/science.aao3290 the whole document	1-19,56, 74, 109-115
A	ARTHUR E. FRANKEL ET AL: "Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients", NEOPLASIA, vol. 19, no. 10, 1 October 2017 (2017-10-01), pages 848-855, XP055540712, US ISSN: 1476-5586, DOI: 10.1016/j.neo.2017.08.004 the whole document	1-19,56, 74, 109-115

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	N. CHAPUT ET AL: "Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab", ANNALS OF ONCOLOGY., vol. 28, no. 6, 1 June 2017 (2017-06-01), pages 1368-1379, XP055563275, NL ISSN: 0923-7534, DOI: 10.1093/annonc/mdx108 the whole document -----	1-19, 56-74, 109-115

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012142605 A1	18-10-2012	NONE	
CN 105296590 A	03-02-2016	NONE	
WO 2016196605 A1	08-12-2016	AU 2016270750 A1	14-12-2017
		BR 112017025813 A2	14-08-2018
		CA 2987129 A1	08-12-2016
		CL 2017003024 A1	06-07-2018
		CN 107847530 A	27-03-2018
		EP 3303401 A1	11-04-2018
		JP 2018521013 A	02-08-2018
		KR 20180011262 A	31-01-2018
		PE 6732018 A1	19-04-2018
		RU 2017141448 A	15-07-2019
		TW 201717975 A	01-06-2017
		US 2016354416 A1	08-12-2016
		US 2018015131 A1	18-01-2018
		US 2019183942 A1	20-06-2019
		UY 36701 A	30-12-2016
		WO 2016196605 A1	08-12-2016
WO 2016063263 A2	28-04-2016	AU 2015334468 A1	08-06-2017
		CA 2966132 A1	28-04-2016
		EP 3209692 A2	30-08-2017
		US 2019282632 A1	19-09-2019
		WO 2016063263 A2	28-04-2016

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-3, 56-58(completely); 4-19, 59-74, 108-115(partially)

A therapeutic composition comprising an effective amount of an isolated population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Its therapeutic use in the treatment of cancer

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2-14. claims: 4-19, 59-74, 108-115(all partially)

A therapeutic composition comprising an effective amount of an isolated population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides; Its therapeutic use in the treatment of cancer.

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15. claims: 20-22, 75-77(completely); 23-55, 78-115(partially)

A therapeutic composition comprising an effective amount of a purified population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Its therapeutic use in the treatment of cancer.

16-28. claims: 23-55, 78-115(all partially)

A therapeutic composition comprising an effective amount of a purified population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises at least Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter, Parabacteroides; Its therapeutic use in the treatment of

cancer

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29. claims: 116-118(completely); 119-131(partially)

A method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy, the method comprising:
determining that the subject is a candidate for the therapy if the microbiome sample comprises bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus.

30-42. claims: 119-131(partially)

A method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy, the method comprising:
determining that the subject is a candidate for the therapy if the microbiome sample comprises bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides

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43. claim: 132

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Ruminococcus, Gemmiger, Faecalibacterium and Subdoligranulum

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44. claim: 133

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter and Parabacteroides

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45. claim: 134

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Barnesiella, Bifidobacterium, Blautia, Erysipelotrichaceae,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Odoribacter and Parabacteroides
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46. claim: 135

A therapeutic composition comprising an effective amount of an isolated population of bacteria species Alistipes senegalensis, Bacteroides dorei, Blautia SC109, Clostridium SC64, Eubacterium biforme and Parabacteroides distasonis
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47. claim: 136

A therapeutic composition comprising an effective amount of an isolated population of bacteria species Barnesiella intestinihominis, Bifidobacterium bifidum, Bifidobacterium longum, Blautia_ SC102, Blautia - SC109, Clostridium innocuum, Odoribacter splanchnicus and Parabacteroides distasonis
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48-116. claims: 137-148

A therapeutic composition comprising an effective amount of a purified population of at least one bacteria of those listed in Tables 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 8A, 8B, 10 or 11

117-123. claims: 149-152

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to one or more of the species in a clade selected from clade 101, clade 14, clade 126, clade 61, clade 125, clade 135 or Fig.6
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124. claims: 153-155, 158-160(completely); 156, 161, 163-169(partially)

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Therapeutic composition thereof and its use in the treatment of cancer
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125-137. claims: 156, 161, 163-169(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides; Therapeutic composition thereof and its use in the treatment of cancer

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138-144. claims: 157, 162(completely); 163-169(partially)

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one or more of the species in a clade selected from clade 101, clade 14, clade 126, clade 61, clade 125 and clade 135; Therapeutic composition thereof and its use in the treatment of cancer

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145. claims: 170-172(completely); 173-180(partially)

A method of treating cancer comprising administering an anticancer treatment to a subject determined to have a microbiome sample comprising bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus.

146-158. claims: 173-180(partially)

A method of treating cancer comprising administering an anticancer treatment to a subject determined to have a microbiome sample comprising bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides

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159. claims: 181, 182(completely); 183-193(partially)

A method comprising evaluating in a sample of a subject its

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

microbiome profile by testing for at least Ruminococcus.

160-172. claims: 183-193(partially)

A method comprising evaluating in a sample of a subject its microbiome profile by testing for at least Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides
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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/US2019/024519	28.03.2019	28.03.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61P35/00 A61K35/742 A61K35/745 A61K35/747

Applicant
SERES THERAPEUTICS, 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	Rodrigo-Simón, Ana Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2019/024519

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:

Exhibit 1002
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 20-55, 75-107, 116-193(completely); 4-19, 59-74, 108-115(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 20-55, 75-107, 116-193(completely); 4-19, 59-74, 108-115(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

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. 1-3, 56-58(completely); 4-19, 59-74, 108-115(partially)

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	109(partially)
	No:	Claims	1-3, 56-58(completely); 4-19, 59-74, 108, 110-115(partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3, 56-58(completely); 4-19, 59-74, 108-115(partially)
Industrial applicability (IA)	Yes:	Claims	1-3, 56-58(completely); 4-19, 59-74, 108-115(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

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1 **The following prior art has been taken into consideration**

D1: WO2012142605

D2: XP002793308

D3: XP55554928

D4: XP55310361

D5: WO2016196605

D6: WO2016063263

D7: XP55522231

D8: XP55554925

D9: XP009512851

D10: XP55564226

D11: XP55540712

D12: XP55563275

D1 describes a pharmaceutical composition comprising a Ruminococcus for use in the treatment of cancer (claims 5-6). D1 also describes pharmaceutical composition comprising at least one of Eubacterium, Alistipes, Clostridium, Bifidobacterium, Subdoligranulum, Bacteroides or Parabacteroidesfor use in the treatment of cancer (claims 1-5).

D2 describes the use of Ruminococcus for the treatment of colorectal cancer (whole doc).

D3 describes that fecal microbiota transplantation from cancer patients who responded to immune checkpoint inhibitors improved antitumour effect of these therapeutics in germ-free antibiotic treated (cancer) mice. Akkermansia muciniphila was found in relative abundance in patients responding to the therapy together with Clostridium, Eubacterium, Alistipes, Erysipelotrichaceae and Bacteroidaceae among others (whole doc).

D4 describes that Bifidobacterium was associated to decreased tumour growth in melanoma and administered alone successfully treated this type of cancer in mice. Furthermore, Bifidobacterium synergized with checkpoint inhibition therapy anti PD-L1 abolishing tumour outgrowth (whole doc).

D5 describes a formulation comprising Alistipes for use in the treatment of cancer (claim 23).

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D6 describes a probiotic bacterial for use in the treatment of cancer composition comprising bacteria selected from Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides salyersiae, Bacteroides acidifaciens, Bacteroides intestinalis, Bacteroides vulgatus, Bacteroides uniformis, Bacteroides massiliensis and Barnesiella intestinihominis (claims 10-13).

D7 describes the administration of Bacteroides fragilis restored checkpoint inhibition therapy anti CTLA-4mAB in the treatment of cancer in mice (P.4605, Col.1, §3).

D8 describes the relative abundance of Ruminococcus in metastatic melanoma patients responding to checkpoint inhibitor anti-PD-1 compared to patients non responding to this therapy. In D8, the authors found that patients with favorable gut microbiome (high diversity and abundance of Ruminococcus and Faecalibacterium) have enhanced systemic antitumour immune responses mediated by increased antigen presentation and improved effector T cell function in the periphery and the tumour micro-environment.

D8 describes a method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy, the method comprisi determining that the subject is a candidate for the therapy if the microbiome sample comprises bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least Ruminococcus, Faecalibacterium, Clostridium, Eubacterium, Odoribacter, Erysipelotrichaceae and Bacteroidaceae among others (whole doc).

D9 describes that gut microbiota stimulate integrated immune and neuroendocrine factors through the body, modulating regulatory T-lymphocite phenotypes, maintaining systemic immune balance and determining the fate of preneoplastic lesions (whole doc).

D10 describes the association of Bifidobacterium longum, Collinsella aerofaciens and Enterococcus faecium with positive clinical response in metastatic melanoma patients as well as their improved effect in combination with checkpoint inhibition therapy anti PD-L1in mice (whole doc).

D11 describes the association of Bacterioides caccae and Faecalibacterium prausnitzii to positive clinical response to checkpoint inhibitors in metastatic melanoma patients (whole doc).

D12 describes the association of Faecalibacterium prausnitzii and other Fimicutes among others to positive clinical response to checkpoint inhibitors in metastatic melanoma patients (whole doc).

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Re Item IV

Lack of Unity of the invention

2 This Authority considers that there are **172 inventions** covered by the claims as follows:

Invention 1 (claims 1-3 and 56-58, completely; claims 4-19, 59-74 and 108-115, partially)

A therapeutic composition comprising an effective amount of an isolated population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Its therapeutic use in the treatment of cancer.

Inventions 2-14 (claims 4-19, 59-74 and 108-115, partially)

A therapeutic composition comprising an effective amount of an isolated population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides; Its therapeutic use in the treatment of cancer.

Invention 15 (claims 20-22 and 75-77, completely; claims 23-55 and 78-115, partially)

A therapeutic composition comprising an effective amount of a purified population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Its therapeutic use in the treatment of cancer.

Inventions 16-28 (claims 23-55 and 78-115, all partially)

A therapeutic composition comprising an effective amount of a purified population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises at least Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter, Parabacteroides; Its therapeutic use in the treatment of cancer.

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Invention 29 (claims 116-118, completely; 119-131, all partially)

A method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy, the method comprising:
determining that the subject is a candidate for the therapy if the microbiome sample comprises bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus.

Invention 30-42 (claims 119-131, all partially)

A method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy, the method comprising:
determining that the subject is a candidate for the therapy if the microbiome sample comprises bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides.

Invention 43 (claim 132, completely)

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Ruminococcus, Gemmiger, Faecalibacterium and Subdoligranulum.

Invention 44 (claim 133, completely)

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter and Parabacteroides.

Invention 45 (claim 134, completely)

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Barnesiella, Bifidobacterium, Blautia, Erysipelotrichaceae, Odoribacter and Parabacteroides.

Invention 46 (claim 135, completely)

A therapeutic composition comprising an effective amount of an isolated population of bacteria species Alistipes senegalensis, Bacteroides dorei, Blautia SC109, Clostridium SC64, Eubacterium biforme and Parabacteroides distasonis.

Invention 47 (claim 136, completely)

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A therapeutic composition comprising an effective amount of an isolated population of bacteria species Barnesiella intestinihominis, Bifidobacterium bifidum, Bifidobacterium longum, Blautia_ SC102, Blautia _SC109, Clostridium innocuum, Odoribacter splanchnicus and Parabacteroides distasonis.

Inventions 48-116 (claims 137-148, completely)

A therapeutic composition comprising an effective amount of a purified population of at least one bacteria of those listed in Tables 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 8A, 8B, 10 or 11.

Inventions 117-123 (claims 149-152, completely)

A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to one or more of the species in a clade selected from clade 101, clade 14, clade 126, clade 61, clade 125, clade 135 and Fig.6.

Invention 124 (claims 153-155 and 158-160, completely; 156,161 and 163-169, partially)

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus; Therapeutic composition thereof and its use in the treatment of cancer.

Inventions 125-137 (claims 156, 161 and 163-169, all partially)

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides; Therapeutic composition thereof and its use in the treatment of cancer.

Inventions 138-144 (claim 157 and 162, completely; 163-169, partially)

A method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer, if the microbiome sample comprises bacterial species that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one or more of the species in a clade selected from clade 101, clade 14, clade 126, clade 61, clade 125 and clade 135; Therapeutic composition thereof and its use in the treatment of cancer.

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Invention 145 (claims 170-172, completely; 173-180, partially)

A method of treating cancer comprising administering an anticancer treatment to a subject determined to have a microbiome sample comprising bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, optionally an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the family Ruminococcaceae, optionally at least Ruminococcus.

Inventions 146-158 (claims 173-180, all partially)

A method of treating cancer comprising administering an anticancer treatment to a subject determined to have a microbiome sample comprising bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, at least one of Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides.

Invention 159 (claims 181-182, completely; 183-193, partially)

A method comprising evaluating in a sample of a subject its microbiome profile by testing for at least Ruminococcus.

Inventions 160-172 (claims 183-193, all partially)

A method comprising evaluating in a sample of a subject its microbiome profile by testing for at least Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides.

3 **The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:**

The present application is concerned with different non-interrelated problems to be solved:

3.1 **Problem 1: Treatment of cancer**

The problem to be solved is seen in the provision of bacterial preparations for the treatment of cancer.

The solutions proposed include the use of:

- Therapeutic compositions comprising a(n) isolated/purified population of at least one of Ruminococcus, Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides (Inventions 1-28).

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- A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter and Parabacteroides (Invention 44).

- A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to the genera Barnesiella, Bifidobacterium, Blautia, Erysipelotrichaceae, Odoribacter and Parabacteroides (Invention 45).

- A therapeutic composition comprising an effective amount of an isolated population of bacteria species Alistipes senegalensis, Bacteroides dorei, Blautia SC109, Clostridium SC64, Eubacterium biforme and Parabacteroides distasonis (Invention 46).

- A therapeutic composition comprising an effective amount of an isolated population of bacteria species Barnesiella intestinihominis, Bifidobacterium bifidum, Bifidobacterium longum, Blautia_ SC102, Blautia _SC109, Clostridium innocuum, Odoribacter splanchnicus and Parabacteroides distasonis (Invention 47).

- A therapeutic composition comprising an effective amount of a purified population of at least one bacteria of those listed in Tables 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 8A, 8B, 10 or 11 (Inventions 48-116).

- A therapeutic composition comprising an effective amount of an isolated population of bacteria belonging to one or more of the species in a clade selected from clade 101, clade 14, clade 126, clade 61, clade 125, clade 135 or Fig.6 (Inventions 117-123).

The solutions proposed are not linked by a single general inventive concept because:

Pharmaceutical composition comprising at least one of the bacteria as specified in the claims as well as their use in the treatment of cancer were known in the art at the filing date as described in D1-D7.

The concept that some gut microbiota stimulate integrated immune and neuroendocrine factors through the body, modulating regulatory T-lymphocyte phenotypes, maintaining systemic immune balance and determining the fate of preneoplastic lesions or synergizing with checkpoint inhibitors in the therapy of cancer was also known in the art at the filing date as described in D1-D12.

The bacteria in the claimed preparations (or combinations thereof) do not seem to share one with another a common feature since they belong to different genera and therefore, have a different nature and behaviour in the gut. Furthermore, the present application does not demonstrate that the claimed bacteria have an equivalent anticancer effect and therefore, they cannot be substituted one for the other with the expectation that the same intended result would be achieved. In summary, the different claimed therapeutic compositions/ bacteria (or combinations thereof) are not equivalents since they have different technical features and therefore constitute different inventions.

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Page 000225

3.2 **Problem 2: Screening methods**

The problems to be solved are seen in the provision of a method of identifying a mammalian subject as a candidate for immune checkpoint therapy in combination with adjuvant microbiome therapy and the treatment of such patient. **An additional problem to be solved lies** in the provision of a method of identifying a mammalian subject as a donor whose feces are useful for fecal matter transfer.

The solutions proposed include the identification in a sample of the patients of at least one of Ruminococcus, Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides (Inventions 29-42 and 124-158), which were already know in the art at the filing date (D8-D12).

3.3 **Problem 3: Microbiome evaluation methods**

The problem to be solved is seen in the provision of a method to evaluate the microbiome profile in a sample from a patient.

The solutions proposed include the identification in the sample of the patient of at least one of Ruminococcus, Gemmiger, Faecalibacterium, Subdoligranulum, Alistipes, Bacteroides, Barnesiella, Bifidobacterium, Blautia, Clostridium, Eubacterium, Erysipelotrichaceae, Odoribacter or Parabacteroides (Inventions 159-172), which were already know in the art at the filing date (D8-D12).

4 The respective solutions to the different non-interrelated problems are not linked among them by a single general inventive concept for the above reasons.

No technical relationship can be identified involving " the same or corresponding special technical features" within the meaning of Rule 13.2 PCT.

Searching inventions 2-172 would have caused a major additional searching and examination effort. In accordance with Art.17(3)(a) and Rule 40 PCT, the search report has been drawn up for those parts of the application which relate to the invention first mentioned in the claims.

The application does not meet the requirements of unity of the invention as defined in Rules 13.1 and 13.2 PCT.

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5 The attention of the applicant is drawn to the fact that inventions directed to specific combinations of bacteria within each genera would not be considered to be clearly and unambiguously disclosed in the application as originally filed and would therefore contravene Art 34(2)(b) PCT.

In case the applicant wishes to pay for a non-searched invention, he is kindly requested to clearly specify the bacteria (combination thereof) in the preparation as well as its basis in the sense of Art 34(2)(b) PCT in the application as originally filed.

Re Item V

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

6 **Invention I (claims 1-19, 56-74 and 108-115)** is directed to a therapeutic composition comprising an effective amount of an isolated population of bacteria that are phylogenetic descendants of the most recent common ancestor (MRCA) of Faecalibacterium prausnitzii and Flavonifractor plautii, wherein the composition comprises at least Ruminococcus and to its therapeutic use in the treatment of cancer.

7 **Claims 56-74 and 108-115 relate to a subject-matter considered by this Authority to be covered by the provision 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 or diagnostic methods practised on the human or animal body, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

NOVELTY of Invention I (Art. 33(1) and (2) PCT)

7.1 **Claims 1-19, 56-74, 108 and 110-115, all partially** are not novel in the sense of Article 33(1)(2) PCT because their subject-matter has been disclosed in **D1** (claims 5-6) or **D2** (whole doc), which describe a pharmaceutical composition comprising a Ruminococcus for use in the treatment of intestinal cancer.

7.2 **Claim 109 is novel in the sense of Art. 33(1) and (2) PCT** because a pharmaceutical composition comprising an isolated population of bacteria that have 16S rDNA sequence identity of at least 94.5% or at least 98.7% to 16S rDNA sequences of species belonging to the

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family Ruminococcaceae for use in the treatment of metastatic melanoma, melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Merkel cell skin cancer (Merkel cell carcinoma) or Hodgkin lymphoma has not been found to be disclosed in the prior art at hand.

8 **INVENTIVE STEP of Invention I (Art. 33(1) and (3) PCT)**

Claim 109 does not meet the criteria of Article 33(1)(3) PCT for the following reasons:

8.1 **The closest prior art, D1 or D2,** describes Ruminococcus for use in the treatment of gastrointestinal cancer.

8.2 **The difference** between D1/D2 and the present application lies in the fact that the present application proposes the treatment of metastatic melanoma, melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Merkel cell skin cancer (Merkel cell carcinoma) or Hodgkin lymphoma.

8.3 **In support of an inventive step** the applicant provided examples describing metagenomic sequencing on samples of fecal microbiome from metastatic melanoma patients who were responders or non-responders to a checkpoint inhibitor. Different bacterial taxa were associated to responder and non-responders, namely:

Type 1 patients (responders) were enriched in Clostridiales, particularly the families of Ruminococcaceae, Lachnospiraceae, Clostridiaceae and Catabacteriaceae while type 2 patients (responders and non-responders) were enriched in Bacteroidia as defined in Table 12.

Ruminococcaceae, Clostridia and Bacteroidia were found to be the strongest predictors of response to checkpoint therapy.

The attention of the applicant is drawn to the fact that the provided experimental evidence does not demonstrate that Ruminococcaceae are able to treat metastatic melanoma, melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, Merkel cell skin cancer (Merkel cell carcinoma) or Hodgkin lymphoma in an unexpected manner compared to intestinal cancer (D1/D2).

8.4 **An unexpected technical effect cannot be acknowledged for the claimed subject-matter.**

8.5 **The problem** *"provision of alternative therapeutic uses of therapeutic compositions comprising Ruminococcaceae"* has not been solved.

8.6 **Invention I (claim 109) does not meet the criteria of Article 33(1)(3) PCT.**

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000228

Electronic Acknowledgement Receipt

EFS ID:	39638629
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Monica Wozniak
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	05-JUN-2020
Filing Date:	28-MAR-2019
Time Stamp:	13:03:36
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		UTSCP1149US_IDS.pdf	263807 f9666b1faa1b3e500d75872e79293854cb03d871	yes	8

	Multipart Description/PDF files in .zip description				
	Document Description	**Start**	**End**		
	Transmittal Letter	1	3		
	Information Disclosure Statement (IDS) Form (SB08)	4	8		
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48	Non Patent Literature	Chen_2016.pdf	14187848 3413464 13a61c9bac51cd06186e1b49c878357d7	no	12
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49	Non Patent Literature	Frankel.pdf	1145827 021907b530730430724c3e7609b73b8ed7ffb827	no	8
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50	Non Patent Literature	Garrett_2015.pdf	2074552 155c3a0003f49d8b9ef12375e3d9ad141d3fb95d	no	8
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51	Non Patent Literature	Gopalakrishnan.pdf	2065205 f0dca13b89c615d3f7419cba4b22face11fd17ea	no	9
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		Total Files Size (in bytes):	558915668		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001074761

CONFIRMATION NO. 2735

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

PUBLICATION NOTICE



Title:METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Publication No.US-2020-0129569-A1
Publication Date:04/30/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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AUSTIN TX 78701-4255

MAILED

MAR 03 2020

INTERNATIONAL PATENT LEGAL ADM.

In re Application of :
The Board Of Regents, The University Of Texas... :
Application No.: 16/337,820 :
PCT No.: PCT/US2017/053717 :
Int. Filing Date: 27 September 2017 : DECISION
Priority Date: 27 September 2016 :
Atty Dkt No.: UTSC.P1149US/1001074761 :
For: Methods For Enhancing Immune Checkpoint :
Blockade Therapy By Modulating The... :

The petition to revive under 37 CFR 1.137(a)(unintentional delay) filed on 24 February2020 (and 28 March 2019) in the above-captioned application is hereby **GRANTED**, as follows:

Petitioner has provided a statement that "the entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(a) was unintentional." This statement is being accepted in satisfaction of 37 CFR 1.137(b)(4).

A review of the application file reveals that applicant has filed the required reply. The petition fee has been paid. No terminal disclaimer is required. Therefore, the request to revive the application abandoned under 35 U.S.C. 371(d) is granted as to the national stage in the United States of America.

This application is being returned to the Office of Patent Application Processing for further processing in accordance with this Decision.

/George Dombroske/
George Dombroske
PCT Legal Examiner
International Patent Legal Administration
Tel: (571) 272-3283

Doc Code: PET.PCT
Document Description: Petition for review by the PCT Legal Office

PTO/SB/64PCT (01-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR REVIVAL OF AN INTERNATIONAL (PCT) APPLICATION FOR PATENT DESIGNATING THE U.S. ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(a) Page 1 of 2	Docket Number (Optional) UTSC.P1149US/ 100106S871

First named inventor: Jennifer WARGO

International (PCT) Application No.: PCT/US2017/053717 U.S. Application No. (if known): _____

Filed: September 27, 2017

Title: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Attention: International Patent Legal Administration
Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

The above-identified application became abandoned as to the United States because the fees and documents required by 35 U.S.C. 371(c) and 37 CFR 1.495 were not filed prior to the expiration of the time set in 37 CFR 1.495(b) or (c) (as applicable). The date of abandonment is the day after the date on which the 35 U.S.C. 371(c) requirements were due. See 37 CFR 1.495(c) and (h).

APPLICANT HEREBY PETITIONS FOR REVIVAL OF THIS APPLICATION.

NOTE: A grantable petition requires the following items:

(1) Petition fee;
(2) Proper reply;
(3) Terminal disclaimer with disclaimer fee which is required for all international applications having an international filing date before June 8, 1995; and
(4) Statement that the entire delay was unintentional.

1. Petition fee

☒ Small entity fee $ 1000 (37 CFR 1.17(m)). Applicant asserts small entity status. See 37 CFR 1.27.

☐ Micro entity fee $ _____ (37 CFR 1.17(m)). Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ Undiscounted fee $ _____ (37 CFR 1.17(m)).

2. Proper reply

The proper reply (the missing requirement(s)) in the form of
371 Nationalization of PCT Application into US (identify the type of reply):

☐ has been filed previously on _____.

☒ is enclosed herewith.

3. Terminal disclaimer with disclaimer fee

☒ Since this international application has an international filing date on or after June 8, 1995, no terminal disclaimer is required.

☐ A terminal disclaimer (and disclaimer fee (37 CFR 1.20(d)) of $ _____ for a small entity or $ _____ for other than a small entity) disclaiming the required period of time is enclosed herewith (see PTO/SB/63).

This collection of information is required by 37 CFR 1.137(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 1 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PET.PCT
Document Description: Petition for review by the PCT Legal Office

PTO/SB/64PCT (01-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR REVIVAL OF AN INTERNATIONAL (PCT) APPLICATION FOR PATENT DESIGNATING THE U.S. ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(a)

4. STATEMENT: The entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(a) was unintentional. [NOTE: The United States Patent and Trademark Office may require additional information if there is a question as to whether either the abandonment or the delay in filing a petition under 37 CFR 1.137(a) was unintentional (MPEP 711.03(c), subsections (III)(C) and (D)).]

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

/Gina Shishima/	February 24, 2020
Signature	Date
Gina Shishima	45,104
Typed or Printed Name	Registration Number, if applicable
98 San Jacinto Blvd, Suite 1100	512-474-5201
Address	Telephone Number
Austin, TX 78701	
Address	

Enclosures:

- ☐ Fee Payment
- ☐ Reply
- ☐ Terminal Disclaimer Form
- ☐ Additional sheet(s) containing statements establishing unintentional delay
- ■ Other (please identify): Associated documents for 371 Nationalization of PCT Application into U.S.

CERTIFICATE OF MAILING OR TRANSMISSION [37 CFR 1.8(a)]

I hereby certify that this correspondence is being:

- ☐ Deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Mail Stop PCT, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.
- ☐ Transmitted to the United States Patent and Trademark Office by EFS-Web, or by facsimile to (571) 273-8300, on the date shown below.

March 28, 2019	/Gina Shishima/
Date	Signature
	Gina Shishima
	Typed or printed name of person signing certificate

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: not yet assigned
Serial No.: 16/337,820	Examiner: not yet assigned
Filed: March 28, 2019	Atty. Dkt. No.: UTSC.P1149US/1001065871
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION (37 C.F.R. § 1.8)
I, Gina Shishima, , hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on February 24, 2020. Signed: Gina Shishima//

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Attached herewith is a petition to revive which has now been executed on behalf of the Applicant. The original petition was filed together with the application under 35 U.S.C. 371 on March 28, 2019 but was unsigned. The required petition fee in the amount of $1,000 was also paid on March 28, 2019. Therefore, it is believe that no additional fees are required. However, the Commissioner is hereby authorized to deduct any underpayment of fees or any additional fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper from Norton Rose Fulbright US LLP Deposit Account No.: 50-1212/UTSC.P1149US/1001065871.

Should this Authority have any questions, please do not hesitate to contact the undersigned.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000243

Respectfully submitted,

/Gina Shishima/

Gina Shishima
Reg. No. 45,104
Agent for Applicant

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd, Suite 1100
Austin, Texas 78701
(512) 474-5201

Date: February 24, 2020

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000244

Electronic Acknowledgement Receipt

EFS ID:	38676848
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Gina N. Shishima/Sherry Stowers
Filer Authorized By:	Gina N. Shishima
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	24-FEB-2020
Filing Date:	28-MAR-2019
Time Stamp:	19:42:28
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the PCT legal office	UTSC_P1149US_Petition_to_Revive_esigned.pdf	107572 c258bf043cce9a26b1b7e38dcb2dcd8d84eefa2c	no	2

Warnings:

Information:					
2	Miscellaneous Incoming Letter	UTSC_P1149US_MiscLetter.pdf	120182 d9dadfa801479cf3a3b50b0a9fa70c66e76c1243	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	227754	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/337,820

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	150		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	70		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8	x 50 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			1000			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	2000		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/337,820	Jennifer WARGO	UTSC.P1149US/1001074761

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

INTERNATIONAL APPLICATION NO.	
PCT/US17/53717	
I.A. FILING DATE	PRIORITY DATE
09/27/2017	09/27/2016

CONFIRMATION NO. 2735
371 ACCEPTANCE LETTER

OC000000114165952

Date Mailed: 01/24/2020

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office, in its capacity as a Designated / Elected Office (37 CFR 1.495), has ACCEPTED the above identified international application for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above. A Filing Receipt will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE or 371(c) DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1) and (c)(2) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN BELOW.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)

03/28/2019
DATE OF RECEIPT OF 35 U.S.C.
371(c)(1) and (c)(2) REQUIREMENTS

The following items have been received:

- Indication of Small Entity Status
- Copy of the International Application filed on 03/28/2019
- Copy of the International Search Report filed on 03/28/2019
- Preliminary Amendments filed on 03/28/2019
- Sequence Listing txt file (EFS or physical medium) filed on 03/28/2019
- Inventor's Oath or Declaration filed on 10/10/2019
- U.S. Basic National Fees filed on 03/28/2019
- Authorize Access to Search Results filed on 03/28/2019
- Priority Documents filed on 03/28/2019
- Power of Attorney filed on 03/28/2019
- Specification filed on 03/28/2019
- Claims filed on 03/28/2019
- Abstracts filed on 03/28/2019
- Drawings filed on 03/28/2019
- Authorization to Permit Access filed on 03/28/2019
- Application Data Sheet (37 CFR 1.76) filed on 03/28/2019

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

MAMYE I WAGSTAFF

Telephone: (571) 272-1057

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000249

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/337,820	03/28/2019		2070	UTSC.P1149US/1001074761	28	3

CONFIRMATION NO. 2735

FILING RECEIPT

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

OC000000114165931

Date Mailed: 01/24/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jennifer WARGO, Houston, TX;
Vancheswaran GOPALAKRISHNAN, Houston, TX;

Applicant(s)

THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, Austin, TX

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US17/53717 09/27/2017
which claims benefit of 62/400,372 09/27/2016
and claims benefit of 62/508,885 05/19/2017
and claims benefit of 62/557,566 09/12/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/23/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/337,820**

Projected Publication Date: 04/30/2020

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000253

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): UTSC.P1149US/1001065871

Application Number: 16/337,820

Filed: March 28, 2019

For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Art Unit: not yet assigned

Examiner: not yet assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☑	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$ 200 ($100 paid previously)
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1212.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 66817.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Laurie Stellman/ — Signature

2019-11-11 — Date

Laurie Stellman — Typed or printed name

512-474-5201 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Ben Horton
Attorney Docket Number:	UTSC.P1149US/1001074761

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
NATL STAGE APPL SZ FEE PER 50 PGS >100	2681	1	200	200
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 2 months with $100 paid	2252	1	200	200
Miscellaneous:				
		Total in USD ($)		**400**

Electronic Acknowledgement Receipt

EFS ID:	37713011
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Ben Horton
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001074761
Receipt Date:	11-NOV-2019
Filing Date:	
Time Stamp:	14:21:58
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
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Payment was successfully received in RAM	$400
RAM confirmation Number	E2019AAE22436104
Deposit Account	
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	Response.pdf	123214 b011757ce2e839b57bf3f5b71418fedb558fbc2d	no	2
Warnings:					
Information:					
2	Supplemental Response or Supplemental Amendment	Prelim.pdf	149415 e529d09d3b358ff527f07d8e866ff624c64389c9	no	8
Warnings:					
Information:					
3	Extension of Time	Extension.pdf	34104 f22a733e27b97118f703c6a7b2182cff4661d56a	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32667 375e333df108c3c2d3e059f338498d9c6846bea8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	339400		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: not yet assigned
Serial No.: 16/337,820	Examiner: not yet assigned
Filed: March 28, 2019	Atty. Dkt. No.: UTSC.P1149US/1001074761
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION (37 C.F.R. § 1.8)
I, Ben Horton, hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on November 11, 2019. Signed: /Ben Horton/

RESPONSE TO NOTICE TO NOTIFICATION OF DEFECTIVE REPLY

In response to the Notification of Defective Reply, dated October 23, 2019, enclosed are:

(a) A Supplemental Preliminary Amendment to the Claims;

(b) Our payment via credit card in the amount of $400.00 to cover the following fees:

1. fee for each 50 pages over 300 ($200 – 15 pages – small entity);
2. two month extension of time fee ($200.00 – small entity – submitted in addition to previously paid $100.00 extension fee for total of $300.00); and

(c) A Request for Extension of Time of two months to and including November 11, 2019. Should such request be absent, consider this such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 as stated below.

Applicants are entitled to small-entity status pursuant to 37 C.F.R. 1.27. Therefore, small-entity fees have been paid accordingly.

The required fees in the amount of $400 in connection with the filing of this paper are being charged to a credit card through EFS-Web concurrently with this submission. The Commissioner

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is hereby authorized to deduct any underpayment of fees or any additional fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper from Norton Rose Fulbright US LLP Deposit Account No.: 50-1212/UTSC.P1149US/1001074761.

Respectfully submitted,

/Laurie Stellman/

Laurie Stellman
Reg. No. 66,817
Agent for Applicant

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd, Suite 1100
Austin, Texas 78701
(512) 474-5201

Date: November 11, 2019

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: not yet assigned
Serial No.: 16/337,820	Examiner: not yet assigned
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SUPPLEMENTAL PRELIMINARY AMENDMENT

Applicants respectfully submit this Supplemental Preliminary Amendment in the above-referenced case. Consideration of this case in view of the amendments made herein is respectfully requested.

Amendments to the Claims beginning on page 2.

Remarks begin on page 8.

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AMENDMENT TO THE CLAIMS

The listing of claims will replace all prior versions, and listing of claims in the application.

1. (Original) A composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

2. (Canceled)

3. (Previously Presented) The composition of claim 1, wherein each of the populations of bacteria is present in the composition at a concentration of at least 10^3 CFU.

4. (Canceled)

5. (Previously Presented) The composition of claim 1, wherein the bacteria are provided as bacterial spores.

6. (Canceled)

7. (Previously Presented) The composition of claim 1, wherein the bacteria belong to the family Ruminococcaceae or the family Clostridiaceae.

8. (Currently Amended) The composition of claim 7, wherein the ~~population of~~ bacteria belong to the genus *Ruminococcus* or [[to]] the genus *Faecalibacterium*.

9. (Previously Presented) The composition of claim 8, wherein the bacteria are selected from the species *Ruminococcus bromii* or *Faecalibacterium prausnitzii*.

10-17. (Canceled)

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18. (Currently Amended) The composition of claim 1, wherein the ~~at least one isolated or purified population of~~ bacteria ~~or the at least two isolated or purified populations of bacteria~~ are a species, subspecies or bacterial strains comprising a 16S rRNA gene sequence that is at least 94% identical to the sequence of SEQ ID NO: 1-876.

19. (Canceled)

20. (Currently Amended) The composition of claim 1, wherein the ~~at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of~~ bacteria are selected from the species in Table 2 designated with a response status of responder (R).

21-24. (Canceled)

25. (Previously Presented) The composition of claim 1, wherein the composition is formulated for oral delivery.

26. (Previously Presented) The composition of claim 25, wherein the composition formulated for oral delivery is a tablet or capsule.

27. (Previously Presented) The composition of claim 26, wherein the tablet or capsule comprises an acid-resistant enteric coating.

28-34. (Canceled)

35. (Previously Presented) A method of treating or preventing cancer in a subject comprising administering to the subject a composition in accordance with claim 1.

36. (Canceled)

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37. (Previously Presented) The method of claim 35, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

38-39. (Canceled)

40. (Original) The method of claim 35, wherein the method further comprises administering at least one additional anticancer treatment.

41-42. (Canceled)

43. (Previously Presented) The method of claim 40, wherein the at least one anticancer treatment is an immune checkpoint inhibitor that is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

44. (Original) A method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*.

45. (Canceled)

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46. (Previously Presented) The method of claim 44, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47-48. (Canceled)

49. (Original) The method of claim 44, wherein the method further comprises administering at least one additional anticancer treatment.

50-65. (Canceled)

66. (Original) The method of claim 44, wherein the composition comprises the bacteria *Faecalibacterium prausnitzii*.

67-72. (Canceled)

73. (Currently Amended) A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition of claim 1~~ or claim 2~~, the response to the immune checkpoint inhibitor is favorable.

74. (Canceled)

75. (Previously Presented) The method of claim 73, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma

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protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

76-78. (Canceled)

79. (Original) The method of claim 73, wherein the microbial profile is a gut microbial profile.

80-128. (Canceled)

129. (Original) A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of butyrate-producing bacteria; (c) one or more bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R), then the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

130. (Canceled)

131. (Previously Presented) The method of claim 129, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

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132-135. (Canceled)

136. (Currently Amended) The method of claim 129, wherein the ~~favorable~~ microbial profile is a ~~favorable~~ gut microbial profile.

137-138. (Canceled)

139. (Original) The method of claim 129, wherein the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

140. (Currently Amended) The method of claim 129, wherein the butyrate-producing ~~bacterial population~~ bacteria comprises one or more bacterial species of the order Clostridiales.

141-142. (Canceled)

143. (Original) The method of claim 140, wherein the one or more species is *Faecalibacterium prausnitzii*.

144-161. (Canceled)

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REMARKS

The claims have been amended without prejudice or disclaimer to manage the claims fees. Claims 2, 4, 6, 10-17, 19, 21-24, 28-34, 36, 38-39, 41-42, 45, 47-48, 50-65, 67-72, 74, 76-78, 80-128, 130, 132-135, 137-138, 141-142 and 144-161 were previously canceled. Claims 8, 18, 20, 73, 136 and 140 have been amended. Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43-44, 46, 49, 66, 73, 75, 79, 129, 131, 136, 139-140 and 143 are pending. Applicants retain the right pursue the subject matter as originally claimed at a later stage in this application or in future applications.

The filing fee has been calculated after amendment of the claims by this supplemental preliminary amendment. No new matter is added by entry of this supplemental preliminary amendment.

It is believed that no fee is due with this communication, however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed document, the Commissioner is authorized to deduct or credit said fees from or to Norton Rose Fulbright US LLP Deposit Account No. 50-1212/UTSC.P1149US/1001074761.

The Examiner is invited to contact the undersigned patent agent with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Laurie Stellman/

Laurie Stellman
Reg. No. 66,817
Agent for Applicants

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(512) 474-5201

Date: November 11, 2019

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/337,820	Filing Date 03/28/2019	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/11/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 28	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CORALIA BETANCOURT/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/337,820

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	150		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	70		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	31 minus 20 =	* 11	x 50 =	550	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			1000			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				410			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	2560		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/337,820	Jennifer WARGO	UTSC.P1149US/1001074761

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INTERNATIONAL APPLICATION NO.	
PCT/US17/53717	
I.A. FILING DATE	PRIORITY DATE
09/27/2017	09/27/2016

CONFIRMATION NO. 2735
371 FORMALITIES LETTER



Date Mailed: 10/23/2019

NOTIFICATION OF DEFECTIVE REPLY

The following items have been submitted by the applicant or the International Bureau to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 03/28/2019
- Copy of the International Search Report filed on 03/28/2019
- Preliminary Amendments filed on 03/28/2019
- Sequence Listing txt file (EFS or physical medium) filed on 03/28/2019
- Inventor's Oath or Declaration filed on 10/10/2019
- U.S. Basic National Fees filed on 03/28/2019
- Authorize Access to Search Results filed on 03/28/2019
- Priority Documents filed on 03/28/2019
- Power of Attorney filed on 03/28/2019
- Specification filed on 03/28/2019
- Claims filed on 03/28/2019
- Abstracts filed on 03/28/2019
- Drawings filed on 03/28/2019
- Authorization to Permit Access filed on 03/28/2019
- Application Data Sheet (37 CFR 1.76) filed on 03/28/2019

Applicant's response filed 10/10/2019 is hereby acknowledged. The following requirements set forth in the NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) mailed 07/11/2019 have not been completed.

The applicant needs to satisfy supplemental fees problems indicated below.

The following items **MUST** be furnished within the period set forth below:

- Additional claim fees of $**560** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Processing fee of $70 for providing the translation of the application and/or the Annexes later than 30 months from the priority date (37 CFR 1.492(i)).

FORM PCT/DO/EO/916 (371 Formalities Notice)

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**830** for a Small Entity:

- The fee for electronically submitting a specification and drawing containing more than 100 pages has not been paid in full. Applicant owes $**200** for **15** pages in excess of **300** pages for a small entity in compliance with 37 CFR 1.27.
- Total additional claim fee(s) for this application is $**560**
- $**70** for English translation surcharge required.

Applicant is required to complete the reply within the time remaining in the period for reply set forth in the notification mailed 07/11/2019 in order to avoid abandonment. Such period for reply may be extended by filing a petition and fee for extension of time under 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
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If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

MAMYE I WAGSTAFF

Telephone: (571) 272-1057

FORM PCT/DO/EO/916 (371 Formalities Notice)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: not yet assigned
Serial No.: 16/337,820	Examiner: not yet assigned
Filed: March 28, 2019	Atty. Dkt. No.: UTSC.P1149US/1001065871
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION (37 C.F.R. § 1.8)
I, Ben Horton, hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on October 10, 2019. Signed: /Ben Horton/

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION FILED UNDER 37 CFR 1.53(b)

In response to the Notice to File Missing Parts of Nonprovisional Application filed under 37 CFR 1.53(b), dated July 11, 2019, enclosed are:

(a) A Preliminary Amendment to the Claims;

(b) Two Declarations executed by Inventors Jennifer WARGO and Vancheswaran GOPALAKRISHNAN;

(c) Our payment via credit card in the amount of $1300 to cover the following fees:

1. fee for each 50 pages over 100 ($800 - 200 pages);
2. fee for total claims over twenty ($400 - 8 claims);
3. one month extension of time fee ($100.00 - 1 month - small); and

(d) A Request for Extension of Time of one month to and including October 11, 2019. Should such request be absent, consider this such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 as stated below.

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000274

Applicants are entitled to small-entity status pursuant to 37 C.F.R. 1.27. Therefore, small-entity fees have been paid accordingly.

The required fees in the amount of $1300 in connection with the filing of this paper are being charged to a credit card through EFS-Web concurrently with this submission. The Commissioner is hereby authorized to deduct any underpayment of fees or any additional fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper from Norton Rose Fulbright US LLP Deposit Account No.: 50-1212/UTSC.P1149US/1001065871.

Respectfully submitted,

/Laurie Stellman/

Laurie Stellman
Reg. No. 66,817
Agent for Applicant

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd, Suite 1100
Austin, Texas 78701
(512) 474-5201

Date: October 10, 2019

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000275

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/337,820 filed on March 28, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Vancheswaran GOPALAKRISHNAN Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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This declaration is directed to:

- ☐ The attached application, or
- ■ United States application or PCT international application number 16/337,820 filed on March 28, 2019.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

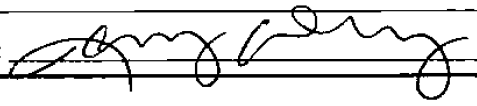
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Jennifer WARGO Date (Optional): 7/22/2019

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/AIA/22 (03-13)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): UTSC.P1149US/1001065871

Application Number: 16/337,820

Filed: March 28, 2019

For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Art Unit: not yet assigned

Examiner: not yet assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 100
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1212.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 66817.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Laurie Stellman/ — Signature

2019-10-10 — Date

Laurie Stellman — Typed or printed name

512-474-5201 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Electronic Patent Application Fee Transmittal

Application Number:	16337820
Filing Date:	
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Laurie B.F. Stellman/Ben Horton
Attorney Docket Number:	UTSC.P1149US/1001065871

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
NATL STAGE APPL SZ FEE PER 50 PGS >100	2681	4	200	800
Claims:				
CLAIMS IN EXCESS OF 20	2615	8	50	400
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
		Total in USD ($)		**1300**

Electronic Acknowledgement Receipt

EFS ID:	37418957
Application Number:	16337820
International Application Number:	
Confirmation Number:	2735
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Customer Number:	32425
Filer:	Laurie B.F. Stellman/Ben Horton
Filer Authorized By:	Laurie B.F. Stellman
Attorney Docket Number:	UTSC.P1149US/1001065871
Receipt Date:	10-OCT-2019
Filing Date:	
Time Stamp:	11:55:46
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1300
RAM confirmation Number	E201900B56110615
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	Response.pdf	126196 10472515faa128c8d44e9d2029ebe25971efe1ec	no	2
Warnings:					
Information:					
2	Preliminary Amendment	Preliminary.pdf	152104 979ee6123f3ff137777b0ce53a540c8d7f22c905	no	9
Warnings:					
Information:					
3	Oath or Declaration filed	Declarations.pdf	90786 53ba7f6e69ffaca78a6f5c4dcdc0a9328097510c	no	2
Warnings:					
Information:					
4	Extension of Time	Extension.pdf	35883 234173133be98d18978b9c55820f8f783ecc186d	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	34259 62214669b704507bd8d5337e2bff524235212bd6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	439228		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: The Board of Regents, the University of Texas System et al.	Group Art Unit: not yet assigned
Serial No.: 16/337,820	Examiner: not yet assigned
Filed: March 28, 2019	Atty. Dkt. No.: UTSC.P1149US/1001065871
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: 2735

CERTIFICATE OF ELECTRONIC TRANSMISSION (37 C.F.R. § 1.8)
I, Ben Horton, hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on October 10, 2019. Signed: /Ben Horton/

PRELIMINARY AMENDMENT

Applicants respectfully submit this Preliminary Amendment in the above-referenced case. Consideration of this case in view of the amendments made herein is respectfully requested.

Amendments to the Claims beginning on page 2.

Remarks begin on page 8.

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AMENDMENT TO THE CLAIMS

The listing of claims will replace all prior versions, and listing of claims in the application.

1. (Original) A composition comprising at least one isolated or purified population of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

2. (Canceled)

3. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein each of the populations of bacteria is present in the composition at a concentration of at least 10^3 CFU.

4. (Canceled)

5. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein the ~~at least one isolated or purified population~~ bacteria ~~or the at least two isolated or purified populations of bacteria~~ are provided as bacterial spores.

6. (Canceled)

7. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein the ~~at least one isolated or purified population bacteria or the at least two isolated or purified populations of~~ bacteria belong to the ~~the~~ family Ruminococcaceae ~~and/~~or [[of]] the family Clostridiaceae.

8. (Currently Amended) The composition of claim 7 ~~1 or claim 2~~, wherein the population of bacteria ~~belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging~~ belong to the genus *Ruminococcus* or to the genus *Faecalibacterium*.

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9. (Currently Amended) The composition of claim 8, wherein the ~~population of bacteria belonging to the genus Ruminococcus is further defined as a population of~~ bacteria ~~belonging to~~ are selected from the species *Ruminococcus bromii* or *Faecalibacterium prausnitzii*.

10-17. (Canceled)

18. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are a species, subspecies or bacterial strains comprising a 16S rRNA gene sequence at least [[80]] 94% identical to the sequence of SEQ ID NO: 1-876.

19. (Canceled)

20. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria are selected from the species in Table 2 designated with a response status of responder (R).

21-24. (Canceled)

25. (Currently Amended) The composition of claim 1 ~~or claim 2~~, wherein the composition is formulated for oral delivery.

26. (Currently Amended) The composition of claim 25 ~~1 or claim 2~~, wherein the composition formulated for oral delivery is a tablet or capsule.

27. (Currently Amended) The composition of claim 26 ~~1 or claim 2~~, wherein the tablet or capsule comprises an acid-resistant enteric coating.

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28-34. (Canceled)

35. (Currently Amended) A method of treating or preventing cancer in a subject comprising administering to the subject a composition in accordance with claim 1~~any one of claims 1-34~~.

36. (Canceled)

37. (Currently Amended) The method of claim 35, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

38-39. (Canceled)

40. (Original) The method of claim 35, wherein the method further comprises administering at least one additional anticancer treatment.

41-42. (Canceled)

43. (Currently Amended) The method of claim 40, wherein the at least one anticancer treatment is an ~~at least one~~ immune checkpoint inhibitor ~~and/or at least one additional anticancer treatment~~ that is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion.

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44. (Original) A method of treating or preventing cancer in a subject comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*.

45. (Canceled)

46. (Currently Amended) The method of claim 44, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

47-48. (Canceled)

49. (Original) The method of claim 44, wherein the method further comprises administering at least one additional anticancer treatment.

50-65. (Canceled)

66. (Original) The method of claim 44, wherein the composition comprises the bacteria *Faecalibacterium prausnitzii*.

67-72. (Canceled)

73. (Original) A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said

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patient, wherein if the microbial profile comprises one or more of the bacterial populations of the composition of claim 1 or claim 2, the response to the immune checkpoint inhibitor is favorable.

74. (Canceled)

75. (Currently Amended) The method of claim 73, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

76-78. (Canceled)

79. (Original) The method of claim 73, wherein the microbial profile is a gut microbial profile.

80-128. (Canceled)

129. (Original) A method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of butyrate-producing bacteria; (c) one or more bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R), then the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

130. (Canceled)

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131. (Currently Amended) The method of claim 129, wherein the cancer is a skin cancer selected from basal-cell skin cancer, squamous-cell skin cancer, melanoma, dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget' s disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

132-135. (Canceled)

136. (Original) The method of claim 129, wherein the favorable microbial profile is a favorable gut microbial profile.

137-138. (Canceled)

139. (Original) The method of claim 129, wherein the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

140. (Original) The method of claim 129, wherein the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales.

141-142. (Canceled)

143. (Original) The method of claim 140, wherein the one or more species is *Faecalibacterium prausnitzii*.

144-161. (Canceled)

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REMARKS

The claims have been amended without prejudice or disclaimer to manage the claims fees. Claims 2, 4, 6, 10-17, 19, 21-24, 28-34, 36, 38-39, 41-42, 45, 47-48, 50-65, 67-72, 74, 76-78, 80-128, 130, 132-135, 137-138, 141-142 and 144-1461 have been canceled. Claims 3, 5, 7-9, 18, 20, 25-27, 35, 37, 43, 46, 75 and 131 have been amended. Claims 1, 3, 5, 7-9, 18, 20, 25-27, 35, 37, 40, 43-44, 46, 49, 66, 73, 75, 79, 129, 131, 136, 139-140 and 143 are pending. Applicants retain the right pursue the subject matter as originally claimed at a later stage in this application or in future applications.

The filing fee has been calculated after amendment of the claims by the preliminary amendment. No new matter is added by entry of this preliminary amendment.

The required fees in the amount of $400.00 for total claims over twenty (8) in connection with the filing of this paper are being charged to a credit card through EFS-Web concurrently with this submission. The Commissioner is hereby authorized to deduct any underpayment of fees or any additional fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper from Norton Rose Fulbright US LLP Deposit Account No.: 50-1212/UTSC.P1149US/1001065871.

The Examiner is invited to contact the undersigned patent agent with any questions, comments or suggestions relating to the referenced patent application.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000291

Respectfully submitted,

/Laurie Stellman/

Laurie Stellman
Reg. No. 66,817
Agent for Applicants

NORTON ROSE FULBRIGHT US LLP
98 San Jacinto Blvd., Suite 1100
Austin, Texas 78701
(512) 474-5201

Date: October 10, 2019

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Microbiotica, Limited v. Board of Reagents, The University of Texas System
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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16337820	

Applicant(s) Jennifer WARGO

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend		Indep	Depend	Indep	Depend	Indep	Depend
1	1						51		1				
2	1						52		1				
3		2					53		1				
4		2					54		1				
5		2					55		1				
6		2					56		1				
7		2					57		1				
8		2					58		1				
9		2					59		1				
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26		2					76		2				
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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16337820	

Applicant(s) Jennifer WARGO

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001065871

CONFIRMATION NO. 2735

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

OC000000109522110

Date Mailed: 07/11/2019

NOTICE OF ACCEPTANCE OF AUTHORIZATION TO PERMIT ACCESS TO SEARCH RESULTS

This is in response to the applicant's authorization to permit access to the search results from the instant application under 37 CFR 1.14(h)(2) submitted on 03/28/2019.

The authorization to permit access to the search results under 37 CFR 1.14(h)(2) is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/miwagstaff/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/337,820

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	150		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	70		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	232 minus 20 =	* 212	x 50 =	10600	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6 minus 3 =	* 3	x 230 =	690			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			1000			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				410			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	13300		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NO.	FIRST NAMED INVENTOR	ATTY. DOCKET NO.
16/337,820	Jennifer WARGO	UTSC.P1149US/1001065871

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

INTERNATIONAL APPLICATION NO.	
PCT/US17/53717	
I.A. FILING DATE	PRIORITY DATE
09/27/2017	09/27/2016

CONFIRMATION NO. 2735
371 FORMALITIES LETTER



Date Mailed: 07/11/2019

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the International Bureau to the United States Patent and Trademark Office as a Designated / Elected Office (37 CFR 1.495).

- Indication of Small Entity Status
- Priority Document
- Copy of the International Application filed on 03/28/2019
- Copy of the International Search Report filed on 03/28/2019
- Preliminary Amendments filed on 03/28/2019
- Sequence Listing txt file (EFS or physical medium) filed on 03/28/2019
- U.S. Basic National Fees filed on 03/28/2019
- Authorize Access to Search Results filed on 03/28/2019
- Priority Documents filed on 03/28/2019
- Power of Attorney filed on 03/28/2019
- Specification filed on 03/28/2019
- Claims filed on 03/28/2019
- Abstracts filed on 03/28/2019
- Drawings filed on 03/28/2019
- Authorization to Permit Access filed on 03/28/2019
- Application Data Sheet (37 CFR 1.76) filed on 03/28/2019

The applicant needs to satisfy supplemental fees problems indicated below.

The following items **MUST** be furnished within the period set forth below:

- Additional claim fees of $**11700** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fees required for this application is $**12700** for a Small Entity:

- The specification and drawings submitted electronically contain the equivalent of more than 100 pages. Applicant owes $**1000** for **215** pages in excess of **100** pages for a small entity in compliance with 37 CFR 1.27.
- Total additional claim fee(s) for this application is $**11700**

FORM PCT/DO/EO/905 (371 Formalities Notice)

- $**690** for **3** independent claims over 3.
- $**10600** for **212** total claims over 20.
- $**410** for multiple dependent claim surcharge.

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.495(c).

- Properly executed inventor's oath or declaration for the following inventor(s) has not been submitted: **Jennifer WARGO** and **Vancheswaran GOPALAKRISHNAN**

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

MAMYE I WAGSTAFF

Telephone: (571) 272-1057

FORM PCT/DO/EO/905 (371 Formalities Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/337,820	03/28/2019	Jennifer WARGO	UTSC.P1149US/1001065871

CONFIRMATION NO. 2735

32425
NORTON ROSE FULBRIGHT US LLP
98 SAN JACINTO BOULEVARD
SUITE 1100
AUSTIN, TX 78701-4255

OC000000109522108

Date Mailed: 07/11/2019

NOTICE OF ACCEPTANCE OF AUTHORIZATION TO PERMIT ACCESS TO APPLICATION VIA PRIORITY DOCUMENT EXCHANGE

This is in response to the applicant's authorization to permit access to the application-as-filed by participating offices under 37 CFR 1.14(h)(1) submitted on 03/28/2019.

The authorization to permit access to the application under 37 CFR 1.14(h)(1) is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/miwagstaff/

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If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anjum, Durreshwar
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Validated By CRFValidator v 1.0.5

Application No: 16337820 Version No: 1.0

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Finished: 2019-03-28 17:24:56.486
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SEQUENCE LISTING

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agtgggcgag aagtgtgcgg aatgtgtggt gtagcggtga aatgcataga tatcacacag 180

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gagtacgcgc aacgccggcg gaattcgtcg tgtagcggtg aaatgcttag atatgacgaa 180

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ggtatcaaac agg 253

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gagttgccga agggtatccg g

DESCRIPTION

METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

[0001] This application claims the benefit of United States Provisional Patent Applications No. 62/400,372, filed September 27, 2016; No. 62/508,885, filed May 19, 2017; and No. 62/557,566, filed September 12, 2017, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The present invention relates generally to the fields of microbiology, immunology, and medicine. More particularly, it concerns the use of the microbiome to improve the efficacy of immune checkpoint blockade therapy

2. Description of Related Art

[0003] Within the past decade, major advances have been made in the treatment of melanoma through the use of targeted therapy and immunotherapy. In particular, the use of immune checkpoint inhibitors has shown tremendous promise, leading to the FDA approval of several agents blocking immuno-modulatory molecules on the surface of T lymphocytes (*e.g.*, anti-CTLA-4 antibody Ipilimumab, and anti-PD-1 antibodies Nivolumab, Pembrolizumab). Importantly, treatment with immune checkpoint blockade may result in durable long-term complete responses, though overall response rates are modest (*i.e.*, 15% with CTLA-4 blockade, and 30-40% with PD-1 blockade).

[0004] However, immune checkpoint inhibitors can be associated with substantial toxicity and only a subset of patients may benefit. Efforts are underway to better understand variation in responses to immune checkpoint blockade; however, it remains unclear what is contributing to this enhanced response in these patients, and there is a critical need to identify actionable strategies to improve responses to therapy in all patients.

[0005] There is an increasing appreciation of the role of the host microbiome in responses to cancer therapy, and studies suggest that bacteria present in the tumor and the gut

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may impact therapeutic responses. There is also a growing appreciation of the role of the gastrointestinal microbiome in shaping immune responses in health and disease. However, there is a significant translational knowledge gap, and there is an unmet need for therapeutic strategies to enhance responses to immune checkpoint blockade in melanoma, and other cancers.

SUMMARY OF THE INVENTION

[0006] In one embodiment, the present disclosure provides a composition comprising at least one isolated or purified population of bacteria belonging to of one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae. In other embodiments, the composition comprises at least two isolated or purified populations of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae. In certain embodiments, the composition is a live bacterial product, live biotherapeutic product or a probiotic composition. In still other embodiments, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are provided as bacterial spores. In another embodiment, the at least one population of bacteria belongs to Clostridiales Family XII and/or Clostridiales Family XIII. In some aspects, the composition comprises at least two isolated or purified populations of bacteria belonging to the family Ruminococcaceae and/or of the family Clostridiaceae. In other embodiments, the composition comprises at least one population belonging to the family Ruminococcaceae and at least one population belonging to the family Clostridiaceae. In some aspects, the two populations of bacteria belonging to the family Ruminococcaceae are further defined as populations of bacteria belonging to the genus *Ruminococcus*. In certain aspects, the at least two isolated or purified populations of bacteria belonging to the family Ruminococcaceae are further defined as populations of bacteria belonging to the genus *Faecalibacterium*. In certain aspects, the population of bacteria belonging to the genus *Faecalibacterium* are further defined as a population of bacteria belonging to the species *Faecalibacterium prausnitzii*. In certain aspects, the population of bacteria belonging to the genus *Ruminococcus* are further defined as a population of bacteria belonging to the species *Ruminococcus bromii*. In some aspects, the at least two isolated or purified populations of bacteria belonging to the family Micrococcaceae are further defined as a population of bacteria belonging to the genus *Rothia*. In additional aspects, the composition further comprises a population of bacteria belonging to the species

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Porphyromonas pasteri, the species *Clostridium hungatei,* the species *Phascolarctobacterium faecium,* the genus *Peptoniphilus,* and/or the class Mollicutes. In certain aspects, the composition does not comprise populations of bacteria belonging to the order Bacteroidales.

[0007] Particular embodiments of the present disclosure provide a method of preventing cancer in a subject comprising administering a composition of the embodiments to the subject. For example, in some aspects, a method is provided for preventing cancer in a subject at risk for developing cancer (*e.g.,* a melanoma) or treating cancer in a subject having a tumor comprising administering to the subject a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*, wherein administration of the composition results in an increase of $CD8^+$ T lymphocytes in the tumor. In particular embodiments, the T lymphocytes are cytotoxic T lymphocytes. In still other embodiments, the method is a method of treating cancer in a subject comprising administerting a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*, wherein administration of the composition results in an increase of effector $CD4^+$, $CD8^+$ T lymphocytes, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood of the subject. In some embodiments, the method is a method of treating cancer in a subject comprising administerting a composition comprising at least one isolated or purified population of bacteria belonging one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium* and/or *Ruminococcus*, wherein administration of the composition results in a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject. In other aspects, the method is a method of treating cancer in a subject having a tumor comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*, wherein administration of the composition to the subject results in an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate. In still other aspects, the method is a method of treating cancer in a subject having a tumor comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus

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Faecalibacterium, wherein administration of the composition to the subject results in an decrease in RORγT expression in a tumor immune infiltrate. Also described are methods of treating a tumor in a subject diagnosed with or suspected of having cancer comprising administering a composition comprising at least one isolated or purified population of bacteria belonging to one or more of the class Clostridia, class Mollicutes, order Clostridiales, family Ruminococcaceae and/or genus *Faecalibacterium*, wherein administration of the composition to the subject results in an increase in $CD45^+$, $CD3^+/CD20^+/CD56^+$, $CD68^+$ and/or HLA-DR^+ cells in the tumor. In some aspects, a composition of the embodiments is administered in a sufficient amount to increase the level of innate effector cells in the subject. In other aspects, administration of the composition to the subject results in an increase in the level of innate effector cells in the subject. For example, administration of the composition can increase innate effector cells such as $CD45^+CD11b^+Ly6G^+$ cells. In some aspects, a composition of the embodiments is administered in a sufficient amount to decrease the level of suppressive myeloid cells in the subject. In additional aspects, administration of the composition to the subject results in a decrease of the level of suppressive myeloid cells in the subject. For example, administration of the composition can decrease the level of suppressive myeloid cells such as $CD45^+CD11b^+CD11c^+$ cells. In particular embodiments, the composition comprises the bacteria *Faecalibacterium prausnitzii.*

[0008] Another embodiment provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial profile in the gut microbiome. In some aspects, a favorable microbial profile is further defined as having one or more of the bacterial populations of the probiotic or live bacterial product compositions of the embodiments. In a further embodiment, there is provided a method of predicting a response (*e.g.,* predicting survival) to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises one or more of the bacterial populations of the probiotic or live bacterial product compositions of the embodiments, the response is favorable. In particular embodiments, a patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In certain embodiments, the favorable microbial profile is a favorable gut microbial profile.

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[0009] In some embodiments, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to one or more of the species, subspecies or bacterial strains selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9. In particular embodiments, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are selected from the group consisting of the species in Table 1 with an "ei" equal to 1.

[0010] In certain aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains identified by NCBI Taxonomy IDs selected from the group consisting of NCBI Taxonomy ID: 717959, 587, 758823, 649756, 44749, 671218, 1264, 1122135, 853, 484018, 46503, 54565, 290052, 216931, 575978, 433321, 1796646, 213810, 228924, 290054, 1509, 1462919, 29375, 337097, 1298596, 487174, 642492, 1735, 1297424, 742766, 46680, 132925, 411467, 1318465, 1852367, 1841857, 169679, 1175296, 259063, 172901, 39488, 57172, 28118, 166486, 28133, 1529, 694434, 1007096, 84030, 56774, 102148, 626947, 216933, 1348613, 1472417, 100176, 824, 1471761, 1297617, 288966, 1317125, 28197, 358743, 264639, 1265, 1335, 66219, 69473, 115117, 341220, 1732, 873513, 396504, 1796619, 45851, 2741, 105841, 86332, 1349822, 84037, 180311, 54291, 1217282, 762984, 1185412, 154046, 663278, 1543, 398512, 69825, 1841867, 1535, 1510, 84026, 1502, 1619234, 39497, 1544, 29343, 649762, 332095, 536633, 1033731, 574930, 742818, 177412, 1121308, 419208, 1673717, 55779, 28117, 626937, 180332, 1776382, 40519, 34062, 40518, 74426, 1216062, 293826, 850, 645466, 474960, 36835, 115544, 1515, 88431, 216932, 1417852, 39492, 1583, 420247, 118967, 169435, 37658, 138595, 31971, 100886, 1197717, 234908, 537007, 319644, 168384, 915173, 95159, 1816678, 626940, 501571, 1796620, 888727, 1147123, 376806, 1274356, 1267, 39495, 404403, 1348, 253314, 258515, 33033, 1118061, 357276, 214851, 320502, 217731, 246787, 29371, 649764, 901, 29374, 33043, 39778, 682400, 871665, 160404, 745368, 408, 1584, 333367, 47246, 1096246, 53342, 438033, 351091, 1796622, 1776384, 817, 48256, 720554, 500632, 36849, 301302, 879970, 655811, 264463, 1532, 285, 995, 242750, 29539, 1432052, 622312, 1796636, 1337051, 328814, 28446, 1492, 820, 39496, 52786, 1549, 1796618, 582, 46507, 109327, 1531, 1382, 33039, 311460, 230143, 216935, 539, 35519, 1681, 328813, 214853, 89014, 1121115, 1585974, 29466, 1363, 292800, 270498, 214856, 142877, 133926, 209880, 179628, 1121102, 105612, 1796615, 39777, 29353, 1579, 163665, 53443, 261299, 1302, 1150298, 938289, 358742, 471875, 938278, 1796613, 1118057, 1077144,

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1737, 218205, 1121298, 684066, 433659, 52699, 204516, 706562, 253257, 328812, 1280, 147802, 58134, 1335613, 891, 585394, 1582, 235931, 308994, 1589, 1682, 1736, 28129, 178001, 551788, 2051, 856, 118562, 101070, 515619, 40215, 187979, 82979, 29363, 1776391, 1285191, 84112, 157688, 38304, 36850, 341694, 287, 75612, 818, 371674, 338188, 88164, 588581, 676965, 546271, 1236512, 178338, 862517, 157687, 158, 51048, 1583331, 529, 888745, 394340, 40545, 855, 553973, 938293, 93063, 708634, 179995, 1351, 476652, 1464038, 555088, 237576, 879566, 1852371, 742727, 1377, 35830, 997353, 218538, 83771, 1605, 28111, 131109, 46609, 690567, 46206, 155615, 51616, 40542, 203, 294, 1034346, 156456, 80866, 554406, 796942, 1002367, 29347, 796944, 61592, 487175, 1050201, 762948, 137732, 1211819, 1019, 272548, 1717, 384636, 216940, 2087, 45634, 466107, 1689, 47678, 575, 979627, 840, 1660, 1236517, 617123, 546, 28135, 82171, 483, 501496, 99656, 1379, 84032, 39483, 1107316, 584, 28124, 1033744, 657309, 536441, 76123, 1118060, 89152, 76122, 303, 1541, 507751, 515620, 38302, 53419, 726, 40324, 1796610, 988946, 1852370, 1017, 1168289, 76936, 94869, 1161098, 215580, 1125779, 327575, 549, 1450648 and 478. In specific aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria are closely related to the species, subspecies or bacterial strains identified by NCBI Taxonomy IDs listed above. For example, in some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of one of the bacteria listed above (*i.e.,* the Set 1 bacteria from Table 1) or bacteria listed in Table 1 and having an ei greater that 0.5 or equal to 1.

[0011] In still other aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to the species, subspecies or bacterial strains selected from the group consisting of *Bacteroides coagulans*, *Clostridium aldenense*, *Clostridium aldrichii*, *Clostridium alkalicellulosi*, *Clostridium amygdalinum*, *Clostridium asparagiforme*, *Clostridium cellulosi*, *Clostridium citroniae*, *Clostridium clariflavum DSM 19732*, *Clostridium clostridioforme*, *Clostridium colinum*, *Clostridium fimetarium*, *Clostridium hiranonis*, *Clostridium hungatei*, *Clostridium hylemonae DSM 15053*, *Clostridium indolis*, *Clostridium lactatifermentans*, *Clostridium leptum*, *Clostridium methylpentosum*, *Clostridium oroticum*, *Clostridium papyrosolvens DSM 2782*, *Clostridium populeti*, *Clostridium propionicum*, *Clostridium saccharolyticum*, *Clostridium scindens*,

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Clostridium sporosphaeroides, *Clostridium stercorarium*, *Clostridium straminisolvens*, *Clostridium sufflavum*, *Clostridium termitidis*, *Clostridium thermosuccinogenes*, *Clostridium viride*, *Clostridium xylanolyticum*, *Desulfotomaculum guttoideum*, *Eubacterium rectale ATCC 33656*, *Eubacterium dolichum*, *Eubacterium eligens ATCC 27750*, *Eubacterium hallii*, *Eubacterium infirmum*, *Eubacterium siraeum*, *Eubacterium tenue*, *Ruminococcus torques*, *Acetanaerobacterium elongatum*, *Acetatifactor muris*, *Acetivibrio cellulolyticus*, *Acetivibrio ethanolgignens*, *Acholeplasma brassicae 0502*, *Acholeplasma parvum*, *Acholeplasma vituli*, *Acinetobacter junii*, *Actinobacillus porcinus*, *Actinomyces bowdenii*, *Actinomyces dentalis*, *Actinomyces odontolyticus*, *Acutalibacter muris*, *Aerococcus viridans*, *Aeromicrobium fastidiosum*, *Alistipes finegoldii*, *Alistipes obesi*, *Alistipes onderdonkii*, *Alistipes putredinis*, *Alistipes shahii*, *Alistipes shahii WAL 8301*, *Alistipes timonensis JC136*, *Alkalibacter saccharofermentans*, *Alkaliphilus metalliredigens QYMF*, *Allisonella histaminiformans*, *Allobaculum stercoricanis DSM 13633*, *Alloprevotella rava*, *Alloprevotella tannerae*, *Anaerobacterium chartisolvens*, *Anaerobiospirillum thomasii*, *Anaerobium acetethylicum*, *Anaerococcus octavius NCTC 9810*, *Anaerococcus provenciensis*, *Anaerococcus vaginalis ATCC 51170*, *Anaerocolumna jejuensis*, *Anaerofilum agile*, *Anaerofustis stercorihominis*, *Anaeroglobus geminatus*, *Anaeromassilibacillus senegalensis*, *Anaeroplasma abactoclasticum*, *Anaerorhabdus furcosa*, *Anaerosporobacter mobilis*, *Anaerostipes butyraticus*, *Anaerostipes caccae*, *Anaerostipes hadrus*, *Anaerotruncus colihominis*, *Anaerovorax odorimutans*, *Anoxybacillus rupiensis*, *Aquabacterium limnoticum*, *Arcobacter butzleri*, *Arthrospira platensis*, *Asaccharobacter celatus*, *Atopobium parvulum*, *Bacteroides caccae*, *Bacteroides caecimuris*, *Bacteroides cellulosilyticus*, *Bacteroides clarus YIT 12056*, *Bacteroides dorei*, *Bacteroides eggerthii*, *Bacteroides finegoldii*, *Bacteroides fragilis*, *Bacteroides gallinarum*, *Bacteroides massiliensis*, *Bacteroides oleiciplenus YIT 12058*, *Bacteroides plebeius DSM 17135*, *Bacteroides rodentium JCM 16496*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides xylanisolvens XB1A*, *Bacteroides xylanolyticus*, *Barnesiella intestinihominis*, *Beduini massiliensis*, *Bifidobacterium bifidum*, *Bifidobacterium dentium*, *Bifidobacterium longum subsp. infantis*, *Blautia caecimuris*, *Blautia coccoides*, *Blautia faecis*, *Blautia glucerasea*, *Blautia hansenii DSM 20583*, *Blautia hydrogenotrophica*, *Blautia luti*, *Blautia luti DSM 14534*, *Blautia wexlerae DSM 19850*, *Budvicia aquatica*, *Butyricicoccus pullicaecorum*, *Butyricimonas paravirosa*, *Butyrivibrio crossotus*, *Caldicoprobacter oshimai*, *Caloramator coolhaasii*, *Caloramator proteoclasticus*, *Caloramator quimbayensis*, *Campylobacter gracilis*, *Campylobacter rectus*, *Campylobacter ureolyticus DSM 20703*, *Capnocytophaga gingivalis*, *Capnocytophaga leadbetteri*,

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Capnocytophaga sputigena, *Casaltella massiliensis*, *Catabacter hongkongensis*, *Catenibacterium mitsuokai*, *Christensenella minuta*, *Christensenella timonensis*, *Chryseobacterium taklimakanense*, *Citrobacter freundii*, *Cloacibacillus porcorum*, *Clostridioides difficile ATCC 9689 = DSM 1296*, *Clostridium amylolyticum*, *Clostridium bowmanii*, *Clostridium butyricum*, *Clostridium cadaveris*, *Clostridium colicanis*, *Clostridium gasigenes*, *Clostridium lentocellum DSM 5427*, *Clostridium oceanicum*, *Clostridium oryzae*, *Clostridium paraputrificum*, *Clostridium pascui*, *Clostridium perfringens*, *Clostridium quinii*, *Clostridium saccharobutylicum*, *Clostridium sporogenes*, *Clostridium ventriculi*, *Collinsella aerofaciens*, *Comamonas testosteroni*, *Coprobacter fastidiosus NSB1*, *Coprococcus eutactus*, *Corynebacterium diphtheriae*, *Corynebacterium durum*, *Corynebacterium mycetoides*, *Corynebacterium pyruviciproducens ATCC BAA-1742*, *Corynebacterium tuberculostearicum*, *Culturomica massiliensis*, *Cuneatibacter caecimuris*, *Defluviitalea saccharophila*, *Delftia acidovorans*, *Desulfitobacterium chlororespirans*, *Desulfitobacterium metallireducens*, *Desulfosporosinus acididurans*, *Desulfotomaculum halophilum*, *Desulfotomaculum intricatum*, *Desulfotomaculum tongense*, *Desulfovibrio desulfuricans subsp. desulfuricans*, *Desulfovibrio idahonensis*, *Desulfovibrio litoralis*, *Desulfovibrio piger*, *Desulfovibrio simplex*, *Desulfovibrio zosterae*, *Desulfuromonas acetoxidans*, *Dethiobacter alkaliphilus AHT 1*, *Dethiosulfatibacter aminovorans*, *Dialister invisus*, *Dialister propionicifaciens*, *Dielma fastidiosa*, *Dietzia alimentaria 72*, *Dorea longicatena*, *Dysgonomonas gadei ATCC BAA-286*, *Dysgonomonas mossii*, *Eggerthella lenta*, *Eikenella corrodens*, *Eisenbergiella tayi*, *Emergencia timonensis*, *Enorma massiliensis phI*, *Enterococcus faecalis*, *Enterorhabdus muris*, *Ethanoligenens harbinense YUAN-3*, *Eubacterium coprostanoligenes*, *Eubacterium limosum*, *Eubacterium oxidoreducens*, *Eubacterium sulci ATCC 35585*, *Eubacterium uniforme*, *Eubacterium ventriosum*, *Eubacterium xylanophilum*, *Extibacter muris*, *Ezakiella peruensis*, *Faecalibacterium prausnitzii*, *Faecalicoccus acidiformans*, *Faecalitalea cylindroides*, *Filifactor villosus*, *Flavonifractor plautii*, *Flintibacter butyricus*, *Frisingicoccus caecimuris*, *Fucophilus fucoidanolyticus*, *Fusicatenibacter saccharivorans*, *Fusobacterium mortiferum*, *Fusobacterium nucleatum subsp. vincentii*, *Fusobacterium simiae*, *Fusobacterium varium*, *Garciella nitratireducens*, *Gemella haemolysans*, *Gemmiger formicilis*, *Gordonibacter urolithinfaciens*, *Gracilibacter thermotolerans JW/YJL-S1*, *Granulicatella elegans*, *Guggenheimella bovis*, *Haemophilus haemolyticus*, *Helicobacter typhlonius*, *Hespellia stercorisuis*, *Holdemanella biformis*, *Holdemania massiliensis AP2*, *Howardella ureilytica*, *Hungatella effluvii*, *Hungatella hathewayi*, *Hydrogenoanaerobacterium saccharovorans*, *Ihubacter massiliensis*, *Intestinibacter bartlettii*, *Intestinimonas*

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butyriciproducens, *Irregularibacter muris*, *Kiloniella laminariae DSM 19542*, *Kroppenstedtia guangzhouensis*, *Lachnoanaerobaculum orale*, *Lachnoanaerobaculum umeaense*, *Lachnoclostridium phytofermentans*, *Lactobacillus acidophilus*, *Lactobacillus algidus*, *Lactobacillus animalis*, *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Lactobacillus fornicalis*, *Lactobacillus iners*, *Lactobacillus pentosus*, *Lactobacillus rogosae*, *Lactococcus garvieae*, *Lactonifactor longoviformis*, *Leptotrichia buccalis*, *Leptotrichia hofstadii*, *Leptotrichia hongkongensis*, *Leptotrichia wadei*, *Leuconostoc inhae*, *Levyella massiliensis*, *Loriellopsis cavernicola*, *Lutispora thermophila*, *Marinilabilia salmonicolor JCM 21150*, *Marvinbryantia formatexigens*, *Mesoplasma photuris*, *Methanobrevibacter smithii ATCC 35061*, *Methanomassiliicoccus luminyensis B10*, *Methylobacterium extorquens*, *Mitsuokella jalaludinii*, *Mobilitalea sibirica*, *Mobiluncus curtisii*, *Mogibacterium pumilum*, *Mogibacterium timidum*, *Moorella glycerini*, *Moorella humiferrea*, *Moraxella nonliquefaciens*, *Moraxella osloensis*, *Morganella morganii*, *Moryella indoligenes*, *Muribaculum intestinale*, *Murimonas intestini*, *Natranaerovirga pectinivora*, *Neglecta timonensis*, *Neisseria cinerea*, *Neisseria oralis*, *Nocardioides mesophilus*, *Novibacillus thermophilus*, *Ochrobactrum anthropi*, *Odoribacter splanchnicus*, *Olsenella profusa*, *Olsenella uli*, *Oribacterium asaccharolyticum ACB7*, *Oribacterium sinus*, *Oscillibacter ruminantium GH1*, *Oscillibacter valericigenes*, *Oxobacter pfennigii*, *Pantoea agglomerans*, *Papillibacter cinnamivorans*, *Parabacteroides faecis*, *Parabacteroides goldsteinii*, *Parabacteroides gordonii*, *Parabacteroides merdae*, *Parasporobacterium paucivorans*, *Parasutterella excrementihominis*, *Parasutterella secunda*, *Parvimonas micra*, *Peptococcus niger*, *Peptoniphilus duerdenii ATCC BAA-1640*, *Peptoniphilus grossensis ph5*, *Peptoniphilus koenoeneniae*, *Peptoniphilus senegalensis JC140*, *Peptostreptococcus stomatis*, *Phascolarctobacterium succinatutens*, *Phocea massiliensis*, *Pontibacter indicus*, *Porphyromonas bennonis*, *Porphyromonas endodontalis*, *Porphyromonas pasteri*, *Prevotella bergensis*, *Prevotella buccae ATCC 33574*, *Prevotella denticola*, *Prevotella enoeca*, *Prevotella fusca JCM 17724*, *Prevotella loescheii*, *Prevotella nigrescens*, *Prevotella oris*, *Prevotella pallens ATCC 700821*, *Prevotella stercorea DSM 18206*, *Prevotellamassilia timonensis*, *Propionispira arcuata*, *Proteus mirabilis*, *Providencia rettgeri*, *Pseudobacteroides cellulosolvens ATCC 35603 = DSM 2933*, *Pseudobutyrivibrio ruminis*, *Pseudoflavonifractor capillosus ATCC 29799*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas mandelii*, *Pseudomonas nitroreducens*, *Pseudomonas putida*, *Raoultella ornithinolytica*, *Raoultella planticola*, *Raoultibacter massiliensis*, *Robinsoniella peoriensis*, *Romboutsia timonensis*, *Roseburia faecis*, *Roseburia hominis A2-183*, *Roseburia intestinalis*, *Roseburia inulinivorans DSM 16841*, *Rothia dentocariosa ATCC 17931*, *Ruminiclostridium*

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thermocellum, *Ruminococcus albus*, *Ruminococcus bromii*, *Ruminococcus callidus*, *Ruminococcus champanellensis 18P13 = JCM 17042*, *Ruminococcus faecis JCM 15917*, *Ruminococcus flavefaciens*, *Ruminococcus gauvreauii*, *Ruminococcus lactaris ATCC 29176*, *Rummeliibacillus pycnus*, *Saccharofermentans acetigenes*, *Scardovia wiggsiae*, *Schlegelella thermodepolymerans*, *Sedimentibacter hongkongensis*, *Selenomonas sputigena ATCC 35185*, *Slackia exigua ATCC 700122*, *Slackia piriformis YIT 12062*, *Solitalea canadensis*, *Solobacterium moorei*, *Sphingomonas aquatilis*, *Spiroplasma alleghenense*, *Spiroplasma chinense*, *Spiroplasma chrysopicola*, *Spiroplasma culicicola*, *Spiroplasma lampyridicola*, *Sporobacter termitidis*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Stomatobaculum longum*, *Streptococcus agalactiae ATCC 13813*, *Streptococcus cristatus*, *Streptococcus equinus*, *Streptococcus gordonii*, *Streptococcus lactarius*, *Streptococcus parauberis*, *Subdoligranulum variabile*, *Succinivibrio dextrinosolvens*, *Sutterella stercoricanis*, *Sutterella wadsworthensis*, *Syntrophococcus sucromutans*, *Syntrophomonas zehnderi OL-4*, *Terrisporobacter mayombei*, *Thermoleophilum album*, *Treponema denticola*, *Treponema socranskii*, *Tyzzerella nexilis DSM 1787*, *Vallitalea guaymasensis*, *Vallitalea pronyensis*, *Vampirovibrio chlorellavorus*, *Veillonella atypica*, *Veillonella denticariosi*, *Veillonella dispar*, *Veillonella parvula*, *Victivallis vadensis*, *Vulcanibacillus modesticaldus and Weissella confusa.*

[0012] In certain aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria selected from the species in Table 2 designated with a response status of responder (R). In still further aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprising a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the species in Table 2 designated with a response status of responder (R). In particular aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the group consisting of the species in Table 2 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01.

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[0013] In certain aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises a 16S ribosomal RNA (rRNA) nucleotide sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the 16S rRNA nucleotide sequence of bacteria selected from the group consisting of the species in Table 1 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01. In particular embodiments, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria are a species, subspecies or bacterial strains comprising a 16S rRNA gene sequence at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of SEQ ID NO: 1-876.

[0014] In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations belong to species of bacteria selected from the species in Table 2 designated with a response status of responder (R). In particular aspects, the at least one isolated or purified population bacteria or the at least two isolated or purified populations of bacteria belong to species of bacteria selected from the group consisting of the species in Table 2 designated with a response status of responder (R) and having an unadjusted p-value less than 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, or 0.01. In still other aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria belong to species, subspecies or strains comprising nucleotide sequences with at least 60%, 65%, 70%, 75%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% percent identity to the co-abundance gene group (CAG) sequences (see, Table 2A) selected from the group consisting of SEQ ID NO: 877-926, SEQ ID NO: 927-976, SEQ ID NO: 977-1026, SEQ ID NO: 1027-1076, SEQ ID NO: 1077-1126, SEQ ID NO: 1127-1176, SEQ ID NO: 1177-1226, SEQ ID NO: 1227-1276, SEQ ID NO: 1277-1326, SEQ ID NO: 1327-1376, SEQ ID NO: 1377-1426, SEQ ID NO: 1427-1476, SEQ ID NO: 1477-1526, SEQ ID NO: 1527-1576, SEQ ID NO: 1577-1626, SEQ ID NO: 1627-1676, SEQ ID NO: 1677-1726, SEQ ID NO: 1727-1776, SEQ ID NO: 1777-1826, SEQ ID NO: 1827-1876, SEQ ID NO: 1877-1926, SEQ ID NO: 1927-1976, SEQ ID NO: 1977-2026, SEQ ID NO: 2027-2076, SEQ ID NO: 2077-2126, SEQ ID NO: 2127-2176, SEQ ID NO: 2177-2226, SEQ ID NO: 2227-2276, SEQ ID NO: 2277-2326, SEQ ID NO: 2327-2376, SEQ ID NO: 2377-2426, SEQ ID NO: 2427-2476, SEQ ID NO: 2477-2526, SEQ ID NO: 2527-2576, SEQ ID NO: 2577-2626 and SEQ ID NO: 2627-2676.

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CAG ID	Sequence Identifiers
CAG00327	SEQ ID NO: 877-926
CAG00659	SEQ ID NO: 927-976
CAG00492	SEQ ID NO: 977-1026
CAG00518	SEQ ID NO: 1027-1076
CAG01146	SEQ ID NO: 1077-1126
CAG00079	SEQ ID NO: 1127-1176
CAG00393	SEQ ID NO: 1177-1226
CAG00766	SEQ ID NO: 1227-1276
CAG00095	SEQ ID NO: 1277-1326
CAG00010_1	SEQ ID NO: 1327-1376
CAG00342	SEQ ID NO: 1377-1426
CAG00303	SEQ ID NO: 1427-1476
CAG00337	SEQ ID NO: 1477-1526
CAG00381	SEQ ID NO: 1527-1576
CAG00559	SEQ ID NO: 1577-1626
CAG00570	SEQ ID NO: 1627-1676
CAG00635	SEQ ID NO: 1677-1726
CAG00636	SEQ ID NO: 1727-1776
CAG00660	SEQ ID NO: 1777-1826
CAG00669	SEQ ID NO: 1827-1876
CAG00708	SEQ ID NO: 1877-1926
CAG00773	SEQ ID NO: 1927-1976
CAG00807	SEQ ID NO: 1977-2026
CAG00880	SEQ ID NO: 2027-2076
CAG00907	SEQ ID NO: 2077-2126
CAG01086	SEQ ID NO: 2127-2176
CAG01215	SEQ ID NO: 2177-2226
CAG01277	SEQ ID NO: 2227-2276
CAG01308	SEQ ID NO: 2277-2326
CAG00577	SEQ ID NO: 2327-2376
CAG00506	SEQ ID NO: 2377-2426
CAG00852	SEQ ID NO: 2427-2476
CAG01046	SEQ ID NO: 2477-2526
CAG00320	SEQ ID NO: 2527-2576
CAG00619	SEQ ID NO: 2577-2626
CAG01366	SEQ ID NO: 2627-2676

[0015] In certain aspects, the at least one isolated or purified population of bacteria or the two populations of bacteria are selected from the group consisting of species, subspecies or strains comprising nucleotide sequences with at least 29% identity to SEQ ID NO: 877-926, at least 16.5% identity to SEQ ID NO: 927-976, at least 48.5% identity to SEQ ID NO: 977-1026,

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at least 28% identity to SEQ ID NO: 1027-1076, at least 93.5% identity to SEQ ID NO: 1077-1126, at least 99.5% identity to SEQ ID NO: 1127-1176, at least 99.5% identity to SEQ ID NO: 1177-1226, at least 99% identity to SEQ ID NO: 1227-1276, 100% identity to SEQ ID NO: 1277-1326, at least 21.5% identity to SEQ ID NO: 1327-1376, 100% identity to SEQ ID NO: 1377-1426, at least 97% identity to SEQ ID NO: 1427-1476, at least 55.5% identity to SEQ ID NO: 1477-1526, 100% identity to SEQ ID NO: 1527-1576, at least 34% identity to SEQ ID NO: 1577-1626, at least 14% identity to SEQ ID NO: 1627-1676, 100% identity to SEQ ID NO: 1677-1726, at least 93% identity to SEQ ID NO: 1727-1776, 100% identity to SEQ ID NO: 1777-1826, at least 45% identity to SEQ ID NO: 1827-1876, at least 99% identity to SEQ ID NO: 1877-1926, at least 74% identity to SEQ ID NO: 1927-1976, 100% identity to SEQ ID NO: 1977-2026, 100% identity to SEQ ID NO: 2027-2076, at least 20% identity to SEQ ID NO: 2077-2126, at least 84% identity to SEQ ID NO: 2127-2176, at least 35.5% identity to SEQ ID NO: 2177-2226, at least 32.5% identity to SEQ ID NO: 2227-2276, at least 70% identity to SEQ ID NO: 2277-2326, 100% identity to SEQ ID NO: 2327-2376, at least 70.5% identity to SEQ ID NO: 2377-2426, at least 99.5% identity to SEQ ID NO: 2427-2476, at least 68.5% identity to SEQ ID NO: 2477-2526, 100% identity to SEQ ID NO: 2527-2576, at least 97.5% identity to SEQ ID NO: 2577-2626 or 100% identity to SEQ ID NO: 2627-2676.

[0016] In certain aspects, the at least one isolated or purified population of bacteria or the two populations of bacteria are selected from the group consisting of species, subspecies or strains comprising nucleotide sequences with at least 29% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to SEQ ID NO: 877-926, at least 16.5% identity to genes of *Clostridiales bacterium* NK3B98 corresponding to SEQ ID NO: 927-976, at least 48.5% identity to genes of Subdoligranulum sp. 4_3_54A2FAA corresponding to SEQ ID NO: 977-1026, at least 28% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to genes of corresponding to SEQ ID NO: 1027-1076, at least 93.5% identity to genes of *Oscillibacter sp.* CAG:155 corresponding to SEQ ID NO: 1077-1126, at least 99.5% identity to genes of *Clostridium sp.* CAG:7 corresponding to SEQ ID NO: 1127-1176, at least 99.5% identity to genes of *Eubacterium sp.* CAG:86 corresponding to SEQ ID NO: 1177-1226, at least 99% identity to genes of *Firmicutes bacterium* CAG:176 corresponding to SEQ ID NO: 1227-1276, 100% identity to genes of *Akkermansia sp.* CAG:344 corresponding to SEQ ID NO: 1277-1326, at least 21.5% identity to genes of *Faecalibacterium sp.* CAG:74 corresponding to SEQ ID NO: 1327-1376, 100% identity to genes of *Bifidobacterium pseudocatenulatum* DSM 20438 = JCM 1200 = LMG 10505 corresponding to SEQ ID NO:

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1377-1426, at least 97% identity to genes of *Clostridium sp.* JCC corresponding to SEQ ID NO: 1427-1476, at least 55.5% identity to genes *of Faecalibacterium prausnitzii* SL3/3 corresponding to SEQ ID NO: 1477-1526, 100% identity to genes of *Clostridium sp.* CAG:242 corresponding to SEQ ID NO: 1527-1576, at least 34% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 1577-1626 , at least 14% identity to genes of *Ruminococcus sp.* CAG:382 corresponding to SEQ ID NO: 1627-1676, 100% identity to genes of *Bifidobacterium bifidum* S17 corresponding to SEQ ID NO: 1677-1726, at least 93% identity to genes of *Roseburia sp.* CAG:309 corresponding to SEQ ID NO: 1727-1776, 100% identity to genes of *Alistipes timonensis* JC136 corresponding to SEQ ID NO: 1777-1826, at least 45% identity to genes of *Firmicutes bacterium* CAG:103 corresponding to SEQ ID NO: 1827-1876, at least 99% identity to genes of *Alistipes senegalensis* JC50 corresponding to SEQ ID NO: 1877-1926, at least 74% identity to genes of *Firmicutes bacterium* CAG:176 corresponding to SEQ ID NO: 1927-1976, 100% identity to genes of *Holdemanella biformis* DSM 3989 corresponding to SEQ ID NO: 1977-2026, 100% identity to genes of *Subdoligranulum sp.* CAG:314 corresponding to SEQ ID NO: 2027-2076, at least 20% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 2077-2126, at least 84% identity to genes of *Firmicutes bacterium* CAG:124 corresponding to SEQ ID NO: 2127-2176, at least 35.5% identity to genes of *Intestinimonas butyriciproducens* corresponding to SEQ ID NO: 2177-2226, at least 32.5% identity to genes of *Clostridium sp.* CAG:226 corresponding to SEQ ID NO: 2227-2276, at least 70% identity to genes of *Firmicutes bacterium* CAG:124 corresponding to SEQ ID NO: 2277-2326, 100% identity to genes of *Faecalibacterium prausnitzii* L2-6 corresponding to SEQ ID NO: 2327-2376, at least 70.5% identity to genes of *Ruminococcaceae bacterium* D16 corresponding to SEQ ID NO: 2377-2426, at least 99.5% identity to genes of *Clostridium spiroforme* DSM 1552 corresponding to SEQ ID NO: 2427-2476, at least 68.5% identity to genes of *Intestinimonas butyriciproducens* corresponding to SEQ ID NO: 2477-2526, 100% identity to genes of *Phascolarctobacterium sp.* CAG:207 corresponding to SEQ ID NO: 2527-2576, at least 97.5% identity to genes of *Faecalibacterium prausnitzii* L2-6 corresponding to SEQ ID NO: 2577-2626 of or 100% identity to genes of *Streptococcus parasanguinis* ATCC 15912 corresponding to SEQ ID NO: 2627-2676.

[0017] In some aspects, the bacteria are lyophilized or freeze dried. In particular aspects, the composition is formulated for oral delivery. For example, the composition formulated for oral delivery is a tablet or capsule. In particular aspects, the tablet or capsule comprises an acid-resistant enteric coating. In certain aspects the composition comprising the

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at least one isolated or purified population of bacteria or the at least two isolated or purified populationss of bacteria is formulated for administration rectally, via colonoscopy, sigmoidoscopy by nasogastric tube, or enema. In some aspects, the composition is lyophilized or is frozen. In certain aspects, the composition is capable of being re-formulated for final delivery as comprising a liquid, a suspension, a gel, a geltab, a semisolid, a tablet, a sachet, a lozenge, a capsule, or as an enteral formulation. In some aspects, the composition is formulated for multiple administrations. In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria comprises an antibiotic resistance gene. In some aspects, the at least one isolated or purified population of bacteria or the at least two isolated or purified populations of bacteria is a short-chain fatty acid-producing population of bacteria. In certain aspects, the short-chain fatty acid-producing population of bacteria is a butyrate-producing population of bacteria. In particular aspects, at least one immune checkpoint inhibitor is administered intravenously and the butyrate-producing population of bacteria is administered orally.

[0018] Embodiments of the present disclosure provide a method of treating cancer in a subject comprising administering a therapeutically effective amount of a short-chain fatty acid, such as butyrate, and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population, to said subject, wherein the subject has been administered an immune checkpoint inhibitor. In some aspects, the method further comprises administering at least one immune checkpoint inhibitor. In certain aspects, more than one checkpoint inhibitor is administered. In some aspects, the method further comprises administering a prebiotic or probiotic.

[0019] In some aspects, the short-chain fatty acid-producing bacterial population comprises bacteria comprising an antibiotic resistance gene. In some aspects, the butyrate-producing bacterial population comprises bacteria comprising an antibiotic resistance gene. In some embodiments, the method further comprises a step of administering such short-chain fatty acid-producing antibiotic resistant bacterial population, for example, such butyrate-producing antibiotic resistant bacterial population, to a subject having cancer. In some embodiments, the method further comprises administering the antibiotic to which the short-chain fatty acid-producing antibiotic resistant bacterial population, such as the butyrate-producing antibiotic resistant bacterial population, are resistant to the subject, wherein the antibiotic resistance gene confers resistance to the antibiotic.

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[0020] In some aspects, the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales. In certain aspects, the one or more bacterial species are from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriaceae. In particular aspects, the one or more bacterial species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti, Ruminococcus obeum, Ruminococcus palustris, Ruminococcus pasteurii, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum,* and *Eubacterium oxidoreducens.* In one specific aspect, the one or more bacterial species is *Faecalibacterium prausnitzii.* In particular aspects, the butyrate-producing bacterial population does not comprise bacterial species of the family Prevotellaceae or the order Bacteriodales.

[0021] In certain aspects, administering the butyrate comprises administering a butyrate prodrug or salt. In particular aspects, administering butyrate comprises administering sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, pivaloyloxymethyl butyrate (AN-9) or butylidenedi-butyrate (AN-10).

[0022] In some aspects, the butyrate or butyrate-producing bacterial population, are administered orally, rectally, via colonoscopy, sigmoidoscopy, enema or by direct injection. In particular aspects, the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

[0023] In some aspects, the at least one checkpoint inhibitor is selected from an inhibitor of CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, BTLA, B7H3, B7H4, TIM3, KIR, or A2aR. In certain aspects, the at least one immune checkpoint inhibitor is a human programmed cell death 1 (PD-1) axis-binding antagonist. In some aspects, the PD-1 axis-binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PDL1-binding antagonist and a PDL2-binding antagonist. In certain aspects, the PD-1 axis-binding antagonist is a PD-1-binding antagonist. In some aspects, the PD-1-binding antagonist inhibits the binding of PD-1 to PDL1 and/or PDL2. In particular aspects, the PD-1-binding antagonist is a monoclonal antibody or antigen binding fragment thereof. In specific aspects, the PD-1-binding antagonist

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is nivolumab, pembrolizumab, pidillizumab, KEYTRUDA®, AMP-514, REGN2810, CT-011, BMS 936559, MPDL328OA or AMP-224. In some aspects, the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody. In particular aspects, the anti-CTLA-4 antibody is tremelimumab, YERVOY®, or ipilimumab. In certain aspects, the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody. In some aspects, the anti-KIR antibody is lirilumab.

[0024] In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In particular aspects, the melanoma is metastatic melanoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

[0025] In certain aspects, the method further comprises administering at least one additional anticancer treatment. In some aspects, the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy. In some aspects, the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

[0026] In some aspects, the at least one immune checkpoint inhibitor and/or at least one additional anticancer treatment is administered intratumorally, intraarterially, intravenously, intravascularly, intrapleuraly, intraperitoneally, intratracheally, intrathecally, intramuscularly, endoscopically, intralesionally, percutaneously, subcutaneously, regionally, stereotactically, orally or by direct injection or perfusion. In particular aspects, the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

[0027] Another embodiment provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to said subject, wherein the subject has been determined to have a favorable microbial

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profile in the gut microbiome. In some aspects, a favorable microbial profile is further defined as having: (a) high alpha-diversity of the gut microbiome; (b) a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, in the gut microbiome; (c) one or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9 or equal to 1 in the gut microbiome; (d) one or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) of the bacteria species in Table 2 designated with a response status of responder (R) in the gut microbiome; and/or (e) clusters centered around R-centroid by beta-diversity (by *e.g.,* weighted unifrac distances).

[0028] In some aspects, a favorable microbial profile is further defined as the presence or high abundance of bacteria of the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, genus *Ruminococcus*, genus *Faecalibacterium*, genus *Hydrogenoanaerobacterium*, phylum Actinobacteria, class Coriobacteriia, order Coriobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota, or family Christensenellaceae. In certain aspects, a favorable microbial profile is further defined as the absence or low abundance of bacteria of the species *Escherichia coli*, species *Anerotruncus colihominis*, genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroidia, order Bacteroidales or family Prevotellaceae. In particular aspects, a favorable microbial profiles is defined as the presence or high abundance of bacteria of the class Clostridiales and the absence or low abundance of bacteria of the order Bacteroidales. In some aspects, a favorable microbial profile is further defined as a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. In certain aspects, the butyrate-producing bacteria comprises one or more species is from the genus *Ruminococcus* or *Faecalibacterium.*

[0029] In some aspects, the subject was determined to comprise a favorable microbial profile or favorable gut microbiome by analyzing the microbiome in a patient sample. In certain aspects, the patient sample is a fecal sample or buccal sample. In some aspects, analyzing comprises performing 16S ribosomal sequencing and/or metagenomics whole genome sequencing.

[0030] In a further embodiment, there is provided a method of predicting a response (*e.g.,* patient survival) to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the

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microbial profile comprises: (a) high alpha-diversity; (b) a high abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria; (c) one or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) bacteria selected from the group consisting of the species in Table 1 with an enrichment index (ei) greater than 0.5, 0.6, 0.7, 0.8 or 0.9 or equal to 1; (d) one or more (*e.g.,* 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) of the bacteria species in Table 2 designated with a response status of responder (R); (e) a low abundance of Bacteriodales; and/or (f) distinct clusters by beta-diversity weighted unifrac distances, then the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In particular embodiments, a patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor. In certain embodiments, a patient is administered a second immune checkpoint inhibitor. In certain embodiments the favorable microbial profile is a favorable gut microbial profile.

[0031] In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma. In particular aspects, the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

[0032] In some aspects, the short-chain fatty acid-producing bacteria, such as butyrate-producing bacterial population, comprises one or more bacterial species of the order Clostridiales. In certain aspects, the one or more species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease. In particular aspects, the one or more species are selected from the group consisting of *Faecalibacterium prausnitzii, Ruminococcus albus, Ruminococcus bromii, Ruminococcus callidus, Ruminococcus flavefaciens, Ruminococcus champanellensis, Ruminococcus faecis, Ruminococcus gauvreauii, Ruminococcus gnavus, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus lactaris, Ruminococcus luti , Ruminococcus obeum, Ruminococcus palustris , Ruminococcus pasteurii,*

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Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum, and Eubacterium oxidoreducens. In certain aspects, the one or more species is *Faecalibacterium prausnitzii.*

[0033] In additional aspects, the method further comprises administering an immune checkpoint inhibitor to a subject predicted to have a favorable response to the immune checkpoint inhibitor. In some aspects, the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

[0034] In some aspects, the method further comprises administering at least one additional anticancer treatment. In certain aspects, the at least one additional anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy or a biological therapy. In particular aspects, the at least one additional anticancer treatment is a short-chain fatty acid, such as butyrate, and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population. In specific aspects, the at least one anticancer treatment is a composition of the embodiments. In some aspects, the method further comprises administering a prebiotic or probiotic.

[0035] In another embodiment, there is provided a method of predicting a response to an immune checkpoint inhibitor in a patient having a cancer comprising detecting a microbial profile in a sample obtained from said patient, wherein if the microbial profile comprises: (a) a low abundance of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria; (b) one or more of the bacteria species in Table 2 designated with a response status of non responder (NR); (c) low alpha diversity; and/or (d) a high amount of the order Bacteriodales, then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In further aspects, the method further comprises administering to the patient a probiotic or live bacterial product composition of the embodiments if the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In still further aspects, a patient predicted to not have a favorable response to an immune checkpoint inhibitor is administered an immune checkpoint inhibitor after administration of a prebiotic or live bacterial product composition of the embodiments.

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[0036] In additional aspects, the method further comprises administering at least one non-immune checkpoint inhibitor additional anticancer treatment to a subject predicted to not have a favorable response to the immune checkpoint inhibitor.

[0037] In further aspects, the method comprises administering at least one anticancer treatment to the subject. In some aspects, the at least one anticancer treatment is surgical therapy, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, small molecule therapy, receptor kinase inhibitor therapy, anti-angiogenic therapy, cytokine therapy, cryotherapy, an immune checkpoint inhibitor, a second immune checkpoint inhibitor or a biological therapy. In particular aspects, the at least one additional anticancer treatment is a short-chain fatty acid, such as butyrate and/or a short-chain fatty acid-producing bacterial population, such as a butyrate-producing bacterial population. In some aspects, the anti-cancer therapy is a prebiotic or probiotic. In specific aspects, the probiotic is a probiotic composition of the embodiments.

[0038] In certain aspects, the cancer is a skin cancer, such as basal-cell skin cancer, squamous-cell skin cancer or melanoma. In other aspects the skin cancer is a skin cancer selected from the group consisting of dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, spindle cell tumors, sebaceous carcinomas, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, and angiosarcoma. In other aspects, the melanoma is Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

[0039] In some aspects, if the microbial profile comprises one or more of the bacteria species in Table 2 designated with a response status of non responder (NR) or a high amount of the order Bacteriodales, then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In some aspects, if the microbial profile comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of the bacteria species in Table 2 designated with a response status of non responder (NR), then the patient is predicted to not have a favorable response to the immune checkpoint inhibitor. In further aspects, the method comprises administering to the patient a probiotic or live bacterial product composition of the embodiments.

[0040] Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the

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detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0041] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0042] FIGS. 1A-G: Increased diversity of the gut microbiome is associated with enhanced responses to PD-1 blockade in patients with metastatic melanoma. (A) Schema of sample collection and analyses. (B) Stacked bar plot of phylogenetic composition of common bacterial taxa (>0.1% abundance) at the order level in oral (n=109, top) and fecal (n=53, bottom) samples by 16S rRNA sequencing. (C) Bipartite network diagram of matched oral and fecal samples from 48 anti-PD-1-treated patients. Edges connect species level OTUs to sample nodes in which they are found. (D) Inverse Simpson diversity scores of the gut microbiome in R (n=30) and NR (n=13) to anti-PD-1 therapy by Mann-Whitney (MW) test. (E) Phylogenetic composition of 39 fecal samples at the family level (>0.1% abundance) at baseline. High (>11.63, n=13), intermediate (7.46-11.63, n=13) and low (<7.46, n=13) diversity groups were determined using tertiles of Inverse Simpson scores. (F) Kaplan-Meier (KM) plot of progression-free survival (PFS) by fecal diversity; high (median PFS undefined), intermediate (median PFS=232 days), and low (median PFS=188 days). High vs intermediate diversity (HR=3.60, 95% C.I.=1.02-12.74) and high vs low (Low HR=3.57, 95% C.I.=1.02-12.52) by univariate Cox model. *p<0.05, **p<0.01. (G) Principal coordinate analysis of fecal samples (n=43) by response using Weighted UniFrac distances.

[0043] FIGS. 2A-F: Compositional differences in the gut microbiome are associated with responses to PD-1 blockade. (A) Heatmap of OTU abundances in R (n=30) and NR (n=13). Columns denote patients and rows denote bacterial species grouped according to their enrichment in R versus NR into 3 sets. **(B)** Phylogenetic composition of OTUs within each set at the order level. **(C)** Taxonomic cladogram from LEfSe showing differences in fecal taxa. Dot size is proportional to the abundance of the taxon. **(D)** LDA scores computed for

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differentially-abundant taxa in the fecal microbiomes of R and NR, as indicated. Length indicates effect size associated with a taxon. p=0.05 for the Kruskal-Wallis test; LDA score > 3. **(E)** Differentially-abundant gut bacteria in R vs NR by MW test (FDR-adjusted) within all taxonomic levels. **(F)** Pairwise comparisons of abundances of bacterial species identified by metagenomic WGS in 25 fecal samples: R (n=14), NR (n=11). *p<0.05, **p<0.01.

[0044] FIGS. 3A-F: Abundance of crOTUs within the gut microbiome is predictive of response to PD-1 blockade. **(A)** Unsupervised hierarchical clustering by complete linkage of crOTU abundances in 43 fecal samples. **(B)** Association of crOTU clusters with response to anti-PD-1 by Fisher's exact test. crOTU Cluster 1 (n=14: R=14, NR=0); Cluster 2 (n=29: R=16, NR=13). **(C)** KM plot of PFS by crOTU cluster. crOTU cluster 1 (median PFS undefined), crOTU cluster 2 (median PFS=242 days). **(D)** Differentially-abundant fecal taxa in crOTU cluster 1 vs crOTU cluster 2, by MW test (FDR-adjusted) within all taxonomic levels. **(E)** PFS in patients with high (n=19, median PFS undefined) or low (n=20, median PFS=242 days) abundance of *F. prausnitzii* (top) or high (n=20, median PFS=188 days) or low (n=19, median PFS=393 days) abundance of Bacteroidales (bottom). **(F)** Unsupervised hierarchical clustering of pathway class abundances inferred from MetaCyc pathways predicted in 28 fecal samples from 25 patients (R=14, NR=11). Regular type: biosynthetic pathways, Bold type: degradative pathways. *p<0.05.

[0045] FIGS. 4A-G: A favorable gut microbiome is associated with systemic anti-tumor immunity. **(A)** Quantification by IHC of the CD8+ infiltrate at pre-treatment in counts/mm^2 in R (n=15) and NR (n=6) by one-sided MW test. *p=0.04. **(B)** Pairwise Spearman rank correlation heatmap of significantly different taxa in fecal samples (n=15) at baseline and CD3, CD8, PD-1, FoxP3, GzmB and RORγT density in counts/mm^2 and PD-L1 by H-score in matched tumors. **(C)** Univariate linear regression between CD8+ counts/mm^2 in the tumor versus *Faecalibacterium* (open circles and dashed line; r^2=0.42, p=0.0067) and Bacteroidales (solid circles and solid line; r^2=0.056, p=0.38) abundance in the gut. **(D)** Pairwise Spearman rank correlation heatmap between significantly different fecal taxa and frequency of CD4$^+$ effector T cells, CD8$^+$ T cells, myeloid dendritic cells, monocytes, B cells, Tregs, and MDSCs by flow cytometry in peripheral blood at baseline. **(E)** Multiplex IHC showing representative images and **(F)** frequency of immune cells, lymphoid cells, myeloid cells, and MHC II in patients having high *Faecalibacterium* or high Bacteroidales in the gut. **(G)** Proposed

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mechanism of action of the gut microbiome on tumor immunity in favorable and unfavorable conditions.

[0046] FIGS. 5A-B. No differences are observed in the mutational landscape of R and NR to PD-1 blockade. (A) Number of mutations per megabase and landscape of driver mutations in tumors of patients with matched fecal microbiome samples (n=7R vs 3NR). **(B)** Total non-synonymous mutational burden in available tumors (n=8R vs 4NR, p=0.683), by two-sided Mann-Whitney (MW) test.

[0047] FIG. 6: Differences in community structure between the oral and fecal microbiomes. Bipartite network diagram of bacterial 16S rRNA derived operational taxonomic units (OTU) from 109 buccal and 53 fecal samples. Edges connect species-level OTUs (diamonds) to sample nodes from oral (open circles) and fecal (filled circles) in which they are found.

[0048] FIGS. 7A-C: Diversity of the fecal microbiome is increased in R to anti-PD-1 therapy. Comparison of alpha-diversity scores in R (n=30, open cirles) and NR (n=13, filled cirles) using the **(A)** Shannon, **(B)** Simpson and **(C)** Chao1 indices by two-sided MW test. * p<0.05, ** p<0.01.

[0049] FIGS. 8A-D: No differences are observed in the diversity of the oral microbiome between R and NR to anti-PD-1 therapy. Comparison of alpha-diversity scores in R (n=54, open cirles) and NR (n=32, filled cirles) using the **(A)** Inverse Simpson (p=0.107), **(B)** Shannon (p=0.139), **(C)** Simpson (p=0.136) and **(D)** Chao1 (p=0.826) indices, by two-sided MW test.

[0050] FIGS. 9A-B: High diversity of the fecal microbiome is associated with longer PFS. Gut microbiota at baseline and subsequent treatment course by subject (n=39). **(A)** Horizontal bars represent alpha diversity scores measured by Inverse Simpson index in each patient. **(B)** Timeline plots showing days elapsed on therapy. x=progressed, o=not progressed at last follow-up.

[0051] FIGS. 10A-D: Diversity of the oral microbiome is not associated with PFS. Oral microbiota and subsequent treatment course by patient (n=86). **(A)** Stacked bars represent the phylogenetic composition of each sample at the family level at baseline. All patients were classified into high (>6.17), intermediate (3.26- 6.17) and low (<3.26) diversity groups, as

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indicated, based on tertiles of Inverse Simpson scores. **(B)** Kaplan-Meier plot of progression-free survival by oral diversity tertiles: high (n=29, median PFS=279 days), intermediate (n=28, median PFS undefined), low (n=29, median PFS=348 days), as indicated. High vs intermediate, p=0.34; high vs low, p=0.54 by log-rank test. **(C)** Horizontal bars represent alpha-diversity scores measured by Inverse Simpson index. **(D)** Timeline plots showing days elapsed on therapy. x=progressed, o=not progressed at last follow-up.

[0052] FIGS. 11A-D: Thresholds for enrichment index (*ei*) scores and relative abundances for OTUs in 86 oral and 43 fecal microbiome samples. Distribution of enrichment scores for bacterial OTUs at the species level in **(A)** fecal and **(B)** oral microbiome samples by Set. The boundaries for each set are indicated. Distribution of $\log_{10}$ relative abundance of species in **(C)** fecal and **(D)** oral microbiome samples. The range for each abundance category is indicated.

[0053] FIGS. 12A-B: No significant differences in oral microbiome OTUs between R and NR to anti- PD-1 therapy by enrichment index *(ei)* score. **(A)** Heatmap of species abundance in R (n=52) and NR (n=34), as indicated, by set of bacterial OTUs based on *ei* scores. Each column denotes a patient and each row denotes a bacterial OTU. High, intermediate, and low are indicated. **(B)** Phylogenetic composition of bacterial OTUs within each set at the order level.

[0054] FIGS. 13A-B: High-dimensional class comparisons using LEfSe reveal increased abundance of Bacteroidales in the oral microbiome of NR to anti-PD-1 therapy. **(A)** Taxonomic Cladogram from LEfSe showing differences in the oral taxa. Taxa enriched in R and NR, respectively, are indciated with size of the dot proportional to abundance of the taxon. **(B)** Histogram of LDA scores computed for differentially abundant taxa between the oral microbiomes of R and NR, where the length of the bar indicates the effect size associated with a taxon. p=0.05 for Kruskal-Wallis test; LDA score > 3.

[0055] FIGS. 14A-C: The diversity and composition of the gut microbiome is stable over time. **(A)** Alpha-diversity of the gut microbiome by Inverse Simpson over time in 3 patients (R) with longitudinal collections. **(B)** Principal component analysis using unweighted UniFrac distances. **(C)** Stacked bars showing the composition of the gut microbiome in patients over time at the order level.

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[0056] FIGS. 15A-B: Clustering by relative OTU abundances shows no association with response to anti-PD-1 therapy. Unsupervised hierarchical by complete linkage using Euclidean distances based on OTU abundance in **(A)** 43 fecal and **(B)** 86 oral microbiome samples. Each column represent a unique microbiome sample whereas each row represents a unique OTU.

[0057] FIGS. 16A-B: Clusters based on oral microbiome crOTU abundances are not associated with response to PD-1 blockade. (A) Unsupervised hierarchical clustering by complete linkage of 86 oral microbiome samples based on crOTU abundances. **(B)** Comparison of clusters by response showing crOTU cluster 1 (n=11, R=9 and NR=2) and Cluster 2 (n=75, R=45 and NR=30). p=0.20 by two-sided Fisher's exact test.

[0058] FIG. 17: Metabolic profiles based on KEGG-orthologs differ in the gut microbiome of R vs NR to PD-1 blockade. Unsupervised hierarchical clustering of common functional pathways (found in at least 20 samples) in 28 fecal samples obtained from 25 patients (n=14R and 11NR) according to KEGGortholog relative abundances.

[0059] FIGS. 18A-F: Responders to PD-1 blockade present an enriched tumor immune infiltrate at baseline. Immunohistochemical quantification and representative images at 40X magnification of **(A)** CD3, **(B)** PD-1, **(C)** FoxP3, **(D)** GzmB, **(E)** PD-L1 and **(F)** RORγT as counts/mm$_2$ or H-Score in responders (R) and non-responders (NR) to anti-PD-1.

[0060] FIG. 19: Patients with a high abundance of *Faecalibacterium* present a favorable antitumor immune infiltrate prior to anti-PD-1 therapy. Spearman rank correlation heatmap of GzmB, CD3, CD8, PD-1, FoxP3, RORγT by counts/mm$_2$, PD-L1 by H-Score by IHC and abundance of all genera within the Ruminococcaceae family in the fecal microbiome (n=15). Positive correlation, negative correlation and no correlation are indicated.

[0061] FIGS. 20A-F: *Faecalibacterium* and Bacteroidales abundance in the fecal microbiome have distinct associations with the tumor immune infiltrate prior to PD-1 blockade. Linear regression between *Faecalibacterium* abundance, Bacteroidales abundance, and density by counts/mm$_2$ or H-score of **(A)** CD3, **(B)** GzmB, **(C)** PD-1, **(D)** PD-L1, **(E)** FoxP3, and **(F)** RORγT by IHC in tumors of patients treated with anti-PD-1 at baseline. Lines show regression for *Faecalibacterium* (thin line, normal type values) and Bacteroidales (thick line, bold type values) with the associated r_2 and p-values.

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[0062] FIG. 21: Gating strategy for flow cytometric analysis of peripheral blood in patients treated with anti-PD-1 therapy. PBMC at baseline in patients treated with anti-PD-1 were analyzed by gating for CD19+ B cells, CD3+CD8+ T cells, CD3+CD4+ T cells (CD3+CD4+FoxP3+ regulatory and CD3+CD4+FoxP3- effector), monocytes (based on CD14/HLA-DR), and MDSC (CD3-CD19-HLADRCD33+ CD11b+).

[0063] FIGS. 22A-D: Patients with high *Faecalibacterium* abundance display a peripheral cytokine profile favorable for response to PD-1 blockade at baseline and enhanced cytokine responses over the course of therapy. (A) Spearman rank correlation heatmap between Clostridiales, *Faecalibacterium*, Ruminococcaceae, and Bacteroidales abundance and peripheral concentration of cytokines in pg/mL by multiplex bead assay. Positive correlation, negative correlation and no correlation is indicated. Change in production of cytokines in serum of responders (n=2) and non-responders (n=2) to anti-PD-1 therapy for **(B)** IP-10 (p=0.042 and p=0.344, respectively), **(C)** MIP-1β (p=0.043 and p=0.898, respectively), and **(D)** IL-17A (p=0.072 and p=0.862, respectively) in fold-change from baseline by ratio paired t-test.

[0064] FIG. 23: Gating strategy for myeloid multiplex IHC in the tumors of patients treated with PD-1 blockade at baseline. Myeloid multiplex immunohistochemistry gating strategy showing immune cells (CD45+), lymphoid cells (CD45+CD3+CD20+CD56+), myeloid cells (CD45+CD3-CD20-CD56-), mast cells (CD45+CD3-CD20-CD56-HLADR-Tryptase+), granulocytes (CD45+CD3-CD20-CD56-HLADRCD66b+), M1 tumor-associated macrophages (CD45+CD3-CD20-CD56-HLADR+CSF1R+CD163-), M2 tumor-associated macrophages (CD45+CD3-CD20-CD56-HLADR+CSF1R+CD163+), mature dendritic cells (CD45+CD3-CD20-CD56-HLADR+CSF1R-DCSIGN-) and immature dendritic cells (CD45+CD3-CD20- CD56-HLADR+CSF1R-DCSIGN+).

[0065] FIGS. 24A-C: High *Faecalibacterium* abundance at baseline is associated with an increased immune infiltrate prior to PD-1 blockade. (A) Multiplex immunohistochemistry showing representative myeloid immune cell staining at 40X magnification. **(B)** Quantification of CD45, CD3/CD20/CD56, CD68, CD66b, Tryptase, HLA-DR, CD163, and DC-SIGN as counts/mm2. **(C)** Quantification of myeloid cells, lymphoid cells, mast cells, granulocytes, M1 and M2 tumor-associated macrophages, immature dendritic cells, and mature dendritic cells as a percentage of total CD45+ immune cells in patients with a high *Faecalibacterium* (n=2) or high Bacteroidales (n=2) abundance.

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[0066] FIGS. 25A-B: Fecal Microbiota Transplantation (FMT) of a favorable gut microbiome in germ-free (GF) mice reduces tumor growth. (A) Experimental design of FMT1 experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection ($8x10^{-5}$ tumor cells). **(B)** Difference in size of tumors implanted in responder (R)-FMT and non-responder (NR)-FMT mice, or control mice. Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse.

[0067] FIGS. 26A-C: Favorable FMT promotes innate effector and reduced myeloid suppressor infiltration in the spleen of GF mice. (A) Flow cytometry quantification showing the frequency of $CD45^+$ immune cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen. **(B)** Flow cytometry quantification showing the frequency of $CD45^+CD11b^+Ly6G^+$ innate effector cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen. **(C)** Flow cytometry quantification showing the frequency of $CD45^+CD11b^+CD11c^+$ suppressive cells in R-FMT (R), NR-FMT (NR), and control mice (C) in the spleen.

[0068] FIGS. 27A-C: Favorable FMT increases CD45+ and CD8+ in the gut and tumor of GF mice. Representative immunofluorescent staining of **(A)** tumor and **(B)** gut from Control (left), NR-FMT (middle), and R-FMT (right) in the tumor of GF mice post-FMT for CD45, CD8, and nuclei (DAPI). **(C)** Quantification of CD8+ density in tumor (top) of R-FMT (n=2, median=433.5 cells/HPF across 12 regions), NR-FMT (NR-FMT n=2, median=325 cells/HPF across 12 regions) and Control mice (n=2, median=412 cells/HPF across 9 regions). p=0.30 (R-FMT vs Control) and gut (bottom) (R-FMT n=2, median=67 cells/HPF across 7 regions, NR-FMT n=2, median=24 cells/HPF across in 5 regions, Control n=2, median=47 cells/HPF across 10 regions). p=0.17 (R-FMT vs Control).

[0069] FIGS. 28A-C: FMT of a favorable gut microbiome in GF mice reduces tumor growth and enhances response to α-PD-L1 therapy. (A) Experimental design of FMT2 experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection ($2.5x10^{-5}$ tumor cells). **(B)** Difference in size of tumors implanted in R-FMT (R, squares) and NR-FMT mice (NR, triangles), or control mice (circles). Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse. **(C)** Tumor growth curves for each GF mouse from α-PD-L1 treated (3x100μg ip every 3 days) R-FMT (squares, n=2, median tumor volume=403.7 mm^3), NR-FMT (triangles, n=2, median tumor volume= 2301 mm^3), and Control (cirlces, n=2, median tumor volume=771.35 mm^3) mice.

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p=0.20 (R-FMT vs NR-FMT), p=0.33 (NR-FMT vs Control by two-sided MW test). Dotted black line marks the tumor size cutoff for α-PD-L1 treatment (500mm^3).

[0070] FIGS. 29A-E: Enhanced therapeutic response upon favorable FMT correlates with increased innate effector and reduced myeloid suppressor infiltration in tumors in GF mice. (A) Flow cytometry quantification showing the frequency of CD45$^+$ immune cells in R-FMT, NR-FMT, and control mice infiltrating the tumor, as indicated. **(B)** Flow cytometry representative plots of CD45$^+$CD11b$^+$Ly6G$^+$ innate effector cells and **(D)** CD11b$^+$CD11c$^+$ suppressive myeloid cells in Control (left), NR-FMT (middle), and R-FMT (right) mice. **(C)** Flow cytometry quantification showing the frequency of CD45$^+$CD11b$^+$Ly6G$^+$ innate effector cells and **(E)** CD45$^+$CD11b$^+$CD11c$^+$ suppressive cells in R-FMT, NR-FMT, and control mice infiltrating the tumor, as indicated.

[0071] FIGS. 30A-D: GF mice receiving FMT from NR-donor have highly activated Th17 compartment. (A) Representative images of IHC staining for Retinoic acid-related orphan receptor gamma t (RORγT) nuclear receptor on tumors from R-FMT (right), NR-FMT (middle), and control (left) mice. Arrows point to RORγT-positive cells. **(B)** IHC quantification showing the number of RORγT+ Th17 cells in R-FMT (R), NR-FMT (NR), and control mice (C) in tumor as counts/mm^2. **(C)** Flow cytometry quantification showing the frequency of CD4+FoxP3+ regulatory T cells in R-FMT (R), NR-FMT (NR), and control mice (C) in spleen. **(D)** Flow cytometry quantification showing the frequency of CD4+IL17+ Th17 cells in R-FMT (R), NR-FMT (NR), and control mice (C) in spleen.

[0072] FIGS. 31A-B: Up-regulation of PD-L1 in the tumor microenvironment of mice receiving R-FMT versus NR-FMT by mass cytometry (CyTOF). (A) t-SNE plot of total live cells (left) isolated from tumors derived from control, NR-, and R- colonized mice, as indicated, by mass cytometry. t-SNE plot of total live cells overlaid with the expression of CD45 (middle) and PD-L1 (right). Equal numbers of cells are displayed from each group. **(B) (top left)** t-SNE plot of total CD45$^+$ cells isolated from tumors derived from control, NR-FMT, and R-FMT mice, as indicated, by CyTOF. **(top right)** Density plots of total CD45$^+$ cells isolated from tumors derived from the indicated experimental groups. **(bottom)** t-SNE plot of total CD45$^+$ cells overlaid with the expression of indicated markers.

[0073] FIGS. 32A-C: FMT from another R-donor in GF mice confirms the impact of a favorable gut microbiome on tumor growth. (A) Experimental design of FMT2

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experiment in germ-free (GF) mice. Time is indicated in days (D) relative to the day of tumor injection ($2.5x10^{-5}$ tumor cells). **(B)** Difference in size of tumors implanted in R-FMT (squares) and NR-FMT mice (triangles), or control mice (circles). Tumor volumes on day 14 post-tumor implantation are plotted, each value representing a single mouse. **(C)** Tumor growth curves for each GF mouse from R-FMT (square, tumor volume=414.3 mm^3), NR-FMT (triangle, tumor volume= 1909.1 mm^3), and Control (circle, n=3, median tumor volume=1049.3 mm^3) mice.

[0074] FIGs. 33A-33F: Genetically-identical C57/BL6 mice from Jackson and Taconic exhibit differential tumor growth (earlier in Jackson) **(A)**, survival (higher in Taconic) **(B-C)**, and microbiome composition (Taconic single-housed upper right; Jackson single-housed lower right) **(D)** after implantation of murine melanoma tumors (BRAF-mutant, PTEN-null). Co-housing of Taconic and Jackson mice resulted in similar tumor outgrowth **(C)** and increased microbiome similarity was observed by principal coordinate analysis **(D)**. Differential abundance at the genus level was observed in singly-housed mice from Jackson and Taconic, but no differences were noted after co-housing **(E)**. Oral administration of butyrate significantly delayed tumor outgrowth in mice implanted with melanoma tumors **(F)**.

[0075] FIGs. 34A-C: 16S analysis of fecal samples from R and NR donors and germ-free recipient mice. Relative abundance comparisons of **(A)** *Faecalibacterium*, **(B)** *Ruminococcaceae* and **(C)** *Bacteroidales* on day 14 post tumor injection. Data from 2 independent experiments are presented. ** $p<0.01$.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0076] Tremendous advances have been made in cancer therapy through the use of molecularly targeted therapy and immunotherapy, however responses are variable and are not always durable. Treatment with immune checkpoint inhibitors is associated with response rates of 15-40% in patients with widespread melanoma, and efforts are underway to identify strategies to enhance responses to checkpoint inhibitor therapy. Thus, methods to improve therapeutic responses as well as increase the number of responders are critically needed.

[0077] The present disclosure overcomes problems with current technologies by providing methods to modulate the microbiome to improve immune response to cancer and therapeutic response to immune checkpoint inhibitors in cancer patients. Studies in the present disclosure used a large cohort of patients with metastatic melanoma undergoing systemic treatment (n=233), a subset of whom were treated with PD-1-based immunotherapy (n=112).

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Oral and gut microbiome samples were characterized in these patients via 16S rRNA gene sequencing and metagenomic whole genome shotgun sequencing. In these analyses, significant differences were observed in the diversity and composition of the gut microbiome in responders versus non-responders to immune checkpoint blockade therapy (*e.g.,* to PD-1-based therapy), with a significantly higher diversity and increased abundance of specific bacteria (*e.g.,* within the order Clostridiales and family Ruminococcaceae) in the gut microbiome of responders versus non-responders. In particular, the species *Faecalibacterium prausnitzii* was found to be more abundant in responders. These bacteria are known to produce short chain fatty acids such as butyrate, which help sustain the integrity of specific cells within the gut (*i.e.,* enterocytes) and may enhance immunity.

[0078] Interestingly, non-responders to therapy were noted to have low levels of these bacteria and significantly higher levels of bacteria of the order Bacteroidales, which has been shown in some studies to down-regulate systemic immune responses. Metagenomic analysis via whole genome shotgun sequencing was performed in a subset of these patients validating these findings, and further demonstrated differences in metabolic processes in bacteria of responders versus non-responders. Furthermore, it was demonstrated that modulation of the gut microbiome by co-housing Taconic and Jackson mice and by oral administration of short chain fatty acids (*e.g.,* butyrate) resulted in delayed tumor outgrowth in mice with a less favorable gut microbiome (Jackson mice). These results from human and murine studies have potentially far-reaching implications to enhance responses to immune checkpoint blockade via modulation of the gut microbiome.

[0079] Importantly, the present studies show that patients with a "favorable" gut microbiome (with high diversity and high relative abundance of bacteria of the order Clostridiales and/or family Ruminococcaceae) have enhanced systemic and anti-tumor immune responses mediated by enhanced antigen presentation at the level of the lymph node and tumor, as well as preserved effector T cell function in the periphery and the tumor microenvironment. In contrast, patients with an "unfavorable" gut microbiome (with low diversity and high relative abundance of bacteria of the order Bacteroidales) have impaired systemic and anti-tumor immune responses mediated by limited intratumoral infiltration of both lymphoid and myeloid elements, weakened antigen presentation capacity, and skewing towards immunoregulatory cellular and humoral elements in the periphery, including Treg and MDSC.

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[0080] Further studies were also undertaken in a mouse melanoma model system. These studies showed mice that received fecal microbiota transplantation from a responder population had decreased tumor growth and increased response to anti-PDL1 therapy. Moreover, mice that received transplantation of a responder microbial popultion had higher percentages of innate effector cells (expressing $CD45^+CD11b^+Ly6G^+$) and lower frequency of suppressive myeloid cells (expressing $CD11b^+CD11c^+$) in the spleen as well as an increased the number of $CD45^+$ immune and $CD8^+$ T cells in the gut. These findings highlight the potential for parallel modulation of the gut microbiome to significantly enhance checkpoint blockade efficacy, warranting prompt evaluation in clinical trials.

[0081] Based on these findings, methods of cancer treatment and diagnosis are provided herein. In one method, short-chain fatty acids, such as butyrate and/or a population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, are administered to patients during treatment with immune checkpoint blockade to enhance therapeutic responses. Also provided herein are methods to use the diversity and composition of the gut microbiome as a predictive biomarker to identify patients who will have a favorable response to immune checkpoint blockade.

I. Definitions

[0082] As used herein, "essentially free," in terms of a specified component, is used herein to mean that none of the specified component has been purposefully formulated into a composition and/or is present only as a contaminant or in trace amounts. The total amount of the specified component resulting from any unintended contamination of a composition is therefore well below 0.01%. Most preferred is a composition in which no amount of the specified component can be detected with standard analytical methods.

[0083] As used herein, "a" or "an" may mean one or more than one.

[0084] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." As used herein, the term "another" may mean at least a second or more.

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[0085] Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

[0086] The phrase "effective amount" or "therapeutically effective amount" or "sufficient amount" means a dosage of a drug or agent sufficient to produce a desired result. The desired result can be a decrease in tumor size, a decrease in the rate of growth of cancer cells, a decrease in metastasis, increase in CD8+ T lymphocytes in the tumor or tumor immune infiltrate, an increase in CD45+, CD3+/CD20+/CD56+, CD68+ and/or HLA-DR+ cells in the tumor, an increase in CD3, CD8, PD1, FoxP3, Granzyme B and/or PD-L1 expression in a tumor immune infiltrate, a decrease in RORγT expression in a tumor immune infiltrate, an increase of effector CD4+, CD8+ T, monocytes and/or myeloid dendritic cell in the systemic circulation or the peripheral blood, a decrease of B cells, regulatory T cells and/or myeloid derived suppressor cells in the systemic circulation or the peripheral blood of the subject or any combination of the above.

[0087] The term "tumor cell" or "cancer cell" denotes a cell that demonstrates inappropriate, unregulated proliferation. A "human" tumor is comprised of cells that have human chromosomes. Such tumors include those in a human patient, and tumors resulting from the introduction into a non-human host animal of a malignant cell line having human chromosomes.

[0088] As used herein, the term "antibody" refers to an immunoglobulin, derivatives thereof which maintain specific binding ability, and proteins having a binding domain which is homologous or largely homologous to an immunoglobulin binding domain. These proteins may be derived from natural sources, or partly or wholly synthetically produced. An antibody may be monoclonal or polyclonal. The antibody may be a member of any immunoglobulin class, including any of the human classes: IgG, IgM, IgA, IgD, and IgE. Antibodies used with the methods and compositions described herein are generally derivatives of the IgG class. The term antibody also refers to antigen-binding antibody fragments. Examples of such antibody fragments include, but are not limited to, Fab, Fab′, F(ab′)2, scFv, Fv, dsFv diabody, and Fd fragments. Antibody fragments may be produced by any means. For instance, the antibody fragment may be enzymatically or chemically produced by fragmentation of an intact antibody, it may be recombinantly produced from a gene encoding the partial antibody sequence, or it may be wholly or partially synthetically produced. The antibody fragment may optionally be

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