a single chain antibody fragment. Alternatively, the fragment may comprise multiple chains which are linked together, for instance, by disulfide linkages. The fragment may also optionally be a multimolecular complex. A functional antibody fragment retains the ability to bind its cognate antigen at comparable affinity to the full antibody.

[0089] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible mutations, *e.g.,* naturally occurring mutations, that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies. In certain embodiments, such a monoclonal antibody typically includes an antibody comprising a polypeptide sequence that binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones, or recombinant DNA clones. It should be understood that a selected target binding sequence can be further altered, for example, to improve affinity for the target, to humanize the target binding sequence, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, *etc.*, and that an antibody comprising the altered target binding sequence is also a monoclonal antibody of this disclosure. In contrast to polyclonal antibody preparations, which typically include several different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. In addition to their specificity, monoclonal antibody preparations are advantageous in that they are typically uncontaminated by other immunoglobulins.

[0090] The phrases "pharmaceutical composition" or "pharmacologically acceptable compisition" refers to molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, such as a human, as appropriate. The preparation of a pharmaceutical composition comprising an antibody or additional active ingredient will be known to those of skill in the art in light of the present disclosure. Moreover, for animal (*e.g.*, human) administration, it will be understood that preparations should meet sterility, pyrogenicity, general safety, and purity standards as required by FDA Office of Biological Standards.

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[0091] As used herein, "pharmaceutically acceptable carrier" includes any and all aqueous solvents (*e.g.,* water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles, such as sodium chloride, and Ringer's dextrose), non-aqueous solvents (*e.g.,* propylene glycol, polyethylene glycol, vegetable oil, and injectable organic esters, such as ethyloleate), dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial or antifungal agents, anti-oxidants, chelating agents, and inert gases), isotonic agents, absorption delaying agents, salts, drugs, drug stabilizers, gels, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, fluid and nutrient replenishers, such like materials and combinations thereof, as would be known to one of ordinary skill in the art. The pH and exact concentration of the various components in a pharmaceutical composition may be adjusted according to well-known parameters.

[0092] The term "unit dose" or "dosage" refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the therapeutic composition calculated to produce the desired responses discussed herein in association with its administration, *i.e.*, the appropriate route and treatment regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the effect desired. The actual dosage amount of a composition of the present embodiments administered to a patient or subject can be determined by physical and physiological factors, such as body weight, the age, health, and sex of the subject, the type of disease being treated, the extent of disease penetration, previous or concurrent therapeutic interventions, idiopathy of the patient, the route of administration, and the potency, stability, and toxicity of the particular therapeutic substance. For example, a dose may also comprise from about 1 µg/kg/body weight to about 1000 mg/kg/body weight (this such range includes intervening doses) or more per administration, and any particular dose derivable therein. In non-limiting examples of a range derivable from the numbers listed herein, a range of about 5 µg/kg/body weight to about 100 mg/kg/body weight, about 5 µg/kg/body weight to about 500 mg/kg/body weight, etc., can be administered. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject.

[0093] An "anti-cancer" agent is capable of negatively affecting a cancer cell/tumor in a subject, for example, by promoting killing of cancer cells, inducing apoptosis in cancer cells, reducing the growth rate of cancer cells, reducing the incidence or number of metastases,

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reducing tumor size, inhibiting tumor growth, reducing the blood supply to a tumor or cancer cells, promoting an immune response against cancer cells or a tumor, preventing or inhibiting the progression of cancer, or increasing the lifespan of a subject with cancer.

[0094] The term "immune checkpoint" refers to a component of the immune system which provides inhibitory signals to its components in order to regulate immune reactions. Known immune checkpoint proteins comprise CTLA-4, PD-l and its ligands PD-Ll and PD-L2 and in addition LAG-3, BTLA, B7H3, B7H4, TIM3, KIR. The pathways involving LAG3, BTLA, B7H3, B7H4, TIM3, and KIR are recognized in the art to constitute immune checkpoint pathways similar to the CTLA-4 and PD-1 dependent pathways (see *e.g.* Pardoll, 2012, *Nature Rev Cancer* 12:252-264; Mellman *et al.*, 2011, *Nature* 480:480- 489).

[0095] The term "PD-1 axis binding antagonist" refers to a molecule that inhibits the interaction of a PD-1 axis binding partner with either one or more of its binding partners, so as to remove T-cell dysfunction resulting from signaling on the PD-1 signaling axis - with a result being to restore or enhance T-cell function (*e.g.*, proliferation, cytokine production, target cell killing). The term "PD-1" axis" refers to any component of the PD-1 immune checkpoint (*e.g.*, PD-1, PD-L1, and PD-L2). As used herein, a PD-1 axis binding antagonist includes a PD-1 binding antagonist, a PD-Ll binding antagonist and a PD-L2 binding antagonist.

[0096] The term "PD-1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-1 with one or more of its binding partners, such as PD-Ll and/or PD-L2. The PD-1 binding antagonist may be a molecule that inhibits the binding of PD-1 to one or more of its binding partners. In a specific aspect, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-Ll and/or PD-L2. For example, PD-1 binding antagonists include anti-PD-1 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-1 with PD-Ll and/or PD-L2. An exemplary PD-1 binding antagonist is an anti-PD-1 antibody. For example the PD-1 binding antagonist is MDX-1106 (nivolumab), MK-3475 (pembrolizumab), CT-011 (pidilizumab), or AMP-224.

[0097] The term "PD-L1 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L1 with either one or more of its binding partners, such as PD-1 or B7-1. For example,

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a PD-L1 binding antagonist is a molecule that inhibits the binding of PD-L1 to its binding partners. In a specific aspect, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or B7-1. The PD-L1 binding antagonists may include anti-PD-Ll antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L1 with one or more of its binding partners, such as PD-1 or B7-1. For example, a PD-L1 binding antagonist reduces the negative co-stimulatory signal mediated by or through cell surface proteins expressed on T lymphocytes mediated signaling through PD-L1 so as to render a dysfunctional T-cell less dysfunctional (*e.g.*, enhancing effector responses to antigen recognition). In one example, a PD-L1 binding antagonist is an anti-PD-Ll antibody. The anti-PD-Ll antibody may be YW243.55.S70, MDX-1105, MPDL3280A, or MEDI4736.

[0098] The term "PD-L2 binding antagonist" refers to a molecule that decreases, blocks, inhibits, abrogates or interferes with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1. A PD-L2 binding antagonist may be a molecule that inhibits the binding of PD-L2 to one or more of its binding partners. For example, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1, such as PD-L2 antagonists including anti-PD-L2 antibodies, antigen binding fragments thereof, immunoadhesins, fusion proteins, oligopeptides and other molecules that decrease, block, inhibit, abrogate or interfere with signal transduction resulting from the interaction of PD-L2 with either one or more of its binding partners, such as PD-1.

[0099] An "immune checkpoint inhibitor" refers to any compound inhibiting the function of an immune checkpoint protein. Inhibition includes reduction of function and full blockade. In particular the immune checkpoint protein is a human immune checkpoint protein. Thus the immune checkpoint protein inhibitor in particular is an inhibitor of a human immune checkpoint protein.

[00100] "Subject" and "patient" refer to either a human or non-human, such as primates, mammals, and vertebrates. In particular embodiments, the subject is a human.

[00101] As used herein, the terms "treat," "treatment," "treating," or "amelioration" when used in reference to a disease, disorder or medical condition, refer to therapeutic treatments for a condition, wherein the object is to reverse, alleviate, ameliorate,

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inhibit, slow down or stop the progression or severity of a symptom or condition. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a condition is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation or at least slowing of progress or worsening of symptoms that would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of the deficit, stabilized (*i.e.*, not worsening) state of a tumor or malignancy, delay or slowing of tumor growth and/or metastasis, and an increased lifespan as compared to that expected in the absence of treatment.

[00102] The "gut microbiota" or "gut microbiome" designates the population of microorganisms living in the intestine of a subject.

[00103] The term "alpha diversity" is a measure of intra-sample diversity and refers to the distribution and assembly patterns of all microbiota within samples and is calculated as a scalar value for each sample. "Beta diversity" is a term for inter-sample diversity, and involves the comparison of samples to each which provides a measure of the distance or dissimilarity between each sample pair.

[00104] The term "relative amount", which can also be designated as the "relative abundance", is defined as the number of bacteria of a particular taxonomic level (from phylum to species) as a percentage of the total number of bacteria of that level in a biological sample. This relative abundance can be assessed, for example, by measuring the percentage of 16S rRNA gene sequences present in the sample which are assigned to these bacteria. It can be measured by any appropriate technique known by the skilled artisan, such as 454 pyrosequencing and quantitative PCR of these specific bacterial 16S rRNA gene markers or quantitative PCR of a specific gene.

[00105] In the present text, a "good responder to a treatment", also called a "responder" or "responsive" patient or in other words a patient who "benefits from" this treatment, refers to a patient who is affected with a cancer and who shows or will show a clinically significant relief in the cancer after receiving this treatment. Conversely, a "bad responder" or "non-responder" is one who does not or will not show a clinically significant

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relief in the cancer after receiving this treatment. The decreased response to treatment may be assessed according to the standards recognized in the art, such as immune- related response criteria (irRC), WHO or RECIST criteria.

[00106] The term "isolated" encompasses a bacterium or other entity or substance that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature or in an experimental setting), and/or (2) produced, prepared, purified, and/or manufactured by the hand of man. Isolated bacteria may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated bacteria are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components.

[00107] The terms "purify," "purifying" and "purified" refer to a bacterium or other material that has been separated from at least some of the components with which it was associated either when initially produced or generated (e.g., whether in nature or in an experimental setting), or during any time after its initial production. A bacterium or a bacterial population may be considered purified if it is isolated at or after production, such as from a material or environment containing the bacterium or bacterial population, and a purified bacterium or bacterial population may contain other materials up to about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or above about 90% and still be considered "isolated." In some embodiments, purified bacteria and bacterial populations are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. In the instance of bacterial compositions provided herein, the one or more bacterial types present in the composition can be independently purified from one or more other bacteria produced and/or present in the material or environment containing the bacterial type. Bacterial compositions and the bacterial components thereof are generally purified from residual habitat products.

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II. Purified Bacterial Population

[00108] Embodiments of the present disclosure concern short-chain fatty acid-containing compositions, such as butyrate-containing compositions and purified bacterial populations (*e.g.,* short-chain fatty acid-containing bacterial populations, such as butyrate-producing bacterial populations) for the treatment of cancer, such as in a subject being or having been administered an immune checkpoint inhibitor. In some embodiments, the subject is administered a prebiotic and/or probiotic to enrich for butyrate-producing bacteria. In certain aspects, the subject undergoes dietary changes to enrich for butyrate-producing bacteria.

[00109] In certain embodiments, the present disclosure provides probiotic compositions and live bacterial products which comprise bacterial populations beneficial for immune checkpoint therapy response. The probiotic composition may comprise bacteria of the phylum Firmicutes. The bacterial population may belong to the class Clostridia, specifically to the order Clostridales, or one or more bacterial populations may belong to the family Clostridiaceae, Ruminococcaceae *(e.g.,* specifically to the genus *Ruminococcus* or the genus *Faecalibacterium*), Micrococcaceae (*e.g.,* specifically to the genus *Rothia),* Lachnospiraceae, and/or Veilonellaceae. In further aspects, the bacterial population may belong to the phylum Tenericutes, particularly to the class Mollicutes. The bacteria may belong to the genus *Peptoniphilus,* particularly to the species *P. asaccharolyticus, P. gorbachii, P. harei, P. ivorii, P. lacrimalis,* and/or *P. olsenii.* Further exemplary bacterial populations for the probiotic composition may include bacterial populations that belong to the genus *Porphyromonas,* particularly to the species *Porphyromonas pasteri,* the species *Clostridium hungatei,* the genus *Phascolarctobacterium* or the species *Phascolarctobacterium faecium.*

[00110] For example, bacterial populations of the genus *Ruminococcus* can include bacteria of the species *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,* and/or *Ruminococcus torques.* Bacterial populations of the genus *Faecalibacterium* can include bacteria of the species *Faecalibacterium prausnitzii.*

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[00111] Exemplary bacterial populations of the genus *Rothia* can include bacteria of the species *R. aeria, R. amarae, R. dentocariosa, R. endophytica, R. mucilaginosa, R. nasimurium,* and/or *R. terrae.*

[00112] Exemplary bacterial populations for inclusion in the probiotic composition include bacterial populations that belong to the phylum Firmicutes, class Clostridia, family Ruminococcaceae, species *Faecalibacterium prausnitzii,* genus *Ruminococcus,* species *Porphyromonas pasteri,* family Veilonellaceae, species *Colostridium hungatei,* genus *Phascolarctobacterium,* species *Phascolarctobacterium faecium,* genus *Peptoniphilus,* family Micrococcaceae, class Mollicutes, and/or genus *Rothia.*

[00113] In particular aspects, the probiotic composition or live bacterial product does not comprise bacterial populations of the order *Bacteroidales,* such as of the genus *Bacteroides,* particularly of the species *B. thetaiotaomicron, B. fragilis, B. vulgatus, B. distasonis, B. ovatus, B. stercoris, B. merda, B. uniformis, B. eggerithii*, or *B. caccae.* In particular, the probiotic composition does not comprise bacterial populations of the genus *Gardnerella* or of the species *Collinsella stercoris, Desulfovibrio alaskensis, Bacteroides mediterraneensis, Prevotella histicola* or *Gardnerella vaginalis.*

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Table 1: Operational taxonomic units of Sets 1-3

OTUs	Set	TAX_id	Phylum	Class	Order	Family	Genus	Species	ei
OTU_219	SET 3	28113	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides heparinolyticus*	-1.00
OTU_140	SET 3	1852370	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotellamassilia*	*Prevotellamassilia timonensis*	-1.00
OTU_320	SET 3	112213	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	-1.00
OTU_166	SET 3	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	-1.00
OTU_1381	SET 3	1348613	Firmicutes	Clostridia	Clostridiales	Defluviitaleaceae	*Vallitalea*	*Vallitalea pronyensis*	-0.64
OTU_2558	SET 3	184185	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides mediterraneensis*	-1.00
OTU_788	SET 3	100236	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella stercorea DSM 18206*	-1.00
OTU_1772	SET 3	184185	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides mediterraneensis*	-1.00
OTU_2085	SET 3	58134	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Desulfotomaculum] guttoideum*	-1.00
OTU_648	SET 3	1527	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerocolumna*	*Anaerocolumna aminovalerica*	-1.00
OTU_623	SET 3	187979	Firmicutes	Negativicutes	Selenomonadales	Selenomonadaceae	*Mitsuokella*	*Mitsuokella jalaludinii*	-1.00
OTU_671	SET 3	184185	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	-1.00
OTU_600	SET 3	387661	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides johnsonii*	-1.00
OTU_1038	SET 3	184185	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	-1.00
OTU_2899	SET 3	357276	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides dorei*	-0.64
OTU_1079	SET 3	45254	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Dysgonomonas*	*Dysgonomonas capnocytophagoides*	-1.00
OTU_546	SET 3	762984	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides clarus YIT 12056*	-1.00

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OTU_1213	SE T3	544645	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Butyricimonas*	*Butyricimonas virosa*	-0.55
OTU_823	SE T3	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-0.55
OTU_954	SE T3	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	-1.00
OTU_886	SE T3	537011	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella copri DSM 18205*	-0.55
OTU_2805	SE T3	52226	Firmicutes	Negativicutes	Selenomonadales	Selenomonadaceae	*Mitsuokella*	*Mitsuokella multacida*	-1.00
OTU_611	SE T3	742742	Actinobacteria	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Collinsella*	*Collinsella tanakaei YIT 12063*	-1.00
OTU_1853	SE T3	291644	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides salyersiae*	-1.00
OTU_1691	SE T3	484018	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides plebeius DSM 17135*	-1.00
OTU_2206	SE T3	484018	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides plebeius DSM 17135*	-1.00
OTU_749	SE T3	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-0.64
OTU_2557	SE T3	184185 6	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides mediterraneensis*	-1.00
OTU_2249	SE T3	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	-1.00
OTU_418	SE T3	179662 0	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acutalibacter*	*Acutalibacter muris*	-0.51
OTU_2640	SE T3	342942	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] glycyrrhizinilyticum*	-1.00
OTU_2555	SE T3	184185 6	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides mediterraneensis*	-1.00
OTU_1263	SE T3	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	-1.00
OTU_1641	SE T3	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	-1.00
OTU_884	SE T3	147206	Actinobacteria	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Collinsella*	*Collinsella stercoris*	-1.00
OTU_2384	SE T3	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	-1.00

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OTU_620	SE T3	253257	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] amygdalinum*	-0.64
OTU_1559	SE T3	817	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides fragilis*	-0.80
OTU_3115	SE T3	47678	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides caccae*	-0.64
OTU_935	SE T3	40545	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Sutterella*	*Sutterella wadsworthensis*	-1.00
OTU_2415	SE T3	645466	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes butyraticus*	-1.00
OTU_876	SE T3	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	-1.00
OTU_1027	SE T3	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	-0.64
OTU_2412	SE T3	1532	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia coccoides*	-1.00
OTU_1305	SE T3	184185 7	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	-1.00
OTU_1554	SE T3	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	-1.00
OTU_567	SE T3	333367	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] asparagiforme*	-0.55
OTU_815	SE T3	544645	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Butyricimonas*	*Butyricimonas virosa*	-1.00
OTU_1898	SE T3	454154	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Paraprevotella*	*Paraprevotella clara*	-0.64
OTU_1143	SE T3	46503	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides merdae*	-1.00
OTU_3106	SE T3	454154	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Paraprevotella*	*Paraprevotella clara*	-1.00
OTU_576	SE T3	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	-0.59
OTU_740	SE T3	156456	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Anaeroglobus*	*Anaeroglobus geminatus*	-1.00
OTU_1827	SE T3	470145	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides coprocola DSM 17136*	-1.00
OTU_3025	SE T3	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	-1.00

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OTU_1709	SEQ ID NO: 46206	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Pseudobutyrivibrio*	*Pseudobutyrivibrio ruminis*	-1.00
OTU_3158	SEQ ID NO: 820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	-1.00
OTU_2145	SEQ ID NO: 544645	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Butyricimonas*	*Butyricimonas virosa*	-0.64
OTU_3211	SEQ ID NO: 449673	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides stercoris ATCC 43183*	-0.64
OTU_2912	SEQ ID NO: 180164	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia schinkii*	-1.00
OTU_3210	SEQ ID NO: 123242 8	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Megasphaera*	*Megasphaera massiliensis*	-0.75
OTU_2843	SEQ ID NO: 449673	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides stercoris ATCC 43183*	-0.75
OTU_1531	SEQ ID NO: 123242 8	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Megasphaera*	*Megasphaera massiliensis*	-1.00
OTU_750	SEQ ID NO: 239935	Verrucomicrobiae	Verrucomicrobiales	Akkermansiaceae	*Akkermansia*	*Akkermansia muciniphila*	-0.55
OTU_1801	SEQ ID NO: 204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-0.80
OTU_1621	SEQ ID NO: 84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	-1.00
OTU_2179	SEQ ID NO: 449673	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides stercoris ATCC 43183*	-1.00
OTU_2121	SEQ ID NO: 1544	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] oroticum*	-0.64
OTU_2070	SEQ ID NO: 204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-1.00
OTU_1071	SEQ ID NO: 585528	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Gardnerella*	*Gardnerella vaginalis ATCC 14018 = JCM 11026*	-1.00
OTU_767	SEQ ID NO: 33039	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*[Ruminococcus] torques*	-0.55
OTU_2257	SEQ ID NO: 821	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides vulgatus*	-0.55
OTU_2072	SEQ ID NO: 339860	Euryarchaeota	Methanobacteria	Methanobacteriales	Methanobacteriaceae	*Methanosphaera*	*Methanosphaera stadtmanae DSM 3091*	-1.00

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OTU_1321	SE T3	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	-1.00
OTU_2533	SE T3	308994	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister propionicifaciens*	-1.00
OTU_1105	SE T3	1796618	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Cuneatibacter*	*Cuneatibacter caecimuris*	-0.64
OTU_2403	SE T3	824	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter gracilis*	-1.00
OTU_1914	SE T3	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-0.55
OTU_2553	SE T3	1841856	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides mediterraneensis*	-1.00
OTU_2977	SE T3	40519	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus callidus*	-1.00
OTU_2988	SE T3	301302	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia faecis*	-1.00
OTU_3116	SE T3	33025	Firmicutes	Negativicutes	Acidaminococcales	Acidaminococcaceae	*Phascolarctobacterium*	*Phascolarctobacterium faecium*	-1.00
OTU_3019	SE T3	487175	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella excrementihominis*	-0.75
OTU_2198	SE T3	39496	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium ventriosum*	-1.00
OTU_46	SE T3	199	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter concisus*	-0.55
OTU_2942	SE T3	871665	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia faecis*	-0.75
OTU_1361	SE T3	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	-0.64
OTU_2636	SE T3	1265	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus flavefaciens*	-1.00
OTU_2285	SE T3	1232428	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Megasphaera*	*Megasphaera massiliensis*	-1.00
OTU_3094	SE T3	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	-0.75
OTU_1358	SE T3	40519	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus callidus*	-0.64
OTU_2259	SE T3	46867	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium chauvoei*	-0.64

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OTU_3181	SE T3	218538	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister invisus*	-0.64
OTU_2642	SE T3	253257	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] amygdalinum*	-1.00
OTU_2552	SE T3	123651 5	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides sartorii JCM 17136 = DSM 21941*	-1.00
OTU_2556	SE T3	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	-1.00
OTU_2616	SE T3	116085	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Coprococcus*	*Coprococcus catus*	-1.00
OTU_2943	SE T3	292800	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flavonifractor*	*Flavonifractor plautii*	-1.00
OTU_2989	SE T3	112111 5	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia wexlerae DSM 19850*	-1.00
OTU_2624	SE T3	357276	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides dorei*	-0.64
OTU_2243	SE T3	109624 6	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella effluvii*	-0.64
OTU_2214	SE T3	123242 8	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Megasphaera*	*Megasphaera massiliensis*	-0.55
OTU_2199	SE T3	454154	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Paraprevotella*	*Paraprevotella clara*	-0.64
OTU_1990	SE T3	537011	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella copri DSM 18205*	-1.00
OTU_3002	SE T3	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	-1.00
OTU_1596	SE T3	172901	Lentisphaerae	Lentisphaeria	Victivallales	Victivallaceae	*Victivallis*	*Victivallis vadensis*	-1.00
OTU_1151	SE T3	76517	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter hominis*	-1.00
OTU_1322	SE T3	168384	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Marvinbryantia*	*Marvinbryantia formatexigens*	-1.00
OTU_2692	SE T3	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	-1.00
OTU_3054	SE T3	147176 1	Firmicutes	Bacilli	Bacillales	Thermoactinomycetaceae	*Novibacillus*	*Novibacillus thermophilus*	-1.00
OTU_3137	SE T3	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-1.00

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OTU_2905	SE T3	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	-1.00
OTU_1783	SE T3	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	-1.00
OTU_1498	SE T3	824	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter gracilis*	-1.00
OTU_2450	SE T3	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	-1.00
OTU_3004	SE T3	69825	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] indolis*	-1.00
OTU_95	SE T3	28135	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella oris*	-0.75
OTU_1368	SE T3	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	-1.00
OTU_1460	SE T3	381308	Proteobacteria	Gammaproteobacteria	Chromatiales	Thioalkalispiraceae	*Thiohalophilus*	*Thiohalophilus thiocyanatoxydans*	-1.00
OTU_1488	SE T3	28446	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] propionicum*	-1.00
OTU_1601	SE T3	181487	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	*Actinomyces cardiffensis*	-1.00
OTU_69	SE T3	505	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Kingella*	*Kingella oralis*	-1.00
OTU_2301	SE T3	515620	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*[Eubacterium] eligens ATCC 27750*	-0.64
OTU_1510	SE T3	113107	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus australis*	-0.75
OTU_2258	SE T3	871665	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia faecis*	-0.64
OTU_2473	SE T3	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	-1.00
OTU_1671	SE T3	40545	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Sutterella*	*Sutterella wadsworthensis*	-1.00
OTU_2545	SE T3	100236 7	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella stercorea DSM 18206*	-1.00
OTU_2620	SE T3	179663 6	Firmicutes	Clostridia	Clostridiales	Lactinospiraceae	*Frisingicoccus*	*Frisingicoccus caecimuris*	-1.00
OTU_2956	SE T3	470145	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides coprocola DSM 17136*	-1.00

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OTU_1598	SEQ_T3	1264	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus albus*	-1.00
OTU_2537	SEQ_T3	745368	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Gemmiger*	*Gemmiger formicilis*	-1.00
OTU_684	SEQ_T3	644	Proteobacteria	Gammaproteobacteria	Aeromonadales	Aeromonadaceae	*Aeromonas*	*Aeromonas hydrophila*	-1.00
OTU_951	SEQ_T3	47847	Actinobacteria	Actinobacteria	Micrococcales	Dermabacteraceae	*Brachybacterium*	*Brachybacterium nesterenkovii*	-1.00
OTU_286	SEQ_T3	888828	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*Haemophilus parainfluenzae ATCC 33392*	-0.64
OTU_1238	SEQ_T3	553973	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] hylemonae DSM 15053*	-0.75
OTU_1135	SEQ_T3	638849	Synergistetes	Synergistia	Synergistales	Synergistaceae	*Pyramidobacter*	*Pyramidobacter piscolens*	-1.00
OTU_1789	SEQ_T3	454154	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Paraprevotella*	*Paraprevotella clara*	-1.00
OTU_526	SEQ_T3	470565	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella histicola*	-0.80
OTU_1166	SEQ_T3	28137	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella veroralis*	-0.64
OTU_1281	SEQ_T3	141785_2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	-0.64
OTU_883	SEQ_T3	134861_3	Firmicutes	Clostridia	Clostridiales	Defluviitaleaceae	*Vallitalea*	*Vallitalea pronyensis*	-1.00
OTU_1445	SEQ_T3	29364	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] polysaccharolyticum*	-1.00
OTU_1582	SEQ_T3	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	-1.00
OTU_1958	SEQ_T3	58134	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Desulfotomaculum] guttoideum*	-1.00
OTU_352	SEQ_T3	52693	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Acetobacterium*	*Acetobacterium paludosum*	-1.00
OTU_941	SEQ_T3	425941	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella nanceiensis*	-1.00
OTU_1495	SEQ_T3	43675	Actinobacteria	Actinobacteria	Micrococcales	Micrococcaceae	*Rothia*	*Rothia mucilaginosa*	-1.00
OTU_2172	SEQ_T3	187326	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Megasphaera*	*Megasphaera micronuciformis*	-1.00

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OTU_511	SE T3	228603	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella shahii*	-1.00
OTU_601	SE T3	1236516	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella saccharolytica JCM 17484*	-1.00
OTU_1074	SE T3	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	-1.00
OTU_48	SE T1	717959	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii WAL 8301*	1.00
OTU_242	SE T1	587	Proteobacteria	Gammaproteobacteria	Enterobacterales	Morganellaceae	*Providencia*	*Providencia rettgeri*	1.00
OTU_194	SE T1	758823	unclassified.NA	unclassified.NA	unclassified.NA	unclassified.NA	*Vampirovibrio*	*Vampirovibrio chlorellavorus*	1.00
OTU_262	SE T1	649756	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes hadrus*	1.00
OTU_1226	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_213	SE T1	671218	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Alloprevotella*	*Alloprevotella rava*	1.00
OTU_350	SE T1	1264	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus albus*	1.00
OTU_249	SE T1	1122135	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_477	SE T1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_356	SE T1	484018	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides plebeius DSM 17135*	1.00
OTU_426	SE T1	46503	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides merdae*	1.00
OTU_143	SE T1	545652	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio simplex*	1.00
OTU_386	SE T1	290052	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio ethanolgignens*	1.00
OTU_387	SE T1	216931	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma alleghenense*	1.00
OTU_1618	SE T1	575978	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio idahonensis*	1.00
OTU_380	SE T1	433321	Firmicutes	Negativicutes	Selenomonadales	Selenomonadaceae	*Propionispira*	*Propionispira arcuata*	1.00

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OTU_359	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_128	SE T1	112213 5	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_536	SE T1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_392	SE T1	112213 5	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_499	SE T1	228924	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XII. Incertae Sedis	*Guggenheimella*	*Guggenheimella bovis*	1.00
OTU_264	SE T1	717959	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii WAL 8301*	1.00
OTU_110	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_215	SE T1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_484	SE T1	1509	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium sporogenes*	1.00
OTU_86	SE T1	146291 9	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Mobilitalea*	*Mobilitalea sibirica*	1.00
OTU_275	SE T1	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_178	SE T1	337097	Firmicutes	Bacilli	Bacillales	Bacillaceae	*Vulcanibacillus*	*Vulcanibacillus modesticaldus*	1.00
OTU_2653	SE T1	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_337	SE T1	487174	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Barnesiella*	*Barnesiella intestinihominis*	1.00
OTU_530	SE T1	642492	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Cellulosilyticum*	*Clostridium lentocellum DSM 5427*	1.00
OTU_123	SE T1	1735	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Holdemanella*	*Holdemanella biformis*	1.00
OTU_1846	SE T1	129742 4	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerobacterium*	*Anaerobacterium chartisolvens*	1.00
OTU_134	SE T1	742766	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Dysgonomonas*	*Dysgonomonas gadei ATCC BAA-286*	1.00
OTU_654	SE T1	146291 9	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Mobilitalea*	*Mobilitalea sibirica*	1.00

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OTU_621	SE T1	46680	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Methylobacillus*	*Pseudomonas nitroreducens*	1.00
OTU_233	SE T1	132925	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium bowmanii*	1.00
OTU_271	SE T1	758823	unclassified.NA	unclassified.NA	unclassified.NA	unclassified.NA	*Vampirovibrio*	*Vampirovibrio chlorellavorus*	1.00
OTU_561	SE T1	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_687	SE T1	112213 5	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_707	SE T1	131846 5	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	*Acholeplasma brassicae 0502*	1.00
OTU_1950	SE T1	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_1113	SE T1	184185 7	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	1.00
OTU_344	SE T1	169679	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium saccharobutylicum*	1.00
OTU_529	SE T1	117529 6	Euryarchaeota	Thermoplasmata	Methanomassiliicoccales	Methanomassiliicoccaceae	*Methanomassiliicoccus*	*Methanomassiliicoccus luminyensis B10*	1.00
OTU_58	SE T1	112213 5	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_2607	SE T1	259063	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerocolumna*	*Anaerocolumna jejuensis*	1.00
OTU_542	SE T1	172901	Lentisphaerae	Lentisphaeria	Victivallales	Victivallaceae	*Victivallis*	*Victivallis vadensis*	1.00
OTU_724	SE T1	39488	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*[Eubacterium] hallii*	1.00
OTU_473	SE T1	57172	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfotomaculum*	*Desulfotomaculum halophilum*	1.00
OTU_2146	SE T1	28118	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Odoribacter*	*Odoribacter splanchnicus*	1.00
OTU_793	SE T1	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	1.00
OTU_90	SE T1	28133	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella nigrescens*	1.00
OTU_593	SE T1	758823	unclassified.NA	unclassified.NA	unclassified.NA	unclassified.NA	*Vampirovibrio*	*Vampirovibrio chlorellavorus*	1.00

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OTU_504	SET1	1529	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium cadaveris*	1.00
OTU_322	SET1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_524	SET1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_805	SET1	100709 6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	1.00
OTU_798	SET1	84030	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_300	SET1	56774	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*unclassified.NA*	*[Eubacterium] infirmum*	1.00
OTU_617	SET1	102148	Firmicutes	Erysipelotrichi a	Erysipelotrichales	Erysipelotrichaceae	*Solobacterium*	*Solobacterium moorei*	1.00
OTU_156	SET1	626947	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella secunda*	1.00
OTU_1449	SET1	129742 4	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerobacterium*	*Anaerobacterium chartisolvens*	1.00
OTU_109	SET1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_1622	SET1	216933	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma chrysopicola*	1.00
OTU_205	SET1	626947	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella secunda*	1.00
OTU_306	SET1	758823	unclassified.NA	unclassified.NA	unclassified.NA	unclassified.NA	*Vampirovibrio*	*Vampirovibrio chlorellavorus*	1.00
OTU_206	SET1	134861 3	Firmicutes	Clostridia	Clostridiales	Defluviitaleaceae	*Vallitalea*	*Vallitalea pronyensis*	1.00
OTU_2657	SET1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_2102	SET1	147241 7	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Butyricimonas*	*Butyricimonas paravirosa*	1.00
OTU_329	SET1	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_1499	SET1	824	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter gracilis*	1.00
OTU_756	SET1	147176 1	Firmicutes	Bacilli	Bacillales	Thermoactinomycetaceae	*Novibacillus*	*Novibacillus thermophilus*	1.00

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OTU_634	SET1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_374	SET1	288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_527	SET1	1317125	Bacteroidetes	Cytophagia	Cytophagales	Hymenobacteraceae	*Pontibacter*	*Pontibacter indicus*	1.00
OTU_772	SET1	28197	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Arcobacter*	*Arcobacter butzleri*	1.00
OTU_2652	SET1	358743	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] citroniae*	1.00
OTU_1352	SET1	642492	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Cellulosibyticum*	*Clostridium lentocellum DSM 5427*	1.00
OTU_678	SET1	264639	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	*Acholeplasma parvum*	1.00
OTU_468	SET1	1265	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus flavefaciens*	1.00
OTU_775	SET1	1122135	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_1526	SET1	1335	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus equinus*	1.00
OTU_2951	SET1	66219	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*Lachnoclostridium phytofermentans*	1.00
OTU_953	SET1	69473	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	*Acholeplasma vituli*	1.00
OTU_431	SET1	115117	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio desulfuricans subsp. desulfuricans*	1.00
OTU_1952	SET1	341220	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lactonifactor*	*Lactonifactor longoviformis*	1.00
OTU_599	SET1	7588235	unclassified.NA	unclassified.NA	unclassified.NA	unclassified.NA	*Vampirovibrio*	*Vampirovibrio chlorellavorus*	1.00
OTU_362	SET1	1732	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium oxidoreducens*	1.00
OTU_340	SET1	873513	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella buccae ATCC 33574*	1.00
OTU_1032	SET1	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2116	SET1	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00

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OTU_1480	SE T1	742766	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Dysgonomonas*	*Dysgonomonas gadei ATCC BAA-286*	1.00
OTU_103	SE T1	487174	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Barnesiella*	*Barnesiella intestinihominis*	0.55
OTU_2458	SE T1	396504	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] sufflavum*	1.00
OTU_1020	SE T1	179661 9	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Irregularibacter*	*Irregularibacter muris*	1.00
OTU_967	SE T1	184185 7	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	1.00
OTU_2801	SE T1	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00
OTU_942	SE T1	1509	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium sporogenes*	1.00
OTU_2995	SE T1	259063	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerocolumna*	*Anaerocolumna jejuensis*	1.00
OTU_865	SE T1	2741	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Peptococcus*	*Peptococcus niger*	1.00
OTU_1158	SE T1	105841	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes caccae*	1.00
OTU_1693	SE T1	86332	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Mogibacterium*	*Mogibacterium pumilum*	1.00
OTU_236	SE T1	134982 2	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Coprobacter*	*Coprobacter fastidiosus NSB1*	1.00
OTU_2554	SE T1	84037	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Syntrophococcus*	*Syntrophococcus sucromutans*	1.00
OTU_558	SE T1	180311	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Hespellia*	*Hespellia stercorisuis*	1.00
OTU_223	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	0.59
OTU_925	SE T1	54291	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	*Raoultella*	*Raoultella ornithinolytica*	1.00
OTU_1965	SE T1	1509	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium sporogenes*	1.00
OTU_608	SE T1	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_836	SE T1	121728 2	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides faecis*	1.00

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OTU_862	SE T1	172901	Lentisphaerae	Lentisphaeria	Victivallales	Victivallaceae	*Victivallis*	*Victivallis vadensis*	1.00
OTU_227	SE T1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_185	SE T1	762984	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides clarus YIT 12056*	1.00
OTU_406	SE T1	118541 2	Firmicutes	Clostridia	Clostridiales	Defluviitaleaceae	*Vallitalea*	*Vallitalea guaymasensis*	1.00
OTU_479	SE T1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_127	SE T1	112213 5	Proteobacteria	Alphaproteobacteria	Kiloniellales	Kiloniellaceae	*Kiloniella*	*Kiloniella laminariae DSM 19542*	1.00
OTU_1344	SE T1	663278	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ethanoligenens*	*Ethanoligenens harbinense YUAN-3*	1.00
OTU_136	SE T1	1543	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium oceanicum*	0.65
OTU_1050	SE T1	626947	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella secunda*	1.00
OTU_995	SE T1	398512	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Pseudobacteroides*	*Pseudobacteroides cellulosolvens ATCC 35603 = DSM 2933*	1.00
OTU_2543	SE T1	129742 4	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerobacterium*	*Anaerobacterium chartisolvens*	1.00
OTU_2983	SE T1	1335	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus equinus*	1.00
OTU_1869	SE T1	587	Proteobacteria	Gammaproteobacteria	Enterobacterales	Morganellaceae	*Providencia*	*Providencia rettgeri*	1.00
OTU_190	SE T1	66219	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*Lachnoclostridium phytofermentans*	1.00
OTU_1714	SE T1	69825	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] indolis*	1.00
OTU_657	SE T1	117529 6	Euryarchaeota	Thermoplasmata	Methanomassiliicoccales	Methanomassiliicoccaceae	*Methanomassiliicoccus*	*Methanomassiliicoccus luminyensis B10*	1.00
OTU_957	SE T1	184186 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00
OTU_346	SE T1	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	1.00
OTU_1979	SE T1	1265	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus flavefaciens*	1.00

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OTU_2606	SE T1	1510	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] stercorarium*	1.00
OTU_989	SE T1	840261	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2820	SE T1	1502	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium perfringens*	1.00
OTU_1434	SE T1	1297424	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerobacterium*	*Anaerobacterium chartisolvens*	1.00
OTU_596	SE T1	1619234	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerobium*	*Anaerobium acetethylicum*	1.00
OTU_1447	SE T1	398512	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Pseudobacteroides*	*Pseudobacteroides cellulosolvens ATCC 35603 = DSM 2933*	1.00
OTU_2980	SE T1	1335	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus equinus*	1.00
OTU_1848	SE T1	394975	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium xylanophilum*	1.00
OTU_1802	SE T1	1544	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] oroticum*	1.00
OTU_2171	SE T1	873513	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella buccae ATCC 33574*	1.00
OTU_1141	SE T1	293433	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] cellulosi*	1.00
OTU_83	SE T1	458511	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00
OTU_627	SE T1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_3010	SE T1	567741	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*unclassified.NA*	*[Eubacterium] infirmum*	1.00
OTU_1055	SE T1	17321	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium oxidoreducens*	1.00
OTU_2647	SE T1	649762	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia luti DSM 14534*	1.00
OTU_1230	SE T1	1540461	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_1549	SE T1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_1985	SE T1	332095	Firmicutes	Tissierellia	unclassified.NA	unclassified.NA	*Dethiosulfatibacter*	*Dethiosulfatibacter aminovorans*	1.00

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OTU_1040	SEQ_T1	536633	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia glucerasea*	1.00
OTU_404	SEQ_T1	1033731	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes timonensis JC136*	1.00
OTU_722	SEQ_T1	129761 7	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_173	SEQ_T1	574930	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides gordonii*	0.55
OTU_932	SEQ_T1	742818	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Slackia*	*Slackia piriformis YIT 12062*	1.00
OTU_1296	SEQ_T1	1264	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus albus*	1.00
OTU_801	SEQ_T1	177412	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobiaceae	*Fucophilus*	*Fucophilus fucoidanolyticus*	1.00	
OTU_1320	SEQ_T1	112130 8	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Clostridioides*	*Clostridioides difficile ATCC 9689 = DSM 1296*	0.50
OTU_2930	SEQ_T1	419208	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella denticariosi*	1.00	
OTU_503	SEQ_T1	167371 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaeromassilibacillus*	*Anaeromassilibacillus senegalensis*	1.00
OTU_708	SEQ_T1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_129	SEQ_T1	180311	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Hespellia*	*Hespellia stercorisuis*	0.59
OTU_385	SEQ_T1	55779	Firmicutes	Clostridia	Thermoanaerobacterales	Thermoanaerobacteraceae	*Moorella*	*Moorella glycerini*	0.55
OTU_279	SEQ_T1	28117	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes putredinis*	1.00
OTU_1489	SEQ_T1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1237	SEQ_T1	180332	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Robinsoniella*	*Robinsoniella peoriensis*	1.00
OTU_1951	SEQ_T1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_2662	SEQ_T1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00

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OTU_3108	SE T1	40519	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus callidus*	1.00
OTU_1201	SE T1	34062	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	*Moraxella osloensis*	1.00
OTU_551	SE T1	40518	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus bromii*	1.00
OTU_1077	SE T1	74426	Actinobacteria	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Collinsella*	*Collinsella aerofaciens*	1.00
OTU_1126	SE T1	121606 2	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfotomaculum*	*Desulfotomaculum tongense*	1.00
OTU_1138	SE T1	293826	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Alkaliphilus*	*Alkaliphilus metalliredigens QYMF*	1.00
OTU_952	SE T1	161923 4	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerobium*	*Anaerobium acetethylicum*	1.00
OTU_2954	SE T1	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00
OTU_1721	SE T1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_1084	SE T1	850	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	*Fusobacterium mortiferum*	1.00
OTU_106	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	0.50
OTU_1013	SE T1	645466	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes butyraticus*	1.00
OTU_1345	SE T1	474960	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Hydrogenoanaerobacterium*	*Hydrogenoanaerobacterium saccharovorans*	1.00
OTU_1775	SE T1	84030	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_666	SE T1	36835	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] colinum*	1.00
OTU_1602	SE T1	115544	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Parasporobacterium*	*Parasporobacterium paucivorans*	1.00
OTU_550	SE T1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_851	SE T1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1982	SE T1	88431	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Dorea*	*Dorea longicatena*	1.00

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OTU_486	SET1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1024	SET1	216932	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma chinense*	1.00
OTU_1262	SET1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_382	SET1	1417852	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	0.73
OTU_472	SET1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_1076	SET1	39492	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Eubacterium] siraeum*	1.00
OTU_686	SET1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_458	SET1	1583	Firmicutes	Bacilli	Lactobacillales	Leuconostocaceae	*Weissella*	*Weissella confusa*	1.00
OTU_449	SET1	663278	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ethanoligenens*	*Ethanoligenens harbinense YUAN-3*	1.00
OTU_555	SET1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_1623	SET1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_703	SET1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_347	SET1	420247	Euryarchaeota	Methanobacteria	Methanobacteriales	Methanobacteriaceae	*Methanobrevibacter*	*Methanobrevibacter smithii ATCC 35061*	0.55
OTU_1139	SET1	118967	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Anaerorhabdus*	*Anaerorhabdus furcosa*	1.00
OTU_1407	SET1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_1414	SET1	37658	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] populeti*	1.00
OTU_791	SET1	138595	Actinobacteria	Coriobacteriia	Coriobacteriales	Atopobiaceae	*Olsenella*	*Olsenella profusa*	1.00
OTU_1246	SET1	319711	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*unclassified.NA*	*[Eubacterium] dolichum*	1.00
OTU_216	SET1	100886	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Catenibacterium*	*Catenibacterium mitsuokai*	1.00

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OTU_1147	SE T1	119771 7	Synergistetes	Synergistia	Synergistales	Synergistaceae	*Cloacibacillus*	*Cloacibacillus porcorum*	1.00
OTU_733	SE T1	234908	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Sutterella*	*Sutterella stercoricanis*	1.00
OTU_2095	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_659	SE T1	2741	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Peptococcus*	*Peptococcus niger*	1.00
OTU_757	SE T1	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_2678	SE T1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_1477	SE T1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	0.68
OTU_1402	SE T1	762984	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides clarus YIT 12056*	1.00
OTU_2277	SE T1	537007	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia hansenii DSM 20583*	1.00
OTU_2566	SE T1	487174	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Barnesiella*	*Barnesiella intestinihominis*	1.00
OTU_2119	SE T1	1732	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium oxidoreducens*	1.00
OTU_1039	SE T1	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	1.00
OTU_1603	SE T1	228924	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XII. Incertae Sedis	*Guggenheimella*	*Guggenheimella bovis*	1.00
OTU_2669	SE T1	319644	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Saccharofermentans*	*Saccharofermentans acetigenes*	1.00
OTU_2044	SE T1	168384	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Marvinbryantia*	*Marvinbryantia formatexigens*	1.00
OTU_411	SE T1	915173	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Faecalicoccus*	*Faecalicoccus acidiformans*	1.00
OTU_357	SE T1	95159	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Caloramator*	*Caloramator coolhaasii*	0.68
OTU_1616	SE T1	31971	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*unclassified.NA*	*[Eubacterium] dolichum*	1.00
OTU_541	SE T1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00

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OTU_1737	SEQ_TAX	1816678	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella timonensis*	1.00
OTU_2707	SEQ_TAX	1417852	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_255	SEQ_TAX	626940	Negativicutes	Acidaminococcales	Acidaminococcaceae	*Phascolarctobacterium*	*Phascolarctobacterium succinatutens*		1.00
OTU_1901	SEQ_TAX	501571	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Butyricicoccus*	*Butyricicoccus pullicaecorum*	0.50
OTU_3081	SEQ_TAX	179662	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acutalibacter*	*Acutalibacter muris*	1.00
OTU_2902	SEQ_TAX	888727	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*unclassified.NA*	*Eubacterium sulci ATCC 35585*	1.00
OTU_2418	SEQ_TAX	114712	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Caloramator*	*Caloramator quimbayensis*	1.00
OTU_2936	SEQ_TAX	129859	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_1244	SEQ_TAX	376806	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides gallinarum*	0.55
OTU_1333	SEQ_TAX	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1340	SEQ_TAX	127435	Firmicutes	Bacilli	Bacillales	Thermoactinomycetaceae	*Kroppenstedtia*	*Kroppenstedtia guangzhouensis*	1.00
OTU_900	SEQ_TAX	1267	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium ventriculi*	1.00
OTU_1684	SEQ_TAX	1335	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus equinus*	1.00
OTU_3012	SEQ_TAX	39495	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium uniforme*	1.00
OTU_3013	SEQ_TAX	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_1300	SEQ_TAX	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_912	SEQ_TAX	185236	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_786	SEQ_TAX	404403	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Howardella*	*Howardella ureilytica*	1.00
OTU_1277	SEQ_TAX	1348	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus parauberis*	1.00

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OTU_1617	SE T1	172901	Lentisphaeriae	Lentisphaeria	Victivallales	Victivallaceae	*Victivallis*	*Victivallis vadensis*	1.00
OTU_1994	SE T1	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00
OTU_1850	SE T1	253314	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] sraminisolvens*	1.00
OTU_2802	SE T1	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00
OTU_581	SE T1	179661	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Irregularibacter*	*Irregularibacter muris*	1.00
OTU_1747	SE T1	258515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetanaerobacterium*	*Acetanaerobacterium elongatum*	0.50
OTU_2428	SE T1	129761	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_157	SE T1	33033	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Parvimonas*	*Parvimonas micra*	1.00
OTU_630	SE T1	100709 6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	0.55
OTU_1366	SE T1	129761 7	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_1247	SE T1	649762	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia luti DSM 14534*	1.00
OTU_1590	SE T1	111806 1	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes obesi*	1.00
OTU_3014	SE T1	357276	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides dorei*	1.00
OTU_489	SE T1	214851	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Subdoligranulum*	*Subdoligranulum variabile*	0.50
OTU_1311	SE T1	320502	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] alkalicellulosi*	1.00
OTU_1389	SE T1	217731	Tenericutes	Mollicutes	Entomoplasmatales	Entomoplasmataceae	*Mesoplasma*	*Mesoplasma photuris*	1.00
OTU_1086	SE T1	246787	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides cellulosilyticus*	0.59
OTU_1131	SE T1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_704	SE T1	184186 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00

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OTU_710	SET1	29371	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] termitidis*	1.00
OTU_2810	SET1	840301	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_921	SET1	649764	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Slackia*	*Slackia exigua ATCC 700122*	1.00
OTU_1159	SET1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_2583	SET1	901	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio piger*	1.00
OTU_1767	SET1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00
OTU_984	SET1	29374	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Filifactor*	*Filifactor villosus*	1.00
OTU_1065	SET1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00
OTU_1763	SET1	29343	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] cellulosi*	1.00
OTU_1768	SET1	33043	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Coprococcus*	*Coprococcus eutactus*	1.00
OTU_1525	SET1	39778	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella dispar*	1.00
OTU_2860	SET1	39778	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella dispar*	1.00
OTU_2297	SET1	86332	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Mogibacterium*	*Mogibacterium pumilum*	1.00
OTU_842	SET1	682400	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Natranaerovirga*	*Natranaerovirga pectinivora*	0.55
OTU_1567	SET1	871665	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia faecis*	1.00
OTU_1774	SET1	160404	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] lactatifermentans*	1.00
OTU_974	SET1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1578	SET1	396504	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] sufflavum*	1.00
OTU_1196	SET1	214851	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Subdoligranulum*	*Subdoligranulum variabile*	0.50

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OTU_1680	SE T 1	1502	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium perfringens*	1.00
OTU_562	SE T 1	405519	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus callidus*	1.00
OTU_1455	SE T 1	745368	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Gemmiger*	*Gemmiger formicilis*	1.00
OTU_2413	SE T 1	408	Proteobacteria	Alphaproteobacteria	Rhizobiales	Methylobacteriaceae	*Methylobacterium*	*Methylobacterium extorquens*	1.00
OTU_575	SE T 1	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	1.00
OTU_294	SE T 1	1584	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus delbrueckii*	1.00
OTU_1362	SE T 1	288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_1931	SE T 1	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_1619	SE T 1	1510	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] stercorarium*	1.00
OTU_779	SE T 1	333367	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] asparagiforme*	1.00
OTU_1119	SE T 1	47246	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] viride*	1.00
OTU_731	SE T 1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	0.59
OTU_403	SE T 1	100709 6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	0.55
OTU_1279	SE T 1	47246	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] viride*	1.00
OTU_1514	SE T 1	109624 6	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella effluvii*	1.00
OTU_1992	SE T 1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_2248	SE T 1	290052	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio ethanolgignens*	1.00
OTU_2668	SE T 1	642492	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Cellulosilyticum*	*Clostridium lentocellum DSM 5427*	1.00
OTU_631	SE T 1	53342	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Caloramator*	*Caloramator proteoclasticus*	0.63

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OTU_1998	SET1	54291	Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	*Raoultella*	*Raoultella ornithinolytica*	1.00
OTU_1031	SET1	438033	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus gauvreauii*	1.00
OTU_2991	SET1	351091	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter valericigenes*	0.55
OTU_2032	SET1	179662 2	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Extibacter*	*Extibacter muris*	1.00
OTU_2641	SET1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_1657	SET1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	0.55
OTU_880	SET1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_405	SET1	177638 4	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Emergencia*	*Emergencia timonensis*	0.50
OTU_809	SET1	39492	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Eubacterium] siraeum*	1.00
OTU_2167	SET1	817	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides fragilis*	1.00
OTU_2670	SET1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2671	SET1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_1056	SET1	411467	Firmicutes	Clostridia	Clostridiales	unclassified NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_1597	SET1	177638 4	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Emergencia*	*Emergencia timonensis*	1.00
OTU_739	SET1	48256	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] hungatei*	1.00
OTU_894	SET1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_961	SET1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_820	SET1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1466	SET1	179662 0	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acutalibacter*	*Acutalibacter muris*	1.00

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OTU_1741	SEQ_T1	720554	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] clariflavum DSM 19732*	1.00
OTU_1984	SEQ_T1	1007096	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	1.00
OTU_2004	SEQ_T1	47246	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] viride*	1.00
OTU_2005	SEQ_T1	500632	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*Tyzzerella nexilis DSM 1787*	1.00
OTU_2655	SEQ_T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_1548	SEQ_T1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1307	SEQ_T1	177638_2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00
OTU_1329	SEQ_T1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_1081	SEQ_T1	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_2028	SEQ_T1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1766	SEQ_T1	36849	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Oxobacter*	*Oxobacter pfennigii*	1.00
OTU_2219	SEQ_T1	301302	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia faecis*	1.00
OTU_2117	SEQ_T1	879970	Firmicutes	Clostridia	Clostridiales	Defluviitaleaceae	*Defluviitalea*	*Defluviitalea saccharophila*	1.00
OTU_410	SEQ_T1	655811	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Anaerococcus*	*Anaerococcus vaginalis ATCC 51170*	1.00
OTU_1411	SEQ_T1	1096246	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella effluvii*	1.00
OTU_2567	SEQ_T1	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	1.00
OTU_864	SEQ_T1	1532	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia coccoides*	1.00
OTU_2001	SEQ_T1	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_1535	SEQ_T1	285	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Comamonas*	*Comamonas testosteroni*	1.00

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OTU_2111	SEQ_TAX_995	Bacteroidetes	Sphingobacteria	Sphingobacteriales	Sphingobacteriaceae	*Solitalea*	*Solitalea canadensis*	1.00
OTU_978	SEQ_TAX_242750	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella bergensis*	1.00
OTU_765	SEQ_TAX_100709_6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	1.00
OTU_2419	SEQ_TAX_29539	Actinobacteria	Thermoleophilia	Thermoleophilales	Thermoleophilaceae	*Thermoleophilum*	*Thermoleophilum album*	1.00
OTU_2853	SEQ_TAX_143205_2	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Eisenbergiella*	*Eisenbergiella tayi*	1.00
OTU_1220	SEQ_TAX_167371_7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaeromassilibacillus*	*Anaeromassilibacillus senegalensis*	1.00
OTU_850	SEQ_TAX_168384	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Marvinbryantia*	*Marvinbryantia formatexigens*	1.00
OTU_777	SEQ_TAX_39492	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Eubacterium] siraeum*	0.50
OTU_713	SEQ_TAX_1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	0.63
OTU_2973	SEQ_TAX_622312	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia inulinivorans DSM 16841*	1.00
OTU_1324	SEQ_TAX_36849	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Oxobacter*	*Oxobacter pfennigii*	1.00
OTU_1061	SEQ_TAX_84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_3167	SEQ_TAX_622312	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia inulinivorans DSM 16841*	0.72
OTU_1337	SEQ_TAX_179663_6	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Frisingicoccus*	*Frisingicoccus caecimuris*	1.00
OTU_2731	SEQ_TAX_214851	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Subdoligranulum*	*Subdoligranulum variabile*	1.00
OTU_2654	SEQ_TAX_100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_2807	SEQ_TAX_133705_1	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Murimonas*	*Murimonas intestini*	1.00
OTU_3041	SEQ_TAX_328814	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii*	0.65
OTU_1861	SEQ_TAX_28446	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] propionicum*	1.00

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OTU_1726	SE T1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00
OTU_2618	SE T1	179662 0	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acutalibacter*	*Acutalibacter muris*	1.00
OTU_2484	SE T1	1492	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium butyricum*	1.00
OTU_1378	SE T1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_2645	SE T1	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	1.00
OTU_1258	SE T1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_1829	SE T1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_1999	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_2796	SE T1	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_2614	SE T1	39496	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium ventriosum*	1.00
OTU_522	SE T1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	0.55
OTU_2071	SE T1	52786	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerofilum*	*Anaerofilum agile*	1.00
OTU_1859	SE T1	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	1.00
OTU_2913	SE T1	39492	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Eubacterium] siraeum*	1.00
OTU_3126	SE T1	39497	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium xylanophilum*	1.00
OTU_2123	SE T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_2676	SE T1	1549	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] sporosphaeroides*	1.00
OTU_2118	SE T1	179661 8	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Cuneatibacter*	*Cuneatibacter caecimuris*	1.00
OTU_1091	SE T1	582	Proteobacteria	Gammaproteobacteria	Enterobacterales	Morganellaceae	*Morganella*	*Morganella morganii*	1.00

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OTU_1800	SET1	160404	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] lactatifermentans*	1.00
OTU_1190	SET1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_2220	SET1	40519	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus callidus*	1.00
OTU_373	SET1	46507	Firmicutes	Tissierellia	unclassified.NA	unclassified.NA	*unclassified.NA*	*[Bacteroides] coagulans*	1.00
OTU_1094	SET1	694434	Firmicutes	Clostridia	Clostridiales	Gracilibacteraceae	*Gracilibacter*	*Gracilibacter thermotolerans JW/YJL-S1*	1.00
OTU_1473	SET1	109327	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Anaerovorax*	*Anaerovorax odorimutans*	1.00
OTU_2273	SET1	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	1.00
OTU_210	SET1	1382	Actinobacteria	Coriobacteriia	Coriobacteriales	Atopobiaceae	*Atopobium*	*Atopobium parvulum*	1.00
OTU_2632	SET1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	0.75
OTU_2850	SET1	33039	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*[Ruminococcus] torques*	1.00
OTU_2808	SET1	143205_2	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Eisenbergiella*	*Eisenbergiella tayi*	1.00
OTU_754	SET1	311460	Firmicutes	Bacilli	Bacillales	Bacillaceae	*Anoxybacillus*	*Anoxybacillus rupiensis*	1.00
OTU_1278	SET1	1264	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus albus*	1.00
OTU_972	SET1	582	Proteobacteria	Gammaproteobacteria	Enterobacterales	Morganellaceae	*Morganella*	*Morganella morganii*	0.50
OTU_3152	SET1	301302	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia faecis*	1.00
OTU_177	SET1	230143	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Scardovia*	*Scardovia wiggsiae*	1.00
OTU_802	SET1	216935	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma culicicola*	1.00
OTU_445	SET1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_1973	SET1	133705_1	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Murimonas*	*Murimonas intestini*	1.00

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OTU_1650	SE T 1	840261	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_1782	SE T 1	539	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Eikenella*	*Eikenella corrodens*	1.00
OTU_310	SE T 1	355191	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Mogibacterium*	*Mogibacterium timidum*	1.00
OTU_2045	SE T 1	1681	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*	*Bifidobacterium bifidum*	1.00
OTU_3178	SE T 1	328813	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes onderdonkii*	1.00
OTU_1468	SE T 1	214853	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Anaerofustis*	*Anaerofustis stercorihominis*	1.00
OTU_2798	SE T 1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_799	SE T 1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_1365	SE T 1	39495	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium uniforme*	1.00
OTU_1773	SE T 1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_3011	SE T 1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_1433	SE T 1	109327	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Anaerovorax*	*Anaerovorax odorimutans*	1.00
OTU_1863	SE T 1	89014	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia luti*	1.00
OTU_2270	SE T 1	33043	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Coprococcus*	*Coprococcus eutactus*	1.00
OTU_2596	SE T 1	216933	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma chrysopicola*	1.00
OTU_826	SE T 1	537007	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia hansenii DSM 20583*	1.00
OTU_2844	SE T 1	1121115	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia wexlerae DSM 19850*	0.55
OTU_2120	SE T 1	1585974	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Bedunii*	*Bedunii massiliensis*	1.00
OTU_2927	SE T 1	29466	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella parvula*	1.00

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OTU_2750	SEQ TAX	290052	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio ethanolgignens*	1.00
OTU_2621	SEQ TAX	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_1996	SEQ TAX	1363	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Lactococcus*	*Lactococcus garvieae*	1.00
OTU_1877	SEQ TAX	54291	Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	*Raoultella*	*Raoultella ornithinolytica*	1.00
OTU_3051	SEQ TAX	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_2033	SEQ TAX	292800	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flavonifractor*	*Flavonifractor plautii*	1.00
OTU_2000	SEQ TAX	270498	Firmicutes	Clostridia	Clostridiales	Catabacteriaceae	*Catabacter*	*Catabacter hongkongensis*	1.00
OTU_945	SEQ TAX	214856	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes finegoldii*	0.70
OTU_1636	SEQ TAX	142877	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfitobacterium*	*Desulfitobacterium metallireducens*	1.00
OTU_2027	SEQ TAX	341220	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lactonifactor*	*Lactonifactor longoviformis*	1.00
OTU_3205	SEQ TAX	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	1.00
OTU_1174	SEQ TAX	109327	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Anaerovorax*	*Anaerovorax odorimutans*	1.00
OTU_1866	SEQ TAX	133926	Actinobacteria	Coriobacteriia	Coriobacteriales	Atopobiaceae	*Olsenella*	*Olsenella uli*	1.00
OTU_2265	SEQ TAX	1583	Firmicutes	Bacilli	Lactobacillales	Leuconostocaceae	*Weissella*	*Weissella confusa*	1.00
OTU_2518	SEQ TAX	844026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2874	SEQ TAX	209880	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Allisonella*	*Allisonella histaminiformans*	1.00
OTU_2877	SEQ TAX	179628	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium colicanis*	1.00
OTU_3077	SEQ TAX	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_980	SEQ TAX	177638	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00

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OTU_1101	SE T1	1510	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] stercorarium*	1.00
OTU_1962	SE T1	84030	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_2309	SE T1	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	0.50
OTU_2282	SE T1	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	1.00
OTU_2151	SE T1	1544	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] oroticum*	1.00
OTU_1068	SE T1	2741	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Peptococcus*	*Peptococcus niger*	1.00
OTU_2427	SE T1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_1148	SE T1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	0.55
OTU_919	SE T1	129742 4	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerobacterium*	*Anaerobacterium chartisolvens*	1.00
OTU_1222	SE T1	871665	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia faecis*	0.63
OTU_2569	SE T1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_1049	SE T1	167371 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaeromassilibacillus*	*Anaeromassilibacillus senegalensis*	1.00
OTU_1496	SE T1	54291	Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	*Raoultella*	*Raoultella ornithinolytica*	1.00
OTU_948	SE T1	28446	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] propionicum*	1.00
OTU_914	SE T1	112110 2	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter ureolyticus DSM 20703*	1.00
OTU_1342	SE T1	69473	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	*Acholeplasma vituli*	1.00
OTU_2210	SE T1	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_1706	SE T1	100709 6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	1.00
OTU_2656	SE T1	105612	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus algidus*	1.00

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OTU_909	SET1	1852367	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_1964	SET1	179661 5	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia caecimuris*	1.00
OTU_1234	SET1	39492	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Eubacterium] siraeum*	1.00
OTU_501	SET1	682400	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Natranaerovirga*	*Natranaerovirga pectinivora*	1.00
OTU_2939	SET1	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	1.00
OTU_556	SET1	39777	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella atypica*	0.63
OTU_1023	SET1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	0.50
OTU_1198	SET1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_2650	SET1	56774	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*unclassified.NA*	*[Eubacterium] infirmum*	1.00
OTU_1338	SET1	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2434	SET1	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_1197	SET1	29353	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] aldrichii*	1.00
OTU_433	SET1	1579	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus acidophilus*	1.00
OTU_394	SET1	1636655	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Dysgonomonas*	*Dysgonomonas mossii*	1.00
OTU_2748	SET1	47246	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] viride*	1.00
OTU_2251	SET1	53443	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia hydrogenotrophica*	1.00
OTU_1272	SET1	261299	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Intestinibacter*	*Intestinibacter bartlettii*	0.59
OTU_1388	SET1	1302	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus gordonii*	1.00
OTU_2677	SET1	115029 8	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Fusicatenibacter*	*Fusicatenibacter saccharivorans*	1.00

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OTU_464	SEQ_T1	938289	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Levyella*	*Levyella massiliensis*	1.00
OTU_1462	SEQ_T1	288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_1871	SEQ_T1	292800	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flavonifractor*	*Flavonifractor plautii*	1.00
OTU_1649	SEQ_T1	288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_2063	SEQ_T1	328814	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii*	1.00
OTU_2525	SEQ_T1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_2422	SEQ_T1	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_1697	SEQ_T1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_3061	SEQ_T1	53342	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Caloramator*	*Caloramator proteoclasticus*	1.00
OTU_2213	SEQ_T1	358742	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] aldenense*	1.00
OTU_1302	SEQ_T1	48256	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] hungatei*	1.00
OTU_811	SEQ_T1	55779	Firmicutes	Clostridia	Thermoanaerobacterales	Thermoanaerobacteraceae	*Moorella*	*Moorella glycerini*	0.55
OTU_3114	SEQ_T1	762984	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides clarus YIT 12056*	1.00
OTU_2828	SEQ_T1	471875	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus lactaris ATCC 29176*	1.00
OTU_2542	SEQ_T1	258515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetanaerobacterium*	*Acetanaerobacterium elongatum*	1.00
OTU_3143	SEQ_T1	53443	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia hydrogenotrophica*	1.00
OTU_2311	SEQ_T1	817	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides fragilis*	1.00
OTU_1588	SEQ_T1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_1881	SEQ_T1	214853	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Anaerofustis*	*Anaerofustis stercorihominis*	1.00

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OTU_1924	SET1	100709 6	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter ruminantium GH1*	1.00
OTU_2816	SET1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_534	SET1	938278	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Casaltella*	*Casaltella massiliensis*	1.00
OTU_2825	SET1	179661 3	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides caecimuris*	0.68
OTU_2142	SET1	341220	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lactonifactor*	*Lactonifactor longoviformis*	1.00
OTU_1605	SET1	184186 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00
OTU_377	SET1	111805 7	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Peptoniphilus*	*Peptoniphilus grossensis ph5*	0.50
OTU_315	SET1	107714 4	Actinobacteria	Coriobacteriia	Coriobacteriales	Dietziaceae	*Dietzia*	*Dietzia alimentaria 72*	1.00
OTU_2544	SET1	1737	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Paeniclostridium*	*[Eubacterium] tenue*	1.00
OTU_2858	SET1	112130 8	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Clostridioides*	*Clostridioides difficile ATCC 9689 = DSM 1296*	1.00
OTU_557	SET1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_1059	SET1	411467	Firmicutes	Clostridia	Clostridiales	unclassified NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_2020	SET1	218205	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Garciella*	*Garciella nitratireducens*	1.00
OTU_931	SET1	112129 8	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium amylolyticum*	1.00
OTU_1695	SET1	684066	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus lacterius*	1.00
OTU_1981	SET1	258515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetanaerobacterium*	*Acetanaerobacterium elongatum*	1.00
OTU_2600	SET1	649756	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes hadrus*	1.00
OTU_1887	SET1	433659	Actinobacteria	Actinobacteria	Propionibacteriales	Nocardioidaceae	*Nocardioides*	*Nocardioides mesophilus*	1.00
OTU_2058	SET1	52699	Actinobacteria	Actinobacteria	Propionibacteriales	Nocardioidaceae	*Aeromicrobium*	*Aeromicrobium fastidiosum*	1.00

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OTU_2235	SET1	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	1.00
OTU_1005	SET1	234908	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Sutterella*	*Sutterella stercoricanis*	1.00
OTU_1910	SET1	706562	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus rogosae*	0.55
OTU_3085	SET1	253257	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] amygdalinum*	0.50
OTU_1583	SET1	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2308	SET1	39496	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium ventriosum*	1.00
OTU_643	SET1	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	0.65
OTU_1191	SET1	115544	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Parasporobacterium*	*Parasporobacterium paucivorans*	1.00
OTU_1997	SET1	84030	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_3166	SET1	706562	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus rogosae*	0.68
OTU_1406	SET1	501571	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Butyricicoccus*	*Butyricicoccus pullicaecorum*	1.00
OTU_3047	SET1	1509	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium sporogenes*	1.00
OTU_2916	SET1	328812	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides goldsteinii*	0.59
OTU_276	SET1	1280	Firmicutes	Bacilli	Bacillales	Staphylococcaceae	*Staphylococcus*	*Staphylococcus aureus*	0.50
OTU_2864	SET1	1121115	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia wexlerae DSM 19850*	1.00
OTU_3131	SET1	762984	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides clarus YIT 12056*	1.00
OTU_414	SET1	147802	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus iners*	1.00
OTU_790	SET1	58134	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Desulfotomaculum] guttoideum*	1.00
OTU_891	SET1	133561 3	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Gordonibacter*	*Gordonibacter urolithinfaciens*	1.00

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OTU_2009	SE T1	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	0.63
OTU_1870	SE T1	745368	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Gemmiger*	*Gemmiger formicilis*	0.50
OTU_1175	SE T1	52786	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerofilum*	*Anaerofilum agile*	1.00
OTU_1395	SE T1	328814	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii*	0.63
OTU_1236	SE T1	891	Proteobacteria	Deltaproteobacteria	Desulfuromonadales	Desulfuromonadaceae	*Desulfuromonas*	*Desulfuromonas acetoxidans*	1.00
OTU_2197	SE T1	585394	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia hominis A2-183*	1.00
OTU_487	SE T1	1582	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus casei*	1.00
OTU_964	SE T1	235931	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Alkalibacter*	*Alkalibacter saccharofermentans*	1.00
OTU_3184	SE T1	308994	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister propionicifaciens*	1.00
OTU_226	SE T1	29466	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella parvula*	1.00
OTU_1037	SE T1	1589	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus pentosus*	1.00
OTU_1021	SE T1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1288	SE T1	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	1.00
OTU_2276	SE T1	1682	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*	*Bifidobacterium longum subsp. infantis*	1.00
OTU_695	SE T1	1736	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium limosum*	1.00
OTU_111	SE T1	28129	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella denticola*	1.00
OTU_1899	SE T1	301302	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia faecis*	1.00
OTU_2162	SE T1	160404	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] lactatifermentans*	1.00
OTU_1053	SE T1	178001	Firmicutes	Bacilli	Lactobacillales	Leuconostocaceae	*Leuconostoc*	*Leuconostoc inhae*	1.00

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OTU_2698	SEQ_TAX	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_934	SEQ_TAX	1509	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium sporogenes*	1.00
OTU_1194	SEQ_TAX	551788	Firmicutes	Clostridia	Clostridiales	Caldicoprobacteraceae	*Caldicoprobacter*	*Caldicoprobacter oshimai*	1.00
OTU_1580	SEQ_TAX	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_645	SEQ_TAX	2051	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Mobiluncus*	*Mobiluncus curtisii*	1.00
OTU_1319	SEQ_TAX	856	Fusobacteriia	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	*Fusobacterium varium*	1.00
OTU_1738	SEQ_TAX	118562	Cyanobacteria	unclassified.NA	Oscillatoriales	Microcoleaceae	*Arthrospira*	*Arthrospira platensis*	1.00
OTU_2168	SEQ_TAX	214856	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes finegoldii*	1.00
OTU_1503	SEQ_TAX	1302	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus gordonii*	1.00
OTU_1185	SEQ_TAX	292800	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flavonifractor*	*Flavonifractor plautii*	1.00
OTU_2365	SEQ_TAX	101070	Firmicutes	Bacilli	Bacillales	Planococcaceae	*Rummeliibacillus*	*Rummeliibacillus pycnus*	1.00
OTU_1822	SEQ_TAX	515619	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Myxococcus*	*[Eubacterium rectale] ATCC 33656*	0.55
OTU_463	SEQ_TAX	40215	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Acinetobacter*	*Acinetobacter junii*	1.00
OTU_3029	SEQ_TAX	745368	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Gemmiger*	*Gemmiger formicilis*	1.00
OTU_2649	SEQ_TAX	187979	Firmicutes	Negativicutes	Selenomonadales	Selenomonadaceae	*Mitsuokella*	*Mitsuokella jalaludinii*	1.00
OTU_2666	SEQ_TAX	82979	Proteobacteria	Gammaproteobacteria	Enterobacterales	Budviciaceae	*Budvicia*	*Budvicia aquatica*	1.00
OTU_2895	SEQ_TAX	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00
OTU_3020	SEQ_TAX	29363	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium paraputrificum*	1.00
OTU_3163	SEQ_TAX	160404	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] lactatifermentans*	1.00

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OTU_1357	SE T1	177639 1	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Romboutsia*	*Romboutsia timonensis*	1.00
OTU_1550	SE T1	128519 1	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfotomaculum*	*Desulfotomaculum intricatum*	1.00
OTU_2275	SE T1	844112	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Eggerthella*	*Eggerthella lenta*	1.00
OTU_1828	SE T1	46503	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides merdae*	1.00
OTU_1647	SE T1	157688	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	*Leptotrichia hofstadii*	1.00
OTU_425	SE T1	38304	Actinobacteria	Actinobacteria	Corynebacteriales	Corynebacteriaceae	*Corynebacterium*	*Corynebacterium tuberculostearicum*	1.00
OTU_3121	SE T1	109624 6	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella effluvii*	1.00
OTU_2982	SE T1	105841	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes caccae*	1.00
OTU_2929	SE T1	292800	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flavonifractor*	*Flavonifractor plautii*	1.00
OTU_2019	SE T1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_508	SE T1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_1664	SE T1	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Ihubacter*	*Ihubacter massiliensis*	1.00
OTU_1854	SE T1	259063	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerocolumna*	*Anaerocolumna jejuensis*	1.00
OTU_2847	SE T1	36850	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium quinii*	1.00
OTU_3191	SE T1	341694	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Peptostreptococcus*	*Peptostreptococcus stomatis*	1.00
OTU_3208	SE T1	287	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	*Pseudomonas aeruginosa*	1.00
OTU_2253	SE T1	75612	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Porphyromonas*	*Pseudomonas mandelii*	1.00
OTU_2511	SE T1	901	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio piger*	1.00
OTU_2002	SE T1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00

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OTU_2524	SET1	818	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides thetaiotaomicron*	1.00
OTU_2530	SET1	371674	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Moryella*	*Moryella indoligenes*	1.00
OTU_2536	SET1	338188	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides finegoldii*	1.00
OTU_2608	SET1	69825	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] indolis*	1.00
OTU_568	SET1	88164	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus fornicalis*	1.00
OTU_2872	SET1	112111_5	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia wexlerae DSM 19850*	1.00
OTU_816	SET1	588581	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] papyrosolvens DSM 2782*	1.00
OTU_1060	SET1	351091	Firmicutes	Clostridia	Clostridiales	Oscillospiraceae	*Oscillibacter*	*Oscillibacter valericigenes*	1.00
OTU_1193	SET1	676965	Firmicutes	Clostridia	Thermoanaerobacterales	Thermoanaerobacteraceae	*Moorella*	*Moorella humiferrea*	1.00
OTU_1639	SET1	358742	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] aldenense*	1.00
OTU_1727	SET1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_221	SET1	546271	Firmicutes	Negativicutes	Selenomonadales	Selenomonadaceae	*Selenomonas*	*Selenomonas spatigena ATCC 35185*	1.00
OTU_2468	SET1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_3057	SET1	47246	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] viride*	1.00
OTU_3093	SET1	123651_2	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides rodentium JCM 16496*	1.00
OTU_3098	SET1	40518	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus bromii*	1.00
OTU_732	SET1	131846_5	Tenericutes	Mollicutes	Acholeplasmatales	Acholeplasmataceae	*Acholeplasma*	*Acholeplasma brassicae 0502*	1.00
OTU_837	SET1	178338	Firmicutes	Tissierellia	unclassified.NA	unclassified.NA	*Sedimentibacter*	*Sedimentibacter hongkongensis*	1.00
OTU_871	SET1	154046	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Hungatella*	*Hungatella hathewayi*	1.00

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OTU_923	SE T1	328813	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes onderdonkii*	1.00
OTU_991	SE T1	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	1.00
OTU_768	SE T1	862517	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Peptoniphilus*	*Peptoniphilus duerdenii ATCC BAA-1640*	1.00
OTU_1251	SE T1	157687	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	*Leptotrichia wadei*	1.00
OTU_160	SE T1	158	Spirochaetes	Spirochaetia	Spirochaetales	Spirochaetaceae	*Treponema*	*Treponema denticola*	1.00
OTU_1633	SE T1	184186 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00
OTU_2294	SE T1	29466	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella parvula*	1.00
OTU_2993	SE T1	84026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_926	SE T1	51048	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Actinobacillus*	*Actinobacillus porcinus*	1.00
OTU_16	SE T1	158333 1	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	*Porphyromonas pasteri*	1.00
OTU_1170	SE T1	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_1566	SE T1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_863	SE T1	529	Proteobacteria	Alphaproteobacteria	Rhizobiales	Brucellaceae	*Ochrobactrum*	*Ochrobactrum anthropi*	1.00
OTU_3206	SE T1	134982 2	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Coprobacter*	*Coprobacter fastidiosus NSB1*	1.00
OTU_1518	SE T1	288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_1678	SE T1	901	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio piger*	1.00
OTU_2086	SE T1	290052	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio ethanolgignens*	1.00
OTU_2560	SE T1	1535	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] leptum*	1.00
OTU_2976	SE T1	536633	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia glucerasea*	1.00

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OTU_3190	SEQ_TAX	706562	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus rogosae*	1.00
OTU_3195	SEQ_TAX	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	1.00
OTU_625	SEQ_TAX	888745	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus agalactiae ATCC 13813*	1.00
OTU_1063	SEQ_TAX	214851	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Subdoligranulum*	*Subdoligranulum variabile*	1.00
OTU_1865	SEQ_TAX	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1926	SEQ_TAX	1732	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium oxidoreducens*	1.00
OTU_3050	SEQ_TAX	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_993	SEQ_TAX	308994	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister propionicifaciens*	1.00
OTU_2923	SEQ_TAX	89014	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia luti*	0.59
OTU_3040	SEQ_TAX	357276	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides dorei*	0.55
OTU_2300	SEQ_TAX	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_940	SEQ_TAX	394340	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Asaccharobacter*	*Asaccharobacter celatus*	0.55
OTU_1116	SEQ_TAX	40545	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Sutterella*	*Sutterella wadsworthensis*	1.00
OTU_1442	SEQ_TAX	1841867	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00
OTU_1656	SEQ_TAX	855	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	*Fusobacterium simiae*	1.00
OTU_2376	SEQ_TAX	357276	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides dorei*	1.00
OTU_2538	SEQ_TAX	515619	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Myxococcus*	*[Eubacterium rectale] ATCC 33656*	1.00
OTU_2602	SEQ_TAX	1619234	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerobium*	*Anaerobium acetethylicum*	1.00
OTU_2603	SEQ_TAX	553973	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] hylemonae DSM 15053*	1.00

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OTU_2604	SET1	213810	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus champanellensis 18P13 = JCM 17042*	1.00
OTU_1658	SET1	253257	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] amygdalinum*	1.00
OTU_1188	SET1	938293	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Anaerococcus*	*Anaerococcus provenciensis*	1.00
OTU_1374	SET1	93063	Proteobacteria	Alphaproteobacteria	Sphingomonadales	Sphingomonadaceae	*Sphingomonas*	*Sphingomonas aquatilis*	1.00
OTU_1558	SET1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2232	SET1	708634	Proteobacteria	Betaproteobacteria	Burkholderiales	unclassified.NA	*Aquabacterium*	*Aquabacterium limnoticum*	1.00
OTU_2563	SET1	179995	Proteobacteria	Gammaproteobacteria	Aeromonadales	Succinivibrionaceae	*Anaerobiospirillu m*	*Anaerobiospirillum thomasii*	1.00
OTU_745	SET1	35519	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Mogibacterium*	*Mogibacterium timidum*	1.00
OTU_1506	SET1	1351	Firmicutes	Bacilli	Lactobacillales	Enterococcaceae	*Enterococcus*	*Enterococcus faecalis*	1.00
OTU_1114	SET1	476652	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfosporosimu s*	*Desulfosporosimus acididuran s*	1.00
OTU_2029	SET1	141785 2	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Flintibacter*	*Flintibacter butyricus*	1.00
OTU_439	SET1	146403 8	Firmicutes	Tissierellia	unclassified.NA	unclassified.NA	*Ezakiella*	*Ezakiella peruensis*	1.00
OTU_1638	SET1	555088	Firmicutes	Clostridia	Clostridiales	Syntrophomonadaceae	*Dethiobacter*	*Dethiobacter alkaliphilus AHT 1*	1.00
OTU_1740	SET1	44749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_1725	SET1	184186 7	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Phocea*	*Phocea massiliensis*	1.00
OTU_2319	SET1	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	1.00
OTU_2322	SET1	237576	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Oribacterium*	*Oribacterium sinus*	1.00
OTU_1301	SET1	177638 2	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Neglecta*	*Neglecta timonensis*	1.00
OTU_1328	SET1	358742	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] aldenense*	1.00

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OTU_1579	SET1	1515	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*Ruminiclostridium thermocellum*	1.00
OTU_1889	SET1	879566	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Acetatifactor*	*Acetatifactor muris*	1.00
OTU_2460	SET1	185237 1	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Raoultibacter*	*Raoultibacter massiliensis*	1.00
OTU_830	SET1	404403	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Howardella*	*Howardella ureilytica*	1.00
OTU_1173	SET1	185236 7	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Inubacter*	*Inubacter massiliensis*	1.00
OTU_2007	SET1	253314	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] straminisolvens*	1.00
OTU_1836	SET1	328814	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii*	1.00
OTU_2353	SET1	742727	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides oleiciplenus YIT 12058*	0.50
OTU_1178	SET1	253314	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] straminisolvens*	1.00
OTU_1463	SET1	626937	Firmicutes	Clostridia	Clostridiales	Christensenellaceae	*Christensenella*	*Christensenella minuta*	1.00
OTU_1977	SET1	1377	Firmicutes	Bacilli	Lactobacillales	Aerococcaceae	*Aerococcus*	*Aerococcus viridans*	1.00
OTU_2610	SET1	588581	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] papyrosolvens DSM 2782*	1.00
OTU_2611	SET1	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	1.00
OTU_2612	SET1	35830	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio cellulolyticus*	1.00
OTU_2615	SET1	844026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_2619	SET1	100176	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Papillibacter*	*Papillibacter cinnamivorans*	1.00
OTU_2799	SET1	626947	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella secunda*	1.00
OTU_3001	SET1	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_3036	SET1	438033	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus gauvreauii*	1.00

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OTU_726	SET1	1732	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium oxidoreducens*	1.00
OTU_138	SET1	997353	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella pallens ATCC 700821*	1.00
OTU_1325	SET1	1432052	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Eisenbergiella*	*Eisenbergiella tayi*	1.00
OTU_1561	SET1	649756	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerostipes*	*Anaerostipes hadrus*	1.00
OTU_512	SET1	33043	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Coprococcus*	*Coprococcus eutactus*	0.50
OTU_2968	SET1	218538	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister invisus*	1.00
OTU_1308	SET1	214856	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes finegoldii*	1.00
OTU_1057	SET1	83771	Proteobacteria	Gammaproteobacteria	Aeromonadales	Succinivibrionaceae	*Succinivibrio*	*Succinivibrio dextrinosolvens*	1.00
OTU_1547	SET1	671218	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Alloprevotella*	*Alloprevotella rava*	1.00
OTU_2298	SET1	1605	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus animalis*	1.00
OTU_2915	SET1	28111	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides eggerthii*	1.00
OTU_461	SET1	131109	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	*Actinomyces bowdenii*	1.00
OTU_959	SET1	1302	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus gordonii*	1.00
OTU_2069	SET1	46609	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium pascui*	1.00
OTU_3092	SET1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_1371	SET1	690567	Firmicutes	Clostridia	Clostridiales	Syntrophomonadaceae	*Syntrophomonas*	*Syntrophomonas zehnderi OL-4*	1.00
OTU_2008	SET1	46206	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Pseudobutyrivibrio*	*Pseudobutyrivibrio ruminis*	1.00
OTU_874	SET1	155615	Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	*Fusobacterium*	*Fusobacterium nucleatum subsp. vincentii*	0.50
OTU_1382	SET1	333367	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] asparagiforme*	1.00

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OTU_2065	SET1	840261	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_1569	SET1	516161	Firmicutes	Clostridia	Clostridiales	Peptococcaceae	*Desulfitobacterium*	*Desulfitobacterium chlororespirans*	1.00
OTU_2838	SET1	1298596	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	0.50
OTU_1890	SET1	1796620	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acutalibacter*	*Acutalibacter muris*	1.00
OTU_112	SET1	40542	Fusobacteriota	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	*Leptotrichia buccalis*	1.00
OTU_2136	SET1	396504	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] sufflavum*	1.00
OTU_1280	SET1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_88	SET1	203	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	*Campylobacter*	*Campylobacter rectus*	1.00
OTU_3193	SET1	328814	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes shahii*	1.00
OTU_810	SET1	294	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	*Pseudomonas fluorescens*	1.00
OTU_2803	SET1	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_2813	SET1	1605	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus animalis*	1.00
OTU_3096	SET1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_2955	SET1	1033446	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Dielma*	*Dielma fastidiosa*	1.00
OTU_395	SET1	156456	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Anaeroglobus*	*Anaeroglobus geminatus*	1.00
OTU_3097	SET1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_819	SET1	80866	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Delftia*	*Delftia acidovorans*	1.00
OTU_1299	SET1	358742	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] aldenense*	0.59
OTU_3058	SET1	840261	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00

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OTU_915	SEQ_TIME1	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2561	SEQ_TIME1	447749	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Sporobacter*	*Sporobacter termitidis*	1.00
OTU_1857	SEQ_TIME1	840026	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_887	SEQ_TIME1	840030	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] saccharolyticum*	1.00
OTU_1593	SEQ_TIME1	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	1.00
OTU_2096	SEQ_TIME1	820	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides uniformis*	1.00
OTU_1572	SEQ_TIME1	169435	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Anaerotruncus*	*Anaerotruncus colihominis*	1.00
OTU_2402	SEQ_TIME1	853	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*	*Faecalibacterium prausnitzii*	1.00
OTU_64	SEQ_TIME1	554406	Fusobacteria	Fusobacteriia	Fusobacteriales	Leptotrichiaceae	*Leptotrichia*	*Leptotrichia hongkongensis*	1.00
OTU_1306	SEQ_TIME1	290054	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*Eubacterium coprostanoligenes*	1.00
OTU_197	SEQ_TIME1	796942	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Stomatobaculum*	*Stomatobaculum longum*	1.00
OTU_2572	SEQ_TIME1	1605	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus animalis*	1.00
OTU_296	SEQ_TIME1	100236	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella stercorea DSM 18206*	0.55
OTU_1711	SEQ_TIME1	29347	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] scindens*	1.00
OTU_254	SEQ_TIME1	796944	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Oribacterium*	*Oribacterium asaccharolyticum ACB7*	1.00
OTU_139	SEQ_TIME1	61592	Actinobacteria	Actinobacteria	Corynebacteriales	Corynebacteriaceae	*Corynebacterium*	*Corynebacterium durum*	1.00
OTU_1332	SEQ_TIME1	184185	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Culturomica*	*Culturomica massiliensis*	1.00
OTU_565	SEQ_TIME1	487175	Proteobacteria	Betaproteobacteria	Burkholderiales	Sutterellaceae	*Parasutterella*	*Parasutterella excrementihominis*	1.00
OTU_569	SEQ_TIME1	45851	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Butyrivibrio*	*Butyrivibrio crossotus*	1.00

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OTU_1956	SEQ ID NO: 69825	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] indolis*	1.00
OTU_1733	SEQ ID NO: 105020	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Allobaculum*	*Allobaculum stercoricanis DSM 13633*	1.00
OTU_3144	SEQ ID NO: 818	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides thetaiotaomicron*	1.00
OTU_8	SEQ ID NO: 762948	Actinobacteria	Actinobacteria	Micrococcales	Micrococcaceae	*Rothia*	*Rothia dentocariosa ATCC 17931*	0.63
OTU_325	SEQ ID NO: 137732	Firmicutes	Bacilli	Lactobacillales	Carnobacteriaceae	*Granulicatella*	*Granulicatella elegans*	1.00
OTU_1651	SEQ ID NO: 103434	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Dielma*	*Dielma fastidiosa*	1.00
OTU_3198	SEQ ID NO: 121181	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Holdemania*	*Holdemania massiliensis AP2*	1.00
OTU_2160	SEQ ID NO: 1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	1.00
OTU_1093	SEQ ID NO: 1019	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*Capnocytophaga sputigena*	1.00
OTU_1655	SEQ ID NO: 288966	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Lutispora*	*Lutispora thermophila*	1.00
OTU_1269	SEQ ID NO: 74426	Actinobacteria	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Collinsella*	*Collinsella aerofaciens*	1.00
OTU_1781	SEQ ID NO: 272548	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	*Actinomyces dentalis*	1.00
OTU_1825	SEQ ID NO: 39777	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella atypica*	1.00
OTU_2240	SEQ ID NO: 46503	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides merdae*	1.00
OTU_3124	SEQ ID NO: 1717	Actinobacteria	Actinobacteria	Corynebacteriales	Corynebacteriaceae	*Corynebacterium*	*Corynebacterium diphtheriae*	1.00
OTU_3151	SEQ ID NO: 84112	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Eggerthella*	*Eggerthella lenta*	1.00
OTU_728	SEQ ID NO: 384636	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides xylanolyticus*	1.00
OTU_939	SEQ ID NO: 216940	Tenericutes	Mollicutes	Entomoplasmatales	Spiroplasmataceae	*Spiroplasma*	*Spiroplasma lampyridicola*	1.00
OTU_947	SEQ ID NO: 2087	Tenericutes	Mollicutes	Anaeroplasmatales	Anaeroplasmataceae	*Anaeroplasma*	*Anaeroplasma abactoclasticum*	1.00

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OTU_1036	SET1	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2880	SET1	45634	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	*Streptococcus*	*Streptococcus cristatus*	1.00
OTU_1594	SET1	89014	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia luti*	1.00
OTU_1852	SET1	253257	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] amygdalinum*	1.00
OTU_969	SET1	466107	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio litoralis*	0.50
OTU_2702	SET1	871665	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*	*Blautia faecis*	1.00
OTU_1134	SET1	938293	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Anaerococcus*	*Anaerococcus provenciensis*	1.00
OTU_1264	SET1	29466	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella parvula*	1.00
OTU_1355	SET1	1689	Actinobacteria	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*	*Bifidobacterium dentium*	1.00
OTU_1422	SET1	47678	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides caccae*	1.00
OTU_1431	SET1	259063	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerocolumna*	*Anaerocolumna jejuensis*	1.00
OTU_1504	SET1	879566	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Acetatifactor*	*Acetatifactor muris*	1.00
OTU_1683	SET1	158333	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	*Porphyromonas pasteri*	1.00
OTU_2033	SET1	575	Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	*Raoultella*	*Raoultella planticola*	1.00
OTU_235	SET1	979627	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoanaerobaculum*	*Lachnoanaerobaculum orale*	1.00
OTU_2479	SET1	33033	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Parvimonas*	*Parvimonas micra*	1.00
OTU_2881	SET1	51048	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Actinobacillus*	*Actinobacillus porcinus*	1.00
OTU_304	SET1	840	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella loescheii*	1.00
OTU_330	SET1	158333	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	*Porphyromonas pasteri*	1.00

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OTU_383	SEQ_TI	1660	Actinobacteria	Actinobacteria	Actinomycetales	Actinomycetaceae	*Actinomyces*	*Actinomyces odontolyticus*	1.00
OTU_549	SEQ_TI	29466	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Veillonella*	*Veillonella parvula*	1.00
OTU_572	SEQ_TI	320502	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] alkalicellulosi*	1.00
OTU_622	SEQ_TI	123651 7	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella fusca JCM 17724*	1.00
OTU_743	SEQ_TI	617123	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoanaerobaculum*	*Lachnoanaerobaculum umeaense*	1.00
OTU_2250	SEQ_TI	546	Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	*Citrobacter*	*Citrobacter freundii*	1.00
OTU_1367	SEQ_TI	129859 6	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus faecis JCM 15917*	1.00
OTU_1067	SEQ_TI	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_1072	SEQ_TI	358743	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] citroniae*	1.00
OTU_1963	SEQ_TI	105020 1	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Allobaculum*	*Allobaculum stercoricanis DSM 13633*	1.00
OTU_1171	SEQ_TI	1264	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus albus*	1.00
OTU_1895	SEQ_TI	471875	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminococcus*	*Ruminococcus lactaris ATCC 29176*	1.00
OTU_211	SEQ_TI	28135	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella oris*	1.00
OTU_2165	SEQ_TI	82171	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio zosterae*	1.00
OTU_2395	SEQ_TI	37658	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] populeti*	1.00
OTU_2682	SEQ_TI	483	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Chromobacterium*	*Neisseria cinerea*	1.00
OTU_2766	SEQ_TI	333367	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] asparagiforme*	1.00
OTU_309	SEQ_TI	501496	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	*Porphyromonas bennonis*	1.00
OTU_723	SEQ_TI	99656	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] fimetarium*	1.00

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OTU_973	SE T1	1379	Firmicutes	Bacilli	Bacillales	unclassified.NA	*Gemella*	*Gemella haemolysans*	1.00
OTU_1231	SE T1	840320	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] thermosuccinogenes*	1.00
OTU_2687	SE T1	1236512	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides rodentium JCM 16496*	1.00
OTU_2840	SE T1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_3053	SE T1	411467	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Pseudoflavonifractor*	*Pseudoflavonifractor capillosus ATCC 29799*	1.00
OTU_3199	SE T1	394837	Firmicutes	Erysipelotrichia	Erysipelotrichales	Erysipelotrichaceae	*Faecalitalea*	*Faecalitalea cylindroides*	1.00
OTU_3207	SE T1	465037	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides merdae*	1.00
OTU_1427	SE T1	879566	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Acetatifactor*	*Acetatifactor muris*	1.00
OTU_901	SE T1	1107316	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Neisseria*	*Neisseria oralis*	1.00
OTU_1223	SE T1	584	Proteobacteria	Gammaproteobacteria	Enterobacterales	Morganellaceae	*Proteus*	*Proteus mirabilis*	1.00
OTU_1608	SE T1	28124	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Porphyromonas*	*Porphyromonas endodontalis*	1.00
OTU_1798	SE T1	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	1.00
OTU_2066	SE T1	109327	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*Anaerovorax*	*Anaerovorax odorimutans*	1.00
OTU_2280	SE T1	1033744	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Peptoniphilus*	*Peptoniphilus senegalensis JC140*	1.00
OTU_2393	SE T1	320502	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] alkalicellulosi*	1.00
OTU_3125	SE T1	901	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio piger*	1.00
OTU_1762	SE T1	483	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Chromobacterium*	*Neisseria cinerea*	1.00
OTU_2848	SE T1	657309	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides xylanisolvens XB1A*	1.00
OTU_298	SE T1	671218	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Alloprevotella*	*Alloprevotella rava*	1.00

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OTU_376	SE T1	536441	Bacteroidetes	Flavobacteria	Flavobacteriales	Flavobacteriaceae	*Chryseobacterium*	*Chryseobacterium taklimakanense*	1.00
OTU_571	SE T1	873513	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella buccae ATCC 33574*	1.00
OTU_618	SE T1	76123	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella enoeca*	1.00
OTU_2595	SE T1	111806 0	Actinobacteria	Coriobacteriia	Coriobacteriales	Coriobacteriaceae	*Enorma*	*Enorma massiliensis phI*	1.00
OTU_266	SE T1	89152	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Achromobacter*	*[Clostridium] hiranonis*	1.00
OTU_514	SE T1	888727	Firmicutes	Clostridia	Clostridiales	Clostridiales Family XIII. Incertae Sedis	*unclassified.NA*	*Eubacterium sulci ATCC 35585*	1.00
OTU_94	SE T1	76122	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Alloprevotella*	*Alloprevotella tannerae*	1.00
OTU_2059	SE T1	303	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	*Pseudomonas putida*	1.00
OTU_3060	SE T1	1541	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Terrisporobacter*	*Terrisporobacter mayombei*	1.00
OTU_1475	SE T1	507751	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Peptoniphilus*	*Peptoniphilus koenoeneniae*	1.00
OTU_1204	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_1626	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_3028	SE T1	515620	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	*Eubacterium*	*[Eubacterium] eligens ATCC 27750*	1.00
OTU_1090	SE T1	38302	Actinobacteria	Actinobacteria	Corynebacteriales	Corynebacteriaceae	*Corynebacterium*	*Corynebacterium mycetoides*	1.00
OTU_186	SE T1	53419	Spirochaetes	Spirochaetia	Spirochaetales	Spirochaetaceae	*Treponema*	*Treponema socranskii*	1.00
OTU_2158	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2205	SE T1	726	Proteobacteria	Gammaproteobacteria	Pasteurellales	Pasteurellaceae	*Haemophilus*	*Haemophilus haemolyticus*	1.00
OTU_2345	SE T1	328812	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Parabacteroides*	*Parabacteroides goldsteinii*	1.00
OTU_1408	SE T1	40324	Proteobacteria	Gammaproteobacteria	Xanthomonadales	Xanthomonadaceae	*Stenotrophomonas*	*Stenotrophomonas maltophilia*	1.00

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OTU_1476	SET1	1297617	Firmicutes	Clostridia	Clostridiales	unclassified.NA	*Intestinimonas*	*Intestinimonas butyriciproducens*	1.00
OTU_1731	SET1	555088	Firmicutes	Clostridia	Clostridiales	Syntrophomonadaceae	*Dethiobacter*	*Dethiobacter alkaliphilus AHT 1*	1.00
OTU_2082	SET1	901	Proteobacteria	Deltaproteobacteria	Desulfovibrionales	Desulfovibrionaceae	*Desulfovibrio*	*Desulfovibrio piger*	1.00
OTU_2114	SET1	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2283	SET1	308994	Firmicutes	Negativicutes	Veillonellales	Veillonellaceae	*Dialister*	*Dialister propionicifaciens*	1.00
OTU_238	SET1	179664	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_2517	SET1	29375	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] xylanolyticum*	1.00
OTU_609	SET1	179661	Actinobacteria	Coriobacteriia	Eggerthellales	Eggerthellaceae	*Enterorhabdus*	*Enterorhabdus muris*	1.00
OTU_1208	SET1	290052	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Acetivibrio*	*Acetivibrio ethanolgignens*	1.00
OTU_1844	SET1	546	Proteobacteria	Gammaproteobacteria	Enterobacterales	Enterobacteriaceae	*Citrobacter*	*Citrobacter freundii*	1.00
OTU_1560	SET1	988946	Cyanobacteria	unclassified.NA	Nostocales	Symphyonemataceae	*Loriellopsis*	*Loriellopsis cavernicola*	1.00
OTU_1819	SET1	1605	Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*	*Lactobacillus animalis*	1.00
OTU_2423	SET1	166486	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Roseburia*	*Roseburia intestinalis*	1.00
OTU_1517	SET1	160404	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Tyzzerella*	*[Clostridium] lactatifermentans*	1.00
OTU_114	SET1	185237	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotellamassilia*	*Prevotellamassilia timonensis*	1.00
OTU_1248	SET1	474960	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Hydrogenoanaerobacterium*	*Hydrogenoanaerobacterium saccharovorans*	1.00
OTU_84	SET1	1017	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*Capnocytophaga gingivalis*	1.00
OTU_1624	SET1	116828	Bacteroidetes	Bacteroidia	Bacteroidales	Marinilabiliaceae	*Marinilabilia*	*Marinilabilia salmonicolor JCM 21150*	1.00
OTU_2918	SET1	246787	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides cellulosilyticus*	1.00

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OTU_1293	SE T1	76936	Proteobacteria	Epsilonproteobacteria	Campylobacterales	Helicobacteraceae	*Helicobacter*	*Helicobacter typhlonius*	1.00
OTU_2664	SE T1	94869	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium gasigenes*	1.00
OTU_2728	SE T1	204516	Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*	*Bacteroides massiliensis*	1.00
OTU_911	SE T1	116109 8	Firmicutes	Tissierellia	Tissierellales	Peptoniphilaceae	*Anaerococcus*	*Anaerococcus octavius NCTC 9810*	1.00
OTU_1930	SE T1	28117	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes putredinis*	1.00
OTU_1625	SE T1	100236 7	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella stercorea DSM 18206*	1.00
OTU_3162	SE T1	261299	Firmicutes	Clostridia	Clostridiales	Peptostreptococcaceae	*Intestinibacter*	*Intestinibacter bartlettii*	1.00
OTU_1255	SE T1	46206	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Pseudobutyrivibrio*	*Pseudobutyrivibrio ruminis*	1.00
OTU_2161	SE T1	515619	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Myxococcus*	*[Eubacterium rectale] ATCC 33656*	1.00
OTU_2320	SE T1	28118	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	*Odoribacter*	*Odoribacter splanchnicus*	1.00
OTU_2674	SE T1	1531	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Lachnoclostridium*	*[Clostridium] clostridioforme*	1.00
OTU_729	SE T1	215580	Proteobacteria	Betaproteobacteria	Burkholderiales	Comamonadaceae	*Schlegelella*	*Schlegelella thermodepolymerans*	1.00
OTU_730	SE T1	179664 6	Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Muribaculum*	*Muribaculum intestinale*	1.00
OTU_994	SE T1	1125779	Actinobacteria	Actinobacteria	Corynebacteriales	Corynebacteriaceae	*Corynebacterium*	*Corynebacterium pyruviciproducens ATCC BAA-1742*	1.00
OTU_1282	SE T1	840261	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Ruminiclostridium*	*[Clostridium] methylpentosum*	1.00
OTU_1717	SE T1	327575	Bacteroidetes	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	*Capnocytophaga*	*Capnocytophaga leadbetteri*	1.00
OTU_2829	SE T1	549	Proteobacteria	Gammaproteobacteria	Enterobacterales	Erwiniaceae	*Pantoea*	*Pantoea agglomerans*	1.00
OTU_398	SE T1	28129	Bacteroidetes	Bacteroidia	Bacteroidales	Prevotellaceae	*Prevotella*	*Prevotella denticola*	1.00

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OTU_971	SE T1	483	Proteobacteria	Betaproteobacteria	Neisseriales	Neisseriaceae	*Chromobacterium*	*Neisseria cinerea*	1.00
OTU_1659	SE T1	145064 8	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	*Clostridium*	*Clostridium oryzae*	1.00
OTU_881	SE T1	214856	Bacteroidetes	Bacteroidia	Bacteroidales	Rikenellaceae	*Alistipes*	*Alistipes finegoldii*	1.00
OTU_1581	SE T1	264463	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Anaerosporobacter*	*Anaerosporobacter mobilis*	1.00
OTU_2148	SE T1	319644	Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Saccharofermentans*	*Saccharofermentans acetigenes*	1.00
OTU_2969	SE T1	515619	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Myxococcus*	*[Eubacterium rectale] ATCC 33656*	1.00
OTU_717	SE T1	478	Proteobacteria	Gammaproteobacteria	Pseudomonadales	Moraxellaceae	*Moraxella*	*Moraxella nonliquefaciens*	1.00

[00114] Table 2: Differences in WGS-derived fecal bacteria species by treatment response status.

CAG Number	Unadjusted p-value	Response status	CAG Number	Taxonomy Level	Species	Genus	Family
CAG00720	0.017	NR	CAG00720	Species	Anaerotruncus colihominis	Anaerotruncus	Ruminococcaceae
CAG00124	0.018	NR	CAG00124	Species	Klebsiella varicola	Klebsiella	Enterobacteriaceae
CAG00011	0.035	NR	CAG00011	Species	Escherichia coli	Escherichia	Enterobacteriaceae
CAG00050	0.043	NR	CAG00050	Species	Bacteroides thetaiotaomicron	Bacteroides	Bacteroidaceae
CAG00834	0.047	NR	CAG00834	Species	Oxalobacter formigenes	Oxalobacter	Oxalobacteraceae
CAG00426	0.06	NR	CAG00426	Species	Paraprevotella clara	Paraprevotella	Prevotellaceae
CAG01272	0.06	NR	CAG01272	Species	Adlercreutzia equolifaciens	Adlercreutzia	Eggerthellaceae
CAG01320	0.066	NR	CAG01320	Species	Clostridium bolteae	Lachnoclostridium	Lachnospiraceae
CAG00012	0.069	NR	CAG00012	Species	Klebsiella pneumoniae	Klebsiella	Enterobacteriaceae
CAG00826	0.089	NR	CAG00826	Genus	unclassified Clostridium	Clostridium	Clostridiaceae
CAG00117	0.092	NR	CAG00117	Species	Parabacteroides merdae	Parabacteroides	Porphyromonadaceae
CAG00093	0.116	NR	CAG00093	Species	Klebsiella quasipneumoniae	Klebsiella	Enterobacteriaceae

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CAG00114	0.116	NR	CAG00114	Genus	unclassified Lachnoclostridium	Lachnoclostridium	Lachnospiraceae	
CAG00161	0.116	NR	CAG00161	Species	Bacteroides coprocola	Bacteroides	Bacteroidaceae	
CAG00163	0.116	NR	CAG00163	Species	Prevotella sp. CAG:255	Prevotella	Prevotellaceae	
CAG00256	0.116	NR	CAG00256	Family	unclassified Lachnospiraceae	unclassified Lachnospiraceae	Lachnospiraceae	
CAG00462	0.116	NR	CAG00462	Species	Streptococcus pasteurianus	Streptococcus	Streptococcaceae	
CAG00815	0.116	NR	CAG00815	Species	Lactococcus lactis	Lactococcus	Streptococcaceae	
CAG00817	0.116	NR	CAG00817	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	
CAG00010_2	0.116	NR	CAG00010_2	NA	unclassified	unclassified	unclassified	
CAG01203	0.116	NR	CAG01203	Species	Streptococcus mutans	Streptococcus	Streptococcaceae	
CAG00949	0.12	NR	CAG00949	Species	Ruminococcaceae bacterium D16	unclassified Ruminococcaceae	Ruminococcaceae	
CAG00775	0.13	NR	CAG00775	Species	Firmicutes bacterium CAG:102	unclassified Firmicutes	unclassified Firmicutes	
CAG00931	0.131	NR	CAG00931	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae	
CAG01263	0.154	NR	CAG01263	Species	Clostridium clostridioforme	Lachnoclostridium	Lachnospiraceae	
CAG00086	0.154	NR	CAG00086	Species	Bacteroides massiliensis	Bacteroides	Bacteroidaceae	
CAG00113	0.157	NR	CAG00113	Species	Clostridium scindens	Lachnoclostridium	Lachnospiraceae	
CAG01323	0.165	NR	CAG01323	Species	Parabacteroides merdae	Parabacteroides	Porphyromonadaceae	
CAG00502	0.184	NR	CAG00502	Species	Eubacterium sp. CAG:161	Eubacterium	Eubacteriaceae	
CAG00254	0.193	NR	CAG00254	Species	Ruminococcus gnavus	Blautia	Lachnospiraceae	
CAG01264	0.197	NR	CAG01264	Species	Clostridium clostridioforme	Lachnoclostridium	Lachnospiraceae	
CAG00327	0.009	R	CAG00327	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae	
CAG00659	0.017	R	CAG00659	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	
CAG00492	0.034	R	CAG00492	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae	
CAG00518	0.034	R	CAG00518	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae	
CAG01146	0.034	R	CAG01146	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae	
CAG00079	0.038	R	CAG00079	Species	Clostridium sp. CAG:7	unclassified Clostridiales	unclassified Clostridiales	
CAG00393	0.048	R	CAG00393	Species	Eubacterium sp. CAG:86	Eubacterium	Eubacteriaceae	
CAG00766	0.065	R	CAG00766	Species	Firmicutes bacterium CAG:176	unclassified Firmicutes	unclassified Firmicutes	
CAG00095	0.065	R	CAG00095	Species	Akkermansia sp. CAG:344	Akkermansia	Akkermansiaceae	
CAG00010_1	0.065	R	CAG00010_1	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	

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CAG00342	0.065	R	CAG00342	Species	Bifidobacterium pseudocatenulatum	Bifidobacterium	Bifidobacteriaceae
CAG00303	0.065	R	CAG00303	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00337	0.065	R	CAG00337	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae
CAG00381	0.065	R	CAG00381	Species	Clostridium sp. CAG:242	unclassified Clostridiales	unclassified Clostridiales
CAG00559	0.065	R	CAG00559	Family	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00570	0.065	R	CAG00570	NA	unclassified	unclassified	unclassified
CAG00635	0.065	R	CAG00635	Species	Bifidobacterium bifidum	Bifidobacterium	Bifidobacteriaceae
CAG00636	0.065	R	CAG00636	Genus	unclassified Roseburia	Roseburia	Lachnospiraceae
CAG00660	0.065	R	CAG00660	Species	Alistipes timonensis	Alistipes	Rikenellaceae
CAG00669	0.065	R	CAG00669	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00708	0.065	R	CAG00708	Species	Alistipes senegalensis	Alistipes	Rikenellaceae
CAG00773	0.065	R	CAG00773	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00807	0.065	R	CAG00807	Genus	unclassified Holdemanella	Holdemanella	Erysipelotrichaceae
CAG00880	0.065	R	CAG00880	Species	Subdoligranulum sp. CAG:314	Subdoligranulum	Ruminococcaceae
CAG00907	0.065	R	CAG00907	Family	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01086	0.065	R	CAG01086	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG01215	0.065	R	CAG01215	Family	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01277	0.065	R	CAG01277	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01308	0.065	R	CAG01308	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00577	0.073	R	CAG00577	Species	Faecalibacterium prausnitzii 3 (L2-6)	Faecalibacterium	Ruminococcaceae
CAG00506	0.083	R	CAG00506	Genus	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae
CAG00852	0.087	R	CAG00852	Species	Clostridium spiroforme	Erysipelatoclostridium	Erysipelotrichaceae
CAG01046	0.091	R	CAG01046	Genus	unclassified Intestinimonas	Intestinimonas	unclassified Clostridiales
CAG00320	0.092	R	CAG00320	Species	Phascolarctobacterium sp. CAG:207	Phascolarctobacterium	Acidaminococcaceae
CAG00619	0.097	R	CAG00619	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae
CAG01366	0.098	R	CAG01366	Species	Streptococcus parasanguinis	Streptococcus	Streptococcaceae
CAG00509	0.1	R	CAG00509	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00441	0.104	R	CAG00441	Genus	unclassified Blautia	Blautia	Lachnospiraceae
CAG00249	0.106	R	CAG00249	Species	Clostridium leptum	Ruminiclostridium	Ruminococcaceae

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CAG50003	0.12	R	CAG50003	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00039	0.121	R	CAG00039	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00127	0.121	R	CAG00127	Family	unclassified Lachnospiraceae	unclassified Lachnospiraceae	Lachnospiraceae
CAG00854	0.121	R	CAG00854	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae
CAG00166	0.121	R	CAG00166	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00272	0.121	R	CAG00272	Species	Faecalibacterium 5 (sp. CAG:74)	Faecalibacterium	Ruminococcaceae
CAG00294	0.121	R	CAG00294	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00367	0.121	R	CAG00367	Species	Firmicutes bacterium CAG:170	unclassified Firmicutes	unclassified Firmicutes
CAG00445	0.121	R	CAG00445	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00452	0.121	R	CAG00452	Species	Clostridium sp. CAG:167	unclassified Clostridiales	unclassified Clostridiales
CAG00497	0.121	R	CAG00497	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00505	0.121	R	CAG00505	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00721	0.121	R	CAG00721	Species	Methanobrevibacter smithii 1	Methanobrevibacter	Methanobacteriaceae
CAG00624	0.121	R	CAG00624	Phylum	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00648	0.121	R	CAG00648	Genus	unclassified Eubacterium	Eubacterium	Eubacteriaceae
CAG00735	0.121	R	CAG00735	Genus	unclassified Eubacterium	Eubacterium	Eubacteriaceae
CAG00770	0.121	R	CAG00770	Family	unclassified Eggerthellaceae	unclassified Eggerthellaceae	Eggerthellaceae
CAG00812	0.121	R	CAG00812	Species	Catenibacterium sp. CAG:290	Catenibacterium	Erysipelotrichaceae
CAG00861	0.121	R	CAG00861	Species	Oscillibacter sp. CAG:241	Oscillibacter	Oscillospiraceae
CAG00863	0.121	R	CAG00863	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00925	0.121	R	CAG00925	NA	unclassified	unclassified	unclassified
CAG00934	0.121	R	CAG00934	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01003	0.121	R	CAG01003	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae
CAG01325	0.121	R	CAG01325	Genus	unclassified Lachnoclostridium	Lachnoclostridium	Lachnospiraceae
CAG02021	0.121	R	CAG02021	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01349	0.121	R	CAG01349	NA	unclassified	unclassified	unclassified
CAG01350	0.121	R	CAG01350	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG01402	0.121	R	CAG01402	Species	Turicibacter sp. H121	Turicibacter	Erysipelotrichaceae
CAG01403	0.121	R	CAG01403	Species	Bacteroides stercorirosoris	Bacteroides	Bacteroidaceae
CAG01551	0.121	R	CAG01551	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae

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CAG01028	0.13	R	CAG01028	Species	Ruminococcaceae bacterium LM158	unclassified Ruminococcaceae	Ruminococcaceae
CAG00121	0.134	R	CAG00121	Species	Bacteroides finegoldii	Bacteroides	Bacteroidaceae
CAG00670	0.134	R	CAG00670	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG00324	0.137	R	CAG00324	Species	Firmicutes bacterium CAG:94	unclassified Firmicutes	unclassified Firmicutes
CAG00218	0.143	R	CAG00218	Species	Barnesiella intestinihominis	Barnesiella	Porphyromonadaceae
CAG00755	0.143	R	CAG00755	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae
CAG00560	0.175	R	CAG00560	Genus	unclassified Subdoligranulum	Subdoligranulum	Ruminococcaceae
CAG00259	0.177	R	CAG00259	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes
CAG01039	0.177	R	CAG01039	Genus	unclassified Faecalibacterium	Faecalibacterium	Ruminococcaceae
CAG00239	0.183	R	CAG00239	Species	Flavonifractor plautii	Flavonifractor	unclassified Clostridiales
CAG00112	0.184	R	CAG00112	Species	Blautia sp. CAG:52	Blautia	Lachnospiraceae
CAG00697	0.196	R	CAG00697	Genus	unclassified Hungatella	Hungatella	Clostridiaceae
CAG00595	0.201	R	CAG00595	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00629	0.213	R	CAG00629	Species	Firmicutes bacterium CAG:124	unclassified Firmicutes	unclassified Firmicutes
CAG00549	0.219	R	CAG00549	Species	Bifidobacterium longum	Bifidobacterium	Bifidobacteriaceae
CAG00328	0.221	R	CAG00328	Species	Alistipes indistinctus	Alistipes	Rikenellaceae
CAG00760	0.222	R	CAG00760	Species	Ruminococcus sp. CAG:177	Ruminococcus	Ruminococcaceae
CAG00031	0.222	R	CAG00031	NA	unclassified	unclassified	unclassified
CAG00102	0.222	R	CAG00102	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00130	0.222	R	CAG00130	Species	Weissella confusa	Weissella	Leuconostocaceae
CAG00134	0.222	R	CAG00134	Species	Cloacibacillus porcorum	Cloacibacillus	Synergistaceae
CAG00145	0.222	R	CAG00145	Genus	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales
CAG00200	0.222	R	CAG00200	Genus	unclassified Flavonifractor	Flavonifractor	unclassified Clostridiales
CAG00179	0.222	R	CAG00179	Species	Blautia sp. CAG:237	Blautia	Lachnospiraceae
CAG00183	0.222	R	CAG00183	Species	Ruminococcus sp. CAG:60	Ruminococcus	Ruminococcaceae
CAG00198	0.222	R	CAG00198	NA	unclassified	unclassified	unclassified
CAG00214	0.222	R	CAG00214	Species	Prevotella corporis	Prevotella	Prevotellaceae
CAG00261	0.222	R	CAG00261	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae
CAG00241	0.222	R	CAG00241	Species	Anaerotruncus sp. CAG:390	Anaerotruncus	Ruminococcaceae
CAG00363	0.222	R	CAG00363	Genus	unclassified Intestinimonas	Intestinimonas	unclassified Clostridiales

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CAG00373	0.222	R	CAG00373	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae	
CAG00436	0.222	R	CAG00436	Species	Clostridium sp. CAG:299	unclassified Clostridiales	unclassified Clostridiales	
CAG00470	0.222	R	CAG00470	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae	
CAG00541	0.222	R	CAG00541	Species	Dorea sp. CAG:105	Dorea	Lachnospiraceae	
CAG00542	0.222	R	CAG00542	Species	Butyrivibrio crossotus	Butyrivibrio	Lachnospiraceae	
CAG00644	0.222	R	CAG00644	Species	Clostridium sp. CAG:226	unclassified Clostridiales	unclassified Clostridiales	
CAG00658	0.222	R	CAG00658	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00676	0.222	R	CAG00676	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00698	0.222	R	CAG00698	Genus	unclassified Ruminococcus	Ruminococcus	Ruminococcaceae	
CAG00703	0.222	R	CAG00703	Species	Candidatus Methanomassiliicoccus intestinalis	Methanomassiliicoccus	Methanomassiliicoccaceae	
CAG00831	0.222	R	CAG00831	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00841	0.222	R	CAG00841	Species	Firmicutes bacterium CAG:345	unclassified Firmicutes	unclassified Firmicutes	
CAG00850	0.222	R	CAG00850	Genus	unclassified Blautia	Blautia	Lachnospiraceae	
CAG00851	0.222	R	CAG00851	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00048_1	0.222	R	CAG00048_1	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	
CAG00866	0.222	R	CAG00866	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00892	0.222	R	CAG00892	Phylum	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00959	0.222	R	CAG00959	Genus	unclassified Alistipes	Alistipes	Rikenellaceae	
CAG00965	0.222	R	CAG00965	Genus	unclassified Firmicutes	unclassified Firmicutes	unclassified Firmicutes	
CAG00988	0.222	R	CAG00988	Species	Clostridium sp. CAG:349	unclassified Clostridiales	unclassified Clostridiales	
CAG01047	0.222	R	CAG01047	Family	unclassified Clostridiales Family XIII. Incertae Sedis	unclassified Clostridiales Family XIII. Incertae Sedis	Clostridiales Family XIII. Incertae Sedis	
CAG01075	0.222	R	CAG01075	Order	unclassified Clostridiales	unclassified Clostridiales	unclassified Clostridiales	
CAG01099	0.222	R	CAG01099	Species	Raoultella ornithinolytica	Raoultella	Enterobacteriaceae	
CAG01108	0.222	R	CAG01108	Species	Clostridium sp. CAG:798	unclassified Clostridiales	unclassified Clostridiales	
CAG01145	0.222	R	CAG01145	Genus	unclassified Bacteroides	Bacteroides	Bacteroidaceae	
CAG01156	0.222	R	CAG01156	Genus	unclassified Eubacterium	Eubacterium	Eubacteriaceae	
CAG01169	0.222	R	CAG01169	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae	
CAG01240	0.222	R	CAG01240	Species	Parabacteroides gordonii	Parabacteroides	Porphyromonadaceae	
CAG00068_2	0.222	R	CAG00068_2	Genus	unclassified Porphyromonas	Porphyromonas	Porphyromonadaceae	

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CAG01372	0.222	R	CAG01372	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae
CAG01394	0.222	R	CAG01394	Genus	unclassified Blautia	Blautia	Lachnospiraceae
CAG00052	0.225	R	CAG00052	Species	Parabacteroides goldsteinii	Parabacteroides	Porphyromonadaceae
CAG00116	0.225	R	CAG00116	Species	Bacteroides nordii	Bacteroides	Bacteroidaceae
CAG00429	0.225	R	CAG00429	Species	Eubacterium sp. CAG:248	Eubacterium	Eubacteriaceae
CAG00702	0.24	R	CAG00702	Species	Bifidobacterium adolescentis	Bifidobacterium	Bifidobacteriaceae
CAG00309	0.243	R	CAG00309	Species	Alistipes onderdonkii	Alistipes	Rikenellaceae
CAG01637	0.259	R	CAG01637	Species	Firmicutes bacterium CAG:65	unclassified Firmicutes	unclassified Firmicutes
CAG01051	0.265	R	CAG01051	Genus	unclassified Oscillibacter	Oscillibacter	Oscillospiraceae
CAG00792	0.265	R	CAG00792	Species	Firmicutes bacterium CAG:65	unclassified Firmicutes	unclassified Firmicutes
CAG00208	0.266	R	CAG00208	Species	Faecalibacterium 8	Faecalibacterium	Ruminococcaceae
CAG01700	0.279	R	CAG01700	Family	unclassified Ruminococcaceae	unclassified Ruminococcaceae	Ruminococcaceae
CAG01371	0.279	R	CAG01371	Species	Escherichia coli	Escherichia	Enterobacteriaceae
CAG00653	0.29	R	CAG00653	Species	Eubacterium siraeum	Ruminiclostridium	Ruminococcaceae
CAG00320	0.29	R	CAG00320	Species	Firmicutes bacterium CAG:56	unclassified Firmicutes	unclassified Firmicutes
CAG00273	0.311	R	CAG00273	Species	Blautia sp. CAG:37	Blautia	Lachnospiraceae

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[00115] Table 2A – Shows the bacterial genes used for characterizing bacteria co-abundance gene groups (CAG) and the corresponding SEQ ID NO for each gene in the bacteria of interest. Each of the listed CAG group and gene is available on the world wide web at meta.genomics.cn/meta/dataTools, and is incorporated herein by reference.

CAG ID	gene_name	SEQ ID
CAG00327	V1.FI20_GL0119476	SEQ ID NO: 877
CAG00327	V1.UC26-4_GL0088915	SEQ ID NO: 878
CAG00327	V1.FI17_GL0037272	SEQ ID NO: 879
CAG00327	V1.FI17_GL0078727	SEQ ID NO: 880
CAG00327	O2.UC24-2_GL0094271	SEQ ID NO: 881
CAG00327	V1.FI17_GL0207542	SEQ ID NO: 882
CAG00327	MH0348_GL0074623	SEQ ID NO: 883
CAG00327	MH0348_GL0010939	SEQ ID NO: 884
CAG00327	MH0373_GL0012294	SEQ ID NO: 885
CAG00327	MH0448_GL0074435	SEQ ID NO: 886
CAG00327	V1.UC26-4_GL0005764	SEQ ID NO: 887
CAG00327	O2.UC52-0_GL0057691	SEQ ID NO: 888
CAG00327	V1.UC26-4_GL0145819	SEQ ID NO: 889
CAG00327	V1.FI17_GL0032281	SEQ ID NO: 890
CAG00327	V1.UC26-4_GL0185580	SEQ ID NO: 891
CAG00327	V1.FI17_GL0175729	SEQ ID NO: 892
CAG00327	V1.UC26-4_GL0030591	SEQ ID NO: 893
CAG00327	MH0343_GL0081662	SEQ ID NO: 894
CAG00327	MH0348_GL0118307	SEQ ID NO: 895
CAG00327	V1.UC26-4_GL0004865	SEQ ID NO: 896
CAG00327	V1.UC26-4_GL0083941	SEQ ID NO: 897
CAG00327	V1.UC26-4_GL0101656	SEQ ID NO: 898
CAG00327	MH0348_GL0087364	SEQ ID NO: 899
CAG00327	V1.FI17_GL0122971	SEQ ID NO: 900
CAG00327	MH0372_GL0069396	SEQ ID NO: 901
CAG00327	MH0366_GL0119156	SEQ ID NO: 902
CAG00327	MH0372_GL0071516	SEQ ID NO: 903
CAG00327	MH0348_GL0064411	SEQ ID NO: 904
CAG00327	MH0343_GL0166170	SEQ ID NO: 905
CAG00327	V1.UC26-4_GL0076251	SEQ ID NO: 906
CAG00327	MH0343_GL0092435	SEQ ID NO: 907
CAG00327	V1.FI17_GL0016953	SEQ ID NO: 908
CAG00327	V1.UC26-4_GL0143205	SEQ ID NO: 909
CAG00327	MH0372_GL0055320	SEQ ID NO: 910

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CAG00327	V1.UC26-4_GL0055452	SEQ ID NO: 911
CAG00327	MH0348_GL0106302	SEQ ID NO: 912
CAG00327	MH0372_GL0097771	SEQ ID NO: 913
CAG00327	764062976-stool1_revised_scaffold12924_1_gene147101	SEQ ID NO: 914
CAG00327	O2.UC48-1_GL0017424	SEQ ID NO: 915
CAG00327	O2.UC48-1_GL0207849	SEQ ID NO: 916
CAG00327	V1.FI17_GL0115124	SEQ ID NO: 917
CAG00327	MH0203_GL0130549	SEQ ID NO: 918
CAG00327	V1.UC26-4_GL0093892	SEQ ID NO: 919
CAG00327	MH0348_GL0072323	SEQ ID NO: 920
CAG00327	MH0348_GL0058041	SEQ ID NO: 921
CAG00327	764062976-stool1_revised_scaffold30750_1_gene162103	SEQ ID NO: 922
CAG00327	764062976-stool1_revised_scaffold4128_1_gene64730	SEQ ID NO: 923
CAG00327	MH0343_GL0169255	SEQ ID NO: 924
CAG00327	MH0343_GL0093310	SEQ ID NO: 925
CAG00327	V1.UC26-4_GL0016002	SEQ ID NO: 926
CAG00659	O2.UC48-0_GL0168719	SEQ ID NO: 927
CAG00659	V1.UC55-0_GL0148491	SEQ ID NO: 928
CAG00659	V1.UC55-0_GL0157646	SEQ ID NO: 929
CAG00659	O2.UC48-0_GL0022850	SEQ ID NO: 930
CAG00659	V1.UC55-0_GL0065136	SEQ ID NO: 931
CAG00659	V1.UC55-0_GL0003249	SEQ ID NO: 932
CAG00659	O2.UC48-0_GL0232704	SEQ ID NO: 933
CAG00659	V1.UC55-0_GL0081417	SEQ ID NO: 934
CAG00659	V1.UC55-0_GL0120641	SEQ ID NO: 935
CAG00659	V1.UC55-0_GL0068968	SEQ ID NO: 936
CAG00659	V1.UC55-0_GL0134495	SEQ ID NO: 937
CAG00659	O2.UC48-0_GL0312586	SEQ ID NO: 938
CAG00659	V1.UC55-0_GL0136172	SEQ ID NO: 939
CAG00659	V1.UC55-0_GL0132419	SEQ ID NO: 940
CAG00659	V1.UC55-0_GL0141266	SEQ ID NO: 941
CAG00659	V1.UC55-0_GL0038453	SEQ ID NO: 942
CAG00659	O2.UC48-0_GL0001916	SEQ ID NO: 943
CAG00659	V1.UC55-0_GL0168942	SEQ ID NO: 944
CAG00659	V1.UC55-0_GL0011960	SEQ ID NO: 945
CAG00659	O2.UC48-0_GL0003471	SEQ ID NO: 946
CAG00659	V1.UC55-0_GL0028121	SEQ ID NO: 947
CAG00659	O2.UC48-0_GL0286932	SEQ ID NO: 948
CAG00659	V1.UC55-0_GL0085245	SEQ ID NO: 949

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CAG00659	V1.UC55-0_GL0230349	SEQ ID NO: 950
CAG00659	V1.UC55-0_GL0020063	SEQ ID NO: 951
CAG00659	V1.UC55-0_GL0185502	SEQ ID NO: 952
CAG00659	O2.UC48-0_GL0167135	SEQ ID NO: 953
CAG00659	V1.UC55-0_GL0188691	SEQ ID NO: 954
CAG00659	V1.UC55-0_GL0039924	SEQ ID NO: 955
CAG00659	O2.UC48-0_GL0301463	SEQ ID NO: 956
CAG00659	V1.UC55-0_GL0135343	SEQ ID NO: 957
CAG00659	O2.UC48-0_GL0045674	SEQ ID NO: 958
CAG00659	V1.UC55-0_GL0250090	SEQ ID NO: 959
CAG00659	V1.UC55-0_GL0100024	SEQ ID NO: 960
CAG00659	V1.UC55-0_GL0027986	SEQ ID NO: 961
CAG00659	V1.UC55-0_GL0144487	SEQ ID NO: 962
CAG00659	O2.UC48-0_GL0091878	SEQ ID NO: 963
CAG00659	V1.UC55-0_GL0027028	SEQ ID NO: 964
CAG00659	O2.UC48-0_GL0166121	SEQ ID NO: 965
CAG00659	V1.UC55-0_GL0002100	SEQ ID NO: 966
CAG00659	V1.UC55-0_GL0248648	SEQ ID NO: 967
CAG00659	V1.UC55-0_GL0200340	SEQ ID NO: 968
CAG00659	V1.UC55-0_GL0184665	SEQ ID NO: 969
CAG00659	V1.UC55-0_GL0206589	SEQ ID NO: 970
CAG00659	V1.UC55-0_GL0195608	SEQ ID NO: 971
CAG00659	V1.UC55-0_GL0195112	SEQ ID NO: 972
CAG00659	O2.UC48-0_GL0293274	SEQ ID NO: 973
CAG00659	V1.UC55-0_GL0148492	SEQ ID NO: 974
CAG00659	V1.UC55-0_GL0095333	SEQ ID NO: 975
CAG00659	O2.UC48-0_GL0215527	SEQ ID NO: 976
CAG00492	V1.FI17_GL0043088	SEQ ID NO: 977
CAG00492	MH0348_GL0110975	SEQ ID NO: 978
CAG00492	MH0348_GL0058897	SEQ ID NO: 979
CAG00492	MH0348_GL0129512	SEQ ID NO: 980
CAG00492	V1.CD46-0_GL0039934	SEQ ID NO: 981
CAG00492	V1.CD46-0_GL0064253	SEQ ID NO: 982
CAG00492	V1.CD46-0_GL0117608	SEQ ID NO: 983
CAG00492	V1.FI08_GL0017847	SEQ ID NO: 984
CAG00492	MH0373_GL0129260	SEQ ID NO: 985
CAG00492	V1.CD46-0_GL0075229	SEQ ID NO: 986
CAG00492	V1.CD46-0_GL0136740	SEQ ID NO: 987
CAG00492	MH0348_GL0008929	SEQ ID NO: 988
CAG00492	V1.CD46-0_GL0135816	SEQ ID NO: 989
CAG00492	V1.CD46-0_GL0068552	SEQ ID NO: 990

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CAG00492	V1.CD46-0_GL0077963	SEQ ID NO: 991
CAG00492	MH0348_GL0074142	SEQ ID NO: 992
CAG00492	V1.FI08_GL0104771	SEQ ID NO: 993
CAG00492	V1.FI17_GL0153167	SEQ ID NO: 994
CAG00492	MH0348_GL0055971	SEQ ID NO: 995
CAG00492	V1.FI08_GL0146851	SEQ ID NO: 996
CAG00492	V1.FI08_GL0053807	SEQ ID NO: 997
CAG00492	V1.CD46-0_GL0112049	SEQ ID NO: 998
CAG00492	V1.CD46-0_GL0089014	SEQ ID NO: 999
CAG00492	MH0348_GL0053234	SEQ ID NO: 1000
CAG00492	V1.FI08_GL0145379	SEQ ID NO: 1001
CAG00492	V1.FI08_GL0165033	SEQ ID NO: 1002
CAG00492	V1.FI08_GL0008571	SEQ ID NO: 1003
CAG00492	V1.FI08_GL0166887	SEQ ID NO: 1004
CAG00492	V1.FI17_GL0066347	SEQ ID NO: 1005
CAG00492	MH0348_GL0136454	SEQ ID NO: 1006
CAG00492	V1.FI08_GL0087488	SEQ ID NO: 1007
CAG00492	MH0348_GL0023440	SEQ ID NO: 1008
CAG00492	V1.FI08_GL0138599	SEQ ID NO: 1009
CAG00492	V1.FI08_GL0073194	SEQ ID NO: 1010
CAG00492	V1.FI08_GL0127100	SEQ ID NO: 1011
CAG00492	MH0348_GL0136728	SEQ ID NO: 1012
CAG00492	V1.FI08_GL0073404	SEQ ID NO: 1013
CAG00492	MH0348_GL0118964	SEQ ID NO: 1014
CAG00492	V1.FI08_GL0131066	SEQ ID NO: 1015
CAG00492	V1.FI08_GL0136903	SEQ ID NO: 1016
CAG00492	V1.CD46-0_GL0141031	SEQ ID NO: 1017
CAG00492	MH0348_GL0074552	SEQ ID NO: 1018
CAG00492	MH0373_GL0093766	SEQ ID NO: 1019
CAG00492	V1.FI17_GL0041765	SEQ ID NO: 1020
CAG00492	V1.FI08_GL0036958	SEQ ID NO: 1021
CAG00492	V1.FI08_GL0034796	SEQ ID NO: 1022
CAG00492	V1.FI08_GL0141490	SEQ ID NO: 1023
CAG00492	MH0348_GL0038049	SEQ ID NO: 1024
CAG00492	V1.CD46-0_GL0006897	SEQ ID NO: 1025
CAG00492	MH0348_GL0128273	SEQ ID NO: 1026
CAG00518	V1.FI17_GL0223127	SEQ ID NO: 1027
CAG00518	V1.FI17_GL0056536	SEQ ID NO: 1028
CAG00518	V1.FI17_GL0151283	SEQ ID NO: 1029
CAG00518	V1.FI17_GL0105002	SEQ ID NO: 1030
CAG00518	V1.FI17_GL0034777	SEQ ID NO: 1031

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CAG00518	V1.FI17_GL0056308	SEQ ID NO: 1032
CAG00518	V1.FI17_GL0174918	SEQ ID NO: 1033
CAG00518	V1.FI17_GL0222796	SEQ ID NO: 1034
CAG00518	V1.FI17_GL0067073	SEQ ID NO: 1035
CAG00518	V1.FI17_GL0178176	SEQ ID NO: 1036
CAG00518	V1.FI17_GL0179703	SEQ ID NO: 1037
CAG00518	V1.FI17_GL0189443	SEQ ID NO: 1038
CAG00518	V1.FI17_GL0084116	SEQ ID NO: 1039
CAG00518	V1.FI17_GL0170320	SEQ ID NO: 1040
CAG00518	V1.FI17_GL0172798	SEQ ID NO: 1041
CAG00518	V1.FI17_GL0080116	SEQ ID NO: 1042
CAG00518	V1.FI17_GL0064860	SEQ ID NO: 1043
CAG00518	V1.FI17_GL0005908	SEQ ID NO: 1044
CAG00518	V1.FI17_GL0081029	SEQ ID NO: 1045
CAG00518	V1.FI17_GL0123216	SEQ ID NO: 1046
CAG00518	V1.FI17_GL0049498	SEQ ID NO: 1047
CAG00518	V1.FI17_GL0096107	SEQ ID NO: 1048
CAG00518	V1.FI17_GL0145670	SEQ ID NO: 1049
CAG00518	V1.FI17_GL0095433	SEQ ID NO: 1050
CAG00518	V1.FI17_GL0098541	SEQ ID NO: 1051
CAG00518	V1.FI17_GL0213327	SEQ ID NO: 1052
CAG00518	V1.FI17_GL0026647	SEQ ID NO: 1053
CAG00518	V1.FI17_GL0130881	SEQ ID NO: 1054
CAG00518	V1.FI17_GL0119514	SEQ ID NO: 1055
CAG00518	V1.FI17_GL0152624	SEQ ID NO: 1056
CAG00518	V1.FI17_GL0230043	SEQ ID NO: 1057
CAG00518	V1.FI17_GL0084105	SEQ ID NO: 1058
CAG00518	V1.FI17_GL0054899	SEQ ID NO: 1059
CAG00518	V1.FI17_GL0090574	SEQ ID NO: 1060
CAG00518	V1.FI17_GL0214395	SEQ ID NO: 1061
CAG00518	V1.FI17_GL0220845	SEQ ID NO: 1062
CAG00518	V1.FI17_GL0050024	SEQ ID NO: 1063
CAG00518	V1.FI17_GL0207008	SEQ ID NO: 1064
CAG00518	V1.FI17_GL0147404	SEQ ID NO: 1065
CAG00518	V1.FI17_GL0175176	SEQ ID NO: 1066
CAG00518	V1.FI17_GL0023173	SEQ ID NO: 1067
CAG00518	V1.FI17_GL0177478	SEQ ID NO: 1068
CAG00518	V1.FI17_GL0061078	SEQ ID NO: 1069
CAG00518	V1.FI17_GL0039499	SEQ ID NO: 1070
CAG00518	V1.FI17_GL0091846	SEQ ID NO: 1071
CAG00518	V1.FI17_GL0224471	SEQ ID NO: 1072

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CAG00518	V1.FI17_GL0118783	SEQ ID NO: 1073
CAG00518	V1.FI17_GL0056307	SEQ ID NO: 1074
CAG00518	V1.FI17_GL0088351	SEQ ID NO: 1075
CAG00518	V1.FI17_GL0073252	SEQ ID NO: 1076
CAG01146	V1.FI28_GL0195377	SEQ ID NO: 1077
CAG01146	O2.UC49-0_GL0025609	SEQ ID NO: 1078
CAG01146	V1.UC38-4_GL0044141	SEQ ID NO: 1079
CAG01146	V1.UC38-4_GL0021935	SEQ ID NO: 1080
CAG01146	O2.UC35-1_GL0026285	SEQ ID NO: 1081
CAG01146	V1.FI06_GL0004599	SEQ ID NO: 1082
CAG01146	V1.UC38-4_GL0034407	SEQ ID NO: 1083
CAG01146	V1.UC38-4_GL0057326	SEQ ID NO: 1084
CAG01146	O2.UC36-1_GL0134634	SEQ ID NO: 1085
CAG01146	V1.UC38-4_GL0088839	SEQ ID NO: 1086
CAG01146	V1.FI34_GL0143132	SEQ ID NO: 1087
CAG01146	V1.UC38-0_GL0106709	SEQ ID NO: 1088
CAG01146	V1.UC38-4_GL0027899	SEQ ID NO: 1089
CAG01146	V1.FI06_GL0061656	SEQ ID NO: 1090
CAG01146	O2.UC35-1_GL0054016	SEQ ID NO: 1091
CAG01146	V1.UC38-0_GL0104749	SEQ ID NO: 1092
CAG01146	V1.UC38-4_GL0045647	SEQ ID NO: 1093
CAG01146	V1.UC38-4_GL0072341	SEQ ID NO: 1094
CAG01146	V1.UC38-0_GL0057730	SEQ ID NO: 1095
CAG01146	V1.FI28_GL0124663	SEQ ID NO: 1096
CAG01146	V1.UC38-0_GL0040549	SEQ ID NO: 1097
CAG01146	V1.FI06_GL0139057	SEQ ID NO: 1098
CAG01146	O2.UC35-1_GL0063806	SEQ ID NO: 1099
CAG01146	V1.UC38-0_GL0149389	SEQ ID NO: 1100
CAG01146	V1.UC38-4_GL0071470	SEQ ID NO: 1101
CAG01146	V1.FI06_GL0051314	SEQ ID NO: 1102
CAG01146	O2.UC35-1_GL0076721	SEQ ID NO: 1103
CAG01146	V1.UC38-4_GL0050715	SEQ ID NO: 1104
CAG01146	V1.FI28_GL0211259	SEQ ID NO: 1105
CAG01146	V1.UC11-0_GL0036916	SEQ ID NO: 1106
CAG01146	V1.UC38-0_GL0052356	SEQ ID NO: 1107
CAG01146	V1.UC38-4_GL0065035	SEQ ID NO: 1108
CAG01146	O2.UC49-0_GL0018610	SEQ ID NO: 1109
CAG01146	V1.UC38-4_GL0056319	SEQ ID NO: 1110
CAG01146	O2.UC49-0_GL0158507	SEQ ID NO: 1111
CAG01146	V1.UC38-0_GL0073167	SEQ ID NO: 1112
CAG01146	O2.UC35-1_GL0026564	SEQ ID NO: 1113

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CAG01146	V1.UC38-4_GL0006756	SEQ ID NO: 1114
CAG01146	V1.FI28_GL0051866	SEQ ID NO: 1115
CAG01146	V1.UC38-0_GL0081759	SEQ ID NO: 1116
CAG01146	V1.UC11-0_GL0026546	SEQ ID NO: 1117
CAG01146	V1.UC38-4_GL0091721	SEQ ID NO: 1118
CAG01146	V1.FI28_GL0206130	SEQ ID NO: 1119
CAG01146	V1.UC38-0_GL0013101	SEQ ID NO: 1120
CAG01146	V1.UC38-4_GL0061996	SEQ ID NO: 1121
CAG01146	V1.UC38-4_GL0142563	SEQ ID NO: 1122
CAG01146	V1.UC38-4_GL0156200	SEQ ID NO: 1123
CAG01146	V1.FI06_GL0070368	SEQ ID NO: 1124
CAG01146	V1.UC38-4_GL0162695	SEQ ID NO: 1125
CAG01146	O2.UC11-1_GL0117762	SEQ ID NO: 1126
CAG00079	N017A_GL0059153	SEQ ID NO: 1127
CAG00079	SZEY-104A_GL0060090	SEQ ID NO: 1128
CAG00079	MH0020_GL0000529	SEQ ID NO: 1129
CAG00079	MH0301_GL0097161	SEQ ID NO: 1130
CAG00079	MH0006_GL0148832	SEQ ID NO: 1131
CAG00079	MH0006_GL0157059	SEQ ID NO: 1132
CAG00079	MH0087_GL0033669	SEQ ID NO: 1133
CAG00079	MH0087_GL0001927	SEQ ID NO: 1134
CAG00079	MH0006_GL0200708	SEQ ID NO: 1135
CAG00079	MH0006_GL0085266	SEQ ID NO: 1136
CAG00079	V1.CD11-0_GL0023861	SEQ ID NO: 1137
CAG00079	MH0087_GL0026189	SEQ ID NO: 1138
CAG00079	MH0020_GL0009728	SEQ ID NO: 1139
CAG00079	MH0305_GL0021042	SEQ ID NO: 1140
CAG00079	MH0087_GL0014945	SEQ ID NO: 1141
CAG00079	MH0087_GL0048780	SEQ ID NO: 1142
CAG00079	MH0087_GL0025847	SEQ ID NO: 1143
CAG00079	MH0109_GL0086398	SEQ ID NO: 1144
CAG00079	SZEY-64A_GL0001256	SEQ ID NO: 1145
CAG00079	MH0006_GL0111726	SEQ ID NO: 1146
CAG00079	MH0420_GL0006194	SEQ ID NO: 1147
CAG00079	MH0074_GL0014285	SEQ ID NO: 1148
CAG00079	MH0006_GL0100867	SEQ ID NO: 1149
CAG00079	SZEY-78A_GL0051586	SEQ ID NO: 1150
CAG00079	MH0087_GL0041527	SEQ ID NO: 1151
CAG00079	MH0274_GL0125787	SEQ ID NO: 1152
CAG00079	MH0087_GL0010722	SEQ ID NO: 1153
CAG00079	MH0006_GL0161952	SEQ ID NO: 1154

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CAG00079	MH0087_GL0047637	SEQ ID NO: 1155
CAG00079	MH0166_GL0060041	SEQ ID NO: 1156
CAG00079	MH0301_GL0099557	SEQ ID NO: 1157
CAG00079	MH0109_GL0002384	SEQ ID NO: 1158
CAG00079	MH0166_GL0024801	SEQ ID NO: 1159
CAG00079	T2D-2A_GL0025065	SEQ ID NO: 1160
CAG00079	MH0087_GL0018284	SEQ ID NO: 1161
CAG00079	MH0020_GL0029215	SEQ ID NO: 1162
CAG00079	MH0006_GL0081754	SEQ ID NO: 1163
CAG00079	MH0087_GL0001908	SEQ ID NO: 1164
CAG00079	MH0088_GL0109554	SEQ ID NO: 1165
CAG00079	MH0006_GL0140990	SEQ ID NO: 1166
CAG00079	MH0119_GL0032882	SEQ ID NO: 1167
CAG00079	MH0020_GL0051592	SEQ ID NO: 1168
CAG00079	MH0222_GL0069273	SEQ ID NO: 1169
CAG00079	MH0109_GL0040568	SEQ ID NO: 1170
CAG00079	MH0006_GL0159123	SEQ ID NO: 1171
CAG00079	MH0006_GL0117755	SEQ ID NO: 1172
CAG00079	T2D-10A_GL0041736	SEQ ID NO: 1173
CAG00079	MH0020_GL0022084	SEQ ID NO: 1174
CAG00079	MH0006_GL0169081	SEQ ID NO: 1175
CAG00079	MH0020_GL0045499	SEQ ID NO: 1176
CAG00393	MH0455_GL0014920	SEQ ID NO: 1177
CAG00393	MH0010_GL0006771	SEQ ID NO: 1178
CAG00393	MH0010_GL0019638	SEQ ID NO: 1179
CAG00393	764285508-stool1_revised_scaffold26788_1_gene82388	SEQ ID NO: 1180
CAG00393	MH0010_GL0008861	SEQ ID NO: 1181
CAG00393	MH0010_GL0038429	SEQ ID NO: 1182
CAG00393	MH0010_GL0039855	SEQ ID NO: 1183
CAG00393	MH0451_GL0172720	SEQ ID NO: 1184
CAG00393	O2.UC58-2_GL0156633	SEQ ID NO: 1185
CAG00393	MH0010_GL0035092	SEQ ID NO: 1186
CAG00393	MH0412_GL0061734	SEQ ID NO: 1187
CAG00393	MH0021_GL0029491	SEQ ID NO: 1188
CAG00393	MH0010_GL0027185	SEQ ID NO: 1189
CAG00393	MH0076_GL0069584	SEQ ID NO: 1190
CAG00393	MH0076_GL0023849	SEQ ID NO: 1191
CAG00393	MH0010_GL0004096	SEQ ID NO: 1192
CAG00393	MH0010_GL0043784	SEQ ID NO: 1193
CAG00393	MH0010_GL0039245	SEQ ID NO: 1194

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CAG00393	O2.UC40-1_GL0172758	SEQ ID NO: 1195
CAG00393	MH0010_GL0000174	SEQ ID NO: 1196
CAG00393	MH0010_GL0044855	SEQ ID NO: 1197
CAG00393	MH0010_GL0016776	SEQ ID NO: 1198
CAG00393	MH0010_GL0017732	SEQ ID NO: 1199
CAG00393	T2D-54A_GL0005082	SEQ ID NO: 1200
CAG00393	MH0010_GL0007485	SEQ ID NO: 1201
CAG00393	DLM008_GL0038553	SEQ ID NO: 1202
CAG00393	MH0345_GL0003914	SEQ ID NO: 1203
CAG00393	MH0010_GL0018041	SEQ ID NO: 1204
CAG00393	MH0010_GL0029248	SEQ ID NO: 1205
CAG00393	MH0316_GL0156730	SEQ ID NO: 1206
CAG00393	O2.UC14-2_GL0059182	SEQ ID NO: 1207
CAG00393	NLF013_GL0025166	SEQ ID NO: 1208
CAG00393	T2D-149A_GL0031274	SEQ ID NO: 1209
CAG00393	MH0148_GL0152134	SEQ ID NO: 1210
CAG00393	MH0224_GL0195949	SEQ ID NO: 1211
CAG00393	MH0454_GL0222405	SEQ ID NO: 1212
CAG00393	MH0094_GL0112338	SEQ ID NO: 1213
CAG00393	MH0010_GL0011210	SEQ ID NO: 1214
CAG00393	MH0010_GL0028548	SEQ ID NO: 1215
CAG00393	MH0010_GL0015291	SEQ ID NO: 1216
CAG00393	MH0345_GL0126419	SEQ ID NO: 1217
CAG00393	O2.UC14-2_GL0085563	SEQ ID NO: 1218
CAG00393	NOF008_GL0002843	SEQ ID NO: 1219
CAG00393	MH0234_GL0001308	SEQ ID NO: 1220
CAG00393	MH0010_GL0029233	SEQ ID NO: 1221
CAG00393	MH0115_GL0015508	SEQ ID NO: 1222
CAG00393	MH0010_GL0035190	SEQ ID NO: 1223
CAG00393	MH0010_GL0017083	SEQ ID NO: 1224
CAG00393	MH0276_GL0232709	SEQ ID NO: 1225
CAG00393	MH0021_GL0021690	SEQ ID NO: 1226
CAG00766	763901136-stool1_revised_scaffold25610_1_gene21731	SEQ ID NO: 1227
CAG00766	MH0012_GL0082825	SEQ ID NO: 1228
CAG00766	MH0012_GL0213577	SEQ ID NO: 1229
CAG00766	MH0224_GL0006730	SEQ ID NO: 1230
CAG00766	MH0012_GL0215773	SEQ ID NO: 1231
CAG00766	MH0142_GL0028426	SEQ ID NO: 1232
CAG00766	MH0118_GL0100408	SEQ ID NO: 1233
CAG00766	MH0185_GL0091951	SEQ ID NO: 1234

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CAG00766	MH0012_GL0000190	SEQ ID NO: 1235
CAG00766	MH0438_GL0006701	SEQ ID NO: 1236
CAG00766	MH0280_GL0150979	SEQ ID NO: 1237
CAG00766	MH0012_GL0069123	SEQ ID NO: 1238
CAG00766	MH0053_GL0026412	SEQ ID NO: 1239
CAG00766	MH0012_GL0226816	SEQ ID NO: 1240
CAG00766	765701615-stool1_revised_scaffold24399_1_gene45416	SEQ ID NO: 1241
CAG00766	MH0117_GL0073357	SEQ ID NO: 1242
CAG00766	MH0142_GL0001380	SEQ ID NO: 1243
CAG00766	MH0378_GL0128532	SEQ ID NO: 1244
CAG00766	MH0329_GL0162954	SEQ ID NO: 1245
CAG00766	MH0004_GL0025979	SEQ ID NO: 1246
CAG00766	MH0012_GL0129416	SEQ ID NO: 1247
CAG00766	MH0012_GL0070480	SEQ ID NO: 1248
CAG00766	MH0446_GL0199336	SEQ ID NO: 1249
CAG00766	O2.UC47-1_GL0073293	SEQ ID NO: 1250
CAG00766	O2.UC57-0_GL0047837	SEQ ID NO: 1251
CAG00766	MH0142_GL0077412	SEQ ID NO: 1252
CAG00766	MH0204_GL0111428	SEQ ID NO: 1253
CAG00766	MH0104_GL0101995	SEQ ID NO: 1254
CAG00766	MH0220_GL0102755	SEQ ID NO: 1255
CAG00766	MH0144_GL0113742	SEQ ID NO: 1256
CAG00766	MH0454_GL0245294	SEQ ID NO: 1257
CAG00766	V1.FI14_GL0156093	SEQ ID NO: 1258
CAG00766	V1.FI07_GL0136264	SEQ ID NO: 1259
CAG00766	MH0006_GL0193781	SEQ ID NO: 1260
CAG00766	MH0012_GL0200508	SEQ ID NO: 1261
CAG00766	MH0012_GL0166994	SEQ ID NO: 1262
CAG00766	MH0012_GL0228079	SEQ ID NO: 1263
CAG00766	MH0383_GL0051378	SEQ ID NO: 1264
CAG00766	MH0193_GL0073874	SEQ ID NO: 1265
CAG00766	MH0012_GL0082824	SEQ ID NO: 1266
CAG00766	MH0193_GL0027357	SEQ ID NO: 1267
CAG00766	O2.UC13-2_GL0031768	SEQ ID NO: 1268
CAG00766	O2.UC40-1_GL0192463	SEQ ID NO: 1269
CAG00766	MH0394_GL0042591	SEQ ID NO: 1270
CAG00766	MH0012_GL0031924	SEQ ID NO: 1271
CAG00766	MH0229_GL0107290	SEQ ID NO: 1272
CAG00766	O2.UC47-1_GL0095795	SEQ ID NO: 1273
CAG00766	MH0220_GL0074700	SEQ ID NO: 1274

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CAG00766	MH0117_GL0107140	SEQ ID NO: 1275
CAG00766	MH0272_GL0100309	SEQ ID NO: 1276
CAG00095	MH0089_GL0046375	SEQ ID NO: 1277
CAG00095	O2.UC28-0_GL0179744	SEQ ID NO: 1278
CAG00095	MH0066_GL0040803	SEQ ID NO: 1279
CAG00095	MH0089_GL0043771	SEQ ID NO: 1280
CAG00095	MH0182_GL0033199	SEQ ID NO: 1281
CAG00095	MH0066_GL0054638	SEQ ID NO: 1282
CAG00095	MH0089_GL0066960	SEQ ID NO: 1283
CAG00095	MH0262_GL0027791	SEQ ID NO: 1284
CAG00095	N034A_GL0043072	SEQ ID NO: 1285
CAG00095	N037A_GL0059379	SEQ ID NO: 1286
CAG00095	MH0089_GL0002779	SEQ ID NO: 1287
CAG00095	763840445-stool2_revised_scaffold52492_2_gene169926	SEQ ID NO: 1288
CAG00095	MH0089_GL0064602	SEQ ID NO: 1289
CAG00095	MH0089_GL0047899	SEQ ID NO: 1290
CAG00095	MH0089_GL0107661	SEQ ID NO: 1291
CAG00095	O2.UC50-0_GL0090229	SEQ ID NO: 1292
CAG00095	MH0089_GL0032534	SEQ ID NO: 1293
CAG00095	MH0089_GL0108397	SEQ ID NO: 1294
CAG00095	MH0066_GL0054655	SEQ ID NO: 1295
CAG00095	MH0089_GL0074632	SEQ ID NO: 1296
CAG00095	159247771-stool1_revised_C643738_1_gene47371	SEQ ID NO: 1297
CAG00095	MH0343_GL0066333	SEQ ID NO: 1298
CAG00095	MH0089_GL0067108	SEQ ID NO: 1299
CAG00095	764588959-stool1_revised_C754420_1_gene104384	SEQ ID NO: 1300
CAG00095	MH0089_GL0056811	SEQ ID NO: 1301
CAG00095	MH0089_GL0099404	SEQ ID NO: 1302
CAG00095	V1.CD2-0-PT_GL0013676	SEQ ID NO: 1303
CAG00095	MH0262_GL0119556	SEQ ID NO: 1304
CAG00095	MH0089_GL0013544	SEQ ID NO: 1305
CAG00095	764184357-stool1_revised_scaffold1841_11_gene14991	SEQ ID NO: 1306
CAG00095	MH0182_GL0006395	SEQ ID NO: 1307
CAG00095	MH0182_GL0048904	SEQ ID NO: 1308
CAG00095	158944319-stool1_revised_scaffold26376_1_gene108987	SEQ ID NO: 1309
CAG00095	MH0395_GL0116427	SEQ ID NO: 1310
CAG00095	MH0262_GL0046339	SEQ ID NO: 1311

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CAG00095	MH0182_GL0017395	SEQ ID NO: 1312
CAG00095	MH0182_GL0056494	SEQ ID NO: 1313
CAG00095	MH0262_GL0136800	SEQ ID NO: 1314
CAG00095	MH0089_GL0013064	SEQ ID NO: 1315
CAG00095	MH0437_GL0086387	SEQ ID NO: 1316
CAG00095	V1.CD2-0-PT_GL0041810	SEQ ID NO: 1317
CAG00095	MH0089_GL0055816	SEQ ID NO: 1318
CAG00095	V1.FI16_GL0098417	SEQ ID NO: 1319
CAG00095	MH0089_GL0074324	SEQ ID NO: 1320
CAG00095	MH0182_GL0040920	SEQ ID NO: 1321
CAG00095	DLF004_GL0024691	SEQ ID NO: 1322
CAG00095	N038A_GL0029176	SEQ ID NO: 1323
CAG00095	MH0089_GL0034070	SEQ ID NO: 1324
CAG00095	V1.CD2-0-PT_GL0091669	SEQ ID NO: 1325
CAG00095	MH0437_GL0249840	SEQ ID NO: 1326
CAG00010_1	MH0217_GL0019688	SEQ ID NO: 1327
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CAG00010_1	MH0217_GL0131423	SEQ ID NO: 1329
CAG00010_1	MH0217_GL0149562	SEQ ID NO: 1330
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CAG00010_1	MH0217_GL0126187	SEQ ID NO: 1338
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CAG00010_1	MH0217_GL0061698	SEQ ID NO: 1341
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CAG00010_1	MH0217_GL0013322	SEQ ID NO: 1346
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CAG00010_1	MH0217_GL0126419	SEQ ID NO: 1348
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CAG00010_1	MH0217_GL0061898	SEQ ID NO: 1350
CAG00010_1	MH0217_GL0049289	SEQ ID NO: 1351
CAG00010_1	MH0217_GL0002063	SEQ ID NO: 1352

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CAG00010_1	MH0217_GL0018343	SEQ ID NO: 1353
CAG00010_1	MH0217_GL0038438	SEQ ID NO: 1354
CAG00010_1	MH0217_GL0004399	SEQ ID NO: 1355
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CAG00010_1	MH0217_GL0176617	SEQ ID NO: 1357
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CAG00010_1	MH0217_GL0052144	SEQ ID NO: 1360
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CAG00010_1	MH0217_GL0025977	SEQ ID NO: 1362
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CAG00010_1	MH0217_GL0062706	SEQ ID NO: 1366
CAG00010_1	MH0217_GL0160566	SEQ ID NO: 1367
CAG00010_1	MH0217_GL0059626	SEQ ID NO: 1368
CAG00010_1	MH0217_GL0127172	SEQ ID NO: 1369
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CAG00010_1	MH0217_GL0163595	SEQ ID NO: 1373
CAG00010_1	MH0217_GL0035863	SEQ ID NO: 1374
CAG00010_1	MH0217_GL0183396	SEQ ID NO: 1375
CAG00010_1	MH0217_GL0127175	SEQ ID NO: 1376
CAG00342	MH0230_GL0150634	SEQ ID NO: 1377
CAG00342	547043.BIFPSEUDO_02724	SEQ ID NO: 1378
CAG00342	MH0356_GL0195431	SEQ ID NO: 1379
CAG00342	MH0356_GL0045072	SEQ ID NO: 1380
CAG00342	V1.CD7-4_GL0062303	SEQ ID NO: 1381
CAG00342	MH0206_GL0250797	SEQ ID NO: 1382
CAG00342	MH0327_GL0032691	SEQ ID NO: 1383
CAG00342	O2.UC26-0_GL0000164	SEQ ID NO: 1384
CAG00342	MH0230_GL0066319	SEQ ID NO: 1385
CAG00342	547043.BIFPSEUDO_03586	SEQ ID NO: 1386
CAG00342	O2.UC50-2_GL0080535	SEQ ID NO: 1387
CAG00342	T2D-51A_GL0104197	SEQ ID NO: 1388
CAG00342	MH0440_GL0182133	SEQ ID NO: 1389
CAG00342	MH0230_GL0057594	SEQ ID NO: 1390
CAG00342	MH0356_GL0185430	SEQ ID NO: 1391
CAG00342	MH0206_GL0011184	SEQ ID NO: 1392
CAG00342	ED19A_GL0013066	SEQ ID NO: 1393

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CAG00342	ED50A_GL0042638	SEQ ID NO: 1394
CAG00342	V1.UC42-0_GL0042202	SEQ ID NO: 1395
CAG00342	T2D-26A_GL0091258	SEQ ID NO: 1396
CAG00342	V1.FI01_GL0085884	SEQ ID NO: 1397
CAG00342	547043.BIFPSEUDO_04297	SEQ ID NO: 1398
CAG00342	MH0410_GL0081324	SEQ ID NO: 1399
CAG00342	MH0356_GL0171913	SEQ ID NO: 1400
CAG00342	BGI-06A_GL0016424	SEQ ID NO: 1401
CAG00342	V1.UC37-0_GL0033386	SEQ ID NO: 1402
CAG00342	V1.FI19_GL0029304	SEQ ID NO: 1403
CAG00342	MH0410_GL0116975	SEQ ID NO: 1404
CAG00342	MH0230_GL0150631	SEQ ID NO: 1405
CAG00342	MH0440_GL0194775	SEQ ID NO: 1406
CAG00342	V1.CD51-0_GL0182145	SEQ ID NO: 1407
CAG00342	O2.UC19-1_GL0006286	SEQ ID NO: 1408
CAG00342	547043.BIFPSEUDO_02929	SEQ ID NO: 1409
CAG00342	MH0356_GL0168645	SEQ ID NO: 1410
CAG00342	V1.UC42-0_GL0019213	SEQ ID NO: 1411
CAG00342	T2D-42A_GL0082631	SEQ ID NO: 1412
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CAG00342	V1.CD2-0-PT_GL0009310	SEQ ID NO: 1416
CAG00342	MH0230_GL0041022	SEQ ID NO: 1417
CAG00342	MH0230_GL0041821	SEQ ID NO: 1418
CAG00342	MH0327_GL0110337	SEQ ID NO: 1419
CAG00342	MH0230_GL0144175	SEQ ID NO: 1420
CAG00342	MH0230_GL0087113	SEQ ID NO: 1421
CAG00342	MH0356_GL0133287	SEQ ID NO: 1422
CAG00342	MH0327_GL0115075	SEQ ID NO: 1423
CAG00342	MH0230_GL0122733	SEQ ID NO: 1424
CAG00342	MH0356_GL0133291	SEQ ID NO: 1425
CAG00342	547043.BIFPSEUDO_04379	SEQ ID NO: 1426
CAG00303	MH0345_GL0025069	SEQ ID NO: 1427
CAG00303	MH0277_GL0043561	SEQ ID NO: 1428
CAG00303	MH0277_GL0017994	SEQ ID NO: 1429
CAG00303	MH0277_GL0035656	SEQ ID NO: 1430
CAG00303	MH0345_GL0168665	SEQ ID NO: 1431
CAG00303	MH0277_GL0005474	SEQ ID NO: 1432
CAG00303	MH0277_GL0014131	SEQ ID NO: 1433
CAG00303	MH0345_GL0161902	SEQ ID NO: 1434

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CAG00303	MH0277_GL0045721	SEQ ID NO: 1435
CAG00303	V1.UC32-0_GL0068347	SEQ ID NO: 1436
CAG00303	MH0277_GL0015253	SEQ ID NO: 1437
CAG00303	MH0277_GL0027237	SEQ ID NO: 1438
CAG00303	MH0277_GL0030721	SEQ ID NO: 1439
CAG00303	MH0277_GL0037357	SEQ ID NO: 1440
CAG00303	MH0277_GL0033151	SEQ ID NO: 1441
CAG00303	MH0277_GL0047657	SEQ ID NO: 1442
CAG00303	MH0277_GL0042255	SEQ ID NO: 1443
CAG00303	MH0277_GL0001264	SEQ ID NO: 1444
CAG00303	MH0345_GL0051193	SEQ ID NO: 1445
CAG00303	MH0277_GL0027760	SEQ ID NO: 1446
CAG00303	MH0277_GL0037876	SEQ ID NO: 1447
CAG00303	MH0277_GL0043562	SEQ ID NO: 1448
CAG00303	MH0277_GL0022738	SEQ ID NO: 1449
CAG00303	MH0277_GL0025210	SEQ ID NO: 1450
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CAG00303	V1.UC22-1_GL0009470	SEQ ID NO: 1452
CAG00303	MH0277_GL0033800	SEQ ID NO: 1453
CAG00303	MH0277_GL0021102	SEQ ID NO: 1454
CAG00303	MH0277_GL0013995	SEQ ID NO: 1455
CAG00303	MH0277_GL0044358	SEQ ID NO: 1456
CAG00303	MH0277_GL0010535	SEQ ID NO: 1457
CAG00303	MH0277_GL0000564	SEQ ID NO: 1458
CAG00303	MH0277_GL0054679	SEQ ID NO: 1459
CAG00303	MH0345_GL0148022	SEQ ID NO: 1460
CAG00303	MH0277_GL0009451	SEQ ID NO: 1461
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CAG00303	MH0277_GL0014642	SEQ ID NO: 1464
CAG00303	MH0277_GL0052775	SEQ ID NO: 1465
CAG00303	V1.CD19-0_GL0089683	SEQ ID NO: 1466
CAG00303	MH0277_GL0002630	SEQ ID NO: 1467
CAG00303	V1.UC32-0_GL0160339	SEQ ID NO: 1468
CAG00303	MH0277_GL0037875	SEQ ID NO: 1469
CAG00303	MH0277_GL0026333	SEQ ID NO: 1470
CAG00303	MH0277_GL0033234	SEQ ID NO: 1471
CAG00303	MH0277_GL0002101	SEQ ID NO: 1472
CAG00303	MH0277_GL0055650	SEQ ID NO: 1473
CAG00303	MH0345_GL0085012	SEQ ID NO: 1474
CAG00303	MH0345_GL0140542	SEQ ID NO: 1475

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CAG00303	MH0277_GL0026993	SEQ ID NO: 1476
CAG00337	MH0212_GL0140047	SEQ ID NO: 1477
CAG00337	MH0212_GL0034625	SEQ ID NO: 1478
CAG00337	MH0088_GL0006484	SEQ ID NO: 1479
CAG00337	V1.FI13_GL0016516	SEQ ID NO: 1480
CAG00337	MH0212_GL0131896	SEQ ID NO: 1481
CAG00337	MH0088_GL0029891	SEQ ID NO: 1482
CAG00337	MH0212_GL0104669	SEQ ID NO: 1483
CAG00337	MH0212_GL0007141	SEQ ID NO: 1484
CAG00337	MH0088_GL0118880	SEQ ID NO: 1485
CAG00337	MH0212_GL0034404	SEQ ID NO: 1486
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CAG00337	MH0212_GL0094592	SEQ ID NO: 1496
CAG00337	MH0212_GL0150396	SEQ ID NO: 1497
CAG00337	MH0212_GL0007716	SEQ ID NO: 1498
CAG00337	MH0358_GL0041328	SEQ ID NO: 1499
CAG00337	V1.FI13_GL0069720	SEQ ID NO: 1500
CAG00337	MH0212_GL0119553	SEQ ID NO: 1501
CAG00337	MH0358_GL0051225	SEQ ID NO: 1502
CAG00337	MH0212_GL0161055	SEQ ID NO: 1503
CAG00337	MH0212_GL0034621	SEQ ID NO: 1504
CAG00337	MH0212_GL0124894	SEQ ID NO: 1505
CAG00337	MH0212_GL0140315	SEQ ID NO: 1506
CAG00337	MH0212_GL0120377	SEQ ID NO: 1507
CAG00337	V1.FI13_GL0107233	SEQ ID NO: 1508
CAG00337	MH0212_GL0024275	SEQ ID NO: 1509
CAG00337	V1.FI11_GL0100921	SEQ ID NO: 1510
CAG00337	MH0212_GL0049197	SEQ ID NO: 1511
CAG00337	MH0088_GL0131171	SEQ ID NO: 1512
CAG00337	V1.FI11_GL0025056	SEQ ID NO: 1513
CAG00337	MH0212_GL0039936	SEQ ID NO: 1514
CAG00337	MH0212_GL0016237	SEQ ID NO: 1515
CAG00337	MH0088_GL0111816	SEQ ID NO: 1516

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CAG00337	MH0212_GL0090580	SEQ ID NO: 1517
CAG00337	MH0212_GL0133270	SEQ ID NO: 1518
CAG00337	MH0212_GL0084814	SEQ ID NO: 1519
CAG00337	MH0088_GL0080625	SEQ ID NO: 1520
CAG00337	MH0212_GL0126560	SEQ ID NO: 1521
CAG00337	MH0088_GL0010923	SEQ ID NO: 1522
CAG00337	MH0358_GL0044332	SEQ ID NO: 1523
CAG00337	MH0212_GL0030833	SEQ ID NO: 1524
CAG00337	MH0088_GL0100711	SEQ ID NO: 1525
CAG00337	MH0212_GL0036263	SEQ ID NO: 1526
CAG00381	MH0233_GL0095998	SEQ ID NO: 1527
CAG00381	MH0233_GL0113533	SEQ ID NO: 1528
CAG00381	MH0233_GL0113359	SEQ ID NO: 1529
CAG00381	MH0233_GL0065305	SEQ ID NO: 1530
CAG00381	MH0233_GL0117231	SEQ ID NO: 1531
CAG00381	MH0233_GL0113826	SEQ ID NO: 1532
CAG00381	MH0233_GL0065304	SEQ ID NO: 1533
CAG00381	MH0233_GL0003883	SEQ ID NO: 1534
CAG00381	MH0233_GL0028807	SEQ ID NO: 1535
CAG00381	MH0233_GL0028855	SEQ ID NO: 1536
CAG00381	MH0233_GL0091862	SEQ ID NO: 1537
CAG00381	MH0233_GL0113327	SEQ ID NO: 1538
CAG00381	MH0233_GL0119203	SEQ ID NO: 1539
CAG00381	O2.UC48-0_GL0255960	SEQ ID NO: 1540
CAG00381	MH0233_GL0030526	SEQ ID NO: 1541
CAG00381	O2.UC19-2_GL0100874	SEQ ID NO: 1542
CAG00381	MH0233_GL0063420	SEQ ID NO: 1543
CAG00381	O2.UC19-2_GL0003982	SEQ ID NO: 1544
CAG00381	MH0233_GL0095983	SEQ ID NO: 1545
CAG00381	MH0233_GL0056899	SEQ ID NO: 1546
CAG00381	O2.UC36-0_GL0021124	SEQ ID NO: 1547
CAG00381	MH0233_GL0011731	SEQ ID NO: 1548
CAG00381	MH0233_GL0082238	SEQ ID NO: 1549
CAG00381	MH0233_GL0113355	SEQ ID NO: 1550
CAG00381	MH0358_GL0105021	SEQ ID NO: 1551
CAG00381	MH0233_GL0007569	SEQ ID NO: 1552
CAG00381	O2.UC36-0_GL0058223	SEQ ID NO: 1553
CAG00381	MH0233_GL0060185	SEQ ID NO: 1554
CAG00381	MH0233_GL0066846	SEQ ID NO: 1555
CAG00381	MH0233_GL0091186	SEQ ID NO: 1556
CAG00381	MH0233_GL0052995	SEQ ID NO: 1557

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CAG00381	MH0233_GL0103619	SEQ ID NO: 1558
CAG00381	MH0233_GL0056698	SEQ ID NO: 1559
CAG00381	O2.UC11-1_GL0112377	SEQ ID NO: 1560
CAG00381	MH0233_GL0019862	SEQ ID NO: 1561
CAG00381	MH0233_GL0103622	SEQ ID NO: 1562
CAG00381	MH0233_GL0091850	SEQ ID NO: 1563
CAG00381	O2.UC19-2_GL0008363	SEQ ID NO: 1564
CAG00381	MH0233_GL0059183	SEQ ID NO: 1565
CAG00381	MH0233_GL0091864	SEQ ID NO: 1566
CAG00381	MH0233_GL0010836	SEQ ID NO: 1567
CAG00381	MH0233_GL0056907	SEQ ID NO: 1568
CAG00381	MH0233_GL0035462	SEQ ID NO: 1569
CAG00381	MH0233_GL0090705	SEQ ID NO: 1570
CAG00381	V1.FI04_GL0104012	SEQ ID NO: 1571
CAG00381	MH0233_GL0066852	SEQ ID NO: 1572
CAG00381	MH0233_GL0047497	SEQ ID NO: 1573
CAG00381	V1.FI12_GL0203479	SEQ ID NO: 1574
CAG00381	MH0233_GL0077085	SEQ ID NO: 1575
CAG00381	MH0233_GL0091179	SEQ ID NO: 1576
CAG00559	MH0012_GL0066180	SEQ ID NO: 1577
CAG00559	MH0012_GL0237518	SEQ ID NO: 1578
CAG00559	O2.UC52-2_GL0048590	SEQ ID NO: 1579
CAG00559	158944319-stool1_revised_C1045997_1_gene109890	SEQ ID NO: 1580
CAG00559	MH0012_GL0074963	SEQ ID NO: 1581
CAG00559	160704339-stool1_revised_C1411799_1_gene84313	SEQ ID NO: 1582
CAG00559	O2.UC47-1_GL0019033	SEQ ID NO: 1583
CAG00559	MH0373_GL0172307	SEQ ID NO: 1584
CAG00559	MH0453_GL0132208	SEQ ID NO: 1585
CAG00559	MH0012_GL0128724	SEQ ID NO: 1586
CAG00559	MH0252_GL0186374	SEQ ID NO: 1587
CAG00559	MH0012_GL0090850	SEQ ID NO: 1588
CAG00559	MH0012_GL0117901	SEQ ID NO: 1589
CAG00559	MH0012_GL0103293	SEQ ID NO: 1590
CAG00559	MH0012_GL0165258	SEQ ID NO: 1591
CAG00559	MH0012_GL0234812	SEQ ID NO: 1592
CAG00559	MH0422_GL0099033	SEQ ID NO: 1593
CAG00559	MH0012_GL0212617	SEQ ID NO: 1594
CAG00559	MH0012_GL0036355	SEQ ID NO: 1595
CAG00559	MH0356_GL0155940	SEQ ID NO: 1596

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CAG00559	MH0193_GL0127486	SEQ ID NO: 1597
CAG00559	MH0262_GL0099379	SEQ ID NO: 1598
CAG00559	O2.UC47-1_GL0011868	SEQ ID NO: 1599
CAG00559	MH0206_GL0124420	SEQ ID NO: 1600
CAG00559	SZEY-62A_GL0068587	SEQ ID NO: 1601
CAG00559	MH0343_GL0006001	SEQ ID NO: 1602
CAG00559	MH0096_GL0061137	SEQ ID NO: 1603
CAG00559	O2.UC40-1_GL0194629	SEQ ID NO: 1604
CAG00559	MH0012_GL0117904	SEQ ID NO: 1605
CAG00559	MH0200_GL0191918	SEQ ID NO: 1606
CAG00559	MH0012_GL0029892	SEQ ID NO: 1607
CAG00559	N022A_GL0074028	SEQ ID NO: 1608
CAG00559	V1.CD30-0_GL0091931	SEQ ID NO: 1609
CAG00559	V1.CD6-0-PT_GL0145486	SEQ ID NO: 1610
CAG00559	MH0303_GL0078484	SEQ ID NO: 1611
CAG00559	MH0197_GL0156714	SEQ ID NO: 1612
CAG00559	MH0434_GL0122412	SEQ ID NO: 1613
CAG00559	MH0012_GL0108748	SEQ ID NO: 1614
CAG00559	MH0012_GL0090852	SEQ ID NO: 1615
CAG00559	MH0012_GL0237521	SEQ ID NO: 1616
CAG00559	MH0193_GL0073226	SEQ ID NO: 1617
CAG00559	SZEY-62A_GL0048973	SEQ ID NO: 1618
CAG00559	MH0193_GL0045020	SEQ ID NO: 1619
CAG00559	MH0430_GL0114903	SEQ ID NO: 1620
CAG00559	MH0197_GL0045605	SEQ ID NO: 1621
CAG00559	MH0012_GL0119351	SEQ ID NO: 1622
CAG00559	MH0197_GL0122038	SEQ ID NO: 1623
CAG00559	MH0012_GL0050082	SEQ ID NO: 1624
CAG00559	MH0012_GL0103291	SEQ ID NO: 1625
CAG00559	MH0451_GL0204212	SEQ ID NO: 1626
CAG00570	158337416-stool1_revised_C1240234_1_gene61382	SEQ ID NO: 1627
CAG00570	MH0366_GL0014438	SEQ ID NO: 1628
CAG00570	MH0366_GL0105096	SEQ ID NO: 1629
CAG00570	MH0366_GL0142970	SEQ ID NO: 1630
CAG00570	158337416-stool1_revised_C1228438_1_gene210576	SEQ ID NO: 1631
CAG00570	158337416-stool1_revised_C1139104_1_gene171934	SEQ ID NO: 1632
CAG00570	158337416-stool1_revised_C1162436_1_gene157074	SEQ ID NO: 1633

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CAG00570	158337416-stool1_revised_scaffold16772_1_gene138838	SEQ ID NO: 1634
CAG00570	158337416-stool1_revised_C1269936_1_gene164544	SEQ ID NO: 1635
CAG00570	158337416-stool1_revised_C1225906_1_gene110954	SEQ ID NO: 1636
CAG00570	160704339-stool1_revised_scaffold28351_1_gene137089	SEQ ID NO: 1637
CAG00570	MH0366_GL0132869	SEQ ID NO: 1638
CAG00570	MH0366_GL0070438	SEQ ID NO: 1639
CAG00570	MH0366_GL0046120	SEQ ID NO: 1640
CAG00570	158337416-stool1_revised_scaffold19851_1_gene97170	SEQ ID NO: 1641
CAG00570	158337416-stool1_revised_C1149190_1_gene133843	SEQ ID NO: 1642
CAG00570	158337416-stool1_revised_C1203284_1_gene113710	SEQ ID NO: 1643
CAG00570	MH0366_GL0009017	SEQ ID NO: 1644
CAG00570	MH0366_GL0127883	SEQ ID NO: 1645
CAG00570	158337416-stool1_revised_scaffold7598_1_gene91220	SEQ ID NO: 1646
CAG00570	MH0366_GL0078392	SEQ ID NO: 1647
CAG00570	158337416-stool1_revised_scaffold24453_1_gene65737	SEQ ID NO: 1648
CAG00570	MH0366_GL0125454	SEQ ID NO: 1649
CAG00570	158337416-stool1_revised_C1254876_1_gene205094	SEQ ID NO: 1650
CAG00570	158337416-stool1_revised_scaffold9058_1_gene230576	SEQ ID NO: 1651
CAG00570	MH0366_GL0089956	SEQ ID NO: 1652
CAG00570	MH0366_GL0066569	SEQ ID NO: 1653
CAG00570	158337416-stool1_revised_scaffold22387_1_gene164973	SEQ ID NO: 1654
CAG00570	158337416-stool1_revised_scaffold22730_1_gene129709	SEQ ID NO: 1655
CAG00570	158337416-stool1_revised_scaffold1855_1_gene49512	SEQ ID NO: 1656
CAG00570	MH0366_GL0141852	SEQ ID NO: 1657
CAG00570	160704339-stool1_revised_C1327971_1_gene36381	SEQ ID NO: 1658
CAG00570	MH0454_GL0090493	SEQ ID NO: 1659
CAG00570	158337416-stool1_revised_C1197272_1_gene97970	SEQ ID NO: 1660

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CAG00570	MH0366_GL0133228	SEQ ID NO: 1661
CAG00570	MH0366_GL0003291	SEQ ID NO: 1662
CAG00570	MH0366_GL0069655	SEQ ID NO: 1663
CAG00570	MH0366_GL0023679	SEQ ID NO: 1664
CAG00570	MH0366_GL0135591	SEQ ID NO: 1665
CAG00570	MH0366_GL0050575	SEQ ID NO: 1666
CAG00570	MH0366_GL0009276	SEQ ID NO: 1667
CAG00570	158337416-stool1_revised_scaffold26304_1_gene216014	SEQ ID NO: 1668
CAG00570	MH0366_GL0140044	SEQ ID NO: 1669
CAG00570	158337416-stool1_revised_C1218172_1_gene176424	SEQ ID NO: 1670
CAG00570	158337416-stool1_revised_C1230400_1_gene160962	SEQ ID NO: 1671
CAG00570	160704339-stool1_revised_C1340293_1_gene152978	SEQ ID NO: 1672
CAG00570	MH0454_GL0213816	SEQ ID NO: 1673
CAG00570	MH0366_GL0045814	SEQ ID NO: 1674
CAG00570	MH0366_GL0128454	SEQ ID NO: 1675
CAG00570	158337416-stool1_revised_C1257214_1_gene57912	SEQ ID NO: 1676
CAG00635	SZEY-74A_GL0013607	SEQ ID NO: 1677
CAG00635	V1.FI13_GL0045803	SEQ ID NO: 1678
CAG00635	398513.BBNG_00128	SEQ ID NO: 1679
CAG00635	O2.UC11-1_GL0162381	SEQ ID NO: 1680
CAG00635	O2.UC11-2_GL0025924	SEQ ID NO: 1681
CAG00635	V1.CD19-0_GL0184168	SEQ ID NO: 1682
CAG00635	MH0341_GL0069432	SEQ ID NO: 1683
CAG00635	MH0341_GL0008211	SEQ ID NO: 1684
CAG00635	883062.BBIF_1015	SEQ ID NO: 1685
CAG00635	O2.UC3-1_GL0087195	SEQ ID NO: 1686
CAG00635	O2.UC11-1_GL0059462	SEQ ID NO: 1687
CAG00635	O2.UC11-1_GL0013718	SEQ ID NO: 1688
CAG00635	O2.UC34-2_GL0006818	SEQ ID NO: 1689
CAG00635	V1.FI17_GL0019390	SEQ ID NO: 1690
CAG00635	MH0203_GL0030664	SEQ ID NO: 1691
CAG00635	V1.CD15-3_GL0025660	SEQ ID NO: 1692
CAG00635	702459.BBPR_0958	SEQ ID NO: 1693
CAG00635	O2.UC11-2_GL0084124	SEQ ID NO: 1694
CAG00635	398513.BBNG_00233	SEQ ID NO: 1695
CAG00635	O2.UC3-0_GL0065679	SEQ ID NO: 1696
CAG00635	O2.UC34-2_GL0070625	SEQ ID NO: 1697

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CAG00635	O2.UC3-0_GL0157811	SEQ ID NO: 1698
CAG00635	MH0203_GL0216381	SEQ ID NO: 1699
CAG00635	O2.UC11-2_GL0118283	SEQ ID NO: 1700
CAG00635	V1.UC54-0_GL0091833	SEQ ID NO: 1701
CAG00635	MH0341_GL0069076	SEQ ID NO: 1702
CAG00635	O2.UC36-0_GL0157758	SEQ ID NO: 1703
CAG00635	O2.UC11-1_GL0160585	SEQ ID NO: 1704
CAG00635	O2.UC20-2_GL0014643	SEQ ID NO: 1705
CAG00635	O2.UC36-0_GL0106717	SEQ ID NO: 1706
CAG00635	398513.BBNG_01392	SEQ ID NO: 1707
CAG00635	883062.BBIF_0260	SEQ ID NO: 1708
CAG00635	BGI-06A_GL0020618	SEQ ID NO: 1709
CAG00635	883062.BBIF_0743	SEQ ID NO: 1710
CAG00635	O2.UC11-1_GL0034723	SEQ ID NO: 1711
CAG00635	O2.UC36-0_GL0135830	SEQ ID NO: 1712
CAG00635	MH0203_GL0243009	SEQ ID NO: 1713
CAG00635	V1.FI17_GL0217323	SEQ ID NO: 1714
CAG00635	398513.BBNG_01505	SEQ ID NO: 1715
CAG00635	MH0161_GL0172217	SEQ ID NO: 1716
CAG00635	O2.UC8-0_GL0116801	SEQ ID NO: 1717
CAG00635	702459.BBPR_1025	SEQ ID NO: 1718
CAG00635	MH0203_GL0035804	SEQ ID NO: 1719
CAG00635	O2.UC19-1_GL0047789	SEQ ID NO: 1720
CAG00635	O2.UC8-0_GL0078403	SEQ ID NO: 1721
CAG00635	O2.UC11-1_GL0067564	SEQ ID NO: 1722
CAG00635	702459.BBPR_0500	SEQ ID NO: 1723
CAG00635	O2.UC11-2_GL0049242	SEQ ID NO: 1724
CAG00635	MH0203_GL0222471	SEQ ID NO: 1725
CAG00635	O2.UC36-0_GL0048522	SEQ ID NO: 1726
CAG00636	MH0205_GL0155444	SEQ ID NO: 1727
CAG00636	MH0098_GL0040145	SEQ ID NO: 1728
CAG00636	MH0006_GL0151219	SEQ ID NO: 1729
CAG00636	MH0205_GL0098023	SEQ ID NO: 1730
CAG00636	MH0098_GL0033699	SEQ ID NO: 1731
CAG00636	MH0098_GL0060936	SEQ ID NO: 1732
CAG00636	MH0205_GL0074663	SEQ ID NO: 1733
CAG00636	MH0006_GL0034135	SEQ ID NO: 1734
CAG00636	MH0205_GL0033937	SEQ ID NO: 1735
CAG00636	MH0098_GL0037973	SEQ ID NO: 1736
CAG00636	MH0205_GL0081238	SEQ ID NO: 1737
CAG00636	MH0098_GL0103935	SEQ ID NO: 1738

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CAG00636	MH0006_GL0103395	SEQ ID NO: 1739
CAG00636	MH0250_GL0001435	SEQ ID NO: 1740
CAG00636	MH0205_GL0038215	SEQ ID NO: 1741
CAG00636	MH0205_GL0155424	SEQ ID NO: 1742
CAG00636	MH0205_GL0105586	SEQ ID NO: 1743
CAG00636	MH0006_GL0015683	SEQ ID NO: 1744
CAG00636	MH0098_GL0133499	SEQ ID NO: 1745
CAG00636	MH0205_GL0073445	SEQ ID NO: 1746
CAG00636	MH0006_GL0160459	SEQ ID NO: 1747
CAG00636	MH0006_GL0105106	SEQ ID NO: 1748
CAG00636	MH0410_GL0068910	SEQ ID NO: 1749
CAG00636	MH0204_GL0106563	SEQ ID NO: 1750
CAG00636	MH0006_GL0175311	SEQ ID NO: 1751
CAG00636	MH0434_GL0073320	SEQ ID NO: 1752
CAG00636	MH0205_GL0113435	SEQ ID NO: 1753
CAG00636	MH0205_GL0143994	SEQ ID NO: 1754
CAG00636	MH0006_GL0222862	SEQ ID NO: 1755
CAG00636	MH0205_GL0041515	SEQ ID NO: 1756
CAG00636	MH0098_GL0003062	SEQ ID NO: 1757
CAG00636	MH0205_GL0146613	SEQ ID NO: 1758
CAG00636	MH0006_GL0146322	SEQ ID NO: 1759
CAG00636	MH0006_GL0198074	SEQ ID NO: 1760
CAG00636	MH0205_GL0047838	SEQ ID NO: 1761
CAG00636	MH0204_GL0009282	SEQ ID NO: 1762
CAG00636	MH0204_GL0194250	SEQ ID NO: 1763
CAG00636	MH0204_GL0144559	SEQ ID NO: 1764
CAG00636	MH0006_GL0018871	SEQ ID NO: 1765
CAG00636	MH0205_GL0158536	SEQ ID NO: 1766
CAG00636	159571453-stool2_revised_C1199086_1_gene7339	SEQ ID NO: 1767
CAG00636	MH0205_GL0144498	SEQ ID NO: 1768
CAG00636	MH0204_GL0176828	SEQ ID NO: 1769
CAG00636	MH0086_GL0081171	SEQ ID NO: 1770
CAG00636	MH0098_GL0073539	SEQ ID NO: 1771
CAG00636	MH0006_GL0191234	SEQ ID NO: 1772
CAG00636	MH0205_GL0068695	SEQ ID NO: 1773
CAG00636	MH0006_GL0018233	SEQ ID NO: 1774
CAG00636	MH0206_GL0061239	SEQ ID NO: 1775
CAG00636	MH0006_GL0164383	SEQ ID NO: 1776
CAG00660	159551223-stool1_revised_scaffold36550_1_gene37802	SEQ ID NO: 1777

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CAG00660	159551223-stool1_revised_scaffold39514_1_gene117926	SEQ ID NO: 1778
CAG00660	159551223-stool1_revised_scaffold34582_1_gene105320	SEQ ID NO: 1779
CAG00660	159551223-stool1_revised_scaffold3298_1_gene168956	SEQ ID NO: 1780
CAG00660	159551223-stool1_revised_scaffold34345_1_gene557	SEQ ID NO: 1781
CAG00660	159551223-stool1_revised_scaffold13073_2_gene99788	SEQ ID NO: 1782
CAG00660	MH0403_GL0183883	SEQ ID NO: 1783
CAG00660	159551223-stool1_revised_scaffold42896_1_gene32050	SEQ ID NO: 1784
CAG00660	159551223-stool1_revised_scaffold39675_1_gene99755	SEQ ID NO: 1785
CAG00660	159551223-stool1_revised_scaffold13073_1_gene107119	SEQ ID NO: 1786
CAG00660	159551223-stool1_revised_scaffold37687_1_gene84758	SEQ ID NO: 1787
CAG00660	159551223-stool1_revised_scaffold13073_2_gene99790	SEQ ID NO: 1788
CAG00660	159551223-stool1_revised_scaffold42962_1_gene51280	SEQ ID NO: 1789
CAG00660	159551223-stool1_revised_scaffold49831_4_gene7345	SEQ ID NO: 1790
CAG00660	159551223-stool1_revised_scaffold38343_1_gene43429	SEQ ID NO: 1791
CAG00660	159551223-stool1_revised_scaffold49831_3_gene104078	SEQ ID NO: 1792
CAG00660	159551223-stool1_revised_scaffold17948_8_gene139490	SEQ ID NO: 1793
CAG00660	159551223-stool1_revised_scaffold17805_1_gene151102	SEQ ID NO: 1794
CAG00660	159551223-stool1_revised_scaffold50270_2_gene111004	SEQ ID NO: 1795
CAG00660	159551223-stool1_revised_scaffold39986_2_gene53942	SEQ ID NO: 1796
CAG00660	159551223-stool1_revised_C1047407_1_gene121290	SEQ ID NO: 1797
CAG00660	159551223-stool1_revised_scaffold34582_1_gene105316	SEQ ID NO: 1798
CAG00660	159551223-stool1_revised_scaffold15409_1_gene119865	SEQ ID NO: 1799

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CAG00660	159551223-stool1_revised_scaffold13073_2_gene99791	SEQ ID NO: 1800
CAG00660	763496533-stool2_revised_scaffold48134_1_gene30793	SEQ ID NO: 1801
CAG00660	159551223-stool1_revised_scaffold17948_7_gene103947	SEQ ID NO: 1802
CAG00660	159551223-stool1_revised_scaffold32985_1_gene115578	SEQ ID NO: 1803
CAG00660	159551223-stool1_revised_scaffold42600_1_gene152210	SEQ ID NO: 1804
CAG00660	159551223-stool1_revised_scaffold19684_1_gene33917	SEQ ID NO: 1805
CAG00660	159551223-stool1_revised_scaffold13073_1_gene107116	SEQ ID NO: 1806
CAG00660	159551223-stool1_revised_C1031143_1_gene28558	SEQ ID NO: 1807
CAG00660	159551223-stool1_revised_scaffold2508_1_gene78321	SEQ ID NO: 1808
CAG00660	159551223-stool1_revised_scaffold40336_1_gene3156	SEQ ID NO: 1809
CAG00660	159551223-stool1_revised_scaffold14052_1_gene127907	SEQ ID NO: 1810
CAG00660	159551223-stool1_revised_scaffold17948_7_gene103950	SEQ ID NO: 1811
CAG00660	159551223-stool1_revised_scaffold35611_1_gene108963	SEQ ID NO: 1812
CAG00660	159551223-stool1_revised_scaffold34582_1_gene105317	SEQ ID NO: 1813
CAG00660	159551223-stool1_revised_scaffold19605_1_gene13629	SEQ ID NO: 1814
CAG00660	159551223-stool1_revised_scaffold36550_2_gene72111	SEQ ID NO: 1815
CAG00660	159551223-stool1_revised_scaffold4271_1_gene139339	SEQ ID NO: 1816
CAG00660	159551223-stool1_revised_scaffold49831_3_gene104079	SEQ ID NO: 1817
CAG00660	159551223-stool1_revised_scaffold34582_1_gene105318	SEQ ID NO: 1818
CAG00660	159551223-stool1_revised_scaffold5822_2_gene908	SEQ ID NO: 1819
CAG00660	159551223-stool1_revised_C1059513_1_gene104605	SEQ ID NO: 1820

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CAG00660	763496533-stool2_revised_scaffold44269_1_gene30449	SEQ ID NO: 1821
CAG00660	159551223-stool1_revised_scaffold22937_2_gene164540	SEQ ID NO: 1822
CAG00660	159551223-stool1_revised_scaffold31901_1_gene90689	SEQ ID NO: 1823
CAG00660	159551223-stool1_revised_scaffold34582_1_gene105319	SEQ ID NO: 1824
CAG00660	159551223-stool1_revised_scaffold22937_3_gene150472	SEQ ID NO: 1825
CAG00660	159551223-stool1_revised_scaffold10714_2_gene35081	SEQ ID NO: 1826
CAG00669	MH0367_GL0070731	SEQ ID NO: 1827
CAG00669	MH0197_GL0129961	SEQ ID NO: 1828
CAG00669	MH0197_GL0146043	SEQ ID NO: 1829
CAG00669	T2D-47A_GL0061723	SEQ ID NO: 1830
CAG00669	MH0197_GL0055241	SEQ ID NO: 1831
CAG00669	MH0366_GL0036354	SEQ ID NO: 1832
CAG00669	MH0197_GL0037877	SEQ ID NO: 1833
CAG00669	MH0303_GL0074511	SEQ ID NO: 1834
CAG00669	MH0197_GL0136603	SEQ ID NO: 1835
CAG00669	MH0229_GL0129914	SEQ ID NO: 1836
CAG00669	MH0197_GL0183681	SEQ ID NO: 1837
CAG00669	MH0229_GL0148590	SEQ ID NO: 1838
CAG00669	MH0197_GL0109522	SEQ ID NO: 1839
CAG00669	V1.FI14_GL0234953	SEQ ID NO: 1840
CAG00669	MH0397_GL0181573	SEQ ID NO: 1841
CAG00669	MH0197_GL0129963	SEQ ID NO: 1842
CAG00669	MH0197_GL0042741	SEQ ID NO: 1843
CAG00669	MH0197_GL0094985	SEQ ID NO: 1844
CAG00669	MH0286_GL0119078	SEQ ID NO: 1845
CAG00669	MH0229_GL0199684	SEQ ID NO: 1846
CAG00669	MH0197_GL0083020	SEQ ID NO: 1847
CAG00669	MH0197_GL0066436	SEQ ID NO: 1848
CAG00669	MH0330_GL0206949	SEQ ID NO: 1849
CAG00669	MH0197_GL0070704	SEQ ID NO: 1850
CAG00669	MH0013_GL0028809	SEQ ID NO: 1851
CAG00669	MH0197_GL0142820	SEQ ID NO: 1852
CAG00669	MH0330_GL0189177	SEQ ID NO: 1853
CAG00669	MH0197_GL0088581	SEQ ID NO: 1854
CAG00669	MH0197_GL0182366	SEQ ID NO: 1855
CAG00669	MH0197_GL0130278	SEQ ID NO: 1856

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CAG00669	MH0197_GL0029501	SEQ ID NO: 1857
CAG00669	MH0197_GL0100655	SEQ ID NO: 1858
CAG00669	MH0373_GL0085470	SEQ ID NO: 1859
CAG00669	MH0229_GL0064007	SEQ ID NO: 1860
CAG00669	MH0197_GL0016425	SEQ ID NO: 1861
CAG00669	MH0197_GL0146041	SEQ ID NO: 1862
CAG00669	V1.FI14_GL0234081	SEQ ID NO: 1863
CAG00669	V1.FI04_GL0219293	SEQ ID NO: 1864
CAG00669	MH0451_GL0015685	SEQ ID NO: 1865
CAG00669	MH0229_GL0083775	SEQ ID NO: 1866
CAG00669	MH0197_GL0130275	SEQ ID NO: 1867
CAG00669	MH0229_GL0058166	SEQ ID NO: 1868
CAG00669	MH0429_GL0191886	SEQ ID NO: 1869
CAG00669	MH0197_GL0093005	SEQ ID NO: 1870
CAG00669	MH0197_GL0079932	SEQ ID NO: 1871
CAG00669	MH0197_GL0125083	SEQ ID NO: 1872
CAG00669	MH0197_GL0094204	SEQ ID NO: 1873
CAG00669	MH0197_GL0113421	SEQ ID NO: 1874
CAG00669	MH0367_GL0043136	SEQ ID NO: 1875
CAG00669	V1.CD50-0_GL0120458	SEQ ID NO: 1876
CAG00708	MH0247_GL0127983	SEQ ID NO: 1877
CAG00708	MH0247_GL0105999	SEQ ID NO: 1878
CAG00708	159632143-stool1_revised_scaffold3172_2_gene50831	SEQ ID NO: 1879
CAG00708	MH0244_GL0114679	SEQ ID NO: 1880
CAG00708	MH0247_GL0039279	SEQ ID NO: 1881
CAG00708	MH0244_GL0135896	SEQ ID NO: 1882
CAG00708	MH0244_GL0155054	SEQ ID NO: 1883
CAG00708	MH0247_GL0159353	SEQ ID NO: 1884
CAG00708	MH0247_GL0106616	SEQ ID NO: 1885
CAG00708	MH0247_GL0068996	SEQ ID NO: 1886
CAG00708	MH0244_GL0064454	SEQ ID NO: 1887
CAG00708	MH0244_GL0080631	SEQ ID NO: 1888
CAG00708	MH0247_GL0184933	SEQ ID NO: 1889
CAG00708	MH0244_GL0122056	SEQ ID NO: 1890
CAG00708	MH0247_GL0180674	SEQ ID NO: 1891
CAG00708	MH0247_GL0063238	SEQ ID NO: 1892
CAG00708	158802708-stool2_revised_scaffold23523_1_gene106103	SEQ ID NO: 1893
CAG00708	MH0244_GL0044729	SEQ ID NO: 1894
CAG00708	MH0244_GL0099222	SEQ ID NO: 1895

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CAG00708	MH0247_GL0093590	SEQ ID NO: 1896
CAG00708	MH0247_GL0178370	SEQ ID NO: 1897
CAG00708	MH0244_GL0103462	SEQ ID NO: 1898
CAG00708	MH0244_GL0057657	SEQ ID NO: 1899
CAG00708	MH0247_GL0149574	SEQ ID NO: 1900
CAG00708	MH0247_GL0198694	SEQ ID NO: 1901
CAG00708	MH0247_GL0063231	SEQ ID NO: 1902
CAG00708	MH0244_GL0149878	SEQ ID NO: 1903
CAG00708	MH0247_GL0119273	SEQ ID NO: 1904
CAG00708	MH0244_GL0003207	SEQ ID NO: 1905
CAG00708	MH0244_GL0057659	SEQ ID NO: 1906
CAG00708	MH0247_GL0168180	SEQ ID NO: 1907
CAG00708	MH0244_GL0051657	SEQ ID NO: 1908
CAG00708	MH0247_GL0179216	SEQ ID NO: 1909
CAG00708	MH0247_GL0126555	SEQ ID NO: 1910
CAG00708	MH0244_GL0112700	SEQ ID NO: 1911
CAG00708	159632143-stool1_revised_scaffold46131_1_gene3651	SEQ ID NO: 1912
CAG00708	MH0247_GL0201508	SEQ ID NO: 1913
CAG00708	MH0244_GL0051655	SEQ ID NO: 1914
CAG00708	MH0244_GL0051247	SEQ ID NO: 1915
CAG00708	MH0247_GL0059767	SEQ ID NO: 1916
CAG00708	MH0244_GL0053868	SEQ ID NO: 1917
CAG00708	MH0244_GL0069611	SEQ ID NO: 1918
CAG00708	MH0247_GL0054726	SEQ ID NO: 1919
CAG00708	MH0247_GL0149581	SEQ ID NO: 1920
CAG00708	159632143-stool1_revised_scaffold2564_1_gene9545	SEQ ID NO: 1921
CAG00708	MH0247_GL0111749	SEQ ID NO: 1922
CAG00708	MH0244_GL0139322	SEQ ID NO: 1923
CAG00708	MH0247_GL0063222	SEQ ID NO: 1924
CAG00708	MH0247_GL0077032	SEQ ID NO: 1925
CAG00708	MH0244_GL0115874	SEQ ID NO: 1926
CAG00773	MH0176_GL0136011	SEQ ID NO: 1927
CAG00773	MH0222_GL0126770	SEQ ID NO: 1928
CAG00773	MH0176_GL0003864	SEQ ID NO: 1929
CAG00773	MH0176_GL0056104	SEQ ID NO: 1930
CAG00773	MH0023_GL0029268	SEQ ID NO: 1931
CAG00773	MH0176_GL0117492	SEQ ID NO: 1932
CAG00773	MH0176_GL0037224	SEQ ID NO: 1933
CAG00773	MH0176_GL0037226	SEQ ID NO: 1934

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CAG00773	O2.UC1-2_GL0103698	SEQ ID NO: 1935
CAG00773	MH0293_GL0180427	SEQ ID NO: 1936
CAG00773	MH0176_GL0046360	SEQ ID NO: 1937
CAG00773	MH0110_GL0070711	SEQ ID NO: 1938
CAG00773	MH0443_GL0014210	SEQ ID NO: 1939
CAG00773	T2D-59A_GL0053779	SEQ ID NO: 1940
CAG00773	V1.FI11_GL0101062	SEQ ID NO: 1941
CAG00773	MH0176_GL0043722	SEQ ID NO: 1942
CAG00773	MH0176_GL0125552	SEQ ID NO: 1943
CAG00773	MH0176_GL0087927	SEQ ID NO: 1944
CAG00773	MH0176_GL0116526	SEQ ID NO: 1945
CAG00773	MH0315_GL0043366	SEQ ID NO: 1946
CAG00773	MH0154_GL0000284	SEQ ID NO: 1947
CAG00773	MH0176_GL0003862	SEQ ID NO: 1948
CAG00773	MH0176_GL0033106	SEQ ID NO: 1949
CAG00773	V1.FI19_GL0065772	SEQ ID NO: 1950
CAG00773	MH0176_GL0090410	SEQ ID NO: 1951
CAG00773	MH0381_GL0041486	SEQ ID NO: 1952
CAG00773	MH0176_GL0116527	SEQ ID NO: 1953
CAG00773	MH0222_GL0102268	SEQ ID NO: 1954
CAG00773	MH0424_GL0113348	SEQ ID NO: 1955
CAG00773	MH0293_GL0145886	SEQ ID NO: 1956
CAG00773	MH0154_GL0003240	SEQ ID NO: 1957
CAG00773	MH0176_GL0117488	SEQ ID NO: 1958
CAG00773	MH0176_GL0006609	SEQ ID NO: 1959
CAG00773	MH0110_GL0065980	SEQ ID NO: 1960
CAG00773	158479027-stool1_revised_scaffold16618_1_gene102199	SEQ ID NO: 1961
CAG00773	MH0176_GL0001208	SEQ ID NO: 1962
CAG00773	MH0245_GL0148135	SEQ ID NO: 1963
CAG00773	MH0381_GL0009741	SEQ ID NO: 1964
CAG00773	MH0396_GL0102547	SEQ ID NO: 1965
CAG00773	MH0176_GL0036856	SEQ ID NO: 1966
CAG00773	MH0176_GL0130995	SEQ ID NO: 1967
CAG00773	MH0293_GL0019828	SEQ ID NO: 1968
CAG00773	MH0293_GL0138546	SEQ ID NO: 1969
CAG00773	V1.FI11_GL0194656	SEQ ID NO: 1970
CAG00773	MH0176_GL0005737	SEQ ID NO: 1971
CAG00773	MH0176_GL0061893	SEQ ID NO: 1972
CAG00773	MH0154_GL0106428	SEQ ID NO: 1973
CAG00773	MH0154_GL0078114	SEQ ID NO: 1974

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CAG00773	MH0222_GL0157669	SEQ ID NO: 1975
CAG00773	MH0222_GL0105590	SEQ ID NO: 1976
CAG00807	MH0301_GL0033725	SEQ ID NO: 1977
CAG00807	MH0165_GL0061412	SEQ ID NO: 1978
CAG00807	MH0301_GL0047494	SEQ ID NO: 1979
CAG00807	MH0092_GL0080106	SEQ ID NO: 1980
CAG00807	MH0165_GL0113700	SEQ ID NO: 1981
CAG00807	MH0148_GL0116445	SEQ ID NO: 1982
CAG00807	MH0148_GL0145001	SEQ ID NO: 1983
CAG00807	MH0148_GL0044463	SEQ ID NO: 1984
CAG00807	MH0041_GL0055082	SEQ ID NO: 1985
CAG00807	MH0148_GL0115069	SEQ ID NO: 1986
CAG00807	MH0148_GL0118383	SEQ ID NO: 1987
CAG00807	MH0102_GL0075586	SEQ ID NO: 1988
CAG00807	MH0148_GL0042336	SEQ ID NO: 1989
CAG00807	MH0093_GL0063769	SEQ ID NO: 1990
CAG00807	V1.FI02_GL0020817	SEQ ID NO: 1991
CAG00807	MH0442_GL0193529	SEQ ID NO: 1992
CAG00807	MH0041_GL0054811	SEQ ID NO: 1993
CAG00807	MH0163_GL0069186	SEQ ID NO: 1994
CAG00807	MH0041_GL0006132	SEQ ID NO: 1995
CAG00807	MH0102_GL0050698	SEQ ID NO: 1996
CAG00807	O2.UC44-0_GL0040348	SEQ ID NO: 1997
CAG00807	MH0148_GL0092929	SEQ ID NO: 1998
CAG00807	MH0148_GL0159142	SEQ ID NO: 1999
CAG00807	764487809-stool1_revised_C1069950_1_gene191231	SEQ ID NO: 2000
CAG00807	MH0148_GL0139776	SEQ ID NO: 2001
CAG00807	MH0041_GL0006131	SEQ ID NO: 2002
CAG00807	MH0187_GL0143210	SEQ ID NO: 2003
CAG00807	MH0260_GL0109822	SEQ ID NO: 2004
CAG00807	V1.CD42-0_GL0096154	SEQ ID NO: 2005
CAG00807	V1.CD16-0_GL0111163	SEQ ID NO: 2006
CAG00807	MH0165_GL0042349	SEQ ID NO: 2007
CAG00807	MH0441_GL0226653	SEQ ID NO: 2008
CAG00807	MH0398_GL0192694	SEQ ID NO: 2009
CAG00807	MH0041_GL0043725	SEQ ID NO: 2010
CAG00807	MH0165_GL0021847	SEQ ID NO: 2011
CAG00807	N037A_GL0072326	SEQ ID NO: 2012
CAG00807	MH0362_GL0079670	SEQ ID NO: 2013
CAG00807	MH0041_GL0005391	SEQ ID NO: 2014

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CAG00807	V1.UC44-0_GL0120843	SEQ ID NO: 2015
CAG00807	MH0298_GL0172386	SEQ ID NO: 2016
CAG00807	O2.UC12-0_GL0044661	SEQ ID NO: 2017
CAG00807	V1.UC22-1_GL0047416	SEQ ID NO: 2018
CAG00807	MH0041_GL0015386	SEQ ID NO: 2019
CAG00807	MH0148_GL0153943	SEQ ID NO: 2020
CAG00807	MH0148_GL0125143	SEQ ID NO: 2021
CAG00807	MH0041_GL0002618	SEQ ID NO: 2022
CAG00807	MH0222_GL0153280	SEQ ID NO: 2023
CAG00807	MH0092_GL0058374	SEQ ID NO: 2024
CAG00807	MH0102_GL0109724	SEQ ID NO: 2025
CAG00807	SZEY-43A_GL0042615	SEQ ID NO: 2026
CAG00880	MH0303_GL0173352	SEQ ID NO: 2027
CAG00880	MH0100_GL0099997	SEQ ID NO: 2028
CAG00880	MH0002_GL0034748	SEQ ID NO: 2029
CAG00880	MH0012_GL0237170	SEQ ID NO: 2030
CAG00880	O2.UC44-0_GL0117257	SEQ ID NO: 2031
CAG00880	MH0012_GL0195203	SEQ ID NO: 2032
CAG00880	MH0262_GL0025010	SEQ ID NO: 2033
CAG00880	MH0012_GL0056991	SEQ ID NO: 2034
CAG00880	MH0012_GL0077956	SEQ ID NO: 2035
CAG00880	MH0220_GL0192349	SEQ ID NO: 2036
CAG00880	MH0012_GL0102653	SEQ ID NO: 2037
CAG00880	MH0012_GL0220969	SEQ ID NO: 2038
CAG00880	MH0012_GL0093821	SEQ ID NO: 2039
CAG00880	MH0012_GL0134845	SEQ ID NO: 2040
CAG00880	MH0012_GL0027380	SEQ ID NO: 2041
CAG00880	MH0343_GL0167330	SEQ ID NO: 2042
CAG00880	MH0012_GL0103710	SEQ ID NO: 2043
CAG00880	O2.UC31-1_GL0033906	SEQ ID NO: 2044
CAG00880	O2.UC29-0_GL0061068	SEQ ID NO: 2045
CAG00880	MH0012_GL0103695	SEQ ID NO: 2046
CAG00880	MH0012_GL0023918	SEQ ID NO: 2047
CAG00880	MH0012_GL0087717	SEQ ID NO: 2048
CAG00880	MH0148_GL0160053	SEQ ID NO: 2049
CAG00880	MH0012_GL0057003	SEQ ID NO: 2050
CAG00880	MH0012_GL0087706	SEQ ID NO: 2051
CAG00880	MH0012_GL0087718	SEQ ID NO: 2052
CAG00880	MH0012_GL0001511	SEQ ID NO: 2053
CAG00880	MH0012_GL0188466	SEQ ID NO: 2054
CAG00880	MH0012_GL0000902	SEQ ID NO: 2055

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CAG00880	MH0174_GL0153781	SEQ ID NO: 2056
CAG00880	MH0012_GL0087712	SEQ ID NO: 2057
CAG00880	MH0012_GL0056938	SEQ ID NO: 2058
CAG00880	MH0012_GL0040034	SEQ ID NO: 2059
CAG00880	MH0280_GL0193689	SEQ ID NO: 2060
CAG00880	MH0012_GL0082084	SEQ ID NO: 2061
CAG00880	MH0012_GL0027391	SEQ ID NO: 2062
CAG00880	MH0012_GL0040027	SEQ ID NO: 2063
CAG00880	MH0012_GL0103688	SEQ ID NO: 2064
CAG00880	MH0012_GL0056935	SEQ ID NO: 2065
CAG00880	MH0012_GL0190522	SEQ ID NO: 2066
CAG00880	MH0012_GL0233883	SEQ ID NO: 2067
CAG00880	MH0012_GL0171998	SEQ ID NO: 2068
CAG00880	MH0012_GL0040024	SEQ ID NO: 2069
CAG00880	MH0012_GL0032203	SEQ ID NO: 2070
CAG00880	MH0002_GL0076942	SEQ ID NO: 2071
CAG00880	MH0012_GL0027390	SEQ ID NO: 2072
CAG00880	MH0348_GL0094114	SEQ ID NO: 2073
CAG00880	MH0012_GL0011994	SEQ ID NO: 2074
CAG00880	MH0012_GL0102651	SEQ ID NO: 2075
CAG00880	MH0012_GL0188458	SEQ ID NO: 2076
CAG00907	MH0406_GL0036577	SEQ ID NO: 2077
CAG00907	MH0406_GL0082730	SEQ ID NO: 2078
CAG00907	MH0406_GL0212707	SEQ ID NO: 2079
CAG00907	MH0406_GL0188937	SEQ ID NO: 2080
CAG00907	MH0406_GL0194580	SEQ ID NO: 2081
CAG00907	V1.FI02_GL0004581	SEQ ID NO: 2082
CAG00907	V1.FI17_GL0111364	SEQ ID NO: 2083
CAG00907	V1.FI02_GL0078865	SEQ ID NO: 2084
CAG00907	V1.FI02_GL0033306	SEQ ID NO: 2085
CAG00907	MH0406_GL0025955	SEQ ID NO: 2086
CAG00907	V1.FI02_GL0193901	SEQ ID NO: 2087
CAG00907	MH0406_GL0150018	SEQ ID NO: 2088
CAG00907	MH0406_GL0159210	SEQ ID NO: 2089
CAG00907	MH0406_GL0050040	SEQ ID NO: 2090
CAG00907	MH0406_GL0056872	SEQ ID NO: 2091
CAG00907	V1.FI17_GL0113355	SEQ ID NO: 2092
CAG00907	MH0252_GL0069372	SEQ ID NO: 2093
CAG00907	MH0406_GL0160700	SEQ ID NO: 2094
CAG00907	MH0406_GL0106290	SEQ ID NO: 2095
CAG00907	MH0406_GL0107270	SEQ ID NO: 2096

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CAG00907	MH0406_GL0140952	SEQ ID NO: 2097
CAG00907	MH0406_GL0198479	SEQ ID NO: 2098
CAG00907	MH0406_GL0114916	SEQ ID NO: 2099
CAG00907	MH0406_GL0098212	SEQ ID NO: 2100
CAG00907	MH0406_GL0109826	SEQ ID NO: 2101
CAG00907	MH0406_GL0050047	SEQ ID NO: 2102
CAG00907	MH0406_GL0010585	SEQ ID NO: 2103
CAG00907	V1.FI17_GL0232428	SEQ ID NO: 2104
CAG00907	MH0406_GL0188934	SEQ ID NO: 2105
CAG00907	V1.FI02_GL0130832	SEQ ID NO: 2106
CAG00907	MH0406_GL0027320	SEQ ID NO: 2107
CAG00907	MH0406_GL0106289	SEQ ID NO: 2108
CAG00907	MH0406_GL0200362	SEQ ID NO: 2109
CAG00907	MH0406_GL0137182	SEQ ID NO: 2110
CAG00907	V1.FI17_GL0052501	SEQ ID NO: 2111
CAG00907	MH0406_GL0160699	SEQ ID NO: 2112
CAG00907	MH0406_GL0130721	SEQ ID NO: 2113
CAG00907	MH0406_GL0004857	SEQ ID NO: 2114
CAG00907	MH0406_GL0036571	SEQ ID NO: 2115
CAG00907	MH0406_GL0103619	SEQ ID NO: 2116
CAG00907	MH0406_GL0001932	SEQ ID NO: 2117
CAG00907	MH0406_GL0179891	SEQ ID NO: 2118
CAG00907	MH0406_GL0036551	SEQ ID NO: 2119
CAG00907	V1.FI02_GL0015755	SEQ ID NO: 2120
CAG00907	V1.FI02_GL0006959	SEQ ID NO: 2121
CAG00907	MH0406_GL0160729	SEQ ID NO: 2122
CAG00907	V1.FI02_GL0057414	SEQ ID NO: 2123
CAG00907	MH0406_GL0203649	SEQ ID NO: 2124
CAG00907	MH0406_GL0179889	SEQ ID NO: 2125
CAG00907	V1.FI02_GL0070231	SEQ ID NO: 2126
CAG01086	MH0272_GL0033692	SEQ ID NO: 2127
CAG01086	MH0272_GL0097741	SEQ ID NO: 2128
CAG01086	MH0272_GL0208037	SEQ ID NO: 2129
CAG01086	MH0272_GL0165135	SEQ ID NO: 2130
CAG01086	MH0272_GL0221196	SEQ ID NO: 2131
CAG01086	MH0272_GL0059874	SEQ ID NO: 2132
CAG01086	MH0272_GL0178997	SEQ ID NO: 2133
CAG01086	MH0272_GL0090046	SEQ ID NO: 2134
CAG01086	MH0197_GL0021730	SEQ ID NO: 2135
CAG01086	MH0197_GL0177498	SEQ ID NO: 2136
CAG01086	MH0197_GL0047997	SEQ ID NO: 2137

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CAG01086	MH0272_GL0018541	SEQ ID NO: 2138
CAG01086	V1.FI12_GL0168719	SEQ ID NO: 2139
CAG01086	MH0272_GL0044864	SEQ ID NO: 2140
CAG01086	MH0272_GL0208142	SEQ ID NO: 2141
CAG01086	V1.FI12_GL0199579	SEQ ID NO: 2142
CAG01086	MH0272_GL0042322	SEQ ID NO: 2143
CAG01086	MH0272_GL0199766	SEQ ID NO: 2144
CAG01086	MH0272_GL0098607	SEQ ID NO: 2145
CAG01086	MH0272_GL0081607	SEQ ID NO: 2146
CAG01086	MH0272_GL0014839	SEQ ID NO: 2147
CAG01086	MH0272_GL0181505	SEQ ID NO: 2148
CAG01086	MH0197_GL0027753	SEQ ID NO: 2149
CAG01086	V1.FI12_GL0102462	SEQ ID NO: 2150
CAG01086	V1.FI12_GL0055721	SEQ ID NO: 2151
CAG01086	MH0272_GL0094548	SEQ ID NO: 2152
CAG01086	MH0272_GL0077413	SEQ ID NO: 2153
CAG01086	MH0197_GL0175920	SEQ ID NO: 2154
CAG01086	MH0197_GL0047836	SEQ ID NO: 2155
CAG01086	MH0272_GL0016746	SEQ ID NO: 2156
CAG01086	V1.FI12_GL0190838	SEQ ID NO: 2157
CAG01086	MH0272_GL0077416	SEQ ID NO: 2158
CAG01086	MH0272_GL0217594	SEQ ID NO: 2159
CAG01086	MH0272_GL0070921	SEQ ID NO: 2160
CAG01086	MH0197_GL0115341	SEQ ID NO: 2161
CAG01086	MH0272_GL0105935	SEQ ID NO: 2162
CAG01086	MH0272_GL0033707	SEQ ID NO: 2163
CAG01086	V1.FI12_GL0185655	SEQ ID NO: 2164
CAG01086	MH0452_GL0230002	SEQ ID NO: 2165
CAG01086	MH0272_GL0051892	SEQ ID NO: 2166
CAG01086	MH0272_GL0040138	SEQ ID NO: 2167
CAG01086	MH0272_GL0172085	SEQ ID NO: 2168
CAG01086	MH0272_GL0106128	SEQ ID NO: 2169
CAG01086	MH0272_GL0077415	SEQ ID NO: 2170
CAG01086	MH0197_GL0111839	SEQ ID NO: 2171
CAG01086	MH0272_GL0126357	SEQ ID NO: 2172
CAG01086	V1.FI12_GL0152693	SEQ ID NO: 2173
CAG01086	MH0197_GL0020164	SEQ ID NO: 2174
CAG01086	MH0272_GL0201993	SEQ ID NO: 2175
CAG01086	MH0272_GL0061438	SEQ ID NO: 2176
CAG01215	MH0433_GL0246310	SEQ ID NO: 2177
CAG01215	MH0433_GL0002323	SEQ ID NO: 2178

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CAG01215	MH0433_GL0182338	SEQ ID NO: 2179
CAG01215	MH0433_GL0059452	SEQ ID NO: 2180
CAG01215	MH0433_GL0151518	SEQ ID NO: 2181
CAG01215	MH0433_GL0179521	SEQ ID NO: 2182
CAG01215	MH0433_GL0117415	SEQ ID NO: 2183
CAG01215	MH0433_GL0046627	SEQ ID NO: 2184
CAG01215	MH0433_GL0141413	SEQ ID NO: 2185
CAG01215	MH0433_GL0006791	SEQ ID NO: 2186
CAG01215	MH0433_GL0222378	SEQ ID NO: 2187
CAG01215	MH0433_GL0231566	SEQ ID NO: 2188
CAG01215	MH0433_GL0058495	SEQ ID NO: 2189
CAG01215	MH0433_GL0011928	SEQ ID NO: 2190
CAG01215	MH0433_GL0237792	SEQ ID NO: 2191
CAG01215	MH0433_GL0142574	SEQ ID NO: 2192
CAG01215	MH0433_GL0083732	SEQ ID NO: 2193
CAG01215	MH0433_GL0134574	SEQ ID NO: 2194
CAG01215	MH0433_GL0012830	SEQ ID NO: 2195
CAG01215	MH0433_GL0218821	SEQ ID NO: 2196
CAG01215	MH0433_GL0222379	SEQ ID NO: 2197
CAG01215	MH0433_GL0037988	SEQ ID NO: 2198
CAG01215	MH0433_GL0191549	SEQ ID NO: 2199
CAG01215	MH0433_GL0233278	SEQ ID NO: 2200
CAG01215	MH0433_GL0162961	SEQ ID NO: 2201
CAG01215	MH0433_GL0172751	SEQ ID NO: 2202
CAG01215	MH0433_GL0218452	SEQ ID NO: 2203
CAG01215	MH0433_GL0047571	SEQ ID NO: 2204
CAG01215	MH0433_GL0199159	SEQ ID NO: 2205
CAG01215	MH0433_GL0103567	SEQ ID NO: 2206
CAG01215	MH0433_GL0165868	SEQ ID NO: 2207
CAG01215	MH0433_GL0191255	SEQ ID NO: 2208
CAG01215	MH0433_GL0145241	SEQ ID NO: 2209
CAG01215	MH0433_GL0079550	SEQ ID NO: 2210
CAG01215	MH0433_GL0182566	SEQ ID NO: 2211
CAG01215	MH0433_GL0069540	SEQ ID NO: 2212
CAG01215	MH0433_GL0007656	SEQ ID NO: 2213
CAG01215	MH0433_GL0010719	SEQ ID NO: 2214
CAG01215	MH0433_GL0235599	SEQ ID NO: 2215
CAG01215	MH0433_GL0151460	SEQ ID NO: 2216
CAG01215	MH0433_GL0049378	SEQ ID NO: 2217
CAG01215	MH0433_GL0086943	SEQ ID NO: 2218
CAG01215	MH0433_GL0055538	SEQ ID NO: 2219

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CAG01215	MH0433_GL0102724	SEQ ID NO: 2220
CAG01215	MH0433_GL0141284	SEQ ID NO: 2221
CAG01215	MH0433_GL0108811	SEQ ID NO: 2222
CAG01215	MH0433_GL0006130	SEQ ID NO: 2223
CAG01215	MH0433_GL0041529	SEQ ID NO: 2224
CAG01215	MH0433_GL0149845	SEQ ID NO: 2225
CAG01215	MH0433_GL0176143	SEQ ID NO: 2226
CAG01277	MH0406_GL0208401	SEQ ID NO: 2227
CAG01277	MH0406_GL0212707	SEQ ID NO: 2228
CAG01277	MH0406_GL0081467	SEQ ID NO: 2229
CAG01277	MH0406_GL0198479	SEQ ID NO: 2230
CAG01277	MH0406_GL0114913	SEQ ID NO: 2231
CAG01277	V1.FI17_GL0113355	SEQ ID NO: 2232
CAG01277	MH0406_GL0159210	SEQ ID NO: 2233
CAG01277	V1.FI17_GL0158312	SEQ ID NO: 2234
CAG01277	MH0406_GL0176325	SEQ ID NO: 2235
CAG01277	MH0406_GL0168102	SEQ ID NO: 2236
CAG01277	MH0406_GL0145969	SEQ ID NO: 2237
CAG01277	MH0406_GL0060237	SEQ ID NO: 2238
CAG01277	MH0406_GL0015582	SEQ ID NO: 2239
CAG01277	MH0406_GL0126250	SEQ ID NO: 2240
CAG01277	MH0406_GL0053950	SEQ ID NO: 2241
CAG01277	MH0406_GL0053951	SEQ ID NO: 2242
CAG01277	MH0406_GL0090592	SEQ ID NO: 2243
CAG01277	MH0406_GL0163333	SEQ ID NO: 2244
CAG01277	MH0406_GL0142881	SEQ ID NO: 2245
CAG01277	MH0406_GL0155754	SEQ ID NO: 2246
CAG01277	MH0406_GL0198480	SEQ ID NO: 2247
CAG01277	MH0406_GL0207882	SEQ ID NO: 2248
CAG01277	MH0433_GL0150353	SEQ ID NO: 2249
CAG01277	MH0406_GL0142889	SEQ ID NO: 2250
CAG01277	MH0406_GL0213396	SEQ ID NO: 2251
CAG01277	MH0406_GL0003826	SEQ ID NO: 2252
CAG01277	MH0406_GL0198478	SEQ ID NO: 2253
CAG01277	MH0406_GL0130721	SEQ ID NO: 2254
CAG01277	MH0433_GL0150751	SEQ ID NO: 2255
CAG01277	MH0406_GL0150228	SEQ ID NO: 2256
CAG01277	MH0406_GL0003626	SEQ ID NO: 2257
CAG01277	MH0406_GL0058550	SEQ ID NO: 2258
CAG01277	MH0406_GL0157472	SEQ ID NO: 2259
CAG01277	MH0406_GL0142885	SEQ ID NO: 2260

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CAG01277	MH0406_GL0114916	SEQ ID NO: 2261
CAG01277	MH0406_GL0168103	SEQ ID NO: 2262
CAG01277	V1.FI02_GL0049212	SEQ ID NO: 2263
CAG01277	V1.FI02_GL0013181	SEQ ID NO: 2264
CAG01277	MH0406_GL0210050	SEQ ID NO: 2265
CAG01277	MH0406_GL0015606	SEQ ID NO: 2266
CAG01277	V1.FI17_GL0005209	SEQ ID NO: 2267
CAG01277	MH0406_GL0211031	SEQ ID NO: 2268
CAG01277	MH0406_GL0133735	SEQ ID NO: 2269
CAG01277	V1.FI02_GL0115051	SEQ ID NO: 2270
CAG01277	MH0406_GL0146427	SEQ ID NO: 2271
CAG01277	V1.FI17_GL0019567	SEQ ID NO: 2272
CAG01277	MH0406_GL0116594	SEQ ID NO: 2273
CAG01277	MH0406_GL0198381	SEQ ID NO: 2274
CAG01277	MH0406_GL0215713	SEQ ID NO: 2275
CAG01277	MH0433_GL0239178	SEQ ID NO: 2276
CAG01308	V1.FI36_GL0162409	SEQ ID NO: 2277
CAG01308	MH0244_GL0125576	SEQ ID NO: 2278
CAG01308	MH0234_GL0080290	SEQ ID NO: 2279
CAG01308	MH0244_GL0062145	SEQ ID NO: 2280
CAG01308	MH0244_GL0014298	SEQ ID NO: 2281
CAG01308	V1.FI36_GL0066337	SEQ ID NO: 2282
CAG01308	MH0244_GL0016761	SEQ ID NO: 2283
CAG01308	MH0244_GL0007228	SEQ ID NO: 2284
CAG01308	MH0244_GL0092742	SEQ ID NO: 2285
CAG01308	MH0234_GL0155898	SEQ ID NO: 2286
CAG01308	MH0244_GL0015948	SEQ ID NO: 2287
CAG01308	MH0244_GL0112042	SEQ ID NO: 2288
CAG01308	MH0325_GL0025548	SEQ ID NO: 2289
CAG01308	MH0364_GL0119824	SEQ ID NO: 2290
CAG01308	T2D-6A_GL0099679	SEQ ID NO: 2291
CAG01308	MH0244_GL0117600	SEQ ID NO: 2292
CAG01308	MH0244_GL0082661	SEQ ID NO: 2293
CAG01308	MH0244_GL0038215	SEQ ID NO: 2294
CAG01308	MH0244_GL0034934	SEQ ID NO: 2295
CAG01308	MH0220_GL0218242	SEQ ID NO: 2296
CAG01308	MH0244_GL0051207	SEQ ID NO: 2297
CAG01308	MH0323_GL0136858	SEQ ID NO: 2298
CAG01308	MH0234_GL0000384	SEQ ID NO: 2299
CAG01308	MH0234_GL0139816	SEQ ID NO: 2300
CAG01308	MH0364_GL0093837	SEQ ID NO: 2301

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CAG01308	MH0244_GL0034936	SEQ ID NO: 2302
CAG01308	MH0244_GL0067087	SEQ ID NO: 2303
CAG01308	V1.FI36_GL0004702	SEQ ID NO: 2304
CAG01308	MH0234_GL0087096	SEQ ID NO: 2305
CAG01308	MH0364_GL0152267	SEQ ID NO: 2306
CAG01308	MH0234_GL0047709	SEQ ID NO: 2307
CAG01308	MH0234_GL0106008	SEQ ID NO: 2308
CAG01308	MH0234_GL0161275	SEQ ID NO: 2309
CAG01308	MH0244_GL0025744	SEQ ID NO: 2310
CAG01308	MH0244_GL0050838	SEQ ID NO: 2311
CAG01308	T2D-6A_GL0189151	SEQ ID NO: 2312
CAG01308	MH0244_GL0033106	SEQ ID NO: 2313
CAG01308	MH0244_GL0093208	SEQ ID NO: 2314
CAG01308	T2D-15A_GL0176051	SEQ ID NO: 2315
CAG01308	MH0244_GL0041878	SEQ ID NO: 2316
CAG01308	MH0244_GL0093260	SEQ ID NO: 2317
CAG01308	MH0244_GL0053442	SEQ ID NO: 2318
CAG01308	MH0244_GL0062146	SEQ ID NO: 2319
CAG01308	MH0244_GL0036596	SEQ ID NO: 2320
CAG01308	V1.UC35-4_GL0069659	SEQ ID NO: 2321
CAG01308	MH0244_GL0050837	SEQ ID NO: 2322
CAG01308	MH0234_GL0165035	SEQ ID NO: 2323
CAG01308	MH0244_GL0044794	SEQ ID NO: 2324
CAG01308	MH0234_GL0109970	SEQ ID NO: 2325
CAG01308	MH0446_GL0183437	SEQ ID NO: 2326
CAG00577	O2.UC53-0_GL0258016	SEQ ID NO: 2327
CAG00577	MH0161_GL0105291	SEQ ID NO: 2328
CAG00577	MH0161_GL0102478	SEQ ID NO: 2329
CAG00577	MH0246_GL0006696	SEQ ID NO: 2330
CAG00577	MH0161_GL0023380	SEQ ID NO: 2331
CAG00577	MH0161_GL0129486	SEQ ID NO: 2332
CAG00577	MH0243_GL0076883	SEQ ID NO: 2333
CAG00577	MH0419_GL0188987	SEQ ID NO: 2334
CAG00577	V1.FI07_GL0058208	SEQ ID NO: 2335
CAG00577	MH0136_GL0032411	SEQ ID NO: 2336
CAG00577	MH0409_GL0012015	SEQ ID NO: 2337
CAG00577	MH0446_GL0261351	SEQ ID NO: 2338
CAG00577	MH0136_GL0100087	SEQ ID NO: 2339
CAG00577	BGI-34A_GL0104891	SEQ ID NO: 2340
CAG00577	MH0243_GL0060327	SEQ ID NO: 2341
CAG00577	MH0161_GL0121426	SEQ ID NO: 2342

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CAG00577	MH0161_GL0155126	SEQ ID NO: 2343
CAG00577	MH0276_GL0081418	SEQ ID NO: 2344
CAG00577	MH0251_GL0168754	SEQ ID NO: 2345
CAG00577	MH0377_GL0014956	SEQ ID NO: 2346
CAG00577	MH0187_GL0110670	SEQ ID NO: 2347
CAG00577	764669880-stool2_revised_scaffold10448_2_gene8524	SEQ ID NO: 2348
CAG00577	638754422-stool2_revised_scaffold8139_1_gene83549	SEQ ID NO: 2349
CAG00577	NOM027_GL0017049	SEQ ID NO: 2350
CAG00577	763901136-stool1_revised_scaffold19007_1_gene87186	SEQ ID NO: 2351
CAG00577	MH0161_GL0124558	SEQ ID NO: 2352
CAG00577	MH0122_GL0017342	SEQ ID NO: 2353
CAG00577	MH0161_GL0140082	SEQ ID NO: 2354
CAG00577	MH0360_GL0039102	SEQ ID NO: 2355
CAG00577	T2D-70A_GL0068462	SEQ ID NO: 2356
CAG00577	SZEY-27A_GL0042977	SEQ ID NO: 2357
CAG00577	MH0205_GL0010899	SEQ ID NO: 2358
CAG00577	V1.UC29-0_GL0089797	SEQ ID NO: 2359
CAG00577	MH0122_GL0103058	SEQ ID NO: 2360
CAG00577	MH0187_GL0139420	SEQ ID NO: 2361
CAG00577	MH0335_GL0015488	SEQ ID NO: 2362
CAG00577	NOM027_GL0026387	SEQ ID NO: 2363
CAG00577	MH0187_GL0161161	SEQ ID NO: 2364
CAG00577	MH0161_GL0136297	SEQ ID NO: 2365
CAG00577	MH0119_GL0032510	SEQ ID NO: 2366
CAG00577	MH0264_GL0010910	SEQ ID NO: 2367
CAG00577	718252.FP2_01730	SEQ ID NO: 2368
CAG00577	MH0176_GL0108424	SEQ ID NO: 2369
CAG00577	DOM001_GL0044227	SEQ ID NO: 2370
CAG00577	N052A_GL0044576	SEQ ID NO: 2371
CAG00577	MH0161_GL0138976	SEQ ID NO: 2372
CAG00577	MH0192_GL0138753	SEQ ID NO: 2373
CAG00577	MH0161_GL0035380	SEQ ID NO: 2374
CAG00577	MH0122_GL0085848	SEQ ID NO: 2375
CAG00577	MH0161_GL0148787	SEQ ID NO: 2376
CAG00506	V1.FI06_GL0142877	SEQ ID NO: 2377
CAG00506	V1.FI06_GL0081750	SEQ ID NO: 2378
CAG00506	MH0245_GL0098106	SEQ ID NO: 2379
CAG00506	MH0193_GL0061145	SEQ ID NO: 2380
CAG00506	O2.UC8-1_GL0071926	SEQ ID NO: 2381

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CAG00506	V1.FI06_GL0177878	SEQ ID NO: 2382
CAG00506	V1.FI28_GL0124123	SEQ ID NO: 2383
CAG00506	MH0245_GL0120503	SEQ ID NO: 2384
CAG00506	MH0245_GL0092011	SEQ ID NO: 2385
CAG00506	V1.FI10_GL0059693	SEQ ID NO: 2386
CAG00506	O2.UC49-0_GL0011326	SEQ ID NO: 2387
CAG00506	MH0203_GL0113000	SEQ ID NO: 2388
CAG00506	V1.FI20_GL0186097	SEQ ID NO: 2389
CAG00506	V1.FI06_GL0107857	SEQ ID NO: 2390
CAG00506	V1.FI06_GL0098842	SEQ ID NO: 2391
CAG00506	O2.UC49-0_GL0130004	SEQ ID NO: 2392
CAG00506	MH0358_GL0115004	SEQ ID NO: 2393
CAG00506	V1.FI06_GL0024747	SEQ ID NO: 2394
CAG00506	MH0239_GL0117717	SEQ ID NO: 2395
CAG00506	MH0239_GL0116017	SEQ ID NO: 2396
CAG00506	MH0233_GL0077458	SEQ ID NO: 2397
CAG00506	O2.UC49-0_GL0070852	SEQ ID NO: 2398
CAG00506	O2.UC49-0_GL0108955	SEQ ID NO: 2399
CAG00506	V1.FI06_GL0203007	SEQ ID NO: 2400
CAG00506	MH0378_GL0199978	SEQ ID NO: 2401
CAG00506	V1.FI06_GL0046835	SEQ ID NO: 2402
CAG00506	MH0245_GL0041180	SEQ ID NO: 2403
CAG00506	MH0203_GL0089458	SEQ ID NO: 2404
CAG00506	MH0245_GL0125120	SEQ ID NO: 2405
CAG00506	MH0203_GL0064889	SEQ ID NO: 2406
CAG00506	MH0245_GL0071752	SEQ ID NO: 2407
CAG00506	MH0203_GL0200298	SEQ ID NO: 2408
CAG00506	V1.FI20_GL0027361	SEQ ID NO: 2409
CAG00506	MH0203_GL0178685	SEQ ID NO: 2410
CAG00506	V1.FI10_GL0046508	SEQ ID NO: 2411
CAG00506	MH0432_GL0047693	SEQ ID NO: 2412
CAG00506	O2.UC49-0_GL0121013	SEQ ID NO: 2413
CAG00506	MH0462_GL0072403	SEQ ID NO: 2414
CAG00506	MH0203_GL0133407	SEQ ID NO: 2415
CAG00506	MH0203_GL0208700	SEQ ID NO: 2416
CAG00506	V1.FI06_GL0090451	SEQ ID NO: 2417
CAG00506	MH0203_GL0189162	SEQ ID NO: 2418
CAG00506	O2.UC11-1_GL0130864	SEQ ID NO: 2419
CAG00506	MH0239_GL0150262	SEQ ID NO: 2420
CAG00506	MH0239_GL0100836	SEQ ID NO: 2421
CAG00506	MH0203_GL0271131	SEQ ID NO: 2422

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CAG00506	MH0378_GL0026482	SEQ ID NO: 2423
CAG00506	V1.FI06_GL0103649	SEQ ID NO: 2424
CAG00506	MH0245_GL0014270	SEQ ID NO: 2425
CAG00506	O2.UC8-1_GL0090917	SEQ ID NO: 2426
CAG00852	428126.CLOSPI_01703	SEQ ID NO: 2427
CAG00852	428126.CLOSPI_01048	SEQ ID NO: 2428
CAG00852	T2D-62A_GL0056517	SEQ ID NO: 2429
CAG00852	V1.UC55-0_GL0234527	SEQ ID NO: 2430
CAG00852	428126.CLOSPI_00163	SEQ ID NO: 2431
CAG00852	T2D-62A_GL0062993	SEQ ID NO: 2432
CAG00852	428126.CLOSPI_02499	SEQ ID NO: 2433
CAG00852	T2D-62A_GL0063552	SEQ ID NO: 2434
CAG00852	T2D-62A_GL0037637	SEQ ID NO: 2435
CAG00852	428126.CLOSPI_01729	SEQ ID NO: 2436
CAG00852	428126.CLOSPI_01154	SEQ ID NO: 2437
CAG00852	T2D-62A_GL0042747	SEQ ID NO: 2438
CAG00852	O2.UC48-0_GL0287483	SEQ ID NO: 2439
CAG00852	T2D-62A_GL0007270	SEQ ID NO: 2440
CAG00852	428126.CLOSPI_01676	SEQ ID NO: 2441
CAG00852	T2D-62A_GL0005689	SEQ ID NO: 2442
CAG00852	428126.CLOSPI_00564	SEQ ID NO: 2443
CAG00852	T2D-62A_GL0018962	SEQ ID NO: 2444
CAG00852	428126.CLOSPI_01979	SEQ ID NO: 2445
CAG00852	T2D-62A_GL0003361	SEQ ID NO: 2446
CAG00852	763820215-stool1_revised_C753290_1_gene28165	SEQ ID NO: 2447
CAG00852	T2D-62A_GL0015998	SEQ ID NO: 2448
CAG00852	428126.CLOSPI_00074	SEQ ID NO: 2449
CAG00852	T2D-62A_GL0003189	SEQ ID NO: 2450
CAG00852	763820215-stool1_revised_C751872_1_gene53758	SEQ ID NO: 2451
CAG00852	428126.CLOSPI_00417	SEQ ID NO: 2452
CAG00852	T2D-62A_GL0002497	SEQ ID NO: 2453
CAG00852	763820215-stool1_revised_C753944_1_gene52720	SEQ ID NO: 2454
CAG00852	428126.CLOSPI_02466	SEQ ID NO: 2455
CAG00852	T2D-62A_GL0035007	SEQ ID NO: 2456
CAG00852	T2D-62A_GL0003764	SEQ ID NO: 2457
CAG00852	V1.UC41-0_GL0059442	SEQ ID NO: 2458
CAG00852	T2D-62A_GL0024874	SEQ ID NO: 2459
CAG00852	428126.CLOSPI_01977	SEQ ID NO: 2460
CAG00852	428126.CLOSPI_02118	SEQ ID NO: 2461

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CAG00852	T2D-62A_GL0037428	SEQ ID NO: 2462
CAG00852	763820215-stool1_revised_C751758_1_gene22231	SEQ ID NO: 2463
CAG00852	T2D-62A_GL0039739	SEQ ID NO: 2464
CAG00852	T2D-62A_GL0058023	SEQ ID NO: 2465
CAG00852	T2D-62A_GL0031255	SEQ ID NO: 2466
CAG00852	T2D-62A_GL0033716	SEQ ID NO: 2467
CAG00852	428126.CLOSPI_00717	SEQ ID NO: 2468
CAG00852	T2D-62A_GL0030287	SEQ ID NO: 2469
CAG00852	428126.CLOSPI_00347	SEQ ID NO: 2470
CAG00852	T2D-62A_GL0037352	SEQ ID NO: 2471
CAG00852	T2D-62A_GL0060825	SEQ ID NO: 2472
CAG00852	428126.CLOSPI_00649	SEQ ID NO: 2473
CAG00852	T2D-62A_GL0036985	SEQ ID NO: 2474
CAG00852	T2D-62A_GL0062259	SEQ ID NO: 2475
CAG00852	T2D-62A_GL0014638	SEQ ID NO: 2476
CAG01046	MH0419_GL0134444	SEQ ID NO: 2477
CAG01046	MH0419_GL0081415	SEQ ID NO: 2478
CAG01046	T2D-11A_GL0089312	SEQ ID NO: 2479
CAG01046	V1.UC26-4_GL0178700	SEQ ID NO: 2480
CAG01046	MH0419_GL0141746	SEQ ID NO: 2481
CAG01046	MH0419_GL0161227	SEQ ID NO: 2482
CAG01046	MH0419_GL0057166	SEQ ID NO: 2483
CAG01046	MH0419_GL0101764	SEQ ID NO: 2484
CAG01046	MH0419_GL0055784	SEQ ID NO: 2485
CAG01046	MH0419_GL0009850	SEQ ID NO: 2486
CAG01046	MH0419_GL0144211	SEQ ID NO: 2487
CAG01046	MH0419_GL0129970	SEQ ID NO: 2488
CAG01046	MH0419_GL0133667	SEQ ID NO: 2489
CAG01046	MH0419_GL0087423	SEQ ID NO: 2490
CAG01046	MH0419_GL0128079	SEQ ID NO: 2491
CAG01046	MH0419_GL0181480	SEQ ID NO: 2492
CAG01046	MH0419_GL0089745	SEQ ID NO: 2493
CAG01046	V1.UC26-4_GL0196540	SEQ ID NO: 2494
CAG01046	MH0402_GL0215165	SEQ ID NO: 2495
CAG01046	MH0419_GL0134445	SEQ ID NO: 2496
CAG01046	MH0419_GL0094834	SEQ ID NO: 2497
CAG01046	MH0419_GL0113310	SEQ ID NO: 2498
CAG01046	MH0419_GL0033530	SEQ ID NO: 2499
CAG01046	MH0419_GL0173114	SEQ ID NO: 2500
CAG01046	MH0419_GL0121366	SEQ ID NO: 2501

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CAG01046	MH0419_GL0188727	SEQ ID NO: 2502
CAG01046	MH0419_GL0167995	SEQ ID NO: 2503
CAG01046	MH0419_GL0109090	SEQ ID NO: 2504
CAG01046	MH0419_GL0139393	SEQ ID NO: 2505
CAG01046	MH0419_GL0028139	SEQ ID NO: 2506
CAG01046	MH0419_GL0134374	SEQ ID NO: 2507
CAG01046	MH0419_GL0129214	SEQ ID NO: 2508
CAG01046	MH0419_GL0015783	SEQ ID NO: 2509
CAG01046	MH0419_GL0136244	SEQ ID NO: 2510
CAG01046	MH0419_GL0058520	SEQ ID NO: 2511
CAG01046	MH0419_GL0093672	SEQ ID NO: 2512
CAG01046	MH0419_GL0081494	SEQ ID NO: 2513
CAG01046	MH0419_GL0071701	SEQ ID NO: 2514
CAG01046	V1.UC26-4_GL0014931	SEQ ID NO: 2515
CAG01046	MH0419_GL0021131	SEQ ID NO: 2516
CAG01046	MH0419_GL0154413	SEQ ID NO: 2517
CAG01046	MH0419_GL0065735	SEQ ID NO: 2518
CAG01046	MH0419_GL0154182	SEQ ID NO: 2519
CAG01046	V1.UC26-4_GL0114982	SEQ ID NO: 2520
CAG01046	MH0419_GL0093098	SEQ ID NO: 2521
CAG01046	MH0419_GL0119499	SEQ ID NO: 2522
CAG01046	MH0419_GL0031857	SEQ ID NO: 2523
CAG01046	MH0419_GL0126857	SEQ ID NO: 2524
CAG01046	V1.UC26-4_GL0009310	SEQ ID NO: 2525
CAG01046	MH0419_GL0189867	SEQ ID NO: 2526
CAG00320	MH0026_GL0048591	SEQ ID NO: 2527
CAG00320	NOM005_GL0026873	SEQ ID NO: 2528
CAG00320	764143897-stool2_revised_scaffold25132_1_gene18467	SEQ ID NO: 2529
CAG00320	MH0425_GL0149489	SEQ ID NO: 2530
CAG00320	158742018-stool1_revised_C792715_1_gene81439	SEQ ID NO: 2531
CAG00320	NOF008_GL0017986	SEQ ID NO: 2532
CAG00320	O2.UC59-2_GL0012634	SEQ ID NO: 2533
CAG00320	MH0016_GL0070979	SEQ ID NO: 2534
CAG00320	MH0184_GL0080481	SEQ ID NO: 2535
CAG00320	158742018-stool1_revised_scaffold24144_1_gene122932	SEQ ID NO: 2536
CAG00320	MH0089_GL0068788	SEQ ID NO: 2537
CAG00320	MH0016_GL0078176	SEQ ID NO: 2538
CAG00320	160421117-stool1_revised_C297599_1_gene60160	SEQ ID NO: 2539

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CAG00320	706846339-stool1_revised_scaffold53564_1_gene171437	SEQ ID NO: 2540
CAG00320	MH0026_GL0006163	SEQ ID NO: 2541
CAG00320	MH0016_GL0036082	SEQ ID NO: 2542
CAG00320	NLM007_GL0004685	SEQ ID NO: 2543
CAG00320	MH0150_GL0154882	SEQ ID NO: 2544
CAG00320	T2D-149A_GL0033867	SEQ ID NO: 2545
CAG00320	MH0016_GL0011934	SEQ ID NO: 2546
CAG00320	NLM017_GL0047166	SEQ ID NO: 2547
CAG00320	764062976-stool1_revised_C1266385_1_gene114204	SEQ ID NO: 2548
CAG00320	MH0026_GL0039721	SEQ ID NO: 2549
CAG00320	DOF013_GL0043028	SEQ ID NO: 2550
CAG00320	MH0016_GL0082126	SEQ ID NO: 2551
CAG00320	MH0089_GL0034565	SEQ ID NO: 2552
CAG00320	O2.UC35-0_GL0081200	SEQ ID NO: 2553
CAG00320	V1.UC11-0_GL0089485	SEQ ID NO: 2554
CAG00320	MH0026_GL0013353	SEQ ID NO: 2555
CAG00320	NOM007_GL0045210	SEQ ID NO: 2556
CAG00320	MH0016_GL0075426	SEQ ID NO: 2557
CAG00320	MH0026_GL0019542	SEQ ID NO: 2558
CAG00320	MH0016_GL0014232	SEQ ID NO: 2559
CAG00320	T2D-178A_GL0095543	SEQ ID NO: 2560
CAG00320	NLM005_GL0019993	SEQ ID NO: 2561
CAG00320	765094712-stool1_revised_C356815_1_gene59944	SEQ ID NO: 2562
CAG00320	DOM020_GL0029204	SEQ ID NO: 2563
CAG00320	DOM019_GL0099701	SEQ ID NO: 2564
CAG00320	O2.UC59-2_GL0006731	SEQ ID NO: 2565
CAG00320	SZEY-68A_GL0089081	SEQ ID NO: 2566
CAG00320	DOM021_GL0005579	SEQ ID NO: 2567
CAG00320	NLF014_GL0047448	SEQ ID NO: 2568
CAG00320	N044A_GL0039024	SEQ ID NO: 2569
CAG00320	764325968-stool2_revised_scaffold4874_1_gene4212	SEQ ID NO: 2570
CAG00320	MH0026_GL0044579	SEQ ID NO: 2571
CAG00320	T2D-140A_GL0085864	SEQ ID NO: 2572
CAG00320	160400887-stool1_revised_C1320145_1_gene238639	SEQ ID NO: 2573
CAG00320	MH0026_GL0018472	SEQ ID NO: 2574
CAG00320	NLM005_GL0048100	SEQ ID NO: 2575
CAG00320	MH0445_GL0034623	SEQ ID NO: 2576

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CAG00619	O2.UC27-1_GL0096976	SEQ ID NO: 2577
CAG00619	MH0230_GL0113758	SEQ ID NO: 2578
CAG00619	MH0425_GL0121626	SEQ ID NO: 2579
CAG00619	MH0244_GL0025967	SEQ ID NO: 2580
CAG00619	MH0244_GL0032296	SEQ ID NO: 2581
CAG00619	MH0271_GL0061023	SEQ ID NO: 2582
CAG00619	O2.UC38-2_GL0069803	SEQ ID NO: 2583
CAG00619	MH0204_GL0120612	SEQ ID NO: 2584
CAG00619	MH0244_GL0010807	SEQ ID NO: 2585
CAG00619	MH0204_GL0179682	SEQ ID NO: 2586
CAG00619	MH0204_GL0036337	SEQ ID NO: 2587
CAG00619	MH0193_GL0128370	SEQ ID NO: 2588
CAG00619	MH0272_GL0006105	SEQ ID NO: 2589
CAG00619	MH0204_GL0007448	SEQ ID NO: 2590
CAG00619	MH0244_GL0123950	SEQ ID NO: 2591
CAG00619	MH0204_GL0176256	SEQ ID NO: 2592
CAG00619	V1.FI28_GL0078516	SEQ ID NO: 2593
CAG00619	MH0230_GL0095497	SEQ ID NO: 2594
CAG00619	MH0204_GL0074260	SEQ ID NO: 2595
CAG00619	MH0230_GL0167508	SEQ ID NO: 2596
CAG00619	MH0204_GL0098332	SEQ ID NO: 2597
CAG00619	MH0244_GL0082048	SEQ ID NO: 2598
CAG00619	MH0204_GL0039377	SEQ ID NO: 2599
CAG00619	MH0244_GL0008613	SEQ ID NO: 2600
CAG00619	MH0244_GL0022447	SEQ ID NO: 2601
CAG00619	MH0412_GL0150687	SEQ ID NO: 2602
CAG00619	MH0244_GL0043838	SEQ ID NO: 2603
CAG00619	MH0204_GL0088591	SEQ ID NO: 2604
CAG00619	MH0204_GL0003543	SEQ ID NO: 2605
CAG00619	MH0244_GL0046019	SEQ ID NO: 2606
CAG00619	MH0230_GL0158262	SEQ ID NO: 2607
CAG00619	MH0305_GL0053525	SEQ ID NO: 2608
CAG00619	MH0230_GL0097229	SEQ ID NO: 2609
CAG00619	MH0204_GL0058174	SEQ ID NO: 2610
CAG00619	MH0204_GL0190107	SEQ ID NO: 2611
CAG00619	MH0425_GL0083676	SEQ ID NO: 2612
CAG00619	MH0162_GL0125751	SEQ ID NO: 2613
CAG00619	MH0193_GL0053644	SEQ ID NO: 2614
CAG00619	MH0230_GL0023755	SEQ ID NO: 2615
CAG00619	MH0193_GL0121539	SEQ ID NO: 2616
CAG00619	V1.FI28_GL0081089	SEQ ID NO: 2617

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CAG00619	MH0230_GL0127895	SEQ ID NO: 2618
CAG00619	MH0193_GL0111037	SEQ ID NO: 2619
CAG00619	MH0162_GL0105293	SEQ ID NO: 2620
CAG00619	764325968-stool2_revised_scaffold26651_2_gene129299	SEQ ID NO: 2621
CAG00619	MH0244_GL0138477	SEQ ID NO: 2622
CAG00619	MH0204_GL0146978	SEQ ID NO: 2623
CAG00619	MH0204_GL0176255	SEQ ID NO: 2624
CAG00619	MH0244_GL0075789	SEQ ID NO: 2625
CAG00619	MH0230_GL0158307	SEQ ID NO: 2626
CAG01366	760570.HMPREF0833_11447	SEQ ID NO: 2627
CAG01366	MH0003_GL0009797	SEQ ID NO: 2628
CAG01366	MH0003_GL0094252	SEQ ID NO: 2629
CAG01366	MH0003_GL0010084	SEQ ID NO: 2630
CAG01366	MH0003_GL0022325	SEQ ID NO: 2631
CAG01366	MH0003_GL0046585	SEQ ID NO: 2632
CAG01366	MH0003_GL0056693	SEQ ID NO: 2633
CAG01366	MH0003_GL0095863	SEQ ID NO: 2634
CAG01366	MH0003_GL0045418	SEQ ID NO: 2635
CAG01366	ED9A_GL0093685	SEQ ID NO: 2636
CAG01366	MH0003_GL0065032	SEQ ID NO: 2637
CAG01366	760570.HMPREF0833_11360	SEQ ID NO: 2638
CAG01366	760570.HMPREF0833_12012	SEQ ID NO: 2639
CAG01366	MH0003_GL0090470	SEQ ID NO: 2640
CAG01366	MH0003_GL0046474	SEQ ID NO: 2641
CAG01366	MH0003_GL0040447	SEQ ID NO: 2642
CAG01366	MH0003_GL0018280	SEQ ID NO: 2643
CAG01366	MH0003_GL0070887	SEQ ID NO: 2644
CAG01366	MH0003_GL0097555	SEQ ID NO: 2645
CAG01366	MH0003_GL0075033	SEQ ID NO: 2646
CAG01366	760570.HMPREF0833_10311	SEQ ID NO: 2647
CAG01366	MH0003_GL0050527	SEQ ID NO: 2648
CAG01366	MH0003_GL0070890	SEQ ID NO: 2649
CAG01366	MH0003_GL0075034	SEQ ID NO: 2650
CAG01366	MH0003_GL0114233	SEQ ID NO: 2651
CAG01366	NLM027_GL0005333	SEQ ID NO: 2652
CAG01366	MH0003_GL0002987	SEQ ID NO: 2653
CAG01366	MH0003_GL0088953	SEQ ID NO: 2654
CAG01366	MH0003_GL0042367	SEQ ID NO: 2655
CAG01366	MH0287_GL0136304	SEQ ID NO: 2656
CAG01366	MH0003_GL0039649	SEQ ID NO: 2657

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CAG01366	MH0003_GL0046477	SEQ ID NO: 2658
CAG01366	MH0003_GL0001128	SEQ ID NO: 2659
CAG01366	MH0003_GL0029627	SEQ ID NO: 2660
CAG01366	MH0003_GL0036396	SEQ ID NO: 2661
CAG01366	MH0003_GL0037301	SEQ ID NO: 2662
CAG01366	MH0287_GL0182172	SEQ ID NO: 2663
CAG01366	MH0003_GL0024528	SEQ ID NO: 2664
CAG01366	MH0003_GL0046587	SEQ ID NO: 2665
CAG01366	760570.HMPREF0833_11647	SEQ ID NO: 2666
CAG01366	MH0003_GL0009545	SEQ ID NO: 2667
CAG01366	MH0003_GL0087011	SEQ ID NO: 2668
CAG01366	760570.HMPREF0833_10973	SEQ ID NO: 2669
CAG01366	MH0003_GL0103117	SEQ ID NO: 2670
CAG01366	MH0003_GL0114020	SEQ ID NO: 2671
CAG01366	MH0003_GL0088954	SEQ ID NO: 2672
CAG01366	MH0003_GL0079951	SEQ ID NO: 2673
CAG01366	MH0003_GL0034625	SEQ ID NO: 2674
CAG01366	ED9A_GL0070789	SEQ ID NO: 2675
CAG01366	MH0003_GL0078182	SEQ ID NO: 2676

[00116] The present disclosure also provides a pharmaceutical composition comprising one or more microbial cultures as described above. The bacterial species therefore are present in the dose form as live bacteria, whether in dried, lyophilized, or sporolated form. This may be preferably adapted for suitable administration; for example, in tablet or powder form, potentially with an enteric coating, for oral treatment.

[00117] In particular aspects, the composition is formulated for oral administration. Oral administration may be achieved using a chewable formulation, a dissolving formulation, an encapsulated/coated formulation, a multi-layered lozenge (to separate active ingredients and/or active ingredients and excipients), a slow release/timed release formulation, or other suitable formulations known to persons skilled in the art. Although the word "tablet" is used herein, the formulation may take a variety of physical forms that may commonly be referred to by other terms, such as lozenge, pill, capsule, or the like.

[00118] While the compositions of the present disclosure are preferably formulated for oral administration, other routes of administration can be employed, however, including, but

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not limited to, subcutaneous, intramuscular, intradermal, transdermal, intraocular, intraperitoneal, mucosal, vaginal, rectal, and intravenous.

[00119] The desired dose of the composition of the present disclosure may be presented in multiple (*e.g.*, two, three, four, five, six, or more) sub-doses administered at appropriate intervals throughout the day.

[00120] In one aspect, the disclosed composition may be prepared as a capsule. The capsule (*i.e.,* the carrier) may be a hollow, generally cylindrical capsule formed from various substances, such as gelatin, cellulose, carbohydrate or the like.

[00121] In another aspect, the disclosed composition may be prepared as a suppository. The suppository may include but is not limited to the bacteria and one or more carriers, such as polyethylene glycol, acacia, acetylated monoglycerides, carnuba wax, cellulose acetate phthalate, corn starch, dibutyl phthalate, docusate sodium, gelatin, glycerin, iron oxides, kaolin, lactose, magnesium stearate, methyl paraben, pharmaceutical glaze, povidone, propyl paraben, sodium benzoate, sorbitan monoleate, sucrose talc, titanium dioxide, white wax and coloring agents.

[00122] In some aspects, the disclosed probiotic may be prepared as a tablet. The tablet may include the bacteria and one or more tableting agents (*i.e.*, carriers), such as dibasic calcium phosphate, stearic acid, croscarmellose, silica, cellulose and cellulose coating. The tablets may be formed using a direct compression process, though those skilled in the art will appreciate that various techniques may be used to form the tablets.

[00123] In other aspects, the disclosed probiotic may be formed as food or drink or, alternatively, as an additive to food or drink, wherein an appropriate quantity of bacteria is added to the food or drink to render the food or drink the carrier.

[00124] The probiotic compositions of the present disclosure may further comprise one or more prebiotics known in the art, such as lactitol, inulin, or a combination thereof.

[00125] 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 aspects, the

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species of bacteria produce butyrate. For example, the bacterial population can comprise one or more bacterial species of the order Clostridiales. The Clostridiales bacteria may be substantially in spore form. In particular aspects, the bacterial species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease. In some embodiments, the Clostridiales bacteria comprise a first family and a second family. In some embodiments, the first family is selected from the group consisting of Ruminococcaceae, Christensenellaceae, Clostridiaceae and Coriobacteriacease, and the second family is not identical to the first family. 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.* In certain embodiments, the bacterial population does not comprise bacterial species of the class Bacteroidia or family Prevotellaceae.

[00126] In some embodiments, the bacterial population comprises bacteria of the order Clostridiales in an amount effective or sufficient to produce one or more metabolites capable of enhancing immune checkpoint therapy in the subject. In some embodiments, the one or more metabolites comprise a short chain fatty acid. In particular aspects, the short chain fatty acid is butyrate. In some embodiments, the order Clostridiales produce one or more short chain fatty acids (*e.g.,* butyrate) in an effective amount to increase the local short chain fatty acid concentration by 2-fold, 4-fold, 5-fold, 10-fold, 50-fold, 100-fold, 1000-fold, or over 1000-fold.

[00127] In some embodiments, the probiotic composition may further comprise a food or a nutritional supplement effective to stimulate the growth of bacteria of the order Clostridiales present in the gastrointestinal tract of the subject. In some embodiments, the nutritional supplement is produced by a bacterium associated with a healthy human gut microbiome. In certain embodiments, the nutritional supplement is produced by bacteria of the

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order Clostridiales. In certain embodiments, the nutritional supplement comprises a short chain fatty acid. In certain embodiments, the short chain fatty acid is selected from butyrate, propionate, or a combination thereof. In particular embodiments, the short chain fatty acid is butyrate.

[00128] Accordingly, certain embodiments of the present disclosure concern administering butyrate prodrugs or salts to a subject who has been or is currently being administered an immune checkpoint inhibitor. For example, the butyrate may be sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, AN-9 or AN-10. Prodrugs and salts of butyrate have been described in WO 96/15660 and in U.S. Patent No. 5,763,488, the disclosures of which are herein incorporated by reference. Other orally available prodrugs and salts of butyrate that may be admnistered include, but are not limited to, isobutyramide, 1-octyl butyrate, orthonitrobenzyl butyrate, monobutyrate-3- monoacetone glucose, monobutyrate-1-monoacetone mannose, monobutyrate xylitol, isobutyramide, 4- phenylbutyrate, and 4-phenyl acetate. Each of these compounds releases butyrate or a butyrate analog into the blood stream upon administration. One or more isoforms of butyrate can include butyl butyrate, amyl butyrate, isobutyl butyrate, benzyl butyrate, a-methylbenzyl butyrate, hexyl butyrate, heptyl butyrate, pennetyl butyrate, methyl butyrate, and 2-hydroxy-3-methylbutanoic acid.

[00129] In further embodiments, the present disclosure concerns methods of obtaining a microbiome profile, comprising the steps of: i) obtaining a sample obtained from a subject (*e.g.,* a human subject), ii) isolating one or more bacterial species from the sample, iii) isolating one or more nucleic acids from at least one bacterial species, iv) sequencing the isolated nucleic acids, and v) comparing the sequenced nucleic acids to a reference nucleic acid sequence. When performing the methods necessitating genotyping, any genotyping assay can be used. For example, this can be done by sequencing the 16S or the 23S ribosomal subunit or by metagenomics shotgun DNA sequencing associated with metatranscriptomics. The biological sample may be selected from the group comprising: whole blood, blood plasma, urine, tears, semen, saliva, buccal mucosa, interstitial fluid, lymph fluid, meningeal fluid, amniotic fluid, glandular fluid, sputum, feces, perspiration, mucous, vaginal secretion, cerebrospinal fluid, hair, skin, fecal material, wound exudate, wound homogenate, and wound fluid. In particular aspects, the sample is fecal material or a buccal sample.

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[00130] In some embodiments, the microbiome profile is identified to be favorable for immune checkpoint therapy. A favorable microbial profile would have a high relative abundance of one or more bacterial species from the phylum Firmicutes, class Clostridia, order Clostridiales, family Ruminococcaceae, genus *Ruminococcus*, genus *Hydrogenoanaerobacterium*, genus *Faecalibacterium*, phylum Actinobacteria, class Coriobacteriia, order Coriaobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota or famly Christensenellaceae. A favorable microbial profile would have a low relative abundance of bacteria from the genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroida, order Bacteroidales or family Prevotellaceae. Accordingly, a favorable microbial profile would have a higher relative abundance of one or more bacterial species from the phylum Firmicutes, class Clostridia, order Clostridiales, famiy Ruminococcaceae, genus *Ruminococcus*, genus *Hydrogenoanaerobacterium*, phylum Actinobacteria, class Coriobacteria, order Coriaobacteriales, family Coriobacteriaceae, domain Archaea, phylum Cyanobacteria, phylum Euryarchaeota or family Christensenellaceae, and would have a decreased abundance of one or more bacterial species from genus *Dialister*, family Veillonellaceae, phylum Bacteroidetes, class Bacteroida, order Bacteroidales and/or family Prevotellaceae.

III. Immune Checkpoint Blockade

[00131] The present disclosure provides methods of enhancing the efficacy of immune checkpoint blockade by modulating the microbiome of a subject, such as by administering a short-chain fatty acid, such as butyrate, and/or a composition comprising one or more populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. Immune checkpoints either turn up a signal (*e.g.,* co-stimulatory molecules) or turn down a signal. Inhibitory immune checkpoint molecules that may be targeted by immune checkpoint blockade include adenosine A2A receptor (A2AR), B7-H3 (also known as CD276), B and T lymphocyte attenuator (BTLA), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, also known as CD152), indoleamine 2,3-dioxygenase (IDO), killer-cell immunoglobulin (KIR), lymphocyte activation gene-3 (LAG3), programmed death 1 (PD-1), T-cell immunoglobulin domain and mucin domain 3 (TIM-3) and V-domain Ig suppressor of T cell activation (VISTA). In particular, the immune checkpoint inhibitors target the PD-1 axis and/or CTLA-4.

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[00132] The immune checkpoint inhibitors may be drugs such as small molecules, recombinant forms of ligand or receptors, or, antibodies, such as human antibodies (*e.g.,* International Patent Publication No. WO2015016718; Pardoll, *Nat Rev Cancer,* 12(4): 252-64, 2012; both incorporated herein by reference). Known inhibitors of the immune checkpoint proteins or analogs thereof may be used, in particular chimerized, humanized or human forms of antibodies may be used. As the skilled person will know, alternative and/or equivalent names may be in use for certain antibodies mentioned in the present disclosure. Such alternative and/or equivalent names are interchangeable in the context of the present invention. For example it is known that lambrolizumab is also known under the alternative and equivalent names MK-3475 and pembrolizumab.

[00133] It is contemplated that any of the immune checkpoint inhibitors that are known in the art to stimulate immune responses may be used. This includes inhibitors that directly or indirectly stimulate or enhance antigen-specific T-lymphocytes. These immune checkpoint inhibitors include, without limitation, agents targeting immune checkpoint proteins and pathways involving PD-L2, LAG3, BTLA, B7H4 and TIM3. For example, LAG3 inhibitors known in the art include soluble LAG3 (IMP321, or LAG3-Ig disclosed in WO2009044273) as well as mouse or humanized antibodies blocking human LAG3 (*e.g.,* IMP701 disclosed in WO2008132601), or fully human antibodies blocking human LAG3 (such as disclosed in EP 2320940). Another example is provided by the use of blocking agents towards BTLA, including without limitation antibodies blocking human BTLA interaction with its ligand (such as 4C7 disclosed in WO2011014438). Yet another example is provided by the use of agents neutralizing B7H4 including without limitation antibodies to human B7H4 (disclosed in WO 2013025779, and in WO2013067492) or soluble recombinant forms of B7H4 (such as disclosed in US20120177645). Yet another example is provided by agents neutralizing B7-H3, including without limitation antibodies neutralizing human B7-H3 (*e.g.* MGA271 disclosed as BRCA84D and derivatives in US 20120294796). Yet another example is provided by agents targeting TIM3, including without limitation antibodies targeting human TIM3 (*e.g.* as disclosed in WO 2013006490 A2 or the anti-human TIM3, blocking antibody F38-2E2 disclosed by Jones *et al.*, J Exp Med. 2008; 205(12):2763-79).

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A. PD-1 Axis Antagonists

[00134] T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). Thus, therapeutic targeting of PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-Ll) and programmed death ligand 2 (PD-L2) is provided herein. PD-Ll is overexpressed in many cancers and is often associated with poor prognosis (Okazaki T *et al.*, Intern. Immun. 2007 19(7):813). Thus, improved methods of treating cancer by inhibiting the PD-Ll/PD-1 interaction in combination with modulating the microbiome is provided herein.

[00135] For example, PD-1 axis binding antagonists include a PD-1 binding antagonist, a PDL1 binding antagonist and a PDL2 binding antagonist. Alternative names for "PD-1" include CD279 and SLEB2. Alternative names for "PDL1" include B7-H1, B7-4, CD274, and B7-H. Alternative names for "PDL2" include B7-DC, Btdc, and CD273. In some embodiments, PD-1, PDL1, and PDL2 are human PD-1, PDL1 and PDL2.

[00136] In some embodiments, the PD-1 binding antagonist is a molecule that inhibits the binding of PD-1 to its ligand binding partners. In a specific aspect, the PD-1 ligand binding partners are PDL1 and/or PDL2. In another embodiment, a PDL1 binding antagonist is a molecule that inhibits the binding of PDL1 to its binding partners. In a specific aspect, PDL1 binding partners are PD-1 and/or B7-1. In another embodiment, the PDL2 binding antagonist is a molecule that inhibits the binding of PDL2 to its binding partners. In a specific aspect, a PDL2 binding partner is PD-1. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. Exemplary antibodies are described in U.S. Patent Nos. US8735553, US8354509, and US8008449, all incorporated herein by reference. Other PD-1 axis antagonists for use in the methods provided herein are known in the art such as described in U.S. Patent Application No. US20140294898, US2014022021, and US20110008369, all incorporated herein by reference.

[00137] In some embodiments, the PD-1 binding antagonist is an anti-PD-1 antibody (*e.g.*, a human antibody, a humanized antibody, or a chimeric antibody). In some embodiments, the anti-PD-1 antibody is selected from the group consisting of nivolumab,

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pembrolizumab, and CT-011. In some embodiments, the PD-1 binding antagonist is an immunoadhesin (*e.g.,* an immunoadhesin comprising an extracellular or PD-1 binding portion of PDL1 or PDL2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 binding antagonist is AMP- 224. Nivolumab, also known as MDX-1106-04, MDX-1106, ONO-4538, BMS-936558, and OPDIVO®, is an anti-PD-1 antibody described in WO2006/121168. Pembrolizumab, also known as MK-3475, Merck 3475, lambrolizumab, KEYTRUDA®, and SCH-900475, is an anti-PD-1 antibody described in WO2009/114335. CT-011, also known as hBAT or hBAT-1, is an anti-PD-1 antibody described in WO2009/101611. AMP-224, also known as B7-DCIg, is a PDL2-Fc fusion soluble receptor described in WO2010/027827 and WO2011/066342. Additional PD-1 binding antagonists include Pidilizumab, also known as CT-011, MEDI0680, also known as AMP-514, and REGN2810.

[00138] In some embodiments, the immune checkpoint inhibitor is a PD-L1 antagonist such as Durvalumab, also known as MEDI4736, atezolizumab, also known as MPDL3280A, or avelumab, also known as MSB00010118C. In certain aspects, the immune checkpoint inhibitor is a PD-L2 antagonist such as rHIgM12B7. In some aspects, the immune checkpoint inhibitor is a LAG-3 antagonist such as, but not limited to, IMP321, and BMS-986016. The immune checkpoint inhibitor may be an adenosine A2a receptor (A2aR) antagonist such as PBF-509.

[00139] In some embodiments, the antibody described herein (such as an anti-PD-1 antibody, an anti-PDLl antibody, or an anti-PDL2 antibody) further comprises a human or murine constant region. In a still further aspect, the human constant region is selected from the group consisting of IgGl, IgG2, IgG2, IgG3, and IgG4. In a still further specific aspect, the human constant region is IgGl. In a still further aspect, the murine constant region is selected from the group consisting of IgGl, IgG2A, IgG2B, and IgG3. In a still further specific aspect, the antibody has reduced or minimal effector function. In a still further specific aspect, the minimal effector function results from production in prokaryotic cells. In a still further specific aspect the minimal effector function results from an "effector-less Fc mutation" or aglycosylation.

[00140] Accordingly, an antibody used herein can be aglycosylated. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the

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carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine- X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxy amino acid, most commonly serine or threonine, although 5- hydroxyproline or 5 -hydroxy lysine may also be used. Removal of glycosylation sites form an antibody is conveniently accomplished by altering the amino acid sequence such that one of the above-described tripeptide sequences (for N-linked glycosylation sites) is removed. The alteration may be made by substitution of an asparagine, serine or threonine residue within the glycosylation site another amino acid residue (*e.g.*, glycine, alanine or a conservative substitution).

[00141] The antibody or antigen binding fragment thereof, may be made using methods known in the art, for example, by a process comprising culturing a host cell containing nucleic acid encoding any of the previously described anti-PDLl, anti-PD-1, or anti-PDL2 antibodies or antigen-binding fragment in a form suitable for expression, under conditions suitable to produce such antibody or fragment, and recovering the antibody or fragment.

B. CTLA-4

[00142] Another immune checkpoint that can be targeted in the methods provided herein is the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also known as CD152. The complete cDNA sequence of human CTLA-4 has the Genbank accession number L15006. CTLA-4 is found on the surface of T cells and acts as an "off" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells. CTLA4 is a member of the immunoglobulin superfamily that is expressed on the surface of Helper T cells and transmits an inhibitory signal to T cells. CTLA4 is similar to the T-cell co-stimulatory protein, CD28, and both molecules bind to CD80 and CD86, also called B7-1 and B7-2 respectively, on antigen-presenting cells. CTLA4 transmits an inhibitory signal to T cells, whereas CD28 transmits a stimulatory signal. Intracellular CTLA4 is also found in regulatory T cells and may be important to their function. T cell activation through the T cell receptor and CD28 leads to increased expression of CTLA-4, an inhibitory receptor for B7 molecules.

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[00143] In some embodiments, the immune checkpoint inhibitor is an anti-CTLA-4 antibody (*e.g.*, a human antibody, a humanized antibody, or a chimeric antibody), an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide.

[00144] Anti-human-CTLA-4 antibodies (or VH and/or VL domains derived therefrom) suitable for use in the present methods can be generated using methods well known in the art. Alternatively, art recognized anti-CTLA-4 antibodies can be used. For example, the anti-CTLA-4 antibodies disclosed in: US 8,119,129, WO 01/14424, WO 98/42752; WO 00/37504 (CP675,206, also known as tremelimumab; formerly ticilimumab), U.S. Patent No. 6,207,156; Hurwitz *et al.*, 1998; can be used in the methods disclosed herein. The teachings of each of the aforementioned publications are hereby incorporated by reference. Antibodies that compete with any of these art-recognized antibodies for binding to CTLA-4 also can be used. For example, a humanized CTLA-4 antibody is described in International Patent Application No. WO2001014424, WO2000037504, and U.S. Patent No. US8017114; all incorporated herein by reference.

[00145] An exemplary anti-CTLA-4 antibody is ipilimumab (also known as 10D1, MDX- 010, MDX- 101, and Yervoy®) or antigen binding fragments and variants thereof (see, *e.g.*, WO0 1/14424). In other embodiments, the antibody comprises the heavy and light chain CDRs or VRs of ipilimumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of ipilimumab, and the CDR1, CDR2 and CDR3 domains of the VL region of ipilimumab. In another embodiment, the antibody competes for binding with and/or binds to the same epitope on CTLA-4 as the above- mentioned antibodies. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with the above-mentioned antibodies (*e.g.*, at least about 90%, 95%, or 99% variable region identity with ipilimumab).

[00146] Other molecules for modulating CTLA-4 include soluble CTLA-4 ligands and receptors such as described in U.S. Patent Nos. US5844905, US5885796 and International Patent Application Nos. WO1995001994 and WO1998042752; all incorporated herein by reference, and immunoadhesins such as described in U.S. Patent No. US8329867, incorporated herein by reference.

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C. Killer Immunoglobulin-like Receptor (KIR)

[00147] Another immune checkpoint inhibitor for use in the present disclosure is an anti-KIR antibody. Anti-human-KIR antibodies (or VH/VL domains derived therefrom) suitable for use in the present methods can be generated using methods well known in the art.

[00148] Alternatively, art recognized anti-KIR antibodies can be used. The anti-KIR antibody can be cross-reactive with multiple inhibitory KIR receptors and potentiates the cytotoxicity of NK cells bearing one or more of these receptors. For example, the anti-KIR antibody may bind to each of KIR2D2DL1, KIR2DL2, and KIR2DL3, and potentiate NK cell activity by reducing, neutralizing and/or reversing inhibition of NK cell cytotoxicity mediated by any or all of these KIRs. In some aspects, the anti-KIR antibody does not bind KIR2DS4 and/or KIR2DS3. For example, monoclonal antibodies 1-7F9 (also known as IPH2101), 14F1, 1-6F1 and 1-6F5, described in WO 2006/003179, the teachings of which are hereby incorporated by reference, can be used. Antibodies that compete with any of these art-recognized antibodies for binding to KIR also can be used. Additional art-recognized anti-KIR antibodies which can be used include, for example, those disclosed in WO 2005/003168, WO 2005/009465, WO 2006/072625, WO 2006/072626, WO 2007/042573, WO 2008/084106, WO 2010/065939, WO 2012/071411 and WO 2012/160448.

[00149] An exemplary anti-KIR antibody is lirilumab (also referred to as BMS-986015 or IPH2102). In other embodiments, the anti-KIR antibody comprises the heavy and light chain complementarity determining regions (CDRs) or variable regions (VRs) of lirilumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the heavy chain variable (VH) region of lirilumab, and the CDR1, CDR2 and CDR3 domains of the light chain variable (VL) region of lirilumab. In another embodiment, the antibody has at least about 90% variable region amino acid sequence identity with lirilumab.

IV. Methods of Treatment

[00150] Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective or suffcicient amount of a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, to a subject who has been or is currently being

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administered immune checkpoint therapy. Also provided herein are methods of selecting subjects who will respond favorably to immune checkpoint therapy by assessing the microbial profile of the subject and administering immune checkpoint inhibitor to a subject identified to have a favorable microbial profile.

[00151] In some embodiments, the treatment results in a sustained response in the individual after cessation of the treatment. The methods described herein may find use in treating conditions where enhanced immunogenicity is desired such as increasing tumor immunogenicity for the treatment of cancer. Also provided herein are methods of enhancing immune function such as in an individual having cancer comprising administering to the individual an effective amount of an immune checkpoint inhibitor (*e.g.,* PD-1 axis binding antagonist and/or CTLA-4 antibody) and a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. In some embodiments, the individual is a human.

[00152] Examples of cancers contemplated for treatment include lung cancer, head and neck cancer, breast cancer, pancreatic cancer, prostate cancer, renal cancer, bone cancer, testicular cancer, cervical cancer, gastrointestinal cancer, lymphomas, pre-neoplastic lesions in the lung, colon cancer, melanoma, metastatic melanoma, basal-cell skin cancer, squamous-cell skin cancer, 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, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma, Desmoplastic Melanoma, and bladder cancer.

[00153] In some embodiments, the individual has cancer that is resistant (has been demonstrated to be resistant) to one or more anti-cancer therapies. In some embodiments, resistance to anti-cancer therapy includes recurrence of cancer or refractory cancer. Recurrence may refer to the reappearance of cancer, in the original site or a new site, after treatment. In some embodiments, resistance to anti-cancer therapy includes progression of the cancer during treatment with the anti-cancer therapy. In some embodiments, the cancer is at early stage or at late stage.

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[00154] The individual may have a cancer that expresses (has been shown to express *e.g.*, in a diagnostic test) PD-L1 biomarker. In some embodiments, the patient's cancer expresses low PD-L1 biomarker. In some embodiments, the patient's cancer expresses high PD-L1 biomarker. The PD-L1 biomarker can be detected in the sample using a method selected from the group consisting of FACS, Western blot, ELISA, immunoprecipitation, immunohistochemistry, immunofluorescence, radioimmunoassay, dot blotting, immunodetection methods, HPLC, surface plasmon resonance, optical spectroscopy, mass spectrometery, HPLC, qPCR, RT-qPCR, multiplex qPCR or RT-qPCR, RNA-seq, microarray analysis, SAGE, MassARRAY technique, and FISH, and combinations thereof.

[00155] In some embodiments of the methods of the present disclosure, the cancer has low levels of T cell infiltration. In some embodiments, the cancer has no detectable T cell infiltrate. In some embodiments, the cancer is a non-immunogenic cancer (*e.g.*, non-immunogenic colorectal cancer and/or ovarian cancer). Without being bound by theory, the combination treatment may increase T cell (*e.g.,* $CD4^+$ T cell, $CD8^+$ T cell, memory T cell) priming, activation, proliferation, and/or infiltration relative to prior to the administration of the combination.

A. Administration

[00156] The therapy provided herein comprises administration of an immune checkpoint inhibitor, a prebiotic or probiotic composition comprising a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria. The therapy may be administered in any suitable manner known in the art. For example, of an immune checkpoint inhibitor (*e.g.,* PD-1 axis binding antagonist and/or CTLA-4 antibody), and a short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered sequentially (at different times) or concurrently (at the same time). In some embodiments, the one or more immune checkpoint inhibitors are in a separate composition as the probiotic therapy. In some embodiments, the immune checkpoint inhibitor is in the same composition as the probiotic composition.

[00157] According to a preferred embodiment, the probiotic bacterial composition is formulated for oral administration. The skilled artisan knows a variety of formulas which can

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encompass living or killed microorganisms and which can present as food supplements (*e.g.*, pills, tablets and the like) or as functional food such as drinks or fermented yogurts.

[00158] The one or more immune checkpoint inhibitors and the short-chain fatty acid, such as butyrate, and/or populations of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered by the same route of administration or by different routes of administration. In some embodiments, the immune checkpoint inhibitor is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In particular aspects, the immune checkpoint inhibitor is administered intravenously and the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, is administered orally. An effective amount of the immune checkpoint inhibitor and the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, may be administered for prevention or treatment of disease. The appropriate dosage of immune checkpoint inhibitor and/or the short-chain fatty acid, such as butyrate, and/or population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria may be determined based on the type of disease to be treated, severity and course of the disease, the clinical condition of the individual, the individual's clinical history and response to the treatment, and the discretion of the attending physician.

[00159] For example, the therapeutically effective or sufficient amount of the immune checkpoint inhibitor, such as an antibody and/or short-chain fatty acid, such as butyrate, that is administered to a human will be in the range of about 0.01 to about 50 mg/kg of patient body weight whether by one or more administrations. In some embodiments, the antibody used is about 0.01 to about 45 mg/kg, about 0.01 to about 40 mg/kg, about 0.01 to about 35 mg/kg, about 0.01 to about 30 mg/kg, about 0.01 to about 25 mg/kg, about 0.01 to about 20 mg/kg, about 0.01 to about 15 mg/kg, about 0.01 to about 10 mg/kg, about 0.01 to about 5 mg/kg, or about 0.01 to

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about 1 mg/kg administered daily, for example. In some embodiments, the antibody is administered at 15 mg/kg. However, other dosage regimens may be useful. In one embodiment, an anti-PDL1 antibody described herein is administered to a human at a dose of about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg or about 1400 mg on day 1 of 21-day cycles. The dose may be administered as a single dose or as multiple doses (*e.g.*, 2 or 3 doses), such as infusions. The progress of this therapy is easily monitored by conventional techniques.

[00160] For example, the therapeutically effective or sufficient amount of each of the at least one isolated or purified population of bacteria or each of the at least two isolated or purified populations of bacteria of the probiotic or live bacterial product compositions of the embodiments that is administered to a human will be at least about $1x10^3$ colony forming units (CFU) of bacteria or at least about $1x10^4$ (CFU). In some embodiments, a single dose will contain about $1x10^4$, $1x10^5$, $1x10^6$, $1x10^7$, $1x10^8$, $1x10^9$, $1x10^{10}$, $1x10^{11}$, $1x10^{12}$, $1x10^{13}$, $1x10^{14}$, $1x10^{15}$ or greater than $1x10^{15}$ CFU of bacteria. In specific embodiments, the bacteria are provided in spore form or as sporulated bacteria. In particular embodiments, the concentration of spores of each isolated or purified population of bacteria, for example of each species, subspecies or strain, is $1x10^4$, $1x10^5$, $1x10^6$, $1x10^7$, $1x10^8$, $1x10^9$, $1x10^{10}$, $1x10^{11}$, $1x10^{12}$, $1x10^{13}$, $1x10^{14}$, $1x10^{15}$ or greater than $1x10^{15}$ viable bacterial spores per gram of composition or per administered dose.

[00161] Intratumoral injection, or injection into the tumor vasculature is specifically contemplated for discrete, solid, accessible tumors. Local, regional or systemic administration also may be appropriate. For tumors of >4 cm, the volume to be administered will be about 4-10 ml (in particular 10 ml), while for tumors of <4 cm, a volume of about 1-3 ml will be used (in particular 3 ml). Multiple injections delivered as single dose comprise about 0.1 to about 0.5 ml volumes. For example, adenoviral particles may advantageously be contacted by administering multiple injections to the tumor.

[00162] Treatment regimens may vary as well, and often depend on tumor type, tumor location, disease progression, and health and age of the patient. Obviously, certain types of tumors will require more aggressive treatment, while at the same time, certain patients cannot

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tolerate more taxing protocols. The clinician will be best suited to make such decisions based on the known efficacy and toxicity (if any) of the therapeutic formulations.

[00163] In certain embodiments, the tumor being treated may not, at least initially, be resectable. Treatments with therapeutic viral constructs may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site.

[00164] The treatments may include various "unit doses." Unit dose is defined as containing a predetermined-quantity of the therapeutic composition. The quantity to be administered, and the particular route and formulation, is within the skill of determination of those in the clinical arts. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time.

B. Additional Anti-Cancer Therapies

[00165] In some embodiments, the immune checkpoint inhibitor, composition comprising a short-chain fatty acid, such as butyrate, and/or composition comprising a population of short-chain fatty acid-producing bacteria, such as butyrate-producing bacteria, provided herein may be administered in combination with at least one additional therapeutic. The additional therapy may be a cancer therapy such as radiation therapy, surgery, chemotherapy, gene therapy, DNA therapy, viral therapy, RNA therapy, immunotherapy, bone marrow transplantation, nanotherapy, monoclonal antibody therapy, or a combination of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy.

[00166] In some embodiments, the additional cancer therapy is the administration of a small molecule enzymatic inhibitor or anti-metastatic agent. In some embodiments, the additional therapy is the administration of side- effect limiting agents (*e.g.*, agents intended to lessen the occurrence and/or severity of side effects of treatment, such as anti-nausea agents, *etc.*). In some embodiments, the additional cancer therapy is radiation therapy. In some embodiments, the additional cancer therapy is surgery. In some embodiments, the additional cancer therapy is a combination of radiation therapy and surgery. In some embodiments, the additional cancer therapy is gamma irradiation. In some embodiments, the additional cancer therapy is therapy targeting

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PBK/AKT/mTOR pathway, HSP90 inhibitor, tubulin inhibitor, apoptosis inhibitor, and/or chemopreventative agent. The additional cancer therapy may be one or more of the chemotherapeutic agents known in the art.

[00167] Various combinations may also be employed. For the example below the immune checkpoint inhibitor, butyrate, and/or butyrate-producing bacterial population is "A" and an additional cancer therapy is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B
B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A
B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

[00168] Administration of any compound or therapy of the present embodiments to a patient will follow general protocols for the administration of such compounds, taking into account the toxicity, if any, of the agents. Therefore, in some embodiments there is a step of monitoring toxicity that is attributable to combination therapy.

1. Chemotherapy

[00169] A wide variety of chemotherapeutic agents may be used in accordance with the present embodiments. The term "chemotherapy" refers to the use of drugs to treat cancer. A "chemotherapeutic agent" is used to connote a compound or composition that is administered in the treatment of cancer. These agents or drugs are categorized by their mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent may be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis.

[00170] Examples of chemotherapeutic agents include alkylating agents, such as thiotepa and cyclosphosphamide; alkyl sulfonates, such as busulfan, improsulfan, and piposulfan; aziridines, such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines, including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues);

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cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards, such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitrosureas, such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics, such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammaI and calicheamicin omegaI1); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites, such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues, such as denopterin, pteropterin, and trimetrexate; purine analogs, such as fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine; pyrimidine analogs, such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens, such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals, such as mitotane and trilostane; folic acid replenisher, such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids, such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSKpolysaccharide complex; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol;

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pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; taxoids, *e.g.*, paclitaxel and docetaxel gemcitabine; 6-thioguanine; mercaptopurine; platinum coordination complexes, such as cisplatin, oxaliplatin, and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (*e.g.,* CPT-11); topoisomerase inhibitor RFS 2000; difluorometlhylornithine (DMFO); retinoids, such as retinoic acid; capecitabine; carboplatin, procarbazine,plicomycin, gemcitabien, navelbine, farnesyl-protein tansferase inhibitors, transplatinum, and pharmaceutically acceptable salts, acids, or derivatives of any of the above.

2. Radiotherapy

[00171] Other factors that cause DNA damage and have been used extensively include what are commonly known as γ-rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated, such as microwaves, proton beam irradiation (U.S. Patents 5,760,395 and 4,870,287), and UV-irradiation. It is most likely that all of these factors affect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 wk), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

3. Immunotherapy

[00172] The skilled artisan will understand that immunotherapies may be used in combination or in conjunction with the methods described herein. In the context of cancer treatment, immunotherapeutics generally rely on the use of immune effector cells and molecules to target and destroy cancer cells. Rituximab (RITUXAN®) is an example of an immunotherapy. The immune effector may be, for example, an antibody specific for a marker on the surface of a tumor cell. The antibody alone may serve as an effector of therapy or it may recruit other cells to actually effect cell killing. The antibody also may be conjugated to a drug or toxin (chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, etc.) and serve as a targeting agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that

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interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells

[00173] Antibody-drug conjugates have emerged as a breakthrough approach to the development of cancer therapeutics. Antibody–drug conjugates (ADCs) comprise monoclonal antibodies (MAbs) that are covalently linked to cell-killing drugs. This approach combines the high specificity of MAbs against their antigen targets with highly potent cytotoxic drugs, resulting in "armed" MAbs that deliver the payload (drug) to tumor cells with enriched levels of the antigen. Targeted delivery of the drug also minimizes its exposure in normal tissues, resulting in decreased toxicity and improved therapeutic index. The approval of two ADC drugs, ADCETRIS® (brentuximab vedotin) in 2011 and KADCYLA® (trastuzumab emtansine or T-DM1) in 2013 by FDA validated the approach. There are currently more than 30 ADC drug candidates in various stages of clinical trials for cancer treatment. As antibody engineering and linker-payload optimization are becoming more and more mature, the discovery and development of new ADCs are increasingly dependent on the identification and validation of new targets that are suitable to this approach and the generation of targeting MAbs. Two criteria for ADC targets are upregulated/high levels of expression in tumor cells and robust internalization.

[00174] In one aspect of immunotherapy, the tumor cell must bear some marker that is amenable to targeting, *i.e.*, is not present on the majority of other cells. Many tumor markers exist and any of these may be suitable for targeting in the context of the present embodiments. Common tumor markers include CD20, carcinoembryonic antigen, tyrosinase (p97), gp68, TAG-72, HMFG, Sialyl Lewis Antigen, MucA, MucB, PLAP, laminin receptor, erb B, and p155. An alternative aspect of immunotherapy is to combine anticancer effects with immune stimulatory effects. Immune stimulating molecules also exist including: cytokines, such as IL-2, IL-4, IL-12, GM-CSF, gamma-IFN, chemokines, such as MIP-1, MCP-1, IL-8, and growth factors, such as FLT3 ligand.

4. Surgery

[00175] Approximately 60% of persons with cancer will undergo surgery of some type, which includes preventative, diagnostic or staging, curative, and palliative surgery. Curative surgery includes resection in which all or part of cancerous tissue is physically removed, excised,

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and/or destroyed and may be used in conjunction with other therapies, such as the treatment of the present embodiments, chemotherapy, radiotherapy, hormonal therapy, gene therapy, immunotherapy, and/or alternative therapies. Tumor resection refers to physical removal of at least part of a tumor. In addition to tumor resection, treatment by surgery includes laser surgery, cryosurgery, electrosurgery, and microscopically-controlled surgery (Mohs' surgery).

[00176] Upon excision of part or all of cancerous cells, tissue, or tumor, a cavity may be formed in the body. Treatment may be accomplished by perfusion, direct injection, or local application of the area with an additional anti-cancer therapy. Such treatment may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. These treatments may be of varying dosages as well.

5. Other Agents

[00177] It is contemplated that other agents may be used in combination with certain aspects of the present embodiments to improve the therapeutic efficacy of treatment. These additional agents include agents that affect the upregulation of cell surface receptors and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion, agents that increase the sensitivity of the hyperproliferative cells to apoptotic inducers, or other biological agents. Increases in intercellular signaling by elevating the number of GAP junctions would increase the anti-hyperproliferative effects on the neighboring hyperproliferative cell population. In other embodiments, cytostatic or differentiation agents can be used in combination with certain aspects of the present embodiments to improve the anti-hyperproliferative efficacy of the treatments. Inhibitors of cell adhesion are contemplated to improve the efficacy of the present embodiments. Examples of cell adhesion inhibitors are focal adhesion kinase (FAKs) inhibitors and Lovastatin. It is further contemplated that other agents that increase the sensitivity of a hyperproliferative cell to apoptosis, such as the antibody c225, could be used in combination with certain aspects of the present embodiments to improve the treatment efficacy.

V. Examples

[00178] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the

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practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1 – Characterization of Microbiome of Melanoma Patients

[00179] To better understand the role of the microbiome in response to immune checkpoint blockade in cancer patients, microbiome samples were prospectively collected from patients with metastatic melanoma going onto treatment with PD-1 blockade (n=112 patients). Oral (buccal) and gut (fecal) microbiome samples were collected at treatment initiation, and tumor biopsies and blood samples were collected when feasible to assess for genomic alterations as well as the density and phenotype of tumor-infiltrating and circulating immune cell subsets (FIG. 1A). Taxonomic profiling via 16S rRNA gene sequencing was performed on all available oral and gut samples, with metagenomic whole genome shotgun sequencing (WGS) on a subset. Patients were classified as responders (R) or non-responders (NR) based on imaging analysis via RECIST 1.1 criteria (Schwartz *et al.,* 2016). Of note, patients in R versus NR groups were relatively similar with respect to age, gender, primary type, prior therapy, concurrent therapy and serum LDH (Table 3). The frequency of specific melanoma driver mutations and total mutational load were also similar between the groups (FIG. 5) (*17*).

[00180] Table 3: Patient characteristics table by microbiome sample type.

Oral Microbiome Samples				**Fecal Microbiome Samples**			
	R	**NR**	**P***		**R**	**NR**	**P***
	n=52 (%)	n=34 (%)			n=30 (%)	n=13 (%)	
Age			0.57				0.60
Median	66.5	64.5		Median	64	70	
Range	21-88	32-87		Range	21-88	42-80	
Gender			0.14				0.74
Male	41 (79)	22 (65)		Male	20 (67)	8 (62)	
Female	11 (21)	12 (35)		Female	10 (33)	5 (38)	
Ethnicity			0.47				0.57
White	48 (92)	29 (85)		White	28 (94)	11 (85)	
Other	4 (6)	5 (6)		Other	2 (6)	2 (15)	

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Primary Type			0.032				0.68
Cutaneous	44 (85)	22 (65)		Cutaneous	25 (83)	10 (77)	
Other**	8 (15)	12 (35)		Other**	5 (17)	3 (23)	
Prior Targeted Therapy			0.76				0.76
Yes	8 (15)	4 (12)		Yes	5 (17)	6 (46)	
No	44 (85)	30 (88)		No			
Prior Checkpoint Therapy			0.81				0.46
Yes	17 (33)	12 (35)		Yes	9 (30)	2 (15)	
No	35 (67)	22 (65)		No	21 (70)	11 (85)	
Disease Stage			0.053				0.0006
III	14 (27)	3 (9)		III	20 (67)	1 (8)	
IV	38 (73)	31 (91)		IV	10 (33)	12 (92)	
Lactate Dehydrogenase****							0.21
< 618 IU	44 (85)	23 (68)	0.11	< 618 IU	26 (87)	9 (69)	
≥ 618 IU	8 (15)	10 (30)		≥ 618 IU	3 (10)	4 (31)	
Treatment Type			0.053				0.22
PD1 Monotherapy	50 (96)	28 (82)		PD1 Monotherapy	29 (97)	11 (85)	
PD1 Combination***	2 (4)	6 (18)		PD1 Combination***	1 (3)	2 (15)	

*p values calculated by Wilcoxon rank sum (age),chi-squared (gender, prior checkpoint) and Fisher's exact (all others)

**other includes acral, mucosal, unknown primaries

***combos include: Abraxane, Urelumanb, Aldera cream

****1 missing value from 1 R who didn't have a baseline LDH read

[00181] The landscape of the oral and fecal microbiota in patients was first assessed with metastatic melanoma via 16S sequencing (V4 region), noting that both communities were relatively diverse, with a high abundance of Lactobacillales in the oral microbiome and Bacteroidales in the fecal microbiome (FIG. 1B). Bipartite network analysis (Muegge *et al.,* 2011) demonstrated a clear separation of community structure between the oral and fecal microbiomes in terms of both matched and aggregate samples (FIGS. 1C and 6), suggesting that these communities are distinct.

[00182] Loss of diversity (dysbiosis) is associated with chronic health conditions (Turnbaugh *et al.,* 2008; Qin *et al.,* 2010) and cancer (Garrett *et al.,* 2015; Segre *et al.,* 2015; Drewes *et al.,* 2016)), and is also associated with poor outcomes to certain forms of cancer therapy including allogeneic stem cell transplant (Taur *et al.,* 2014). Based on these data diversity of the oral and gut microbiomes was tested in patients on PD-1 blockade, and found that diversity of the

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gut microbiome was significantly higher in R compared to NR using several indices (p=0.009, FIGS. 1D and 7). No significant differences were observed in the oral microbiome (p=0.11, FIG. 8). The relationship of diversity with progression-free survival (PFS) was tested in the cohort, demonstrating that patients with a high diversity in the fecal microbiome had significantly prolonged PFS compared to those with intermediate or low diversity (p=0.021 and 0.041, respectively; FIGS. 1E-F and 9). No differences in PFS were noted when comparing diversity of the oral microbiome (FIG. 10A-D).

[00183] Compositional differences in the microbiome may also influence cancer development and response to therapy (Sivan *et al.,* 2015; Iida *et al.,* 2013; Viaud *et al.,* 2013; Vetizou *et al.,* 2015), thus it was also sought to determine if differences existed in component microbiota in the oral or gut microbiomes of R and NR to PD-1 blockade. To test this, enrichment index (*ei*) of operational taxonomic units (OTUs) was calculated and compared R versus NR, demonstrating that distinct sets of bacteria were associated with response to anti-PD-1 therapy, with enrichment of Clostridiales in R and Bacteroidales in NR in the gut microbiome (p<0.001, FIG. 2A-B and 11). No significant differences in enrichment were noted in the oral microbiome of R versus NR (FIG. 12A-B). To further explore these findings, high dimensional class comparisons were performed via linear discriminant analysis of effect size (LEfSe) (Segata *et al.,* 2011), which again demonstrated differentially abundant bacteria in the fecal microbiome of R versus NR to PD-1 blockade, with Clostridiales/Ruminococcaceae enriched in R and Bacteroidales enriched in NR (FIG. 2C-D). No significant differences were observed in the oral microbiome between R and NR, with the exception of higher Bacteroidales in NR to PD-1 blockade (FIG. 13A-B). Pairwise comparisons were then performed for bacterial taxa at all levels by response. In addition to confirming the previous taxonomic differences, these analyses identified *Faecalibacterium prausnitzii* species as significantly enriched in R (FIG. 2E, Table 4). Metagenomic WGS further revealed enrichment of *Faecalibacterium* species in addition to others including *Akkermansia* in R, whilst *Bacteroides thetaiotaomicron*, *Escherichia coli*, and *Anaerotruncus colihominis* were enriched in NR (FIG. 2F, Table 4). Of note, the gut microbiome was shown to be relatively stable over time in a limited number of longitudinal samples tested (FIG. 14A-C).

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[00184] Based on these insights, it was next asked whether bacterial composition and abundances within the gut and/or oral microbiomes could predict response to PD-1 blockade in the inventors' cohort. To do this, all identified OTUs were grouped into clusters of related OTUs (crOTUs) via construction of a phylogenetic tree from sequence alignment data (Peled *et al.,* 2017). This technique involves comparison of abundances of different potential groupings of bacteria based on 16S sequence similarity and helps address the sparse distribution of OTU abundances observed in the absence of this approach (FIG. 15A-B). Unsupervised hierarchical clustering of crOTU abundances within the gut and oral microbiomes was then performed without input of response data. Results demonstrated that patients segregated into 2 distinct clusters, with one cluster (cluster 1) comprised entirely of R and the other (cluster 2) comprised of a mixture of R and NR (p=0.02) with enrichment of Clostridiales in cluster 1 and Bacteroidales in cluster 2 (FIG. 3A-B). PFS was then assessed in each of these clusters, demonstrating a significantly shorter time to progression on PD-1 blockade among patients in cluster 1 compared to those in cluster 2 (p=0.02) (FIG. 3C). To better understand compositional differences in these clusters, pairwise comparisons of the gut microbiota were performed, and identified a pattern very similar to that seen when clustering by response, with Clostridiales/Ruminococcaceae enriched in cluster 1, and Bacteroidales enriched in cluster 2 (FIG. 3D, Table 5). Analysis of crOTUs in the oral microbiome revealed no apparent relationship to treatment response (FIG. 16A-B).

[00185] To explore the association of specific bacterial taxa and treatment response, the inventors compared PFS to anti-PD-1 therapy as it related to the "top hits" consistently observed across analyses (*F. prausnitzii* in R and Bacteroidales in NR), dichotomizing patients into high versus low categories based on the median relative abundance of these taxa in the gut microbiome. Patients with high *F. prausnitzii* abundance had a significantly prolonged PFS versus those with a low abundance (p=0.03). Conversely, patients with a high abundance of Bacteroidales had a shortened PFS compared to those with a low abundance (p=0.05) (FIG. 3E). This is in line with recently published data in a small cohort of patients on CTLA-4 blockade, where patients with a higher abundance of *Faecalibacterium* had a prolonged PFS compared to those with a higher abundance of Bacteroides in the gut microbiome (Chaput *et al.,* 2017)). In addition, Cox proportional hazards analyses were performed in the inventors' cohort, demonstrating that the strongest predictors of response to PD-1 blockade were alpha-diversity (HR= 3.94; 95% C.I. =1.02-12.52), abundance of *F.prausnitzii* (HR= 2.92; 95% C.I. =1.08-7.89) and crOTU clusters

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(HR=3.80; 95% C.I. =1.09-13.21) in the fecal microbiome. These effects remained significant in multivariate analyses after adjusting for prior treatment with immunotherapy (Table 6).

[00186] Table 4: Pairwise comparisons of bacterial taxa between R and NR by 2-sided MW test within each level of taxonomy.

Taxon	p-value	Effect Size	FDR-Adjusted p-Value	Taxonomy Level
Bacteroidetes	0.000939	19.06232	0.002664	Phylum
Firmicutes	0.001776	-16.9273	0.002664	Phylum
Proteobacteria	0.927224	0	0.927224	Phylum
Bacteroidia	0.000939	21.3498	0.002165	Class
Clostridia	0.001443	-14.9449	0.002165	Class
Gammaproteobacteria	0.628911	0	0.628911	Class
Bacteroidales	0.000939	19.67232	0.002165	Order
Clostridiales	0.001443	-16.6223	0.002165	Order
Enterobacterales	0.842779	0	0.842779	Order
Bacteroidaceae	0.159028	9.721784	0.307087	Family
Clostridiaceae	0.175479	-6.44306	0.307087	Family
Enterobacteriaceae	0.863521	0.419371	0.863521	Family
Lachnospiraceae	0.48832	-2.6306	0.683647	Family
Porphyromonadaceae	0.061699	-9.34054	0.215948	Family
Rikenellaceae	0.750983	-0.41937	0.863521	Family
Ruminococcaceae	0.000118	-19.5579	0.000827	Family
Alistipes	0.750983	-3.43122	0.844806	Genus
Bacteroides	0.159028	6.709937	0.424075	Genus
Blautia	0.844806	-0.305	0.844806	Genus
Escherichia	0.551319	1.982481	0.844806	Genus
Faecalibacterium	0.005128	-17.3848	0.041026	Genus
Lachnoclostridium	0.539046	2.13498	0.844806	Genus
Parabacteroides	0.098795	-11.1324	0.395182	Genus
Roseburia	0.804154	0	0.844806	Genus
Alistipes onderdonkii	0.577459	0.038125	0.577459	Species
Bacteroides caccae	0.569645	-0.03812	0.577459	Species
Bacteroides ovatus	0.397414	-1.63936	0.577459	Species
Bacteroides thetaiotaomicron	0.412328	8.120549	0.577459	Species
Bacteroides uniformis	0.475213	7.510555	0.577459	Species
Bacteroides vulgatus	0.300376	-2.7831	0.577459	Species
Escherichia coli	0.551319	6.824311	0.577459	Species

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Faecalibacterium prausnitzii	0.005128	-12.543	0.046155	Species
Parabacteroides merdae	0.440288	-1.18186	0.577459	Species

[00187] Table 5: Pairwise comparisons of 16S-derived bacterial taxa between crOTU community type 1 and crOTU community type 2 by 2 sided Mann-Whitney test within each level of taxonomy.

Taxon	p-value	Effect Size	FDR-adjusted p-value[a]	Taxonomic Level
Bacteroidetes	6.95e-10	-25.62	2.09e-09	Phylum
Firmicutes	3.37e-08	26.53	5.06e-08	Phylum
Proteobacteria	0.86	0.00	0.86	Phylum
Bacteroidia	6.95e-10	-37.97	2.09e-09	Class
Clostridia	9.42e-08	13.72	1.41e-07	Class
Gammaproteobacteria	0.04	0.00	0.04	Class
Bacteroidales	6.95e-10	-38.12	2.09e-09	Order
Clostridiales	9.42e-08	13.57	1.41e-07	Order
Enterobacterales	0.04	0.00	0.04	Order
Bacteroidaceae	4.83e-08	-27.75	3.38e-07	Family
Ruminococcaceae	0.00	15.55	0.00	Family
Clostridiaceae	0.0011	14.79	0.00	Family
Lachnospiraceae	0.01	11.59	0.02	Family
Enterobacteriaceae	0.04	8.84	0.06	Family
Rikenellaceae	0.36	-7.55	0.42	Family
Porphyromonadaceae	0.67	0.00	0.67	Family
Bacteroides	4.83e-08	-28.52	3.87e-07	Genus
Blautia	0.07	6.86	0.19	Genus
Faecalibacterium	0.07	6.71	0.19	Genus
Roseburia	0.18	4.27	0.36	Genus
Alistipes	0.36	-8.31	0.57	Genus
Lachnoclostridium	0.57	0.00	0.76	Genus
Escherichia	0.71	-1.07	0.79	Genus
Parabacteroides	0.79	-4.73	0.79	Genus
Bacteroides.vulgatus	0.00	-20.47	0.00	Species
Bacteroides.uniformis	0.00	-18.72	0.01	Species
Bacteroides.thetaiotaomicron	0.00	-17.80	0.01	Species
Bacteroides.ovatus	0.07	-11.86	0.13	Species
Faecalibacterium.prausnitzii	0.07	8.20	0.13	Species
Bacteroides.caccae	0.21	-8.73	0.31	Species
Alistipes.onderdonkii	0.36	-6.82	0.46	Species

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Escherichia.coli	0.71	0.42	0.80	Species
Parabacteroides.merdae	0.82	-0.42	0.82	Species

[a]FDR *p*-values are adjusted within each level of taxonomy level

[00188] Next, it was sought to gain insight into the mechanism through which the gut microbiome may influence response to anti-PD-1 therapy, and first conducted functional genomic profiling of gut microbiome samples via metagenomic WGS in R vs NR to therapy. Organism-specific gene hits were assigned to the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthology (KO), and based on these annotations, metagenomes for each sample were reconstructed into metabolic pathways using the MetaCyc hierarchy of pathway classifications (Caspi *et al.,* 2008; Kanehisa *et al.,* 2000). Unsupervised hierarchical clustering on relative abundances of both KOs and predicted pathways identified three groups of patient samples, with response rates of 72.7%, 57.1%, and 42.9%. Comparisons of gene function abundances across these groups showed changes in metabolic functions, with anabolic functions predominating in R including amino acid biosynthesis (FIG. 3F), which may promote host immunity (Blacher *et al.,*2017), whereas catabolic functions predominated in NR (FIG. 3F, 17, Table 7).

[00189] There is clear evidence in pre-clinical models that differential composition of the gut microbiome may influence therapeutic responses to PD-1 blockade at the level of the tumor microenvironment (Sivan *et al.,* 2015), thus the relationship between the gut microbiota and systemic and anti-tumor immune responses was interrogated in the cohort of patients on PD-1 blockade. To do this the tumor associated immune infiltrates were compared via multi-parameter IHC, and observed a higher density of $CD8^+$ T lymphocytes in baseline samples of R versus NR (p=0.04), consistent with prior reports (FIG. 4A and 18A-F) (Tumeh *et al.,* 2014; Chen *et al.,* 2016). 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

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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). To better understand the influence of compositional differences in the gut microbiome on antigen processing and presentation within the tumor microenvironment, multiplex IHC targeting the myeloid compartment was performed (Tsujikawa *et al.,* 2017). In these studies, patients with a high abundance of *Faecalibacterium* in the gut microbiome had a higher density of immune cells and markers of antigen processing and presentation compared to those with a high abundance of Bacteroidales (FIG. 4E-F and 23-24), suggesting a possible mechanism through which the gut microbiome may modulate anti-tumor immune responses (Sivan *et al.,* 2015).

[00190] Placing these insights in the context of published literature, it was proposed that the gut microbiome modulates responses to treatment with anti-PD-1 therapy (FIG. 4G). Specifically, it was proposed that patients with a "favorable" gut microbiome (with high diversity and abundance of Ruminococcaceae/*Faecalibacterium*) 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 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. These findings highlight the potential for parallel modulation of the gut microbiome to significantly enhance checkpoint blockade efficacy.

[00191] Table 6: Univariate and multivariate Cox proportional hazards models for progression-free survival in the fecal analysis cohort.

Variable	Univariate HR[a] (95% C.I.)	*p*-value	HR[a]- Final model[b] (95% C.I.)[a]	*p*-value
alpha-diversity (Inverse Simpson)[c]				
High (ref)				
Intermediate	3.57 (1.01-12.74)	**0.05**		
Low	3.94 (1.02-12.52)	**0.05**		

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***Faecalibacterium* abundance**[d]				
High (ref)				
Low	2.92 (1.08-7.89)	**0.03**	3.64 (1.28-10.40)	**0.02**
Bacteroidales abundance[d]				
High (ref)				
Low	0.39 (0.15-1.03)	0.06		
crOTU Cluster				
Cluster 1 (ref)				
Cluster 2	3.80 (1.09-13.21)	**0.04**		
Sex				
Male (ref)				
Female	0.84 (0.30-2.35)	0.11		
Ethnicity				
White (ref)				
Other	3.23 (0.86-12.09)	0.08		
Age	1.01 (0.98-1.03)	0.10		
Primary Site				
Cutaneous (ref)				
Other	1.02 (0.23-4.52)	0.98		
Stage				
III (ref)				
IV	1.18 (0.34-4.16)	0.08		
Baseline LDH				
Normal (ref)				
Elevated[c]	2.24 (0.79-6.32)	0.13		
Prior Immunotherapy				
No (ref)				
Yes	2.28 (1.11-7.18)	**0.03**		
Prior Targeted therapy				
No (ref)				
Yes	1.88 (0.66-5.31)	0.24		
Anti-PD-1 combination vs monotherapy				
Monotherapy (ref)				
Combinations	1.40 (0.23-6.13)	0.20		
CD8+ density in baseline tumor[d]	0.99 (0.99-1.00)	0.07		

a HRs represent 4 patients excluded from analysis due to insufficient follow up data
b Final model determine by forwards selection and best subsets approach. Alpha Diversity was included as a binary variable based on the median cut point.
c elevated LDH: exceeding the upper limit of normal (618 IU/mL), all samples assayed in a common laboratory
d CD8+ density based on samples from 15 patients with baseline tumor available

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[00192] Table 7: Pairwise comparison of MetaCyc pathway class by response.

Pathway	Estimate[a]	p-value	Enrichment Index	Enriched In
glycolate and glyoxylate degradation I	0.05	0.00	-0.52	NR
oxalate degradation II	0.08	0.03	-0.36	NR
formate to trimethylamine N-oxide electron transfer	0.11	0.04	-0.29	NR
D-sorbitol degradation II	0.00	0.05	-0.22	NR
ketogluconate metabolism	0.00	0.05	-0.22	NR
phenylacetate degradation I (aerobic)	0.14	0.09	-0.23	NR
pyridoxal 5'-phosphate biosynthesis I	0.18	0.10	-0.31	NR
superpathway of pyridoxal 5'-phosphate biosynthesis and salvage	0.18	0.10	-0.31	NR
4-aminobutanoate degradation III	0.00	0.11	-0.17	NR
hydrogen to trimethylamine N-oxide electron transfer	0.00	0.11	-0.17	NR
4-hydroxybenzoate biosynthesis II (microbes)	0.22	0.11	-0.34	NR
glycocholate metabolism (bacteria)	0.24	0.12	-0.38	NR
malonate decarboxylase activation	0.21	0.18	-0.52	NR
4-aminobutanoate degradation II	0.19	0.18	-0.17	NR
aspartate superpathway	0.19	0.18	-0.17	NR
D-malate degradation	0.19	0.18	-0.17	NR
formate to dimethyl sulfoxide electron transfer	0.19	0.18	-0.17	NR
L-lysine degradation I	0.19	0.18	-0.17	NR
NAD biosynthesis I (from aspartate)	0.19	0.18	-0.17	NR
nitrate reduction III (dissimilatory)	0.19	0.18	-0.17	NR
2-methylcitrate cycle I	0.24	0.21	-0.24	NR
GDP-D-glycero-alpha-D-manno-heptose biosynthesis	0.24	0.21	-0.24	NR
sulfoquinovose degradation I	0.24	0.21	-0.24	NR
superpathway of 4-aminobutanoate degradation	0.24	0.21	-0.24	NR
tetrahydromonapterin biosynthesis	0.24	0.21	-0.24	NR
mevalonate pathway I	0.30	0.23	-0.26	NR
superpathway of geranylgeranyldiphosphate biosynthesis I (via mevalonate)	0.30	0.23	-0.26	NR
D-galactonate degradation	0.00	0.23	-0.12	NR
trehalose degradation I (low osmolarity)	0.00	0.23	-0.12	NR
4-aminobutanoate degradation I	0.31	0.23	-0.18	NR
adenine and adenosine salvage V	0.31	0.23	-0.18	NR
guanine and guanosine salvage III	0.31	0.23	-0.18	NR
superpathway of guanine and guanosine salvage	0.31	0.23	-0.18	NR
L-ascorbate degradation II (bacterial, aerobic)	0.33	0.24	-0.28	NR
fatty acid beta-oxidation I	0.26	0.34	-0.12	NR
glucose and glucose-1-phosphate degradation	0.26	0.34	-0.12	NR
glyoxylate cycle	0.26	0.34	-0.12	NR

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L-gulonate degradation	0.26	0.34	-0.12	NR
superpathway of glyoxylate bypass and TCA	0.26	0.34	-0.12	NR
3-phenylpropanoate and 3-(3-hydroxyphenyl)propanoate degradation to 2-oxopent-4-enoate	0.34	0.39	-0.36	NR
L-phenylalanine biosynthesis II	0.34	0.39	-0.36	NR
tetrathionate reduction I (to thiosulfate)	0.34	0.39	-0.36	NR
urate degradation to allantoin II	0.34	0.39	-0.36	NR
cob(II)yrinate a,c-diamide biosynthesis I (early cobalt insertion)	0.41	0.41	-0.12	NR
glycerol-3-phosphate to cytochrome bo oxidase electron transfer	0.41	0.41	-0.12	NR
NADH to cytochrome bo oxidase electron transfer I	0.41	0.41	-0.12	NR
proline to cytochrome bo oxidase electron transfer	0.41	0.41	-0.12	NR
pyruvate to cytochrome bo oxidase electron transfer	0.41	0.41	-0.12	NR
succinate to cytochrome bo oxidase electron transfer	0.41	0.41	-0.12	NR
cinnamate and 3-hydroxycinnamate degradation to 2-oxopent-4-enoate	0.39	0.41	-0.19	NR
Entner-Doudoroff pathway I	0.39	0.41	-0.19	NR
superpathway of glycolysis and Entner-Doudoroff	0.39	0.41	-0.19	NR
glycerol degradation II	0.44	0.43	-0.20	NR
L-threonine degradation III (to methylglyoxal)	0.44	0.43	-0.20	NR
neurosporene biosynthesis	0.44	0.43	-0.20	NR
phenylethylamine degradation I	0.44	0.43	-0.20	NR
trans-lycopene biosynthesis I (bacteria)	0.44	0.43	-0.20	NR
acetate formation from acetyl-CoA II	0.49	0.43	-0.23	NR
crotonate fermentation (to acetate and cyclohexane carboxylate)	0.49	0.43	-0.23	NR
D-allose degradation	0.49	0.43	-0.23	NR
2-O-alpha-mannosyl-D-glycerate degradation	0.48	0.43	-0.21	NR
galactitol degradation	0.48	0.43	-0.21	NR
malonate degradation I (biotin-independent)	0.48	0.43	-0.21	NR
(R)-acetoin biosynthesis I	0.48	0.43	-0.21	NR
(R,R)-butanediol biosynthesis	0.48	0.43	-0.21	NR
(R,R)-butanediol degradation	0.48	0.43	-0.21	NR
aerobactin biosynthesis	0.00	0.44	-1.00	NR
benzoyl-CoA degradation I (aerobic)	0.00	0.44	-1.00	NR
glutaryl-CoA degradation	0.00	0.44	-1.00	NR
nitrate reduction I (denitrification)	0.00	0.44	-1.00	NR
pectin degradation II	0.00	0.44	-1.00	NR
fluoroacetate and fluorothreonine biosynthesis	0.00	0.49	-0.08	NR
catechol degradation to beta-ketoadipate	0.36	0.56	-0.44	NR
chondroitin sulfate degradation I (bacterial)	0.36	0.56	-0.44	NR
dermatan sulfate degradation I (bacterial)	0.36	0.56	-0.44	NR
L-methionine salvage cycle III	0.36	0.56	-0.44	NR
phenylmercury acetate degradation	0.36	0.56	-0.44	NR

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urea degradation I	0.36	0.56	-0.44	NR
4-hydroxyphenylpyruvate biosynthesis	0.38	0.60	-0.07	NR
glutathionylspermidine biosynthesis	0.38	0.60	-0.07	NR
L-phenylalanine biosynthesis I	0.38	0.60	-0.07	NR
methylerythritol phosphate pathway II	0.38	0.60	-0.07	NR
nitrate reduction IX (dissimilatory)	0.38	0.60	-0.07	NR
nitrate reduction X (periplasmic, dissimilatory)	0.38	0.60	-0.07	NR
paraoxon degradation	0.38	0.60	-0.07	NR
parathion degradation	0.38	0.60	-0.07	NR
superpathway of aromatic amino acid biosynthesis	0.38	0.60	-0.07	NR
3-methylthiopropanoate biosynthesis	0.49	0.66	-0.26	NR
allantoin degradation to glyoxylate III	0.49	0.66	-0.26	NR
gallate degradation I	0.49	0.66	-0.26	NR
sulfoacetaldehyde degradation III	0.49	0.66	-0.26	NR
syringate degradation	0.49	0.66	-0.26	NR
(5Z)-dodec-5-enoate biosynthesis	0.57	0.66	-0.07	NR
fatty acid beta-oxidation III (unsaturated, odd number)	0.57	0.66	-0.07	NR
formaldehyde oxidation II (glutathione-dependent)	0.57	0.66	-0.07	NR
oleate biosynthesis IV (anaerobic)	0.57	0.66	-0.07	NR
superpathway of fatty acids biosynthesis (E. coli)	0.57	0.66	-0.07	NR
superpathway of unsaturated fatty acids biosynthesis (E. coli)	0.57	0.66	-0.07	NR
NAD salvage pathway III	0.51	0.68	-0.12	NR
NAD salvage pathway IV	0.51	0.68	-0.12	NR
superpathway of ubiquinol-8 biosynthesis (prokaryotic)	0.51	0.68	-0.12	NR
ubiquinol-7 biosynthesis (prokaryotic)	0.51	0.68	-0.12	NR
ubiquinol-8 biosynthesis (prokaryotic)	0.51	0.68	-0.12	NR
ubiquinol-9 biosynthesis (prokaryotic)	0.51	0.68	-0.12	NR
dTDP-N-acetylthomosamine biosynthesis	0.58	0.69	-0.12	NR
putrescine degradation II	0.58	0.69	-0.12	NR
taurine degradation IV	0.58	0.69	-0.12	NR
bile acids degradation	0.64	0.70	-0.12	NR
guanine and guanosine salvage II	0.64	0.70	-0.12	NR
guanosine nucleotides degradation II	0.64	0.70	-0.12	NR
superpathway of phenylethylamine degradation	0.64	0.70	-0.12	NR
formaldehyde assimilation I (serine pathway)	0.68	0.70	-0.12	NR
L-arginine degradation II (AST pathway)	0.68	0.70	-0.12	NR
S-methyl-5'-thioadenosine degradation II	0.68	0.70	-0.12	NR
superpathway of (R,R)-butanediol biosynthesis	0.68	0.70	-0.12	NR
2,3-dihydroxybenzoate biosynthesis	0.94	1.00	-0.01	NR
2-oxoisovalerate decarboxylation to isobutanoyl-CoA	0.00	1.00	-0.04	NR
acyl carrier protein metabolism	0.77	1.00	-0.05	NR

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allantoin degradation IV (anaerobic)	0.61	1.00	-0.03	NR
allantoin degradation to ureidoglycolate II (ammonia producing)	0.61	1.00	-0.03	NR
allantoin degradation to ureidoglycolate I (urea producing)	0.78	1.00	-0.12	NR
anthranilate degradation I (aerobic)	0.78	1.00	-0.12	NR
Bifidobacterium shunt	0.69	1.00	-0.06	NR
cyanate degradation	0.71	1.00	-0.12	NR
D-glucarate degradation II	0.00	1.00	-0.04	NR
D-gluconate degradation	0.00	1.00	-0.04	NR
D-glucosaminate degradation	0.76	1.00	-0.12	NR
D-serine degradation	0.00	1.00	-0.04	NR
glucose degradation (oxidative)	0.84	1.00	-0.04	NR
glutathione-glutaredoxin redox reactions	0.00	1.00	-0.04	NR
heme biosynthesis I (aerobic)	0.94	1.00	-0.01	NR
heptadecane biosynthesis	0.61	1.00	-0.03	NR
lactose and galactose degradation I	0.71	1.00	-0.12	NR
L-methionine degradation I (to L-homocysteine)	0.74	1.00	-0.12	NR
L-methionine salvage cycle I (bacteria and plants)	0.76	1.00	-0.12	NR
maltose degradation	0.00	1.00	-0.04	NR
mannitol degradation I	0.00	1.00	-0.04	NR
mannosylglycerate biosynthesis I	0.90	1.00	-0.03	NR
PRPP biosynthesis II	0.77	1.00	-0.05	NR
pseudouridine degradation	0.69	1.00	-0.06	NR
purine nucleotides degradation II (aerobic)	0.00	1.00	-0.04	NR
pyrimidine deoxyribonucleotides de novo biosynthesis III	0.94	1.00	-0.01	NR
pyrimidine deoxyribonucleotides dephosphorylation	0.90	1.00	-0.03	NR
pyrimidine nucleobases salvage II	0.00	1.00	-0.04	NR
pyrroloquinoline quinone biosynthesis	0.76	1.00	-0.12	NR
pyruvate decarboxylation to acetyl CoA	0.00	1.00	-0.04	NR
quinate degradation I	0.90	1.00	-0.03	NR
(R)-acetoin biosynthesis II	0.82	1.00	-0.02	NR
(S)-acetoin biosynthesis	0.77	1.00	-0.05	NR
salicylate biosynthesis I	0.90	1.00	-0.03	NR
shikimate degradation I	0.90	1.00	-0.03	NR
S-methyl-5'-thioadenosine degradation I	0.90	1.00	-0.03	NR
S-methyl-5-thio-alpha-D-ribose 1-phosphate degradation	0.76	1.00	-0.12	NR
(S,S)-butanediol biosynthesis	0.77	1.00	-0.05	NR
(S,S)-butanediol degradation	0.77	1.00	-0.05	NR
sulfate reduction I (assimilatory)	0.00	1.00	-0.04	NR
sulfate reduction III (assimilatory)	0.00	1.00	-0.04	NR
sulfite oxidation III	0.00	1.00	-0.04	NR
sulfur reduction II (via polysulfide)	0.78	1.00	-0.12	NR

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superpathway of L-arginine, putrescine, and 4-aminobutanoate degradation	0.90	1.00	-0.03	NR
superpathway of ornithine degradation	0.90	1.00	-0.03	NR
TCA cycle I (prokaryotic)	0.00	1.00	-0.04	NR
trehalose biosynthesis IV	0.00	1.00	-0.04	NR
trehalose biosynthesis V	0.78	1.00	-0.12	NR
trehalose degradation II (trehalase)	0.61	1.00	-0.03	NR
trehalose degradation VI (periplasmic)	0.61	1.00	-0.03	NR
two-component alkanesulfonate monooxygenase	0.94	1.00	-0.01	NR
UDP-2,3-diacetamido-2,3-dideoxy-alpha-D-mannuronate biosynthesis	0.61	1.00	-0.03	NR
urate biosynthesis/inosine 5'-phosphate degradation	0.00	1.00	-0.04	NR
vanillin and vanillate degradation II	0.90	1.00	-0.03	NR
vancomycin resistance II	Inf	0.02	1.00	R
inosine-5'-phosphate biosynthesis III	Inf	0.11	1.00	R
fructan biosynthesis	4.48	0.11	0.40	R
putrescine degradation I	6.84	0.13	0.19	R
L-cysteine degradation II	4.66	0.18	0.22	R
D-serine metabolism	5.21	0.18	0.59	R
bis(guanylyl molybdenum cofactor) biosynthesis	Inf	0.18	0.10	R
gentisate degradation I	Inf	0.23	1.00	R
kojibiose degradation	Inf	0.23	1.00	R
methanogenesis from H2 and CO2	Inf	0.23	1.00	R
phosphopantothenate biosynthesis III	Inf	0.23	1.00	R
reductive acetyl coenzyme A pathway II (autotrophic methanogens)	Inf	0.23	1.00	R
(R)-cysteate degradation	3.00	0.24	0.28	R
L-cysteine biosynthesis III (from L-homocysteine)	2.86	0.24	0.22	R
glycolysis IV (plant cytosol)	3.26	0.35	0.15	R
UDP-N-acetyl-D-galactosamine biosynthesis I	2.91	0.39	0.18	R
formaldehyde oxidation I	2.41	0.41	0.33	R
trehalose degradation IV	2.41	0.41	0.33	R
heme biosynthesis II (anaerobic)	2.56	0.41	0.29	R
superpathway of heme biosynthesis from uroporphyrinogen-III	2.56	0.41	0.29	R
8-amino-7-oxononanoate biosynthesis III	2.25	0.43	0.22	R
2-oxoglutarate decarboxylation to succinyl-CoA	Inf	0.44	0.05	R
CMP-N-acetylneuraminate biosynthesis II (bacteria)	Inf	0.44	0.05	R
cob(II)yrinate a,c-diamide biosynthesis II (late cobalt incorporation)	Inf	0.44	0.05	R
cyclopropane fatty acid (CFA) biosynthesis	Inf	0.44	0.05	R
guanylyl molybdenum cofactor biosynthesis	Inf	0.44	0.05	R
hydrogen production III	Inf	0.44	0.05	R
hydrogen production VI	Inf	0.44	0.05	R
L-arginine degradation I (arginase pathway)	Inf	0.44	0.05	R
L-arginine degradation VI (arginase 2 pathway)	Inf	0.44	0.05	R

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L-citrulline biosynthesis	Inf	0.44	0.05	R
L-ornithine biosynthesis II	Inf	0.44	0.05	R
L-proline biosynthesis III	Inf	0.44	0.05	R
pectin degradation III	Inf	0.44	0.05	R
putrescine biosynthesis IV	Inf	0.44	0.05	R
adenine and adenosine salvage VI	Inf	0.49	1.00	R
alginate degradation	Inf	0.49	1.00	R
glycine biosynthesis III	Inf	0.49	1.00	R
sulfolactate degradation I	Inf	0.49	1.00	R
superpathway of L-cysteine biosynthesis (mammalian)	Inf	0.49	1.00	R
L-histidine degradation III	2.77	0.56	0.06	R
nitrogen fixation I (ferredoxin)	2.77	0.56	0.06	R
chlorosalicylate degradation	2.63	0.60	0.40	R
methylsalicylate degradation	2.63	0.60	0.40	R
salicylate degradation I	2.63	0.60	0.40	R
acrylate degradation	2.18	0.62	0.08	R
L-methionine degradation II	2.18	0.62	0.08	R
cyanophycin metabolism	1.76	0.66	0.22	R
TCA cycle VII (acetate-producers)	1.76	0.66	0.22	R
Kdo transfer to lipid IVA II	1.95	0.68	0.22	R
aminopropanol phosphate biosynthesis I	1.71	0.69	0.16	R
hopanoid biosynthesis (bacteria)	1.57	0.70	0.11	R
D-galactarate degradation I	1.48	0.70	0.08	R
D-glucarate degradation I	1.48	0.70	0.08	R
formaldehyde assimilation II (RuMP Cycle)	1.48	0.70	0.08	R
ribose degradation	1.48	0.70	0.08	R
superpathway of D-glucarate and D-galactarate degradation	1.48	0.70	0.08	R
1,2-dichloroethane degradation	Inf	1.00	1.00	R
1,4-dihydroxy-2-naphthoate biosynthesis	0.00	1.00	0.00	R
2-aminoethylphosphonate degradation I	0.00	1.00	0.00	R
2'-deoxy-alpha-D-ribose 1-phosphate degradation	0.00	1.00	0.00	R
[2Fe-2S] iron-sulfur cluster biosynthesis	0.00	1.00	0.00	R
2-heptyl-3-hydroxy-4(1H)-quinolone biosynthesis	Inf	1.00	1.00	R
3-dehydroquinate biosynthesis I	0.00	1.00	0.00	R
4-amino-2-methyl-5-diphosphomethylpyrimidine biosynthesis	0.00	1.00	0.00	R
4-aminobenzoate biosynthesis	0.00	1.00	0.00	R
4-deoxy-L-threo-hex-4-enopyranuronate degradation	0.00	1.00	0.00	R
5-aminoimidazole ribonucleotide biosynthesis I	0.00	1.00	0.00	R
6-hydroxymethyl-dihydropterin diphosphate biosynthesis I	0.00	1.00	0.00	R
8-amino-7-oxononanoate biosynthesis I	0.00	1.00	0.00	R
acetate conversion to acetyl-CoA	0.00	1.00	0.00	R

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acetate formation from acetyl-CoA I	0.00	1.00	0.00	R
adenine and adenosine salvage I	0.00	1.00	0.00	R
adenine and adenosine salvage III	0.00	1.00	0.00	R
adenine salvage	0.00	1.00	0.00	R
adenosine deoxyribonucleotides de novo biosynthesis	0.00	1.00	0.00	R
adenosine deoxyribonucleotides de novo biosynthesis II	0.00	1.00	0.00	R
adenosine nucleotides degradation II	0.00	1.00	0.00	R
adenosine nucleotides degradation III	0.00	1.00	0.00	R
adenosine ribonucleotides de novo biosynthesis	0.00	1.00	0.00	R
adenosylcobalamin biosynthesis from cobyrinate a,c-diamide I	0.00	1.00	0.00	R
adenosylcobalamin biosynthesis from cobyrinate a,c-diamide II	0.00	1.00	0.00	R
adenosylcobalamin salvage from cobalamin	0.00	1.00	0.00	R
adenosylcobalamin salvage from cobinamide I	0.00	1.00	0.00	R
ADP-L-glycero-beta-D-manno-heptose biosynthesis	1.32	1.00	0.02	R
aerobic respiration I (cytochrome c)	1.63	1.00	0.22	R
allantoin degradation to glyoxylate I	Inf	1.00	1.00	R
ammonia assimilation cycle III	0.00	1.00	0.00	R
androstenedione degradation	Inf	1.00	1.00	R
anhydromuropeptides recycling	0.00	1.00	0.00	R
arginine dependent acid resistance	0.00	1.00	0.00	R
arsenate detoxification II (glutaredoxin)	0.00	1.00	0.00	R
autoinducer AI-2 biosynthesis I	0.00	1.00	0.00	R
autoinducer AI-2 degradation	0.00	1.00	0.00	R
base-degraded thiamine salvage	0.00	1.00	0.00	R
beta-alanine biosynthesis II	Inf	1.00	1.00	R
beta-alanine biosynthesis III	0.00	1.00	0.00	R
beta-D-glucuronide and D-glucuronate degradation	0.00	1.00	0.00	R
biotin biosynthesis from 8-amino-7-oxononanoate I	0.00	1.00	0.00	R
biotin biosynthesis I	0.00	1.00	0.00	R
biotin-carboxyl carrier protein assembly	0.00	1.00	0.00	R
C4 photosynthetic carbon assimilation cycle, NAD-ME type	0.00	1.00	0.00	R
Calvin-Benson-Bassham cycle	Inf	1.00	1.00	R
CDP-diacylglycerol biosynthesis I	0.00	1.00	0.00	R
CDP-diacylglycerol biosynthesis II	0.00	1.00	0.00	R
cellulose and hemicellulose degradation (cellulolosome)	1.29	1.00	0.01	R
cellulose biosynthesis	1.32	1.00	0.02	R
chitin degradation II	0.00	1.00	0.00	R
chitobiose degradation	0.00	1.00	0.00	R
chorismate biosynthesis from 3-dehydroquinate	0.00	1.00	0.00	R
chorismate biosynthesis I	0.00	1.00	0.00	R
cis-genanyl-CoA degradation	1.63	1.00	0.22	R

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cis-vaccenate biosynthesis	0.00	1.00	0.00	R
citrate degradation	0.00	1.00	0.00	R
citrate lyase activation	0.00	1.00	0.00	R
CMP-3-deoxy-D-manno-octulosonate biosynthesis	0.00	1.00	0.00	R
CMP phosphorylation	0.00	1.00	0.00	R
coenzyme A biosynthesis I	0.00	1.00	0.00	R
creatinine degradation I	0.00	1.00	0.00	R
cytidylyl molybdenum cofactor biosynthesis	0.00	1.00	0.00	R
D-arabinose degradation I	0.00	1.00	0.00	R
demethylmenaquinol-6 biosynthesis I	0.00	1.00	0.00	R
demethylmenaquinol-8 biosynthesis I	0.00	1.00	0.00	R
demethylmenaquinol-9 biosynthesis	0.00	1.00	0.00	R
D-fructuronate degradation	0.00	1.00	0.00	R
D-galactarate degradation II	0.00	1.00	0.00	R
D-galactose degradation I (Leloir pathway)	0.00	1.00	0.00	R
D-galactose degradation V (Leloir pathway)	0.00	1.00	0.00	R
D-galacturonate degradation I	0.00	1.00	0.00	R
di-trans,poly-cis-undecaprenyl phosphate biosynthesis	0.00	1.00	0.00	R
D-mannose degradation	0.00	1.00	0.00	R
D-sorbitol degradation I	0.00	1.00	0.00	R
dTDP-L-rhamnose biosynthesis I	0.00	1.00	0.00	R
ethanolamine utilization	0.00	1.00	0.00	R
ethanol degradation I	0.00	1.00	0.00	R
ethanol degradation II	0.00	1.00	0.00	R
fatty acid biosynthesis initiation I	0.00	1.00	0.00	R
fatty acid biosynthesis initiation III	Inf	1.00	1.00	R
fatty acid elongation -- saturated	0.00	1.00	0.00	R
fatty acid salvage	Inf	1.00	1.00	R
flavin biosynthesis I (bacteria and plants)	0.00	1.00	0.00	R
fluoroacetate degradation	Inf	1.00	1.00	R
folate polyglutamylation	0.00	1.00	0.00	R
folate transformations I	0.00	1.00	0.00	R
formate assimilation into 5,10-methylenetetrahydrofolate	0.00	1.00	0.00	R
formate oxidation to CO2	0.00	1.00	0.00	R
fructose degradation	0.00	1.00	0.00	R
fucose degradation	0.00	1.00	0.00	R
GABA shunt	Inf	1.00	1.00	R
GDP-L-fucose biosynthesis I (from GDP-D-mannose)	0.00	1.00	0.00	R
GDP-mannose biosynthesis	0.00	1.00	0.00	R
geranyl diphosphate biosynthesis	0.00	1.00	0.00	R
geranylgeranyl diphosphate biosynthesis	0.00	1.00	0.00	R

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gluconeogenesis I	0.00	1.00	0.00	R
glutaminyl-tRNAgln biosynthesis via transamidation	0.00	1.00	0.00	R
glutathione biosynthesis	0.00	1.00	0.00	R
glutathione-peroxide redox reactions	0.00	1.00	0.00	R
glycerol-3-phosphate to fumarate electron transfer	0.00	1.00	0.00	R
glycerol and glycerophosphodiester degradation	0.00	1.00	0.00	R
glycerol degradation I	0.00	1.00	0.00	R
glycerophosphodiester degradation	0.00	1.00	0.00	R
glycine biosynthesis I	0.00	1.00	0.00	R
glycine cleavage	0.00	1.00	0.00	R
glycogen biosynthesis I (from ADP-D-Glucose)	0.00	1.00	0.00	R
glycolysis I (from glucose 6-phosphate)	0.00	1.00	0.00	R
glycolysis III (from glucose)	0.00	1.00	0.00	R
gondoate biosynthesis (anaerobic)	0.00	1.00	0.00	R
guanine and guanosine salvage	0.00	1.00	0.00	R
guanosine deoxyribonucleotides de novo biosynthesis I	0.00	1.00	0.00	R
guanosine deoxyribonucleotides de novo biosynthesis II	0.00	1.00	0.00	R
guanosine nucleotides degradation III	0.00	1.00	0.00	R
guanosine ribonucleotides de novo biosynthesis	0.00	1.00	0.00	R
heptaprenyl diphosphate biosynthesis	0.00	1.00	0.00	R
histamine biosynthesis	1.36	1.00	0.04	R
homolactic fermentation	0.00	1.00	0.00	R
hyaluronan degradation	0.00	1.00	0.00	R
hydrogen oxidation I (aerobic)	0.00	1.00	0.00	R
hydrogen oxidation III (anaerobic, NADP)	0.00	1.00	0.00	R
hydrogen to dimethyl sulfoxide electron transfer	0.00	1.00	0.00	R
hydrogen to fumarate electron transfer	0.00	1.00	0.00	R
hydroxymethylpyrimidine salvage	0.00	1.00	0.00	R
hypotaurine degradation	Inf	1.00	1.00	R
incomplete reductive TCA cycle	0.00	1.00	0.00	R
inosine-5'-phosphate biosynthesis I	0.00	1.00	0.00	R
L-1,2-propanediol degradation	1.03	1.00	0.01	R
lactose degradation III	0.00	1.00	0.00	R
L-alanine biosynthesis I	0.00	1.00	0.00	R
L-alanine biosynthesis II	0.00	1.00	0.00	R
L-alanine biosynthesis III	0.00	1.00	0.00	R
L-alanine degradation IV	0.00	1.00	0.00	R
L-arabinose degradation I	0.00	1.00	0.00	R
L-arginine biosynthesis II (acetyl cycle)	0.00	1.00	0.00	R
L-arginine biosynthesis I (via L-ornithine)	0.00	1.00	0.00	R
L-arginine degradation III (arginine decarboxylase/agmatinase pathway)	0.00	1.00	0.00	R

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L-arginine degradation V (arginine deiminase pathway)	0.00	1.00	0.00	R
L-asparagine biosynthesis I	0.00	1.00	0.00	R
L-asparagine biosynthesis II	0.00	1.00	0.00	R
L-asparagine biosynthesis III (tRNA-dependent)	0.00	1.00	0.00	R
L-asparagine degradation I	0.00	1.00	0.00	R
L-aspartate biosynthesis	0.00	1.00	0.00	R
L-aspartate degradation I	0.00	1.00	0.00	R
L-citrulline degradation	0.00	1.00	0.00	R
L-cysteine biosynthesis I	0.00	1.00	0.00	R
leucine degradation IV	Inf	1.00	1.00	R
L-glutamate biosynthesis I	0.00	1.00	0.00	R
L-glutamate biosynthesis II	0.00	1.00	0.00	R
L-glutamate biosynthesis III	0.00	1.00	0.00	R
L-glutamate degradation I	0.00	1.00	0.00	R
L-glutamate degradation II	0.00	1.00	0.00	R
L-glutamate degradation IX (via 4-aminobutanoate)	0.00	1.00	0.00	R
L-glutamate degradation X	0.00	1.00	0.00	R
L-glutamine biosynthesis I	0.00	1.00	0.00	R
L-glutamine biosynthesis III	0.00	1.00	0.00	R
L-glutamine degradation I	0.00	1.00	0.00	R
L-glutamine degradation II	0.00	1.00	0.00	R
L-histidine biosynthesis	0.00	1.00	0.00	R
L-histidine degradation I	0.00	1.00	0.00	R
L-homocysteine biosynthesis	0.00	1.00	0.00	R
L-homoserine and L-methionine biosynthesis	0.00	1.00	0.00	R
L-homoserine biosynthesis	0.00	1.00	0.00	R
L-idonate degradation	0.00	1.00	0.00	R
lipid IVA biosynthesis	0.00	1.00	0.00	R
lipoate biosynthesis and incorporation I	0.00	1.00	0.00	R
lipoate biosynthesis and incorporation II	0.00	1.00	0.00	R
lipoate salvage I	0.00	1.00	0.00	R
L-isoleucine biosynthesis I (from threonine)	0.00	1.00	0.00	R
L-isoleucine degradation I	0.00	1.00	0.00	R
L-lactaldehyde degradation (anaerobic)	0.00	1.00	0.00	R
L-leucine biosynthesis	0.00	1.00	0.00	R
L-leucine degradation I	1.63	1.00	0.22	R
L-lysine biosynthesis I	0.00	1.00	0.00	R
L-lysine biosynthesis III	0.00	1.00	0.00	R
L-lysine biosynthesis VI	0.00	1.00	0.00	R
L-lysine fermentation to acetate and butanoate	0.00	1.00	0.00	R
L-malate degradation II	0.00	1.00	0.00	R

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L-methionine biosynthesis I	0.00	1.00	0.00	R
L-methionine biosynthesis III	0.00	1.00	0.00	R
long-chain fatty acid activation	0.00	1.00	0.00	R
L-ornithine biosynthesis I	0.00	1.00	0.00	R
L-phenylalanine degradation I (aerobic)	Inf	1.00	1.00	R
L-proline biosynthesis I	0.00	1.00	0.00	R
L-proline degradation	0.00	1.00	0.00	R
L-rhamnose degradation I	0.00	1.00	0.00	R
L-selenocysteine biosynthesis I (bacteria)	0.00	1.00	0.00	R
L-serine biosynthesis	0.00	1.00	0.00	R
L-serine degradation	0.00	1.00	0.00	R
L-threonine biosynthesis	0.00	1.00	0.00	R
L-threonine degradation II	0.00	1.00	0.00	R
L-threonine degradation IV	0.00	1.00	0.00	R
L-tryptophan biosynthesis	0.00	1.00	0.00	R
L-tryptophan degradation II (via pyruvate)	0.00	1.00	0.00	R
L-tryptophan degradation I (via anthranilate)	Inf	1.00	1.00	R
L-tryptophan degradation to 2-amino-3-carboxymuconate semialdehyde	Inf	1.00	1.00	R
L-tyrosine biosynthesis I	0.00	1.00	0.00	R
L-valine biosynthesis	0.00	1.00	0.00	R
mannan degradation	0.00	1.00	0.00	R
melibiose degradation	0.00	1.00	0.00	R
menaquinol-6 biosynthesis	0.00	1.00	0.00	R
menaquinol-7 biosynthesis	0.00	1.00	0.00	R
menaquinol-8 biosynthesis	0.00	1.00	0.00	R
menaquinol-9 biosynthesis	0.00	1.00	0.00	R
methylerythritol phosphate pathway I	0.00	1.00	0.00	R
methylglyoxal degradation I	0.00	1.00	0.00	R
methylphosphonate degradation I	0.00	1.00	0.00	R
mevalonate degradation	1.32	1.00	0.02	R
mixed acid fermentation	0.00	1.00	0.00	R
molybdenum cofactor biosynthesis	0.00	1.00	0.00	R
myo-, chiro- and scillo-inositol degradation	0.00	1.00	0.00	R
myo-inositol biosynthesis	0.00	1.00	0.00	R
myo-inositol degradation I	0.00	1.00	0.00	R
N10-formyl-tetrahydrofolate biosynthesis	0.00	1.00	0.00	R
N6-L-threonylcarbamoyladenosine37-modified tRNA biosynthesis	0.00	1.00	0.00	R
N-acetylglucosamine degradation I	0.00	1.00	0.00	R
N-acetylglucosamine degradation II	1.03	1.00	0.01	R
N-acetylneuraminate and N-acetylmannosamine degradation I	0.00	1.00	0.00	R
NAD biosynthesis from 2-amino-3-carboxymuconate semialdehyde	0.00	1.00	0.00	R

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NAD biosynthesis II (from tryptophan)	Inf	1.00	1.00	R
NAD biosynthesis III	1.22	1.00	0.08	R
NADH repair	0.00	1.00	0.00	R
NADH to cytochrome bd oxidase electron transfer I	0.00	1.00	0.00	R
NAD phosphorylation and dephosphorylation	0.00	1.00	0.00	R
NAD salvage pathway II	0.00	1.00	0.00	R
octane oxidation	Inf	1.00	1.00	R
octaprenyl diphosphate biosynthesis	0.00	1.00	0.00	R
oleate beta-oxidation	0.00	1.00	0.00	R
oxidized GTP and dGTP detoxification	0.00	1.00	0.00	R
palmitate biosynthesis II (bacteria and plants)	0.00	1.00	0.00	R
palmitoleate biosynthesis I (from (5Z)-dodec-5-enoate)	0.00	1.00	0.00	R
pantothenate and coenzyme A biosynthesis I	0.00	1.00	0.00	R
partial TCA cycle (obligate autotrophs)	0.00	1.00	0.00	R
pentose phosphate pathway	0.00	1.00	0.00	R
pentose phosphate pathway (non-oxidative branch)	0.00	1.00	0.00	R
pentose phosphate pathway (oxidative branch)	0.00	1.00	0.00	R
peptidoglycan biosynthesis I (meso-diaminopimelate containing)	0.00	1.00	0.00	R
peptidoglycan maturation (meso-diaminopimelate containing)	0.00	1.00	0.00	R
phosphate acquisition	0.00	1.00	0.00	R
phosphatidylethanolamine biosynthesis I	0.00	1.00	0.00	R
phosphatidylglycerol biosynthesis II (non-plastidic)	0.00	1.00	0.00	R
phosphatidylglycerol biosynthesis I (plastidic)	0.00	1.00	0.00	R
phospholipases	0.00	1.00	0.00	R
phosphopantothenate biosynthesis I	0.00	1.00	0.00	R
polyisoprenoid biosynthesis (E. coli)	0.00	1.00	0.00	R
ppGpp biosynthesis	0.00	1.00	0.00	R
preQ0 biosynthesis	0.00	1.00	0.00	R
propanoyl CoA degradation I	0.00	1.00	0.00	R
protocatechuate degradation II (ortho-cleavage pathway)	0.00	1.00	0.00	R
PRPP biosynthesis I	0.00	1.00	0.00	R
purine deoxyribonucleosides degradation I	0.00	1.00	0.00	R
purine ribonucleosides degradation	0.00	1.00	0.00	R
putrescine biosynthesis I	0.00	1.00	0.00	R
putrescine biosynthesis III	0.00	1.00	0.00	R
pyridoxal 5'-phosphate biosynthesis II	0.00	1.00	0.00	R
pyridoxal 5'-phosphate salvage I	0.00	1.00	0.00	R
pyrimidine deoxyribonucleosides degradation	0.00	1.00	0.00	R
pyrimidine deoxyribonucleosides salvage	0.00	1.00	0.00	R
pyrimidine deoxyribonucleotide phosphorylation	0.00	1.00	0.00	R
pyrimidine deoxyribonucleotides de novo biosynthesis I	0.00	1.00	0.00	R

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pyrimidine deoxyribonucleotides de novo biosynthesis II	0.00	1.00	0.00	R
pyrimidine nucleobases salvage I	0.00	1.00	0.00	R
pyrimidine ribonucleosides degradation	0.00	1.00	0.00	R
pyrimidine ribonucleosides salvage I	0.00	1.00	0.00	R
pyruvate fermentation to acetate and lactate II	0.00	1.00	0.00	R
pyruvate fermentation to acetate I	0.00	1.00	0.00	R
pyruvate fermentation to acetate IV	0.00	1.00	0.00	R
pyruvate fermentation to ethanol I	0.00	1.00	0.00	R
pyruvate fermentation to ethanol III	0.00	1.00	0.00	R
pyruvate fermentation to lactate	0.00	1.00	0.00	R
pyruvate to cytochrome bd terminal oxidase electron transfer	0.00	1.00	0.00	R
queuosine biosynthesis	0.00	1.00	0.00	R
reactive oxygen species degradation	0.00	1.00	0.00	R
reductive acetyl coenzyme A pathway I (homoacetogenic bacteria)	0.00	1.00	0.00	R
reductive monocarboxylic acid cycle	0.00	1.00	0.00	R
rhamnogalacturonan type I degradation II (bacteria)	0.00	1.00	0.00	R
Rubisco shunt	Inf	1.00	1.00	R
S-adenosyl-L-methionine biosynthesis	0.00	1.00	0.00	R
S-adenosyl-L-methionine cycle I	0.00	1.00	0.00	R
S-adenosyl-L-methionine cycle II	0.00	1.00	0.00	R
salicylate degradation II	Inf	1.00	1.00	R
selenate reduction	0.00	1.00	0.00	R
siroheme biosynthesis	0.00	1.00	0.00	R
S-methyl-5'-thioadenosine degradation III	1.06	1.00	0.02	R
spermidine biosynthesis I	0.00	1.00	0.00	R
stearate biosynthesis II (bacteria and plants)	0.00	1.00	0.00	R
succinate to cytochrome bd oxidase electron transfer	0.00	1.00	0.00	R
sucrose degradation III (sucrose invertase)	0.00	1.00	0.00	R
sucrose degradation IV (sucrose phosphorylase)	0.00	1.00	0.00	R
sulfate activation for sulfonation	0.00	1.00	0.00	R
sulfate reduction IV (dissimilatory)	Inf	1.00	1.00	R
sulfoacetaldehyde degradation I	Inf	1.00	1.00	R
sulfolactate degradation III	Inf	1.00	1.00	R
superoxide radicals degradation	0.00	1.00	0.00	R
superpathway of acetate utilization and formation	0.00	1.00	0.00	R
superpathway of adenosine nucleotides de novo biosynthesis I	0.00	1.00	0.00	R
superpathway of adenosine nucleotides de novo biosynthesis II	0.00	1.00	0.00	R
superpathway of beta-D-glucuronide and D-glucuronate degradation	0.00	1.00	0.00	R
superpathway of branched chain amino acid biosynthesis	0.00	1.00	0.00	R
superpathway of demethylmenaquinol-8 biosynthesis	0.00	1.00	0.00	R
superpathway of geranylgeranyl diphosphate biosynthesis II (via MEP)	0.00	1.00	0.00	R

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superpathway of glucose and xylose degradation	0.00	1.00	0.00	R
superpathway of guanosine nucleotides de novo biosynthesis I	0.00	1.00	0.00	R
superpathway of guanosine nucleotides de novo biosynthesis II	0.00	1.00	0.00	R
superpathway of L-alanine biosynthesis	0.00	1.00	0.00	R
superpathway of L-asparagine biosynthesis	0.00	1.00	0.00	R
superpathway of L-aspartate and L-asparagine biosynthesis	0.00	1.00	0.00	R
superpathway of L-isoleucine biosynthesis I	0.00	1.00	0.00	R
superpathway of L-lysine, L-threonine and L-methionine biosynthesis I	0.00	1.00	0.00	R
superpathway of L-methionine biosynthesis (by sulfhydrylation)	0.00	1.00	0.00	R
superpathway of L-methionine biosynthesis (transsulfuration)	0.00	1.00	0.00	R
superpathway of L-serine and glycine biosynthesis I	0.00	1.00	0.00	R
superpathway of L-threonine biosynthesis	0.00	1.00	0.00	R
superpathway of menaquinol-7 biosynthesis	0.00	1.00	0.00	R
superpathway of menaquinol-8 biosynthesis I	0.00	1.00	0.00	R
superpathway of N-acetylglucosamine, N-acetylmannosamine and N-acetylneuraminate degradation	0.00	1.00	0.00	R
superpathway of purine deoxyribonucleosides degradation	0.00	1.00	0.00	R
superpathway of pyrimidine deoxyribonucleoside salvage	0.00	1.00	0.00	R
superpathway of pyrimidine deoxyribonucleosides degradation	0.00	1.00	0.00	R
superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis	0.00	1.00	0.00	R
superpathway of pyrimidine deoxyribonucleotides de novo biosynthesis (E. coli)	0.00	1.00	0.00	R
superpathway of pyrimidine nucleobases salvage	0.00	1.00	0.00	R
superpathway of pyrimidine ribonucleotides de novo biosynthesis	0.00	1.00	0.00	R
superpathway of sulfate assimilation and cysteine biosynthesis	0.00	1.00	0.00	R
superpathway of tetrahydrofolate biosynthesis	0.00	1.00	0.00	R
superpathway of thiamine diphosphate biosynthesis I	0.00	1.00	0.00	R
superpathway of UDP-glucose-derived O-antigen building blocks biosynthesis	0.00	1.00	0.00	R
taurine degradation I	Inf	1.00	1.00	R
taurine degradation III	1.32	1.00	0.02	R
TCA cycle VIII (helicobacter)	1.36	1.00	0.04	R
tetrahydrofolate biosynthesis	0.00	1.00	0.00	R
tetrahydrofolate salvage from 5,10-methenyltetrahydrofolate	0.00	1.00	0.00	R
tetrapyrrole biosynthesis I (from glutamate)	0.00	1.00	0.00	R
thiamine diphosphate biosynthesis I (E. coli)	0.00	1.00	0.00	R
thiamine diphosphate biosynthesis II (Bacillus)	0.00	1.00	0.00	R
thiamine salvage II	0.00	1.00	0.00	R
thiamine salvage III	0.00	1.00	0.00	R
thiamine salvage IV (yeast)	0.00	1.00	0.00	R
thiazole biosynthesis I (facultative anaerobic bacteria)	0.00	1.00	0.00	R
thioredoxin pathway	0.00	1.00	0.00	R
thiosulfate disproportionation III (rhodanese)	1.29	1.00	0.01	R

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thymine degradation	0.00	1.00	0.00	R
trans, trans-farnesyl diphosphate biosynthesis	0.00	1.00	0.00	R
trehalose biosynthesis I	0.00	1.00	0.00	R
triacylglycerol degradation	1.22	1.00	0.08	R
tRNA charging	0.00	1.00	0.00	R
tRNA processing	0.00	1.00	0.00	R
UDP-alpha-D-glucuronate biosynthesis (from UDP-glucose)	0.00	1.00	0.00	R
UDP-D-galactose biosynthesis	0.00	1.00	0.00	R
UDP-D-galacturonate biosynthesis I (from UDP-D-glucuronate)	0.00	1.00	0.00	R
UDP-galactofuranose biosynthesis	0.00	1.00	0.00	R
UDP-glucose biosynthesis	0.00	1.00	0.00	R
UDP-N-acetyl-alpha-D-galactosaminuronate biosynthesis	Inf	1.00	1.00	R
UDP-N-acetyl-alpha-D-mannosaminouronate biosynthesis	0.00	1.00	0.00	R
UDP-N-acetyl-D-glucosamine biosynthesis I	0.00	1.00	0.00	R
UDP-N-acetylmuramoyl-pentapeptide biosynthesis II (lysine-containing)	1.32	1.00	0.02	R
UDP-N-acetylmuramoyl-pentapeptide biosynthesis I (meso-diaminopimelate containing)	0.00	1.00	0.00	R
UMP biosynthesis	0.00	1.00	0.00	R
uracil degradation III	1.63	1.00	0.22	R
urea cycle	0.00	1.00	0.00	R
urea degradation II	0.00	1.00	0.00	R
UTP and CTP de novo biosynthesis	0.00	1.00	0.00	R
UTP and CTP dephosphorylation I	0.00	1.00	0.00	R
xanthine and xanthosine salvage	0.00	1.00	0.00	R
xylose degradation I	0.00	1.00	0.00	R

[a]Estimates apply to a subset of 25 patients who had Metagenomic WGS data available

[00193] Table 8: Individual values and summary statistics of metabolic reconstructions.

Sample	Genes	Genes of known or predicted molecular function	Pathways	Metabolic Reactions	Transport Reactions	Compounds
1	36475	23417	451	2016	276	1669
2	36914	23811	459	2089	281	1751
3	44948	28820	498	2312	323	1895
4	31710	20446	397	1861	234	1583
5	25541	15702	500	2272	339	1877
6	41761	26459	507	2372	324	1943

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7	27071	17620	404	1851	245	1559
8	29091	18566	481	2163	328	1793
9	27740	17946	486	2255	328	1854
10	44204	27899	523	2471	344	2009
11	26897	17433	400	1814	240	1547
12	22879	14385	490	2248	334	1857
13	37311	24090	435	2017	274	1708
14	35781	22589	444	2094	287	1770
15	23732	15066	491	2253	331	1886
16	19793	12789	395	1899	240	1619
17	23184	14702	436	2020	276	1695
18	31203	19760	517	2329	354	1919
19	24237	15593	458	2117	311	1785
20	35021	22007	498	2251	336	1853
21	32373	21032	492	2218	314	1825
22	30518	19678	463	2114	277	1792
23	29535	19148	467	2165	316	1793
24	24410	15301	506	2305	349	1894
25	38701	24639	515	2325	358	1928
26	28840	18767	399	1879	245	1601
27	26919	17486	439	2012	306	1684
28	28250	18066	449	2004	282	1715
Mean	30894	19758	464	2133	302	1779

Example 2 – Materials and Methods

[00194] **Patient cohort:** An initial cohort of 112 patients with metastatic melanoma were included in this study. These patients were treated with anti-PD1 immune checkpoint blockade therapy at The University of Texas (UT) MD Anderson Cancer Center between April 2015 and March 2016 and signed voluntary informed consent for collection and analysis of tumor, blood and microbiome samples under Institutional Review Board (IRB)–approved protocols. Patients who were diagnosed with uveal melanoma (n=10), or who got anti-PD1 in combination with targeted agents or with adoptive T-cell transfer therapy (n=8), or in whom response could not be determined (n=6) were excluded from this analysis. Electronic medical charts were reviewed independently by three investigators to assign clinical response group and document other clinical parameters (Table 3). The primary outcome of clinical response (responder) (R) was defined by radiographic evidence of complete response (CR), partial response (PR) or stable disease (SD) per RECIST 1.1 criteria for at least 6 months. Lack of a clinical response (non responder) (NR) was

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defined by disease progression (PD) on serial CT scans or a clinical benefit lasting less than 6 months (minimal benefit).

[00195] **Microbiome sample collection:** Bucccal samples were collected during routine pre-treatment clinic visits using the Catch-All Sample Collection Swab (Epicentre, Madison, WI). All patients were also given outpatient OMNIgene GUT kit (OMR-200) (DNA Genotek fecal sample collection kits and asked to return). Importantly, this kit helps maintain microbiome profile stability at room temperature for up to 60 days. All samples were frozen at -80 degree C before DNA extraction and analysis.

[00196] The final cohort consisted of buccal samples collected from 87 patients, of whom 52 were R and 34 were NR, and fecal samples collected from 43 patients (of whom 30 were R and 13 were NR. All but 2 buccal and 2 fecal samples were collected at baseline. These were included as a baseline surrogate as a subset analysis on longitudinal samples which showed no change after treatment intervention in this cohort.

[00197] **Tumor and blood sample collection:** Available tumor samples (n=23) at matched pre-treatment time points were obtained from the MD Anderson Cancer Center Department of Pathology archive and Institutional Tissue Bank. After samples underwent quality control checks for percent tumor viability by an MD Anderson pathologist, the inventors included 17 samples from R and 6 from NR. Blood samples collected and stored for research (protocols previously listed) at baseline (n=11) were also queried for study inclusion yielding samples from 8R and 3 NR.

[00198] **DNA extraction and bacterial 16S sequencing:** Preparation and sequencing was done in collaboration with the Center for Metagenomics and Microbiome Research (CMMR) at The Baylor College of Medicine. 16S rRNA gene sequencing methods were adapted from the methods developed for the NIH-Human Microbiome Project (A framework for human microbiome research, 2012).

[00199] Briefly, bacterial genomic DNA was extracted using MO BIO PowerSoil DNA Isolation Kit (MO BIO Laboratories, USA). The 16S rDNA V4 region was amplified by PCR and sequenced in the MiSeq platform (Illumina, Inc, San Diego, CA) using the 2x250 bp

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paired-end protocol yielding pair-end reads that overlap almost completely. The primers used for amplification contain adapters for MiSeq sequencing and single-end barcodes allowing pooling and direct sequencing of PCR products (Caporaso *et al.,* 2012).

[00200] Quality filtered sequences with >97% identity were clustered into bins known as *Operational Taxonomic Units (OTUs)*, using open-reference OTU picking (Edgar, 2010; Rognes *et al.,* 2016; Caporaso *et al.,* 2010), and classified at the species level against the NCBI 16S ribosomal RNA 16S sequence database using ncbi-blast+ package 2.5.0. Phylogenetic classification was obtained from the NCBI taxonomy database. The relative abundance of each OTU was determined for all samples. Taxonomic classification was validated using the Greengenes, SILVA and RDP databases.

[00201] A phylogenetic tree was empirically constructed using the FastTree algorithm (Price *et al.,* 2010) in the QIIME software package, as described previously (Peled *et al.,* 2016). Briefly, all nodes of the tree were considered as *clusters of related OTU (crOTU)*, where the abundance of each crOTU was the sum of abundances of its member OTUs. The trees were constructed from a sequence alignment of all observed OTU's within both oral 1152 (97.5%% of 1182 OTUs) and gut 1434 (98.6% of 1455 OTUs) microbiomes. The resultant oral and gut microbiome crOTU trees contained 1152 and 1434 nodes respectively.

[00202] Taxonomical alpha-diversity was estimated using the Inverse Simpson Index. Rarefaction limits were set based on the least number of reads in all oral (13000) and fecal samples (8000) that were analyzed, where $D=1/\sum_{k=1}^{S} pi^2$, where pi is the proportion of the total species S that is comprised by the species i. Since, it captures variance of the taxonomical abundance distribution, it is often considered to be among the most meaningful and robust diversity metrics (Shannon *et al.,* 2013).

[00203] **Bipartite network to compare and contrast the oral and gut microbiota:** The biparitie network was constructed using *make_biparitite_network.py* script in QIIME using default parameters (Caporaso *et al.,* 2010) and then visualized in Cytoscape using edge-weighted spring-embedded layout. 2 networks were generated, using all buccal and fecal samples (FIG. 6) and using only paired samples (FIG. 1A), when both samples were obtained from the same patients.

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[00204] **Enrichment Index to visualize differences in oral and gut microbiome between R and NR:** *OTU representation index (ri)*: is used to quantify the representation of each species in R; (*ri*R), and NR (*ri*NR), as the proportion of samples within each group that had non-zero abundance for a particular species. The values of ri ranged from 0 (OTU not found in any sample within a group) to 1 (OTU found in all samples within a group).

[00205] *OTU enrichment index (ei):* was used to quantify and compare the enrichment of each OTU in R vs NR, where $ei=(ri\text{R} - ri\text{NR}) / (ri\text{R} + ri\text{NR})$. This index has values ranging from -1 and +1. When a species is identified in all R samples but not in any NR samples, $ei=+1$. The contrary is true for $ei= -1$.

[00206] The distribution *ei* scores was used to classify all species into 3 sets, Set 1- differentially enriched in R, Set 2 – found in both groups, and Set 3- differentially enriched in NR. Within each set, all OTU's were sorted by abundance and then visualized as a heatmap of log(10)-transformed OTU abundances in all sample given as columns. Thresholds for the OTU abundances (low, medium and high) were derived from the distribution of the abundances for all OTUs.

[00207] **Statistical assessment of biomarkers using LEfSe:** The LEfSe method of analysis first compares abundances of all bacterial clades between R and NR in the oral and gut microbiomes, using the Kruskal-Wallis test at a pre-defined α of 0.05, Significantly different vectors resulting from the comparison of abundances (*e.g.*, *Faecalibacterium* relative abundance) between groups are used as input to linear discriminant analysis (LDA), which produces an effect size (FIG. 2B). The primary advantage of LEfSe 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 of the difference between groups. In the case of hierarchically organized bacterial clades, there may be a lack of correlation between p values and effect sizes due to differences in the number of hypotheses considered at different levels since a greater number of comparisons would need to be made at the genus and species levels when compared to the phylum and class levels.

[00208] **Metagenomic whole genome shotgun (WGS) sequencing:** This was also done in collaboration with CMMR and Metagenopolis (MGP). Briefly, metagenomic sequencing

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data provides species-level resolution of the bacteria, and the near-complete genomic content of the collection of microbes in a particular sample, also referred to as the pangenome (depth of sequencing directly relates to the amount of the pangenome that is covered in a particular dataset).

[00209] Whole Genome Shotgun (WGS) sequencing utilizes the same extracted bacterial genomic DNA used for 16S rRNA gene compositional analysis. However, WGS sequencing achieves a higher depth of sequencing by employing a more powerful sequencing platform. Individual libraries were constructed from each sample and loaded into the HiSeq platform (Illumina) and sequenced using the 2x100 bp pair-end read protocol. The process of quality filtering, trimming, and demultiplexing was carried out by in-house pipeline developed by assembling publicly available tools such as Casava v1.8.3 (Illumina) for the generation of fastqs, Trim Galore and cutadapt for adapter and quality trimming, and PRINSEQ for sample demultiplexing.

[00210] Gut microbiota analysis was performed using the quantitative metagenomics pipeline developed at MGP. This approach allow the analysis of the microbiota at the gene and species level. High quality reads were selected and cleaned to eliminate possible contaminants as human reads. These were mapped and counted using the MetaHIT hs_9.9M genes catalogue (Li *et al.,* 2014) using the METEOR Studio in house pipeline using a two steps procedure : first using uniquely mapping reads, then attributing shared reads (mapping different genes from the catalogue) according to their mapping ratio using unique reads. Mapping was performed using a > 95% identity threshold to account gene variability and the no redundant nature of the catalogue.

[00211] After a downsizing step at 14M reads (to correct for the different sequencing depth) and normalization (RPKM), a gene frequency profile matrix was obtained which was used as the reference to perform the analyses using MetaOMineR, a suite of R packages developed at MGP and dedicated to the analysis of large quantitative metagenomics datasets.

[00212] The hs_9.9M gene catalogue has been clustered into 1438 MGS (MetaGenomic Species, groups of >500 genes that co-vary in abundance among hundreds samples and thus belong to the same microbial species (Nielson *et al.,* 2014). The taxonomical annotation of the MGS was performed using the homology of its genes with previously sequenced organisms (using blastN against nt and wgs databanks). MGS signal among samples was calculated as the

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mean or median signal of 50 marker genes. A MGS frequency profile matrix was constructed using the MGS mean signals and after normalization (sum of the MGS frequency of a sample = 1).

[00213] Reads whose genomic coordinates overlap with known KEGG orthologs were tabulated, and KEGG modules were calculated step-wise and determined to be complete if 65% of the reaction steps were present per detected species and for the metagenome. Pathways were constructed for each taxa and metagenome by calculating the minimum set through MinPath resulting from the gene orthologs present.

[00214] **Pathway Metagenome Databases (PGDB):** Databases were generated for each WGS sample using the PathoLogic program from the Pathway Tools software [PMID:26454094]. Inputs for the program were produced using predicted gene functions based on KEGG orthology and their taxonomy assignment in the metagenomes Thus, if the same function (KO group) had several taxonomic annotations, each of the annotations was considered as a separate gene. The definition of the KO group in KEGG was used as the gene function and the first name of the KO group, if available, was used as the gene name. EC numbers were assigned to the gene according to annotations of the KO group by the numbers in KEGG. The metabolic reconstructions were made in the automatic mode as described in the Pathway Tools manual with the option –tip to automatically predict transport reactions. The DOMAIN value 'TAX-2 (Bacteria)' was used as the organism class for the PGDB and the CODON-TABLE value to be equal 1. The generated PGDB were summarized and compared using Pathway Tools. The generated PGDBs are available upon request.

[00215] **Statistical Analyses:** Alpha-diversity was compared between R and NR using the Wilcoxon rank-sum or Mann-Whitney (MW) test. All patients were classified into high, intermediate or low diversity groups based on tertiles of the distribution. Pairwise comparisons of taxonomic abundances by both response and cluster were conducted using the MW test. Within each level (phylum, class, order, family, genus and species), the low abundance (<0.1%) and low variance taxa (<0.001) were excluded. Adjustments for multiple comparisons were done using the false-discovery rate method at an alpha level of 0.05. An effect size was estimated for each taxon as $U/\sqrt{n}$, where U is test statistic for the MW test, and n is the total sample size (n=43) (Fritz *et al.,* 2012), and volcano plots were generated for log10(FDR-adjusted p values) on the y-axis and

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median-adjusted effect sizes on the x-axis. In addition, patients were also classified as having high or low abundance of *Faecalibacterium prausnitzii* or *Bacteroidales* based on the median abundance of these taxa in the gut microbiome. Kaplan-Meier estimates were estimated for each group and compared using the log-rank test. Hazard ratios were estimated using the Cox-proportional hazard model.

[00216] In general the MW test was used for comparisons between binary outcome variables (R vs NR), and the Spearman correlation test was used to compare continuous variables. Additionally, the Fishers exact test was used when proportions were compared between binary variables. Hypothesis testing was done using both one-sided and two-sided tests as appropriate at a 95% significance level. All analyses were conducted in R and GraphPad Prism (La Jolla, CA).

[00217] **Immunohistochemistry:** Briefly, sections (4μm thickness) were prepared from formalin fixed paraffin embedded (FFPE) tissues. The presence of tumor was confirmed by a pathologist on hematoxylin & eosin-stained slides (H&E). Slides were then stained using a Leica Bond RX automated slide stainer (Leica Biosystems, Buffalo Grove, IL) for CD3 (n=17)(DAKO, Santa Clara, CA, 1:100), CD8 (n=21)(Thermo Scientific, Waltham, MA, 1:100), PD-1 (n=16)(Abcam, Cambridge, UK, 1:250), PD-L1(n=15)(1:100, Cell Signaling, Danvers, MA), GzmB (n=17), RORγT (n=14)(1:800, EMD Millipore, Billerica, MA), FoxP3 (n=16)(1:50, BioLegend, San Diego, CA) and counter-stained with hematoxylin. Stained slides were then scanned using an automated Aperio Slide Scanner (Leica), and the density of the immune infiltrate was quantified in tumor regions using a modified version of the default "Nuclear v9" algorithm and expressed as positive counts/mm2 for CD3, CD8, PD-1, FoxP3, and RORγT and as an H-score for PD-L1 which takes into account a percentage of positive cells multiplied by their intensity on a scale of 1 to 3 for a score between 1-300.

[00218] Flow cytometry was performed on peripheral blood mononuclear cells (PBMC). PBMCs were stained with CD3 (UCHT1, BioLegend), CD4 (SK3, eBioscience, Thermo Scientific), CD8 (RPAT8, BD Biosciences, Mississauga, Canada), FoxP3 (PCH101, eBioscience), CD127 (HIL-7R-M21, BD Biosciences), CD19 (HIB-19, BioLegend), CD14 (61D3, eBioscience), HLA-DR (L243, BD Biosciences), CD33 (WM53, BD Biosciences), CD56 (NCAM1, BD Biosciences), and CD11b (ICRF44, BD Biosciences) and acquisition was carried out on a Fortessa

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Flow Cytometer (BD Biosciences). Analysis was performed with FlowJo version 10 (Tree Star Inc., Ashland, OR).version 10 (Tree Star Inc., Ashland, OR).

[00219] **Multiplex Immunohistochemistry:** Sequential 12-marker myeloid multiplex immunohistochemistry was performed as described previously (Tsujikawa, *Cell Reports*, 2017). Briefly, FFPE sections underwent sequential staining, scanning and destaining cycles using AEC as chromagen and scanned with an Aperio Slide Scanner (Leica). Following staining and scanning with hematoxylin for nuclei, CD68, Tryptase, CSF1R, DC-SIGN, CD66b, CD83, CD163, HLA-DR, PD-L1, CD3/CD20/CD56, and CD45. CD45-positive regions of all images were then extracted using ImageScope, aligned, overlayed and segmented using CellProfiler and layers pseudocolored for analysis and quantification using FCS Express.

[00220] **Cytokine Multiplexing:** 41 plasma cytokine levels were assessed using multiplex bead assay (Bio-Rad, Hercules, CA). Cytokines, chemokines and soluble mediators quantified included IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, Eotaxin, FGF basic, G-CSF, GM-CSF, IFN-g, IP-10, MIP-1a, PDGF-bb, MIP-1b, RANTES, TNF-a, VEGF, IL-2ra, HGF, TRAIL, IL-17A, IL-17F, IL-23, SDF1/CXCL12, CCL22, MCP-1/CCL2, Gro-a/CXCL1, ENA78/CXCL5, EGF, TGF-b1, TGF-b2, and TGF-b3.

Example 3 – Modulation of the Gut Microbiome Enhances Anti-Tumor Responses in a Murine Melanoma Model

[00221] Next, it was sought to use insights gained from human studies to test the hypothesis that modulating the gut microbiome could enhance anti-tumor responses in a murine model of melanoma. Studies were performed to determine if modulation of the gut microbiome to enrich for short-chain fatty acid producing bacteria would enhance anti-tumor responses.

[00222] In these studies, a murine tumor model with a common driver mutation that is found in melanoma (BRAF) was used. The cells were implanted into genetically identical mice (C57BL6) purchased from 2 different vendors (Taconic farms versus Jackson laboratories) that differ significantly in their microbiome (with enriched short chain fatty acid producing bacteria in Taconic mice). The BRAF(V600E)/Pten$^{-/-}$ tumor cells were implanted into Taconic and Jackson mice, and substantial differences were observed in tumor growth (FIG. 33A) and survival (FIG. 33B) in these genetically identical mice with differing microbiomes. Interestingly, modulation of

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the gut microbiome by co-housing Taconic and Jackson (FIG. 33C) (as mice are normally copropahgic) or by fecal transplant abrogated these differences, suggesting that modulation of the gut microbiome can alter tumor growth in the BRAF-mutant tumor model. As mice are copraphagic, cohousing leads the emrgence of a merged microbiome that draws from both individual microbiomes. 16S sequencing was performed on single-housed versus co-housed Taconic and Jackson mice, demonstrating distinct microbiomes in the single-housed mice and co-housed mice (FIGs. 33D & E), confirming modulation of the gut microbiome in these mice.

[00223] Based on the data in human patients, it was tested whether oral administration of butyrate (a short chain fatty acid) would enhance anti-tumor responses by providing adequate substrate to facilitate a favorable gut microbiome. In these studies, butyrate was administered orally to Taconic and Jackson mice. Treatment with butyrate was associated with an enhanced anti-tumor response in these studies (FIG. 33F), further suggesting that modulation of the gut microbiome may enhance anti-tumor responses.

[00224] Thus, these studies provide novel data regarding the diversity and composition of the oral and gut microbiome in patients with metastatic melanoma on systemic therapy, and importantly demonstrate that differential bacterial "signatures" exist in responders versus non-responders to immune checkpoint blockade (specifically PD-1 based therapy).

Example 4 – Fecal Microbiota Transplantation

[00225] **Fecal Microbiota Transplantation (FMT) of a favorable gut microbiome in germ-free (GF) mice reduces tumor growth (FMT1):** To investigate a causal link between a "favorable" gut microbiome and response to immune checkpoint blockade, Fecal Microbiome Transplantation (FMT) experiments were performed in germ-free (GF) recipient mice. A well-established syngeneic model of injectable murine melanoma driven by oncogenic $BRAF^{V600E}$ expression and PTEN deletion (BP cells) was used. In the first experiment (FMT1), it was sought to determine if FMT could have any impact on tumor growth. GF mice (n=3 per group) were transplanted by oral gavage with stool from a responder (R-FMT group) or from a non-responder (NR-FMT group) to anti-PD-1 therapy. Control group mice were transplanted with PBS alone. Two weeks after FMT, each mouse was injected subcutaneously with $8x10^5$ BP cells, and

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tumor growth was checked twice a week (FIG. 25A). Blood and fecal pellets were collected at different time points during the experiment.

[00226] Results from FMT1 demonstrated significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 ($p=0.04$, Figure 1B).

[00227] Next, the systemic impact of FMT on the immune system was investigated using multicolor fluorescence activated cell sorting (FACS) analysis. Notably, mice receiving R-FMT had 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 (FIG. 26). These data 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.

[00228] This conclusion was further confirmed by quantitative confocal imaging on gut and tumor sections from mice that received FMT. Indeed, tumors of mice receiving R-FMT had a higher density of $CD45^+$ and $CD8^+$ T cells than mice receiving NR-FMT (FIG. 27A, and 27C upper panel). Moreover, FMT from R locally increased the number of $CD45^+$ immune and $CD8^+$ T cells in the gut compared to NR-FMT (FIG. 27B and 27C lower panel).

[00229] Additionally, taxonomic characterization using 16S sequencing revealed stark differences in the gut microbiome of germ-free mice before and after fecal microbiota transplantation (FMT), with major increases in Bacteroidales and Clostridiales taxa. As expected, control mice that received PBS, harbored markedly different taxa in their gut microbiome when compared to mice that received stool from responders (R-FMT) or non-responders (NR-FMT) to anti-PD1 therapy. Furthermore, the gut microbiomes of mice receiving R-FMT and NR-FMT remained fairly stable over time post transplantation.

[00230] **FMT of a favorable gut microbiome in GF mice reduces tumor growth and enhances response to α-PD-L1 therapy (FMT2):** In the second FMT experiment (FMT2), it was asked if the microbiome from an R patient could enhance response to immune therapy when transplanted in mouse model of melanoma. To address this question, GF mice were transplanted

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by oral gavage with stool from a responder (n=2, R-FMT group) or from a non-responder (n=3, NR-FMT group) to anti-PD-1 therapy. Control group mice (n=2) were transplanted with PBS alone. Two weeks after FMT, each mouse was injected with $8x10^5$ BP cells and tumor growth was checked twice a week. When tumor volume reached 250-500 mm^3, mice were treated with anti-PD-L1 antibody, administered by intra-peritoneal injection (FIG. 28A).

[00231] Results from FMT2 demonstrated significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 (p=0.04, FIG. 28B). Importantly, mice transplanted with R-FMT also exhibited improved responses to anti-PD-L1 therapy (FIG. 28C) compared to mice that were transplanted with stool from NR (NR-FMT).

[00232] Next, the mechanism through which the gut microbiome may influence systemic and anti-tumor immune responses was determined. FACS analysis of tumors and spleen immune infiltrates demonstrated that mice receiving R-FMT had higher percentage of $CD45^+$ myeloid cells infiltrating the tumor compared to mice in the NR-FMT group (FIG. 29A). In particular, a higher percentage of innate effector cells (expressing $CD45^+CD11b^+Ly6G^+$) and lower frequency of suppressive myeloid cells (expressing $CD11b^+CD11c^+$) were found in tumor immune infiltrates from R-FMT compared to NR-FMT (FIG. 29B-E). These data correlated specific subpopulations of the innate immune compartment to the anti-tumoral response induced by FMT from an R patient, both at peripheral (as showed in FMT1) and tumor level.

[00233] An increase in the frequency of $ROR\gamma T^+$ Th17 cells in the tumor was also detected in NR-FMT mice (FIG. 30A and B), in line with observations made in tumors from patients who failed to respond to PD-1 blockade. Moreover, mice receiving NR-FMT also demonstrated higher levels of regulatory $CD4^+$ $FOXP3^+$ T cells (FIG. 30C) and $CD4^+$ $IL\text{-}17^+$ (FIG. 31D) cells in the spleen, suggesting impaired host immune responses.

[00234] Mass cytometry (CyTOF) analysis using t-SNE dimension reduction was performed on tumors from mice, and demonstrated up-regulation of PD-L1 in the tumor microenvironment of mice receiving R-FMT versus NR-FMT (FIG. 31A), suggesting the development of a "hot" tumor microenvironment. CyTOF analysis also confirmed that distinct

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myeloid subpopulation preferentially infiltrate tumors in R-FMT or non-responders NR-FMT (FIG. 31B)

[00235] Longitudinal sampling and microbiome characterization of fecal pellets from FMT2 experiment showed results similar to FMT1, with relative stability in the gut microbiome over time.

[00236] **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 abundant orders over time suggested that the engrafted microbiome was stable during the whole experiment.

[00237] Based on the hypotheses that certain bacteria within the R-FMT mice flora help slow tumor growth, and that certain bacteria in NR-FMT mice flora help stimulate tumor growth, we compared OTUs that were either present in R-FMT mice or NR-FMT mice only (or also missing from control mice). These were done in representative mice from each group from the 2 FMT experiments. The inventors also looked at the OTUs that showed consistent transfer results in both FMT experiments. This analysis revealed that OTUs classified as *Acetanaerobacterium elongatum, Alistipes timonensis, Anaerocolumna jejuensis, Anaerocolumna xylanovorans, Bacteroides fragilis, Bacteroides nordii, Bacteroides stercoris, Blautia faecis, Blautia glucerasea, Blautia hansenii, Blautia obeum, Blautia schinkii, Caproiciproducens galactitolivorans, Christensenella minuta, Clostridium aldenense, Clostridium alkalicellulosi, Clostridium amygdalinum, Clostridium oroticum, Clostridium polysaccharolyticum, Clostridium xylanolyticum, Coprobacillus cateniformis, Emergencia timonensis, Eubacterium hallii, Extibacter muris, Faecalibacterium prausnitzii, Ihubacter massiliensis, Neglecta timonensis, Novibacillus thermophilus, Oscillibacter ruminantium, Papillibacter cinnamivorans, Parabacteroides johnsonii, Parasporobacterium paucivorans, Peptococcus niger, Pseudoflavonifractor capillosus, Robinsoniella peoriensis, Ruminococcus gauvreauii,*

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Ruminococcus gnavus, Ruminococcus torques, and *Slackia piriformis* were found only in R-FMT mice in both experiments.

[00238] FMT from different R and NR donors in germ-free GF mice confirms the link between R microbiota and reduced tumor growth (FMT3). To validate the finding that a "favorable" gut microbiome restrains tumor growth when transplanted in GF mice, an experiment was performed similar to FMT1 using stools from different R and NR patients. In this third experiment (FMT3), GF mice were transplanted by oral gavage with stool from one responder ((n=1, R-FMT group) or from one non-responder ((n=1, NR-FMT group) to anti-PD-1 therapy. Control group mice were transplanted with PBS alone (n=3, Control group). Two weeks after FMT, each mouse was injected subcutaneously with $2.5x10^5$ BP cells, and tumor growth was checked twice a week (Figure 32A). Blood and fecal pellets were collected at different time points during the experiment.

[00239] Results from FMT3 confirmed significantly delayed tumor growth by day 14 in R-FMT group compared to mice in those transplanted with stool from NR to anti-PD-1 (Figure 32B). Importantly, this difference was maintained over time until the end point (FIG. 32C).

Example 5 – Fecal Microbiota Transplantation Methods

[00240] Fecal microbiota transplantation (FMT): All animal studies were approved by the Animal Care and Use Committee, The UT at MD Anderson Cancer Center, in compliance with the Guide for the Care and Use of Laboratory Animals. B6 germ-free mice for murine studies were bought from the gnotobiotic facility of Baylor College of Medicine (Houston). All mice were transported in specialized autoclaved shipping cages, and were housed at MD Anderson Cancer Center mouse facility. All cages, bottles with stoppers and animal drinking water were autoclaved before being used. Food and bedding were double irradiated and tested to ensure sterility prior to being used in the experiment. Within each treatment category, a control group of mice received only pre-reduced PBS. All other mice from experimental groups received FMT from either an R donor or a NR donor, with each donor sample delivered to one, two or three mice. 200µl cleared supernatant from 0.1 g/µl human fecal suspension was obtained using a 100 µm strainer and gavaged into mice for 3 doses over 1 week, followed by a break of 1-week to allow

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microbiome establishment. Mice were then injected with BP syngeneic tumor cell line (Day 14), and animals were treated with anti-PD-L1 monoclonal antibody (purified low endotoxin, functional formulation, B7-H1, CD274, Leinco Technologies Inc.) once tumors reached ~250-500 mm^3. Tumor growth/survival was assessed. Fecal specimens, blood, spleens and tumors were harvested and processed for further analysis.

[00241] Flow cytometry of mouse tumor and spleen: Tumors were isolated and minced into small pieces and digested for 1 hour in RPMI containing collagenase A (2 mg/mL; Roche, Cat.No. 11 088 793 001) and DNase I (40 units/mL; Sigma-Aldrich, Cat.No. D5025) with agitation at 37°C. Cell suspensions were passed through a cell strainer, washed in 2% RPMI supplemented with 2 mmol/L EDTA and resuspended in FACS buffer (PBS containing 2% heat-inactivated FBS with 2 mM EDTA supplementation). Spleens were smashed in FACS buffer and red blood cells lysed by incubation in ACK buffer (Gibco) for 2 minutes at room temperature. The pellet was then washed and resuspended in FACS buffer. For analysis of cell surface markers, the following antibodies were used: CD45 (30-F11, BD Biosciences), CD11b (M1/70, eBioscience), CD11c (HL3, BD Pharmigen), Ly6G (RB6-8C5, eBioscience), Ly6C (AL-21, BD Bioscience), F4/80 (BM8, eBioscience). Cells were labeled with LIVE/DEAD viability stain (Life Technologies) and samples were acquired on a LSR Fortessa X20 flow cytometry (BD). Doublets were distinguished and excluded by plotting FSC area versus FSC height and data analyzed using FlowJo software (Tree Star).

[00242] Immunofluorescence on FFPE samples: Xenograft tumors, mouse gut and spleens were harvested, fixed in buffered 10% formalin first (4 hours at room temperature), then switched to 70% ethanol and stored at 4°C. Tissues were embedded in paraffin and 5 μm sections were mounted on positively charged slides. Tissues were deparaffinized and antigen retrieval was performed in pH 6.0 Citrate buffer (Dako) using a microwave. Sections were blocked in blocking buffer (5% Goat Serum/0.3% BSA/0.01%Triton in PBS) followed by primary antibody incubation overnight at 4°C. Sections were washed and then incubated with Alexa-conjugated secondary antibody (1:500, Molecular Probes) for 1 hour at room temperature. Coverslips were washed 3 times in PBS/0.01% Triton and then incubated for 15 minutes at room temperature in Hoechst stain (1:5000, Invitrogen). After 3 washes in PBS, the samples were mounted in ProLog

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Diamond mounting media (Molecular Probe). Images where captured using a Nikon A1R+ confocal microscope equipped with a four solid state laser system and a 20× objective.

[00243] **CyTOF:** Tumors were manually dissociated, digested using liberase TL (Roche) and DNase I for 30 minutes at 37°C, and passed through a 70 μm mesh filter. Samples were then centrifuged using a discontinuous gradient of Histopaque 1119 (Sigma-Aldrich) and RMPI media. Single cell suspensions of up to 2.5 x 10^6 cells per sample were Fc-receptor blocked and stained with a surface antibody mixture for 30 minutes at 4°C. Metal-conjugated antibodies were purchased from Fluidigm or conjugated using X8 polymer antibody labeling kits according to the manufacturer's protocol (Fluidigm). Samples were stained using 2.5 μM ^{194}Pt-cisplatin (Fluidigm) for 1 minute and washed twice with 2% FCS PBS. Cells were barcoded using a palladium mass tag barcoding approach according to the manufacturer's protocol (Fluidigm) and combined after two washes with 2% FCS PBS. Cells were then fixed and permeabilized using FoxP3 transcription factor staining kit according to the manufacturer's protocol (eBioscience). Samples were then stained using a mixture of antibodies against intracellular targets for 30 minutes at room temperature. Samples were washed twice with 2% FCS PBS and then incubated overnight in a 1.6% PFA/100 nM iridium/PBS solution prior to acquisition using a Helios mass cytometer (Fluidigm).

[00244] Mass cytometry data were bead normalized and debarcoded using Fluidigm software. Total live and CD45+ cells were manually gated using FlowJo. t-SNE analyses were performed on total live and CD45+ cells using the Cyt package in Matlab. Data were arcsinh transformed using a co-efficient of 4 and randomly down-sampled to 50,000 events per sample prior to t-SNE analysis. t-SNE plots for each experimental group were then generated by merging samples from each group and displaying an equal number of randomly down-sampled events (50,000) from each treatment group.

[00245] Table 9: CyTOF panel.

Target	Clone	Metal Tag	Stain	Source
CD45	30-F11	89Y	Surface	Fluidigm
c-MYC	9E10	115In	Intracellular	eBioscience

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MHC-II	M5/114.15.2	139La	Surface	Biolegend
NK1.1	PK136	141Pr	Surface	Biolegend
CD11c	N418	142Nd	Surface	Biolegend
CD80	16-10A1	143Nd	Surface	Biolegend
MHC-I	28-14-8	144Nd	Surface	Fluidigm
CD4	RM4-5	145Nd	Surface	Fluidigm
CD8a	53-6.7	146Nd	Surface	Fluidigm
CD86	GL-1	147Sm	Surface	Biolegend
CD27	LG.3A10	148Nd	Surface	Biolegend
OX40	OX-86	149Sm	Surface	eBioscience
CD25	3C7	150Nd	Surface	Fluidigm
TIGIT	1G9	151Eu	Surface	Biolegend
CD3ε	145-2C11	152Sm	Intracellular	Fluidigm
PD-L1	10F.9G2	153Eu	Surface	Fluidigm
BATF	D7C5	154Sm	Intracellular	Fluidigm
ICOS	7E.17G9	155Gd	Surface	eBioscience
CD69	H1.2F3	156Gd	Surface	Biolegend
CXCR5	2G8	158Gd	Surface	BD
PD-1	29F.1A12	159Tb	Surface	Fluidigm
CD62L	MEL-14	160Gd	Surface	Fluidigm
CXCR3	CXCR3-173	161Dy	Surface	Biolegend
TIM3	RMT3-23	162Dy	Surface	Fluidigm
LAG3	C9B7W	163Dy	Surface	Biolegend
LAP-TGFβ	TW7-16B4	164Dy	Surface	Fluidigm
FoxP3	FJK-16s	165Ho	Intracellular	Fluidigm
BCL2	BCL/10C4	166Er	Intracellular	Biolegend
GATA3	L50-823	167Er	Intracellular	BD
BCL6	K112-91	168Er	Intracellular	BD
CD117	2B8	169Tm	Surface	Biolegend
CD127	A7R34	170Er	Surface	Biolegend

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CTLA-4	UC10-4B9	171Yb	Intracellular	Biolegend
CD11b	M1/70	172Yb	Surface	Fluidigm
TBET	4B10	173Yb	Intracellular	Biolegend
RORγT	Q31-378	174Yb	Intracellular	BD
CD28	37.51	175Lu	Surface	Biolegend
EOMES	Dan11mag	176Yb	Intracellular	eBioscience
Live/Dead	N/A	194Pt	Surface	Fluidigm
CD19	6D5	195Pt	Surface	Biolegend
TCRγδ	GL3	196Pt	Surface	Biolegend
KLRG1	2F1	198Pt	Surface	BD
CD44	IM7	209Bi	Surface	Fluidigm

* * *

[00246] All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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U.S. Patent No. 5844905

U.S. Patent No. 6,207,156

U.S. Patent No. 8,008,449

U.S. Patent No. 8,017,114

U.S. Patent No. 8,119,129

U.S. Patent No. 8,329,867

U.S. Patent No. 8,354,509

U.S. Patent No. 8,735,553

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

(57) Abstract: Provided herein are methods and compositions for the treatment of cancer by modulating the microbiome to enhance the efficacy of immune checkpoint blockade. The microbiome may be modulated by the administration of butyrate and/or butyrate-producing bacteria. Also provided herein are methods of determining a response to an immune checkpoint inhibitor by identifying if a subject has a favorable microbial profile.

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PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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To:

SHISHIMA, Gina, N.
Norton Rose Fulbright US LLP
98 San Jacinto Blvd., Suite 1100
Austin, TX 78701-4255
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
26 February 2019 (26.02.2019)

Applicant's or agent's file reference
UTFC.P1305WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2017/053717

International filing date *(day/month/year)*
27 September 2017 (27.09.2017)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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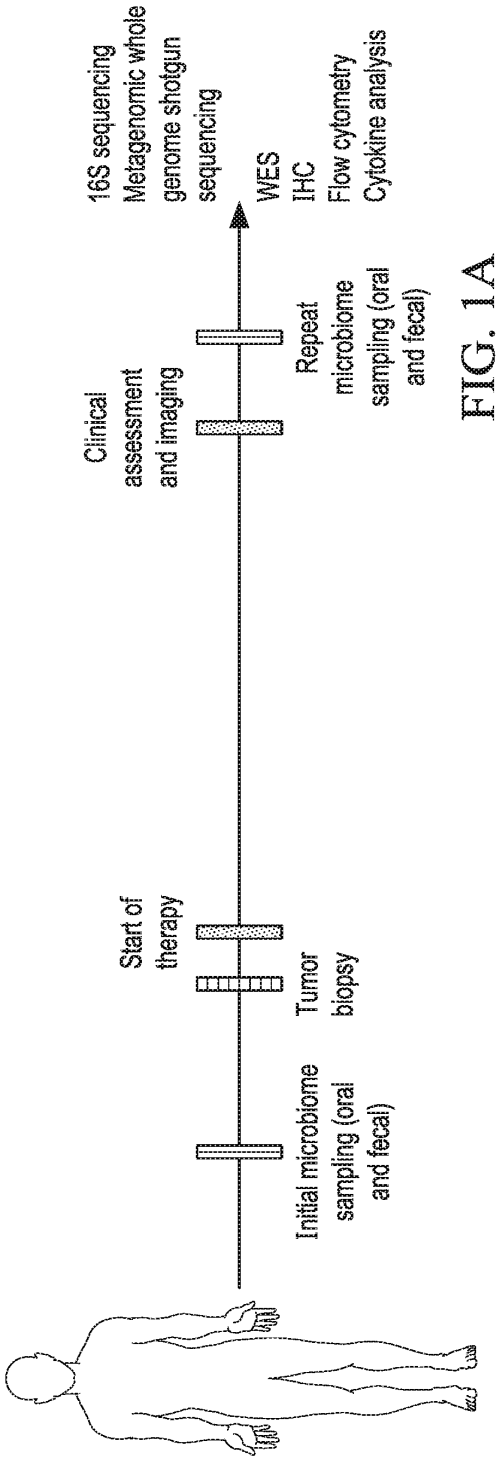

Initial microbiome sampling (oral and fecal)
Tumor biopsy
Start of therapy
Clinical assessment and imaging
Repeat microbiome sampling (oral and fecal)
WES
IHC
Flow cytometry
Cytokine analysis
16S sequencing
Metagenomic whole genome shotgun sequencing

FIG. 1A

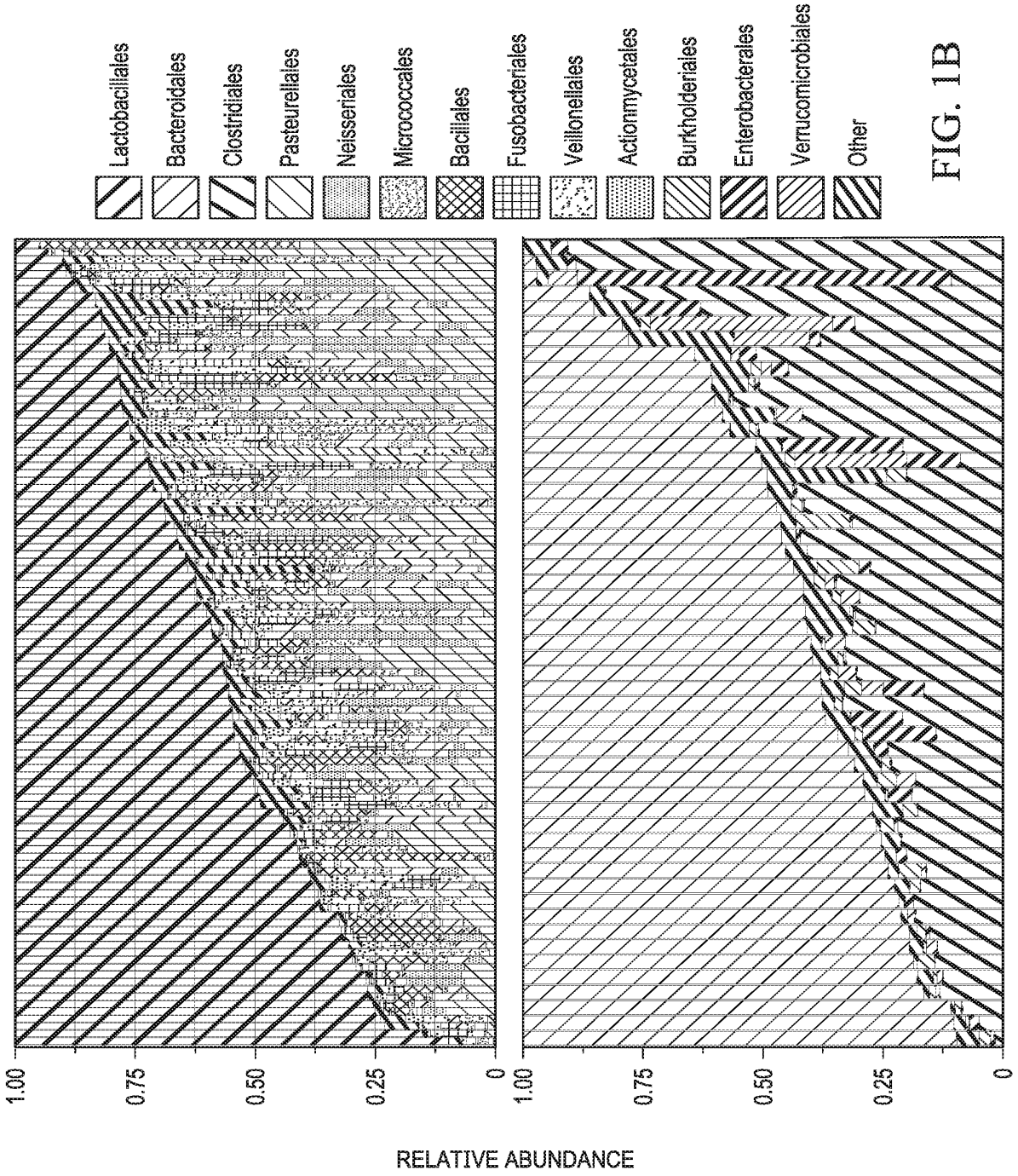

Lactobacillales
Bacteroidales
Clostridiales
Pasteurellales
Neisseriales
Micrococcales
Bacillales
Fusobacteriales
Veillonellales
Actinomycetales
Burkholderiales
Enterobacterales
Verrucomicrobiales
Other
1.00
0.75
0.50
0.25
0
RELATIVE ABUNDANCE

FIG. 1B

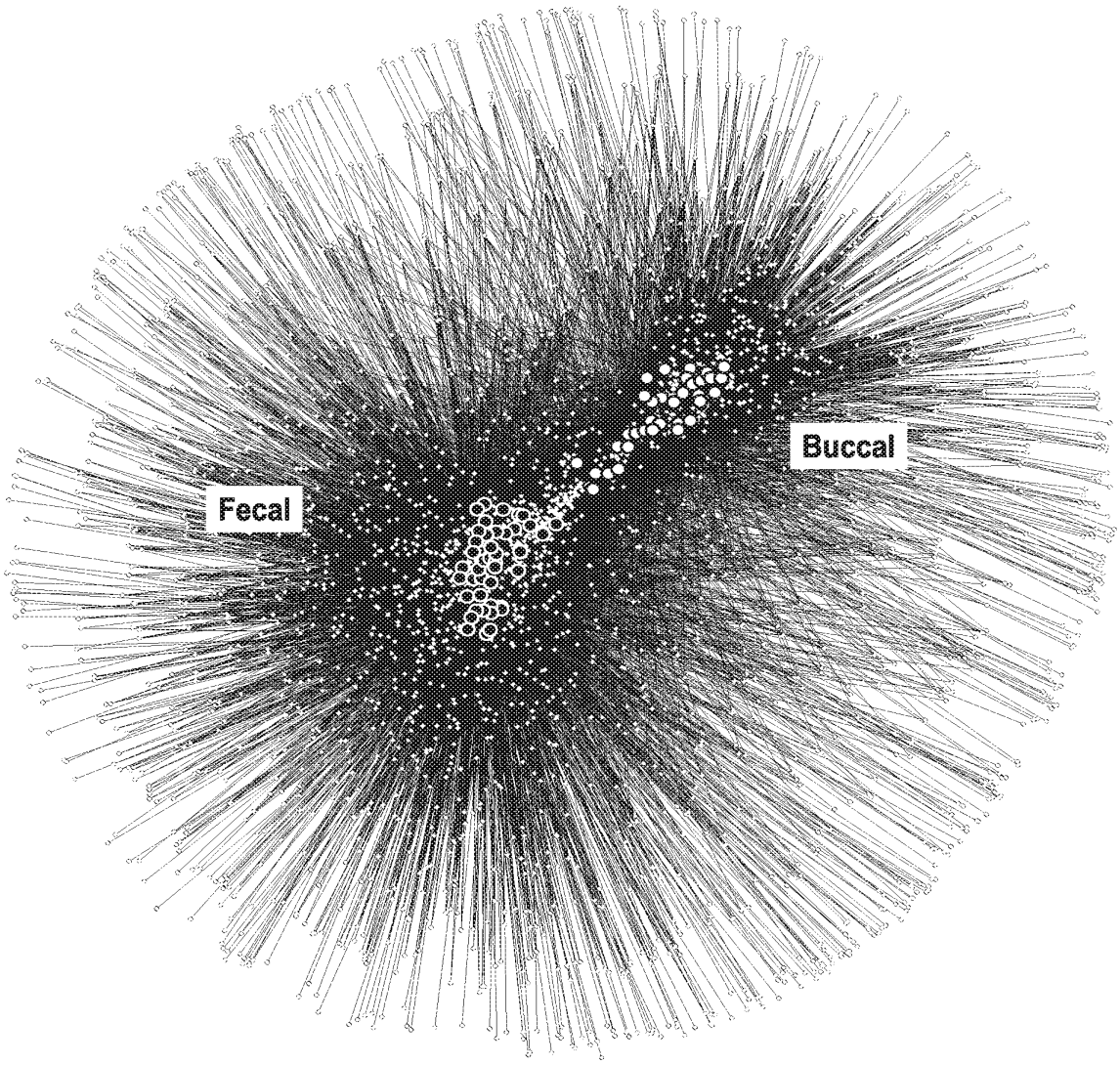
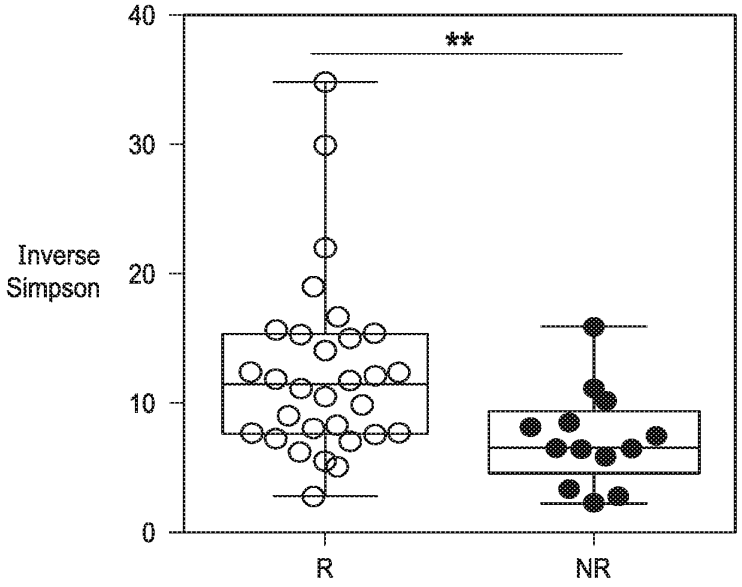


FIG. 1C

FIG. 1D



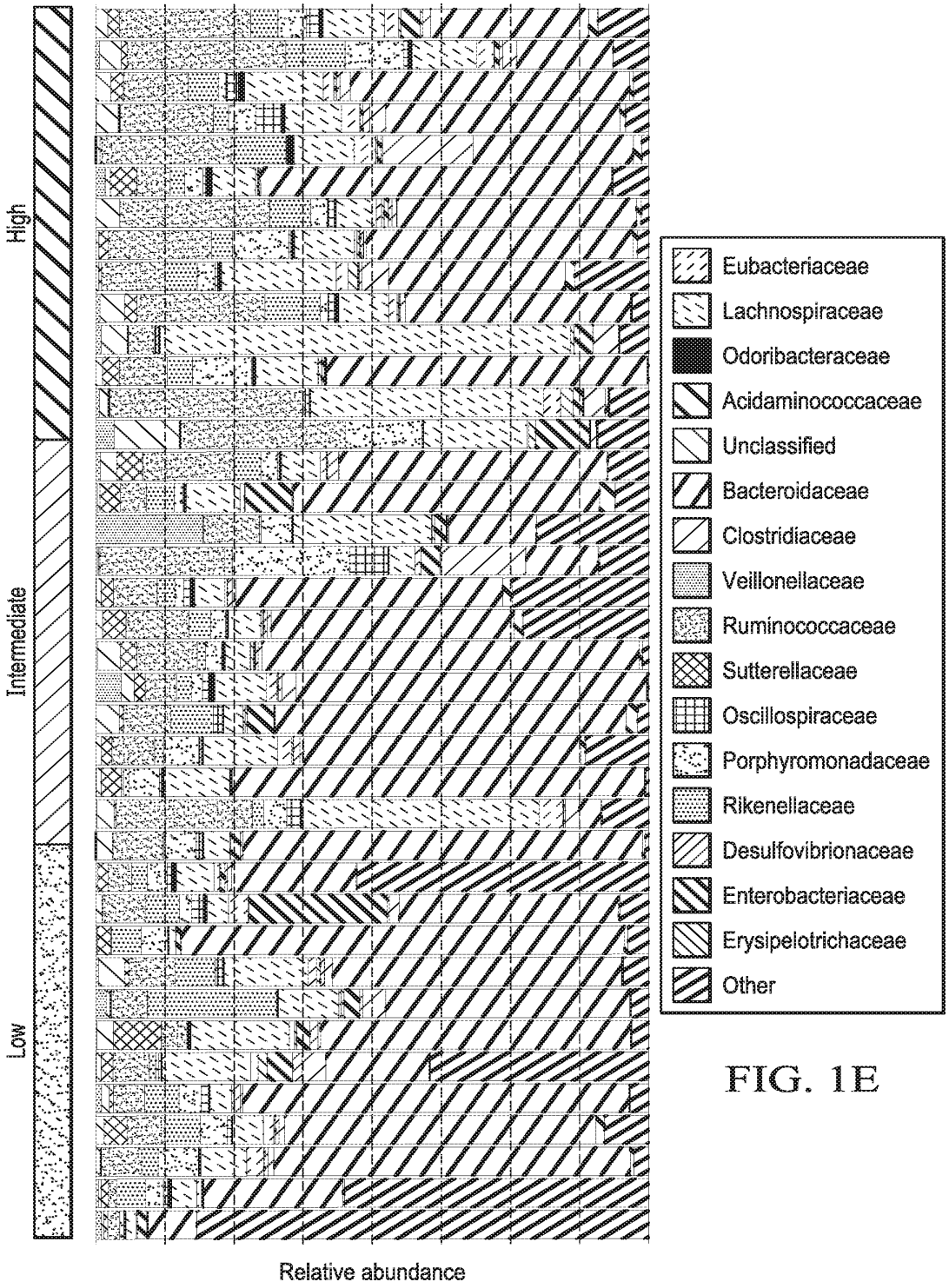

High
Intermediate
Low
Relative abundance
Eubacteriaceae
Lachnospiraceae
Odoribacteraceae
Acidaminococcaceae
Unclassified
Bacteroidaceae
Clostridiaceae
Veillonellaceae
Ruminococcaceae
Sutterellaceae
Oscillospiraceae
Porphyromonadaceae
Rikenellaceae
Desulfovibrionaceae
Enterobacteriaceae
Erysipelotrichaceae
Other

FIG. 1E

FIG. 1F

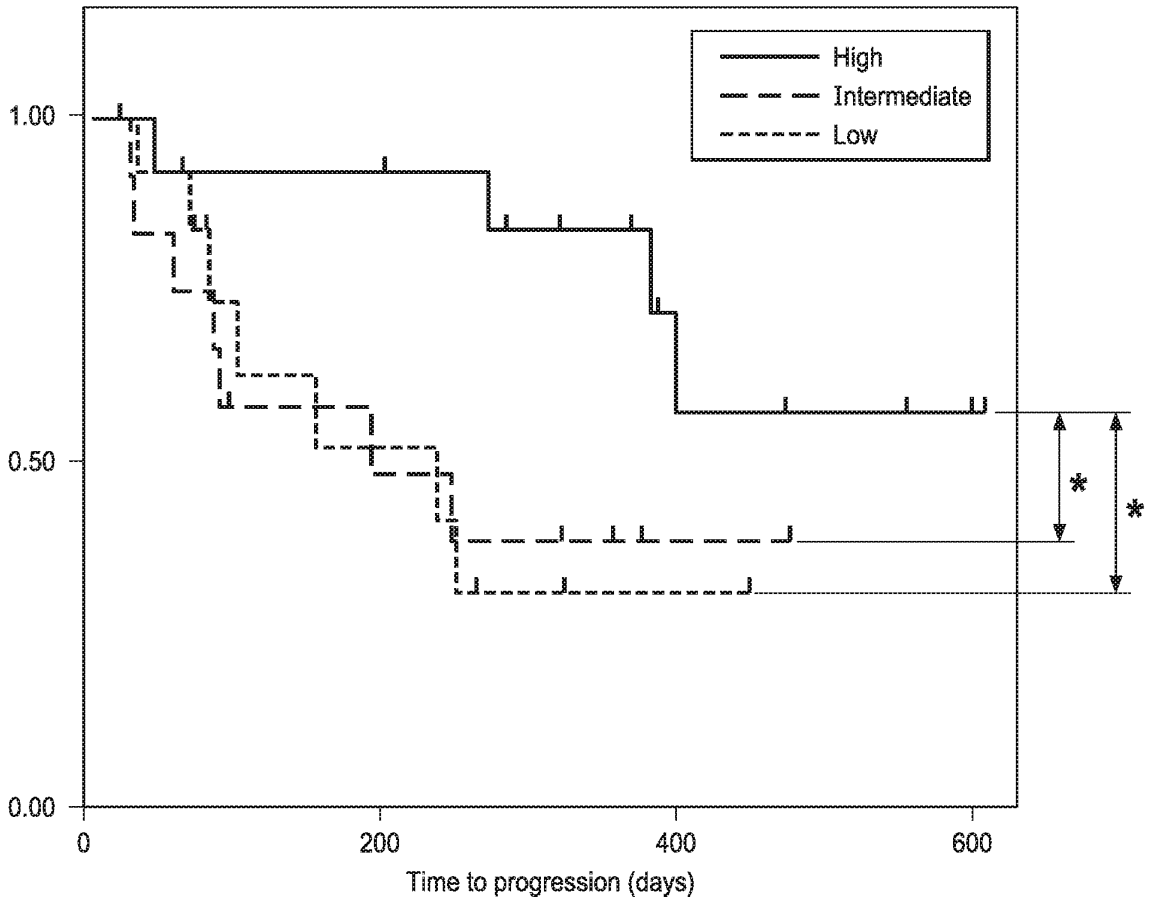
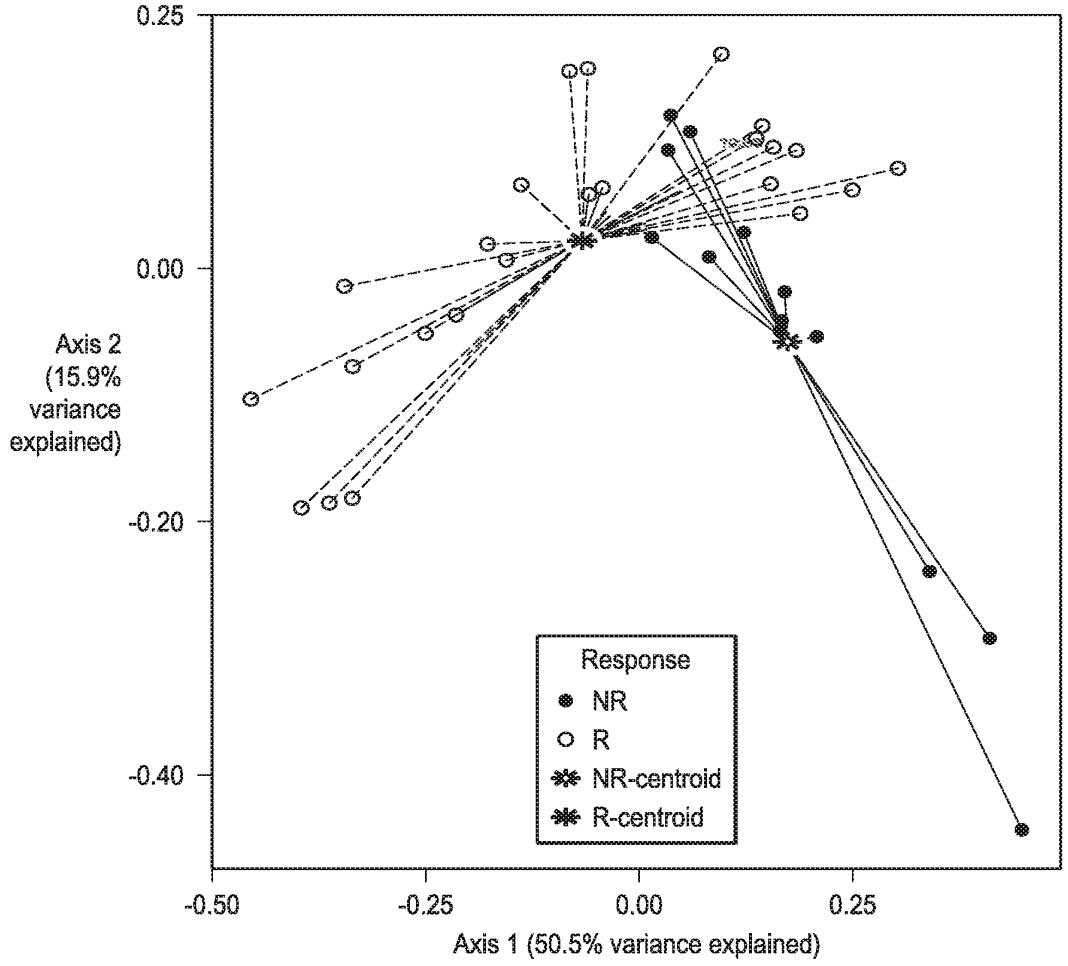

High
Intermediate
Low
1.00
0.50
0.00
0
200
400
600
Time to progression (days)
*
*

FIG. 1G


0.25
0.00
-0.20
-0.40
Axis 2
(15.9%
variance
explained)
-0.50
-0.25
0.00
0.25
Axis 1 (50.5% variance explained)
Response
NR
R
NR-centroid
R-centroid

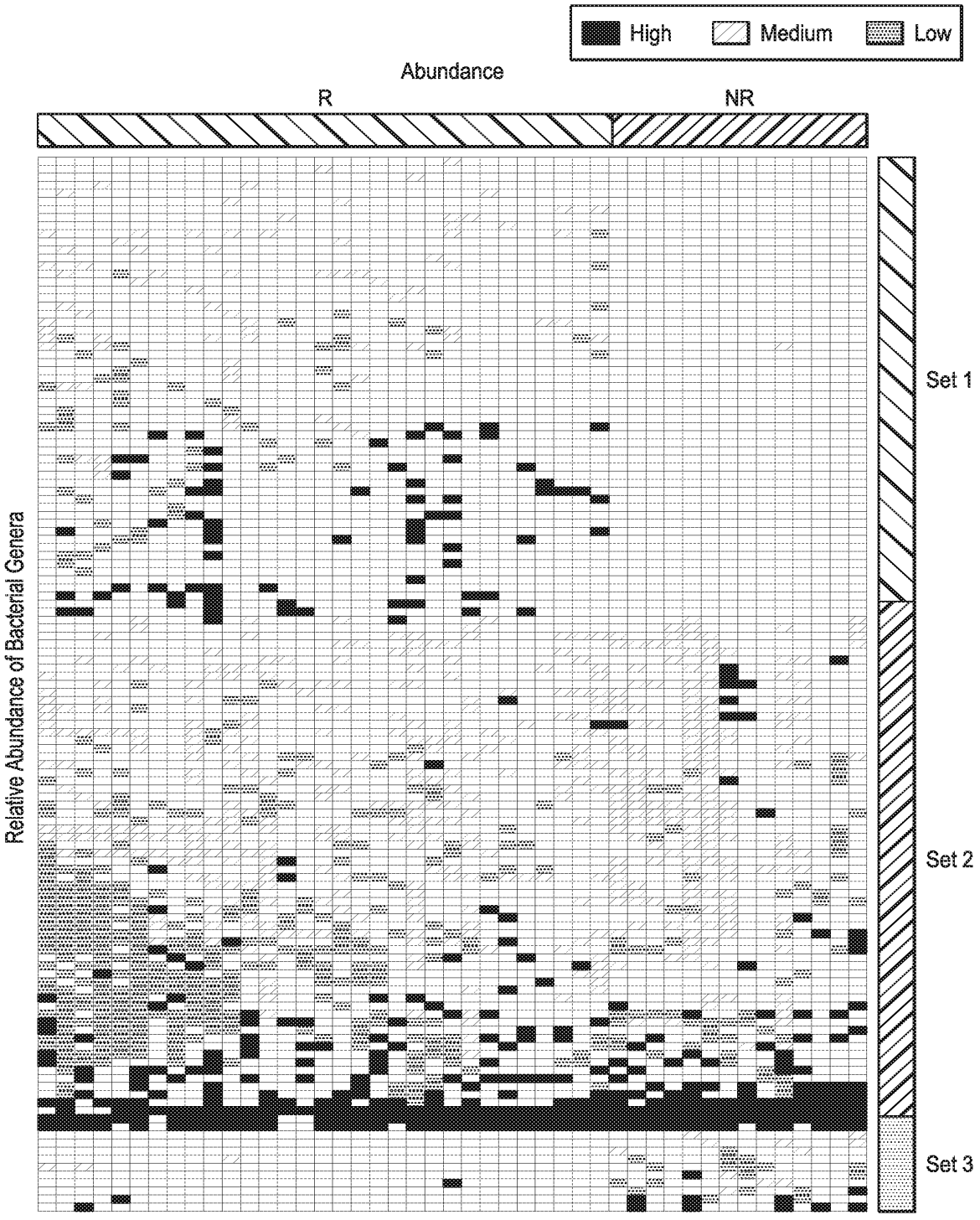

High
Medium
Low
Abundance
R
NR
Relative Abundance of Bacterial Genera
Set 1
Set 2
Set 3

FIG. 2A

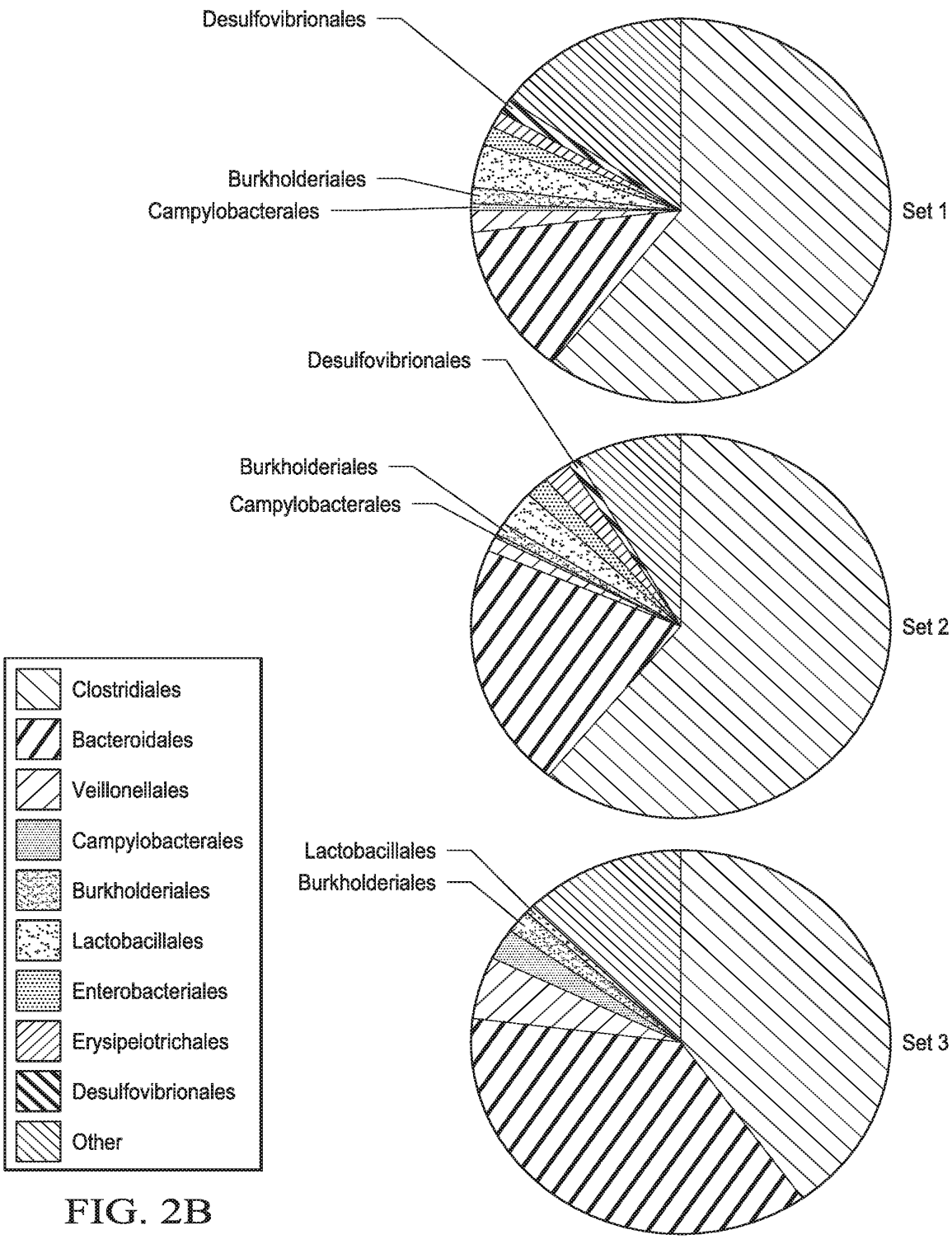

Desulfovibrionales
Burkholderiales
Campylobacterales
Set 1
Desulfovibrionales
Burkholderiales
Campylobacterales
Set 2
Lactobacillales
Burkholderiales
Set 3
Clostridiales
Bacteroidales
Veillonellales
Campylobacterales
Burkholderiales
Lactobacillales
Enterobacteriales
Erysipelotrichales
Desulfovibrionales
Other

FIG. 2B

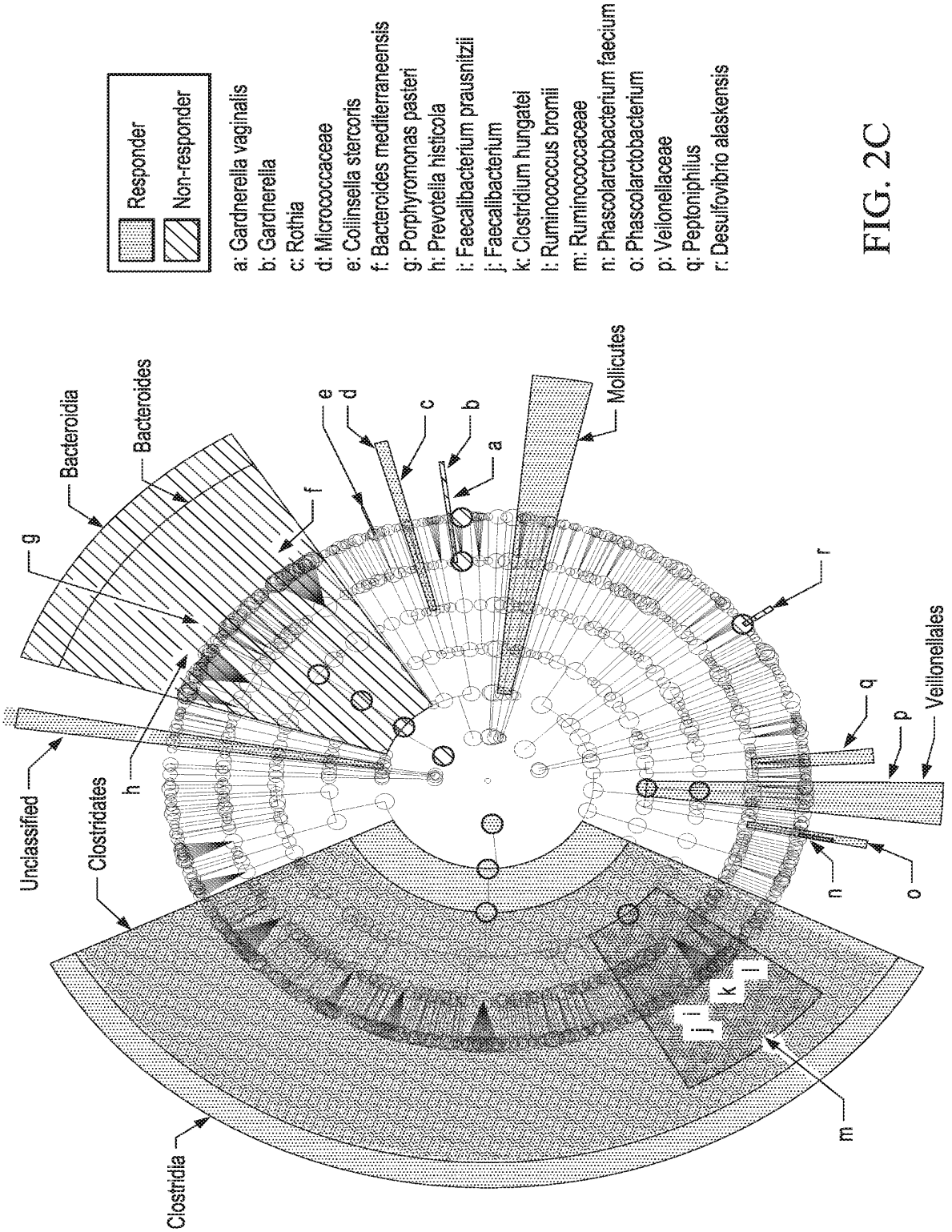

Responder
Non-responder
a: Gardnerella vaginalis
b: Gardnerella
c: Rothia
d: Micrococcaceae
e: Collinsella stercoris
f: Bacteroides mediterraneensis
g: Porphyromonas pasteri
h: Prevotella histicola
i: Faecalibacterium prausnitzii
j: Faecalibacterium
k: Clostridium hungatei
l: Ruminococcus bromii
m: Ruminococcaceae
n: Phascolarctobacterium faecium
o: Phascolarctobacterium
p: Veillonellaceae
q: Peptoniphilus
r: Desulfovibrio alaskensis
Bacteroidia
Bacteroides
Mollicutes
Unclassified
Clostridates
Clostridia
Veillonellales

FIG. 2C

FIG. 2D

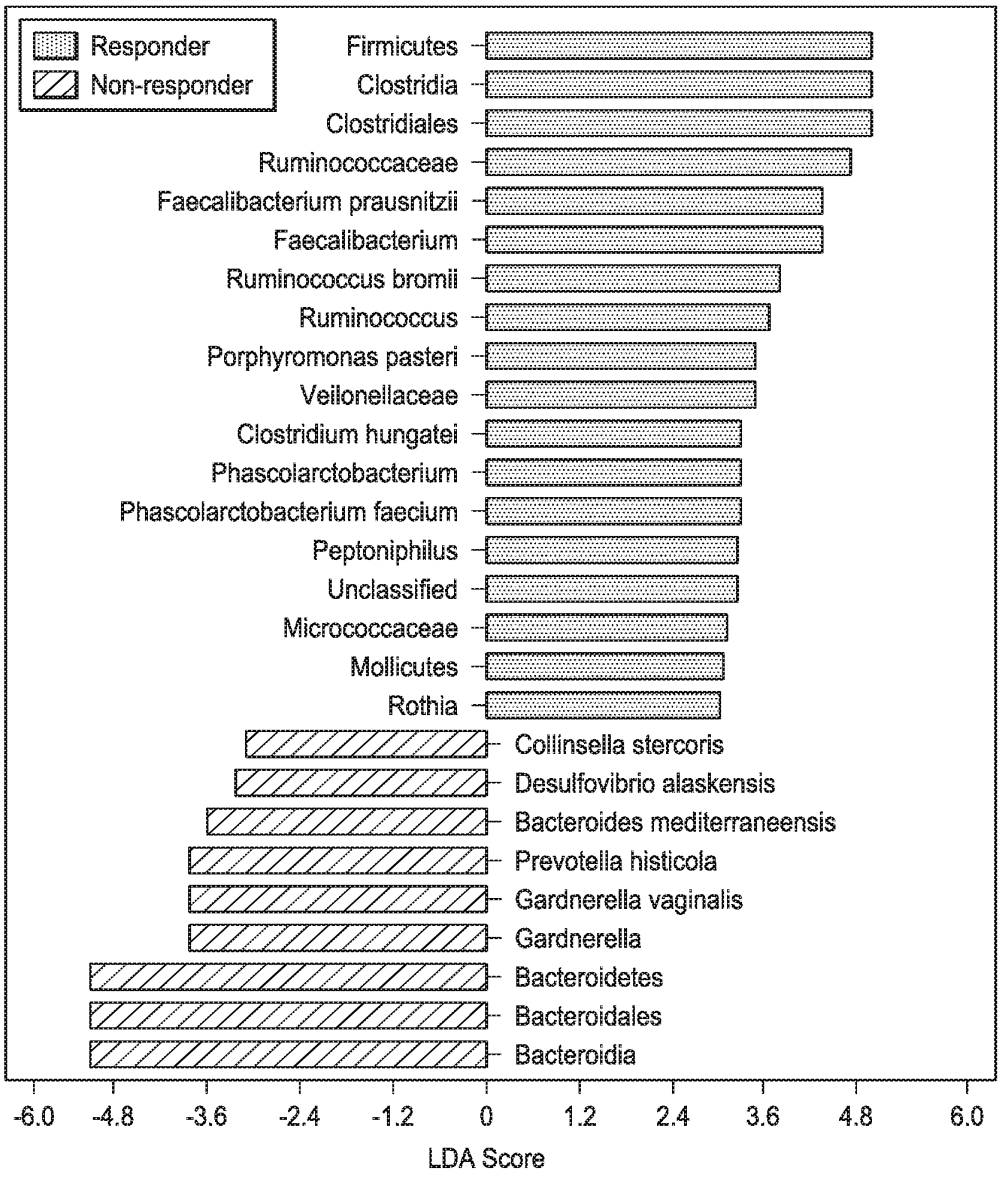
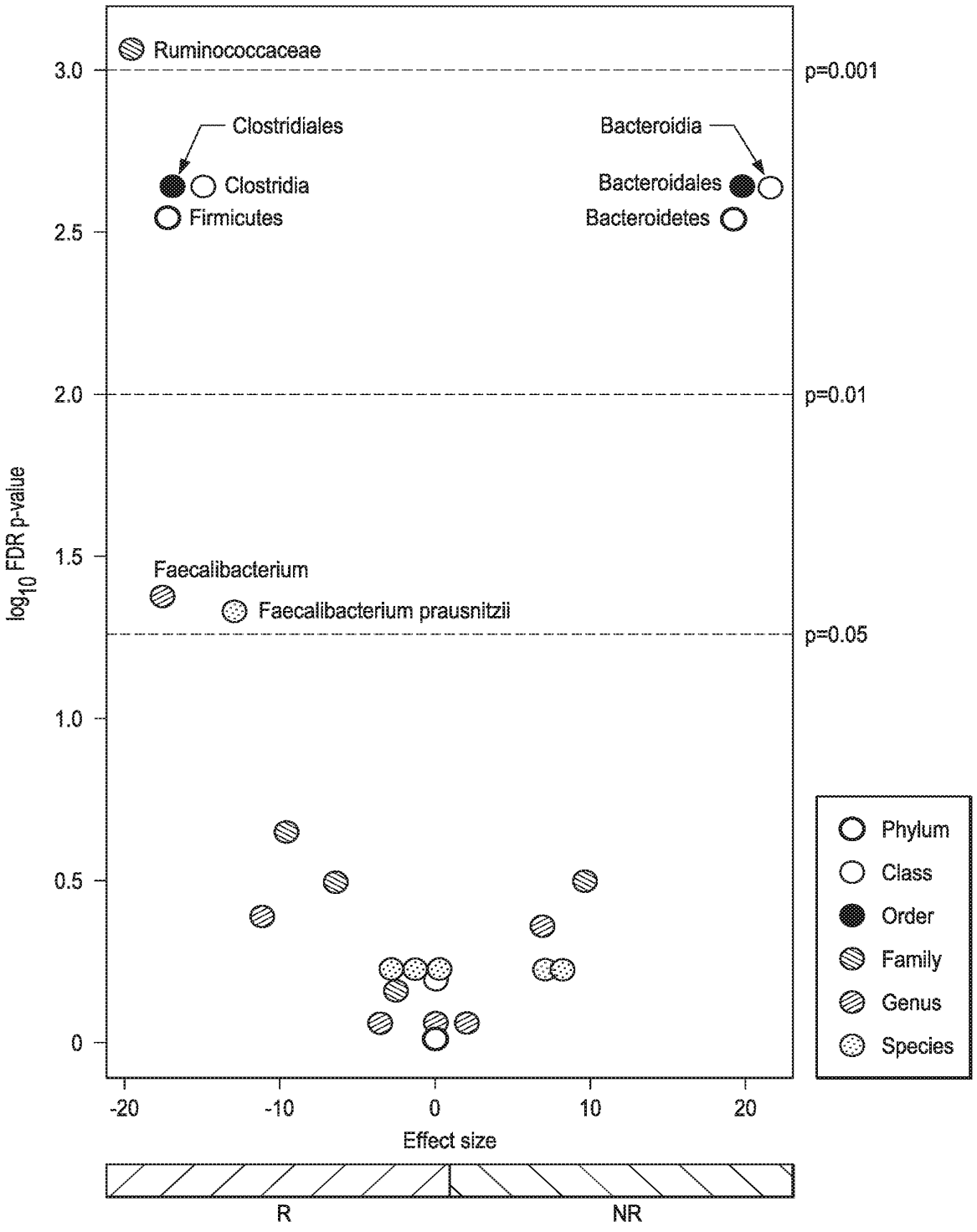

Responder
Non-responder
Firmicutes
Clostridia
Clostridiales
Ruminococcaceae
Faecalibacterium prausnitzii
Faecalibacterium
Ruminococcus bromii
Ruminococcus
Porphyromonas pasteri
Veilonellaceae
Clostridium hungatei
Phascolarctobacterium
Phascolarctobacterium faecium
Peptoniphilus
Unclassified
Micrococcaceae
Mollicutes
Rothia
Collinsella stercoris
Desulfovibrio alaskensis
Bacteroides mediterraneensis
Prevotella histicola
Gardnerella vaginalis
Gardnerella
Bacteroidetes
Bacteroidales
Bacteroidia
-6.0
-4.8
-3.6
-2.4
-1.2
0
1.2
2.4
3.6
4.8
6.0
LDA Score

FIG. 2E


Ruminococcaceae
p=0.001
Clostridiales
Clostridia
Firmicutes
Bacteroidia
Bacteroidales
Bacteroidetes
p=0.01
Faecalibacterium
Faecalibacterium prausnitzii
p=0.05
log10 FDR p-value
3.0
2.5
2.0
1.5
1.0
0.5
0
-20
-10
0
10
20
Effect size
R
NR
Phylum
Class
Order
Family
Genus
Species

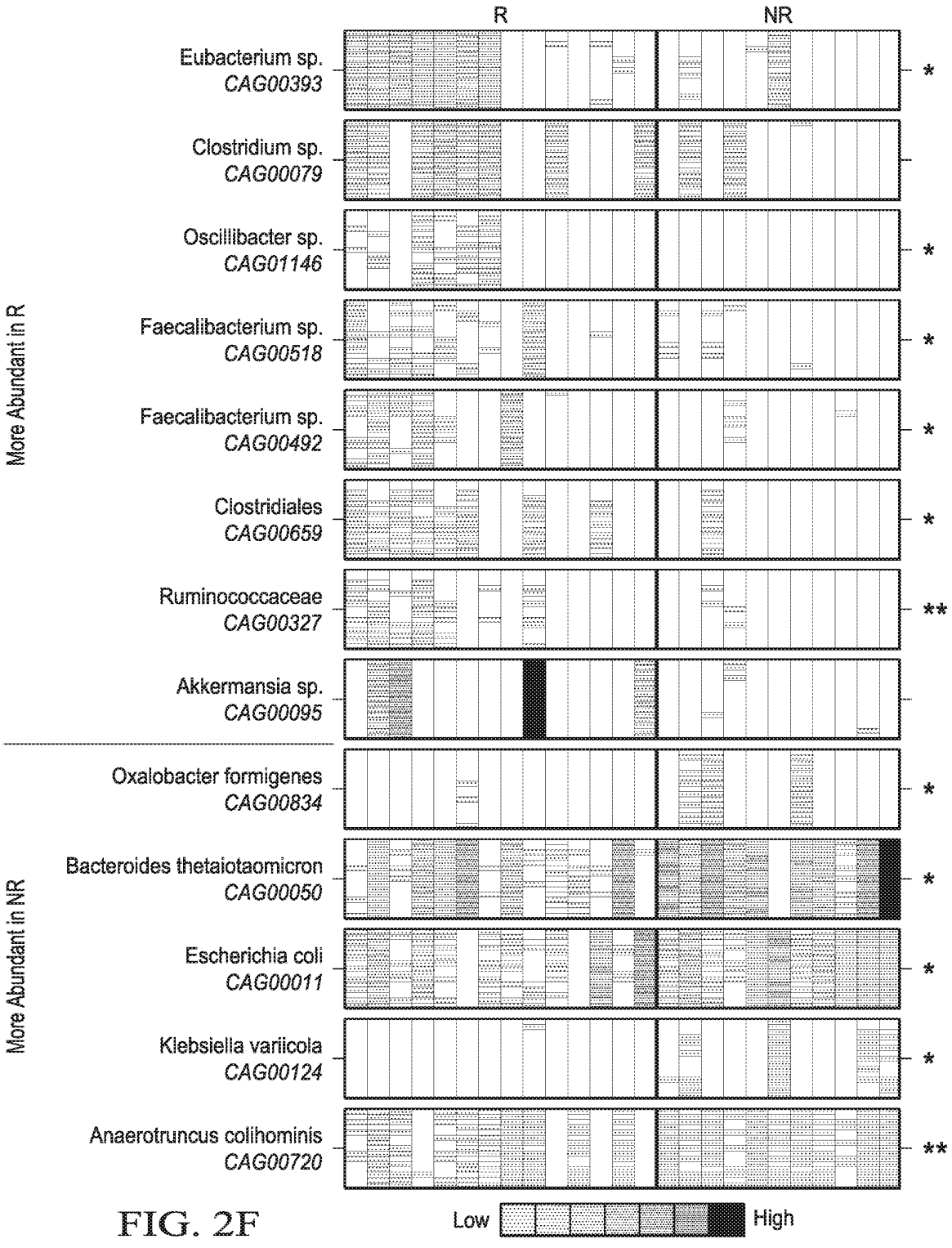

R
NR
More Abundant in R
More Abundant in NR
Eubacterium sp. CAG00393
Clostridium sp. CAG00079
Oscillibacter sp. CAG01146
Faecalibacterium sp. CAG00518
Faecalibacterium sp. CAG00492
Clostridiales CAG00659
Ruminococcaceae CAG00327
Akkermansia sp. CAG00095
Oxalobacter formigenes CAG00834
Bacteroides thetaiotaomicron CAG00050
Escherichia coli CAG00011
Klebsiella variicola CAG00124
Anaerotruncus colihominis CAG00720
*
*
*
*
*
*
**
*
*
*
*
**
Low
High

FIG. 2F

FIG. 3A

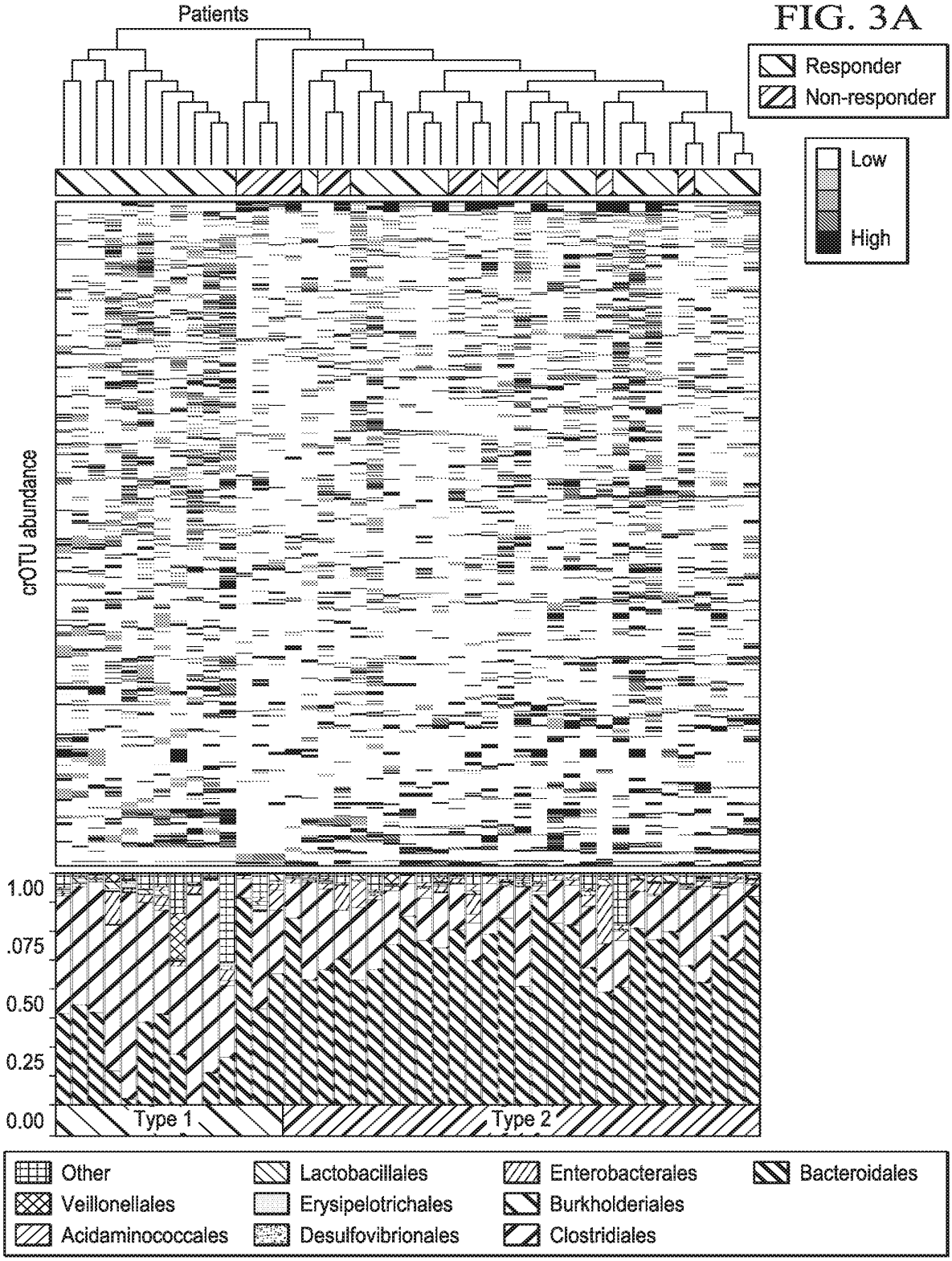

Patients
Responder
Non-responder
Low
High
crOTU abundance
1.00
.075
0.50
0.25
0.00
Type 1
Type 2
Other
Veillonellales
Acidaminococcales
Lactobacillales
Erysipelotrichales
Desulfovibrionales
Enterobacterales
Burkholderiales
Clostridiales
Bacteroidales

FIG. 3B

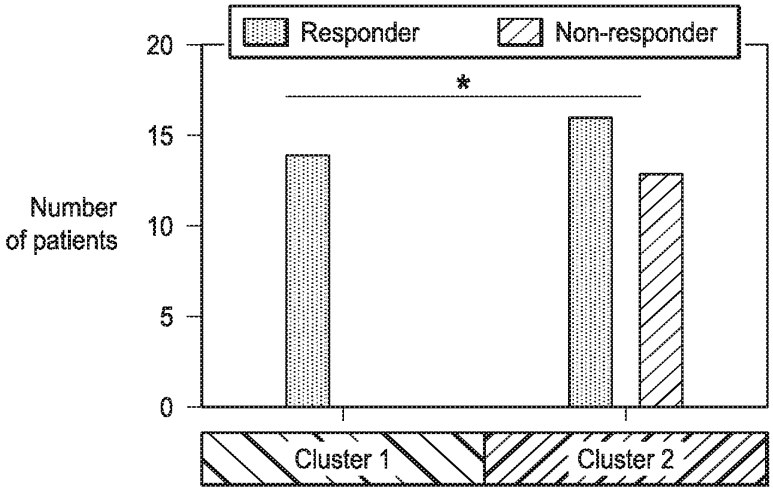

Responder
Non-responder
*
20
15
10
5
0
Number of patients
Cluster 1
Cluster 2

FIG. 3C

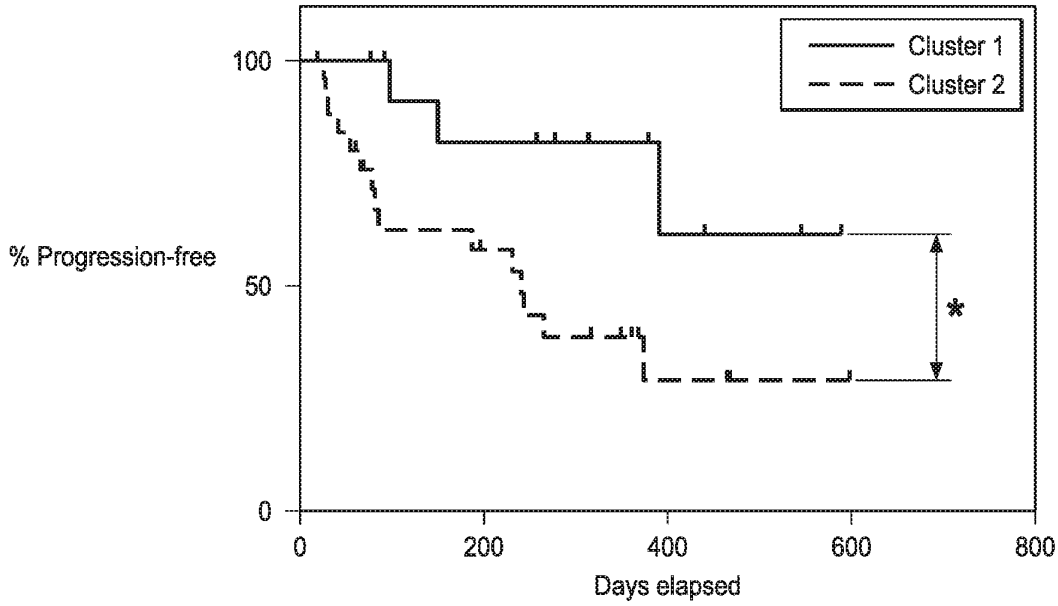

Cluster 1
Cluster 2
100
50
0
% Progression-free
*
0
200
400
600
800
Days elapsed

FIG. 3D

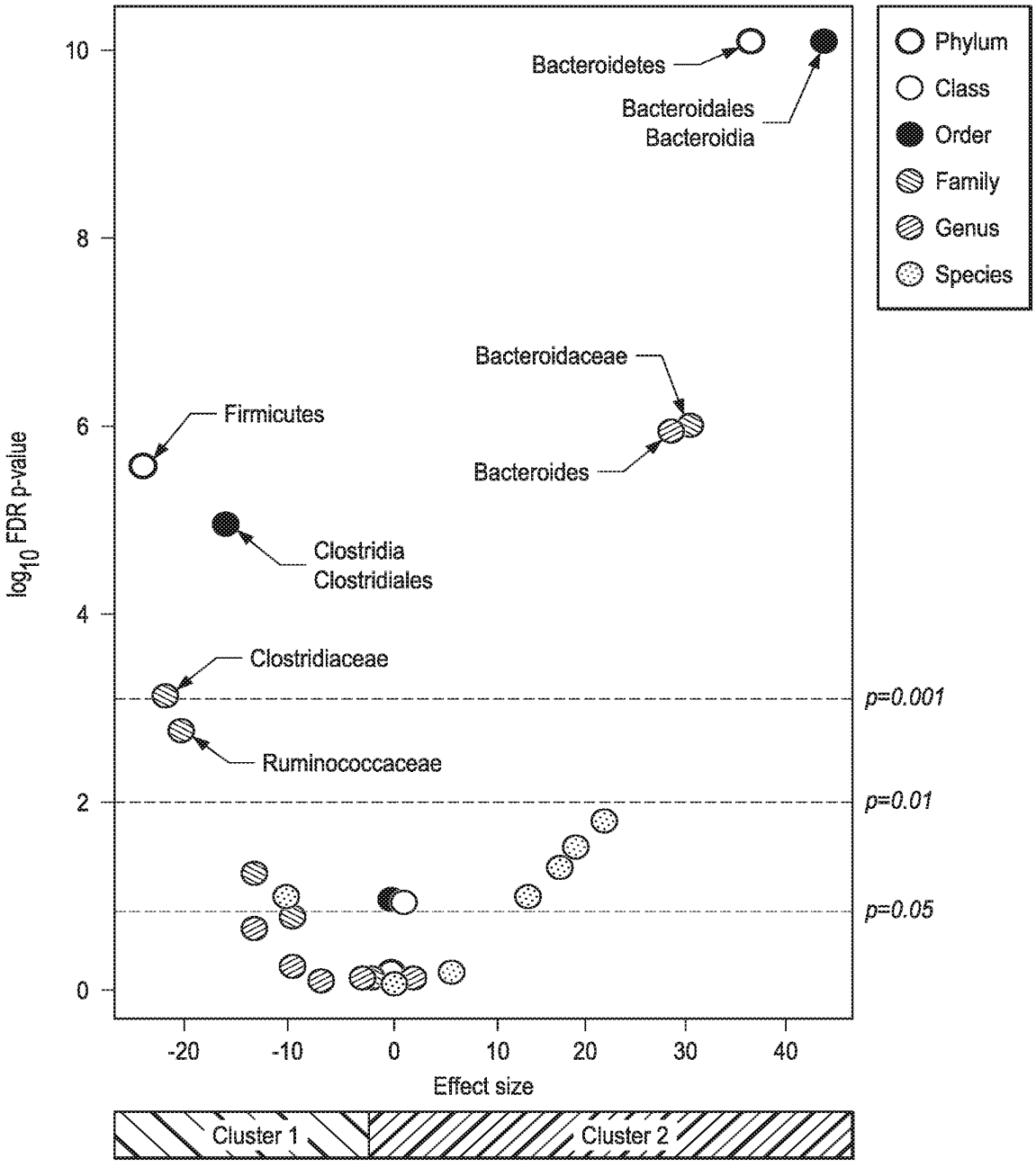
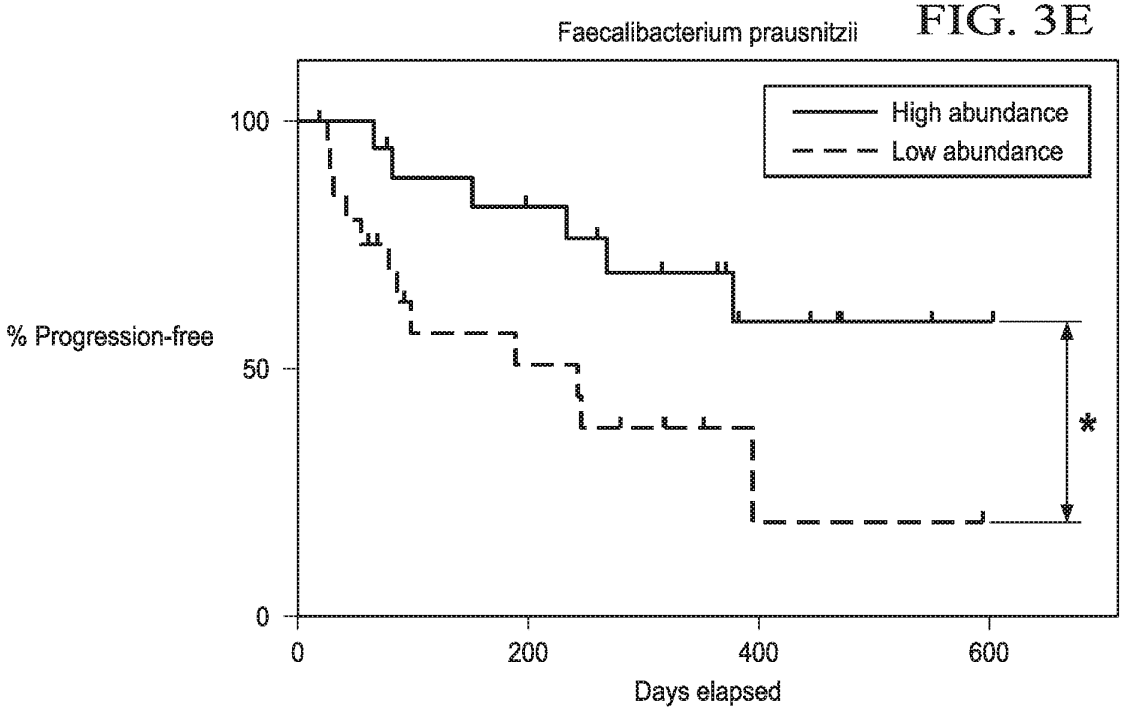
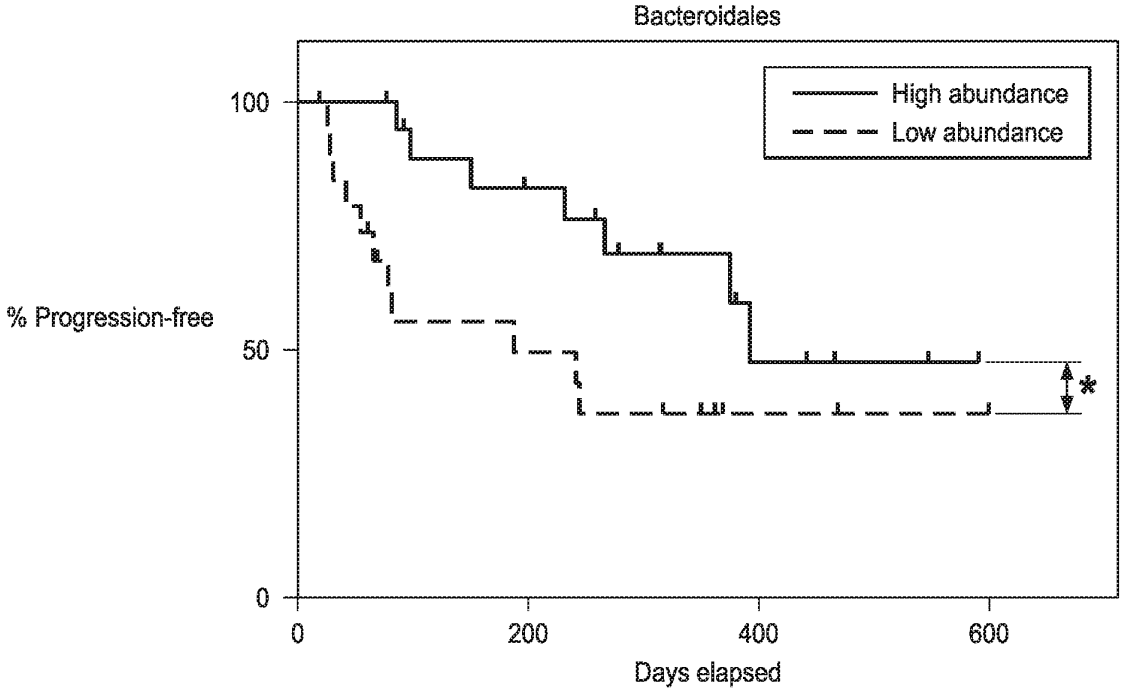

Phylum
Class
Order
Family
Genus
Species
Bacteroidetes
Bacteroidales
Bacteroidia
Bacteroidaceae
Bacteroides
Firmicutes
Clostridia
Clostridiales
Clostridiaceae
Ruminococcaceae
p=0.001
p=0.01
p=0.05
log10 FDR p-value
10
8
6
4
2
0
-20
-10
0
10
20
30
40
Effect size
Cluster 1
Cluster 2

FIG. 3E


Faecalibacterium prausnitzii
High abundance
Low abundance
% Progression-free
100
50
0
0
200
400
600
Days elapsed
*


Bacteroidales
High abundance
Low abundance
% Progression-free
100
50
0
0
200
400
600
Days elapsed
*

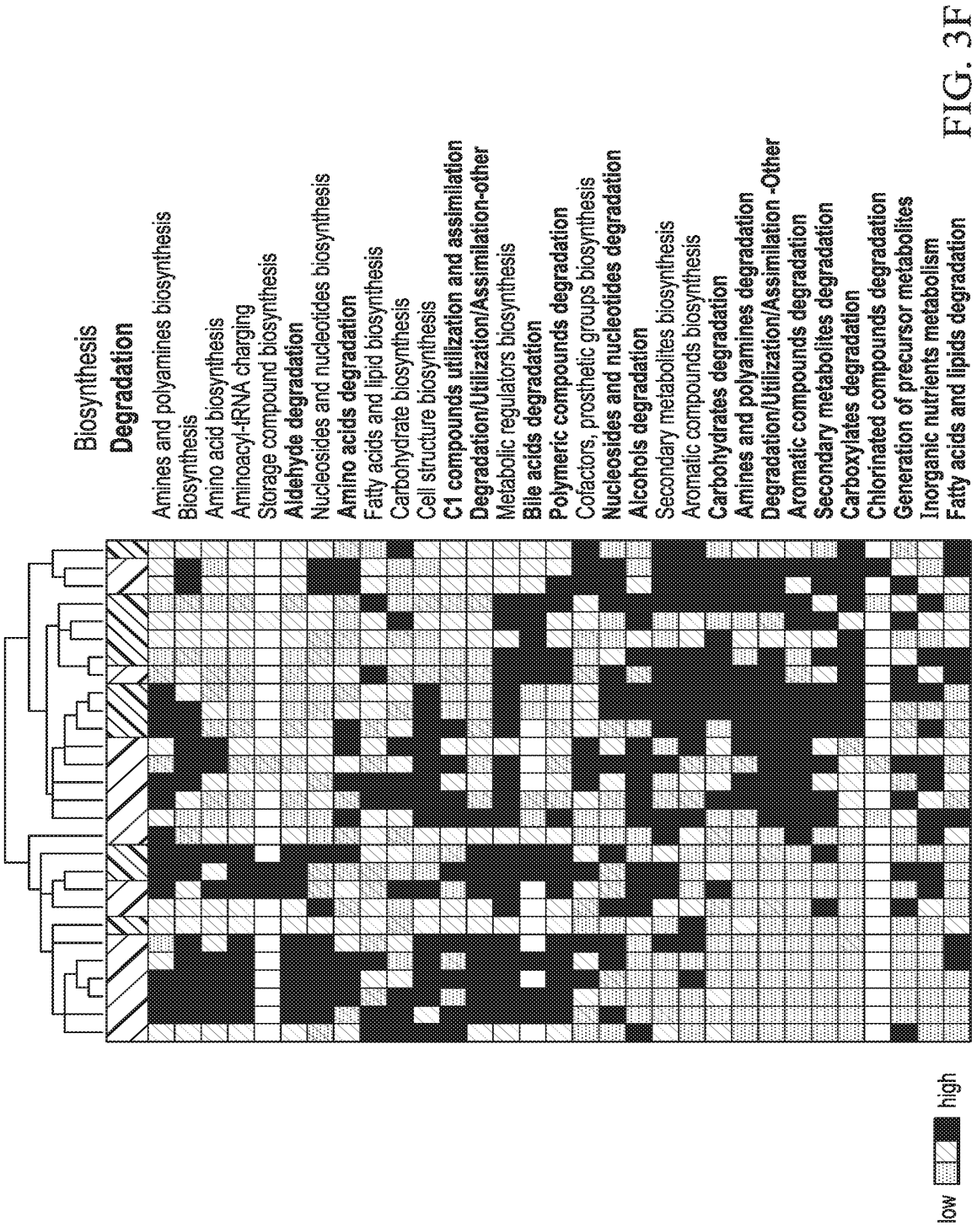

Biosynthesis
Degradation
Amines and polyamines biosynthesis
Biosynthesis
Amino acid biosynthesis
Aminoacyl-tRNA charging
Storage compound biosynthesis
Aldehyde degradation
Nucleosides and nucleotides biosynthesis
Amino acids degradation
Fatty acids and lipid biosynthesis
Carbohydrate biosynthesis
Cell structure biosynthesis
C1 compounds utilization and assimilation
Degradation/Utilization/Assimilation-other
Metabolic regulators biosynthesis
Bile acids degradation
Polymeric compounds degradation
Cofactors, prosthetic groups biosynthesis
Nucleosides and nucleotides degradation
Alcohols degradation
Secondary metabolites biosynthesis
Aromatic compounds biosynthesis
Carbohydrates degradation
Amines and polyamines degradation
Degradation/Utilization/Assimilation -Other
Aromatic compounds degradation
Secondary metabolites degradation
Carboxylates degradation
Chlorinated compounds degradation
Generation of precursor metabolites
Inorganic nutrients metabolism
Fatty acids and lipids degradation
low
high

FIG. 3F

FIG. 4A

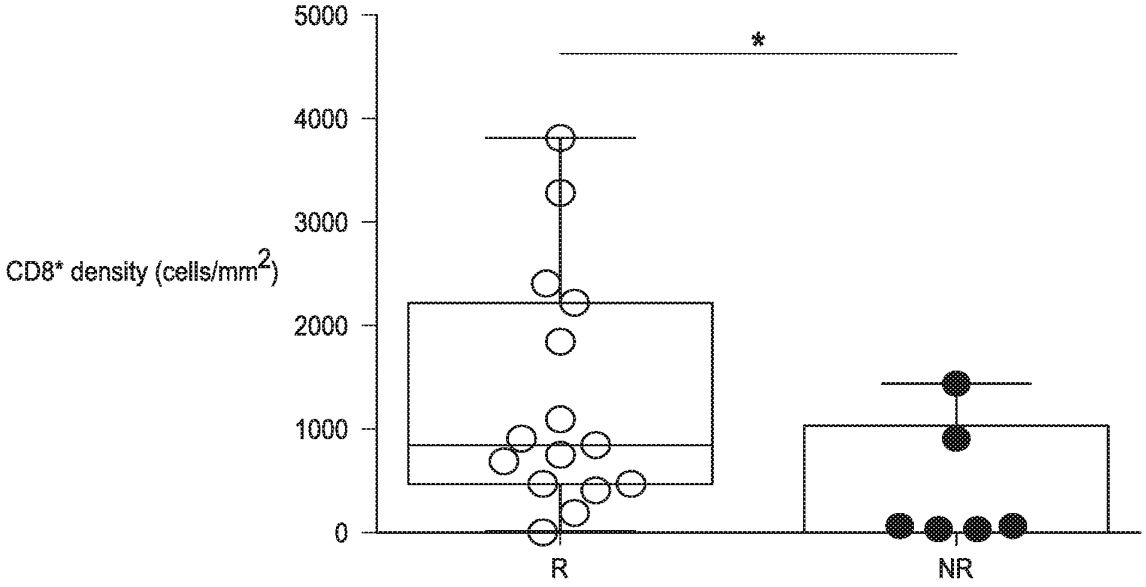

5000
4000
3000
2000
1000
0
CD8* density (cells/mm2)
*
R
NR

FIG. 4B

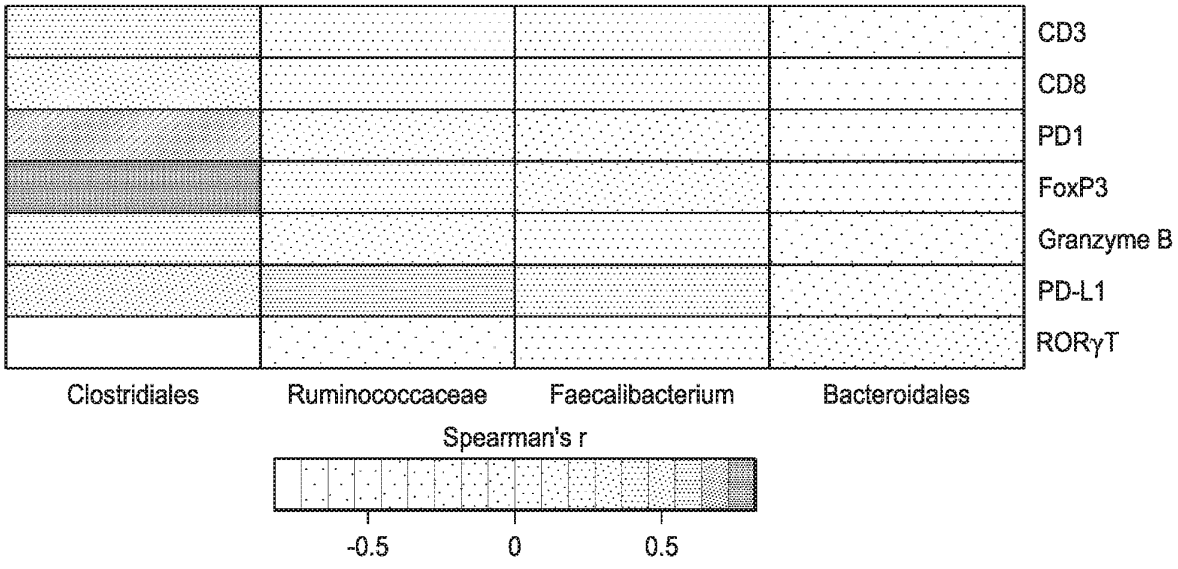

CD3
CD8
PD1
FoxP3
Granzyme B
PD-L1
RORγT
Clostridiales
Ruminococcaceae
Faecalibacterium
Bacteroidales
Spearman's r
-0.5
0
0.5

FIG. 4C

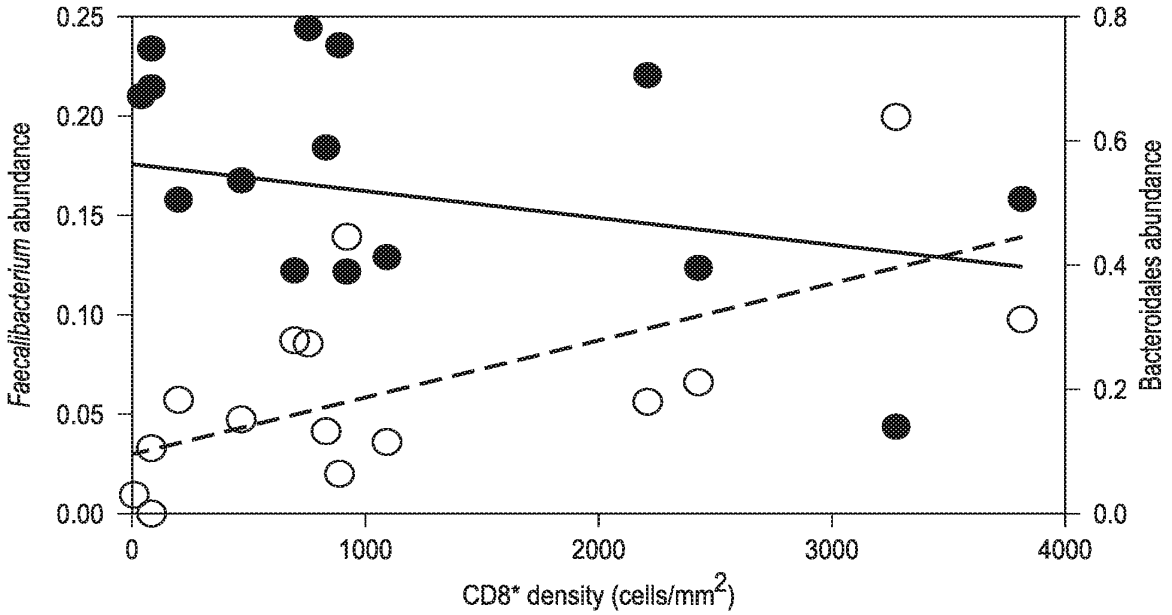

0.25
0.20
0.15
0.10
0.05
0.00
Faecalibacterium abundance
0.8
0.6
0.4
0.2
0.0
Bacteroidales abundance
0
1000
2000
3000
4000
CD8* density (cells/mm2)

FIG. 4D

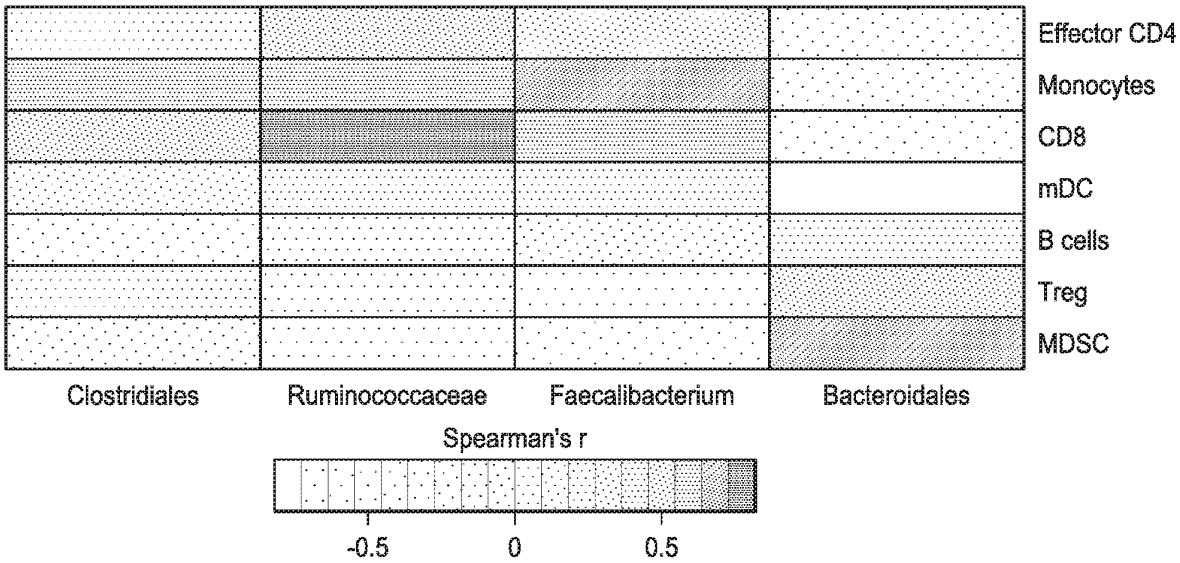

Effector CD4
Monocytes
CD8
mDC
B cells
Treg
MDSC
Clostridiales
Ruminococcaceae
Faecalibacterium
Bacteroidales
Spearman's r
-0.5
0
0.5

FIG. 4E

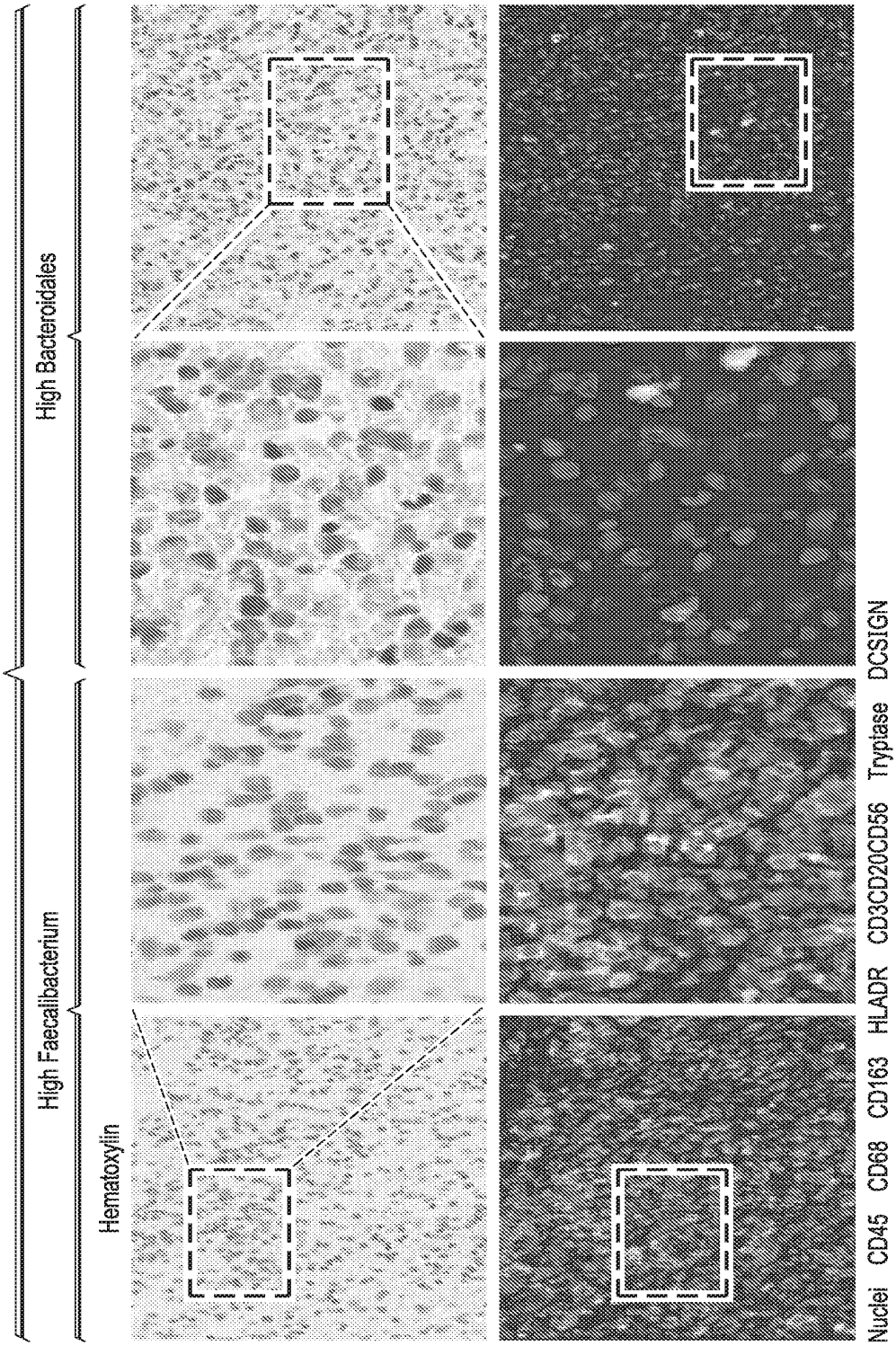
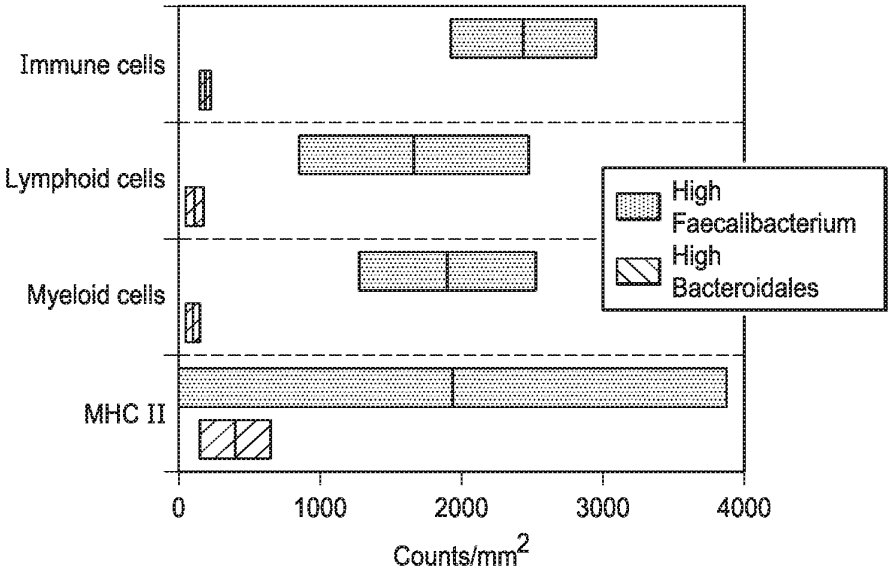

High Faecalibacterium
High Bacteroidales
Hematoxylin
Nuclei CD45 CD68 CD163 HLADR CD3CD20CD56 Tryptase DCSIGN

FIG. 4F


Immune cells
Lymphoid cells
Myeloid cells
MHC II
High Faecalibacterium
High Bacteroidales
0
1000
2000
3000
4000
Counts/mm2

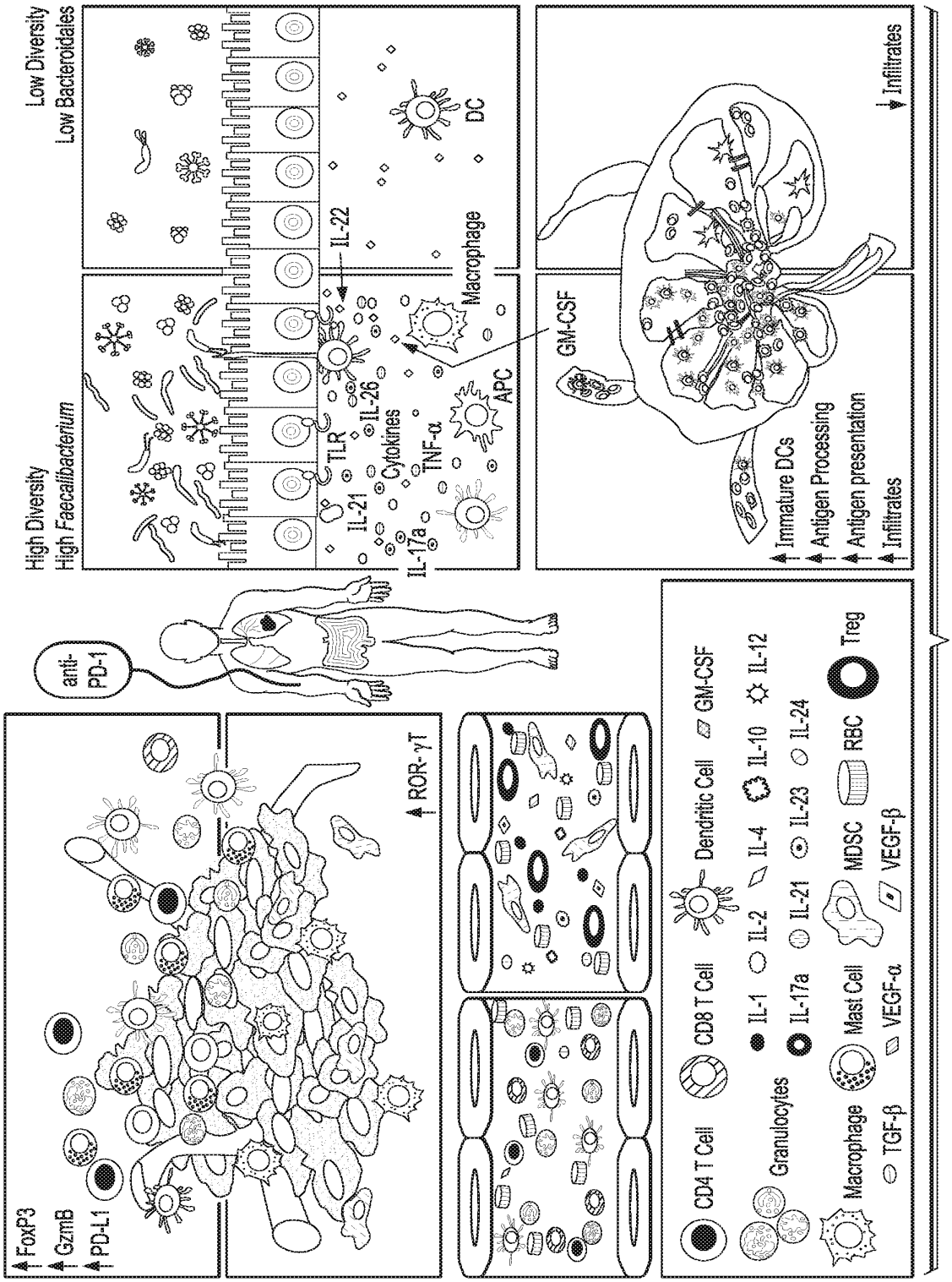

High Diversity
High Faecalibacterium
Low Diversity
Low Bacteroidales
anti-PD-1
FoxP3
GzmB
PD-L1
ROR-γT
TLR
IL-21
IL-26
Cytokines
IL-17a
TNF-α
APC
IL-22
Macrophage
DC
GM-CSF
Immature DCs
Antigen Processing
Antigen presentation
Infiltrates
Infiltrates
CD4 T Cell
CD8 T Cell
Dendritic Cell
GM-CSF
Granulocytes
IL-1
IL-2
IL-4
IL-10
IL-12
Macrophage
Mast Cell
IL-17a
IL-21
IL-23
IL-24
MDSC
RBC
Treg
TGF-β
VEGF-α
VEGF-β

FIG. 4G

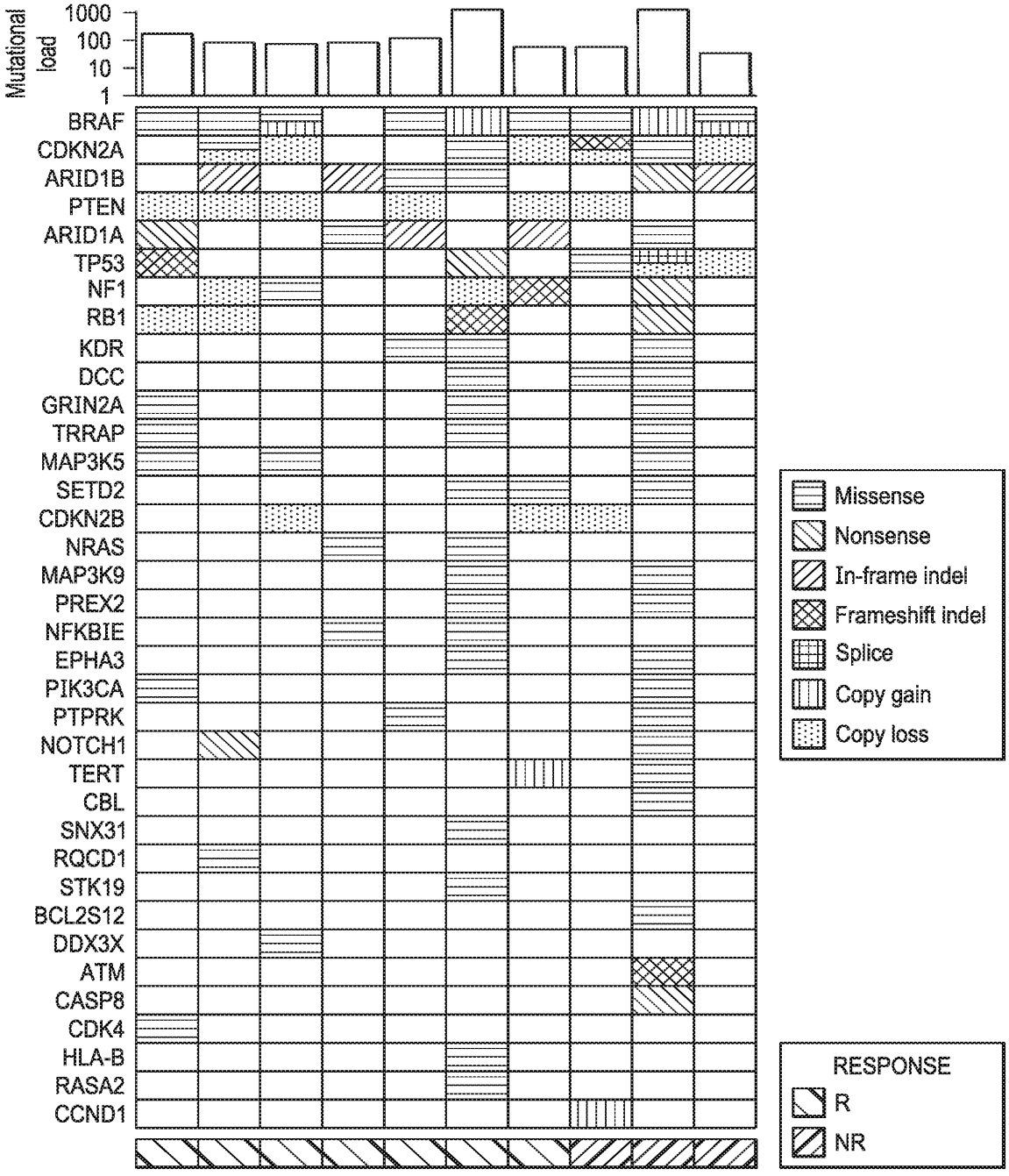
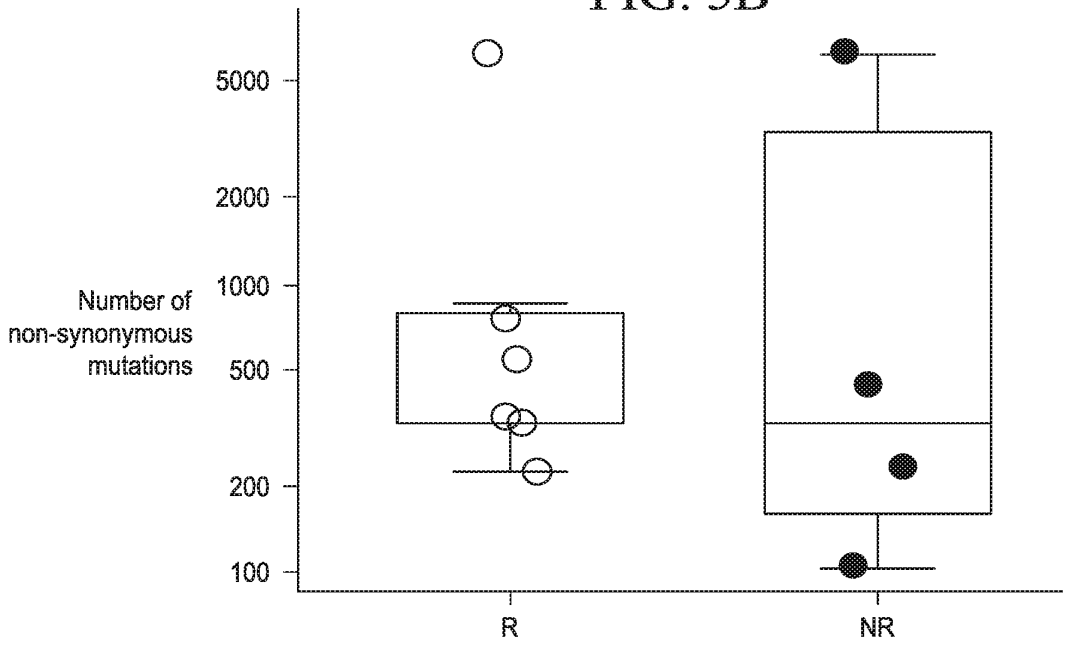

Mutational load
1000
100
10
1
BRAF
CDKN2A
ARID1B
PTEN
ARID1A
TP53
NF1
RB1
KDR
DCC
GRIN2A
TRRAP
MAP3K5
SETD2
CDKN2B
NRAS
MAP3K9
PREX2
NFKBIE
EPHA3
PIK3CA
PTPRK
NOTCH1
TERT
CBL
SNX31
RQCD1
STK19
BCL2S12
DDX3X
ATM
CASP8
CDK4
HLA-B
RASA2
CCND1
Missense
Nonsense
In-frame indel
Frameshift indel
Splice
Copy gain
Copy loss
RESPONSE
R
NR

FIG. 5A

FIG. 5B


Number of non-synonymous mutations
5000
2000
1000
500
200
100
R
NR

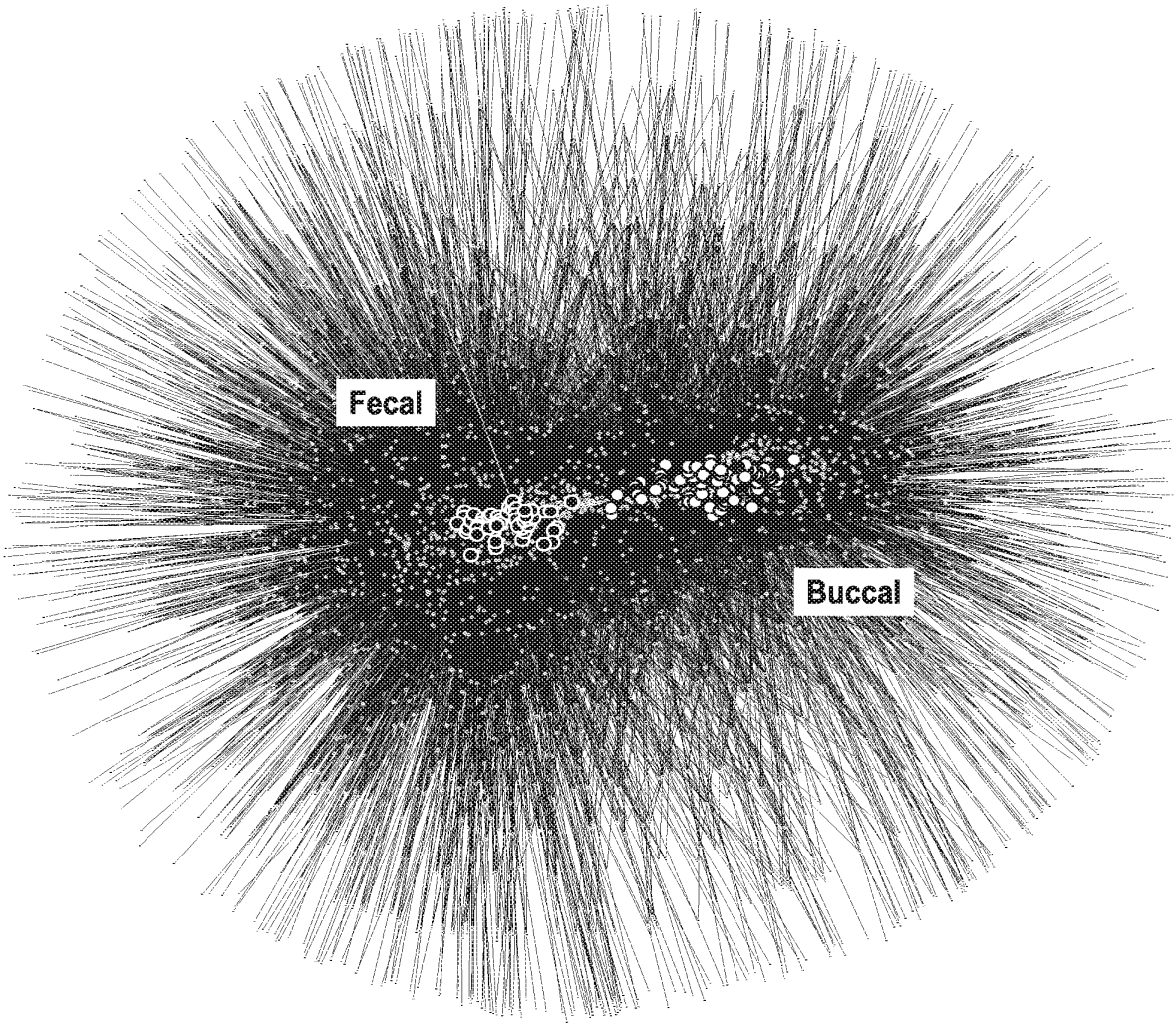


FIG. 6

FIG. 7A

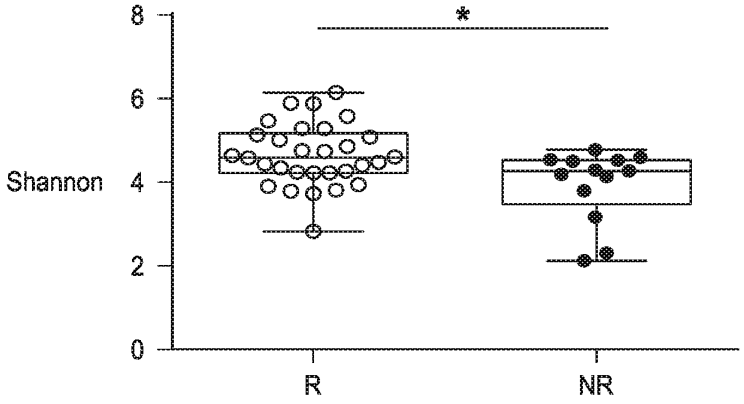


FIG. 7B

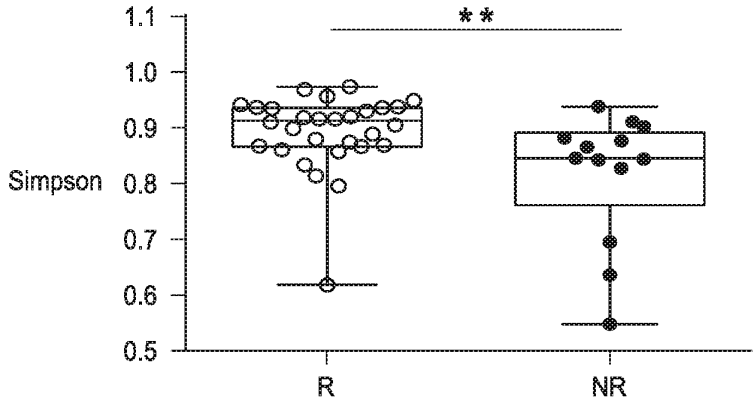


FIG. 7C

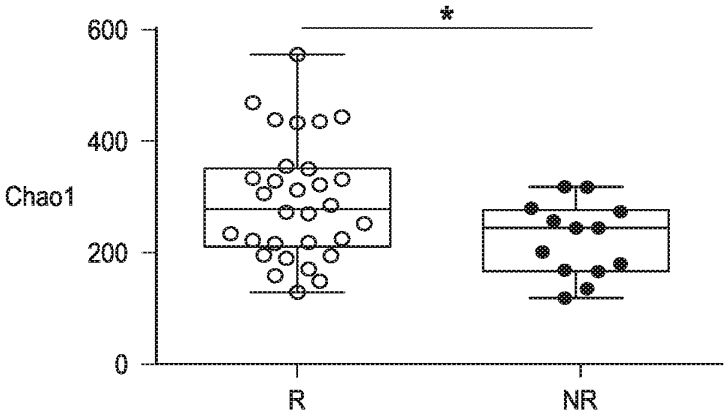


FIG. 8A

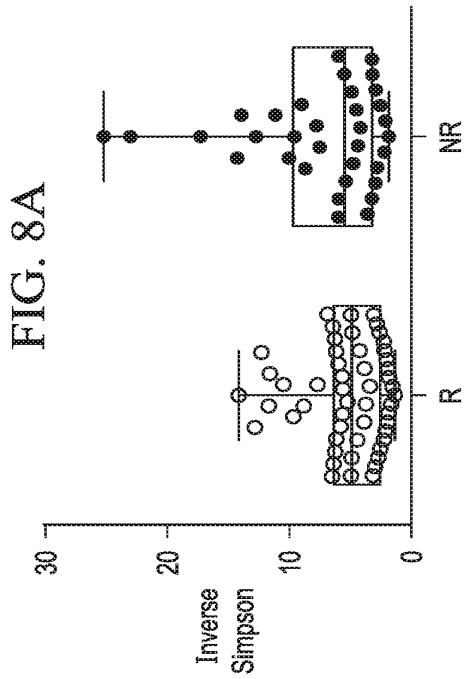


FIG. 8B

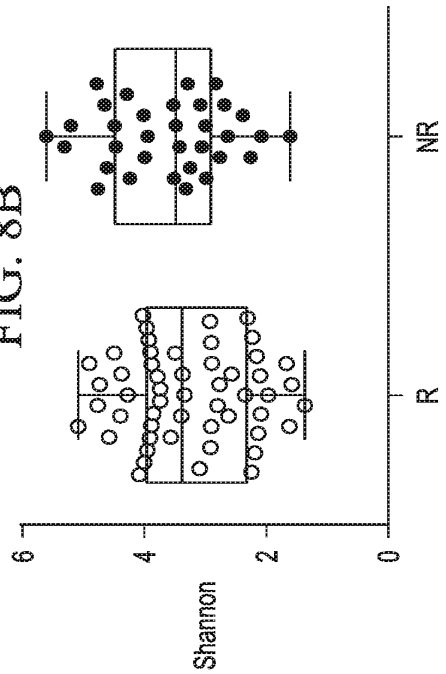


FIG. 8C

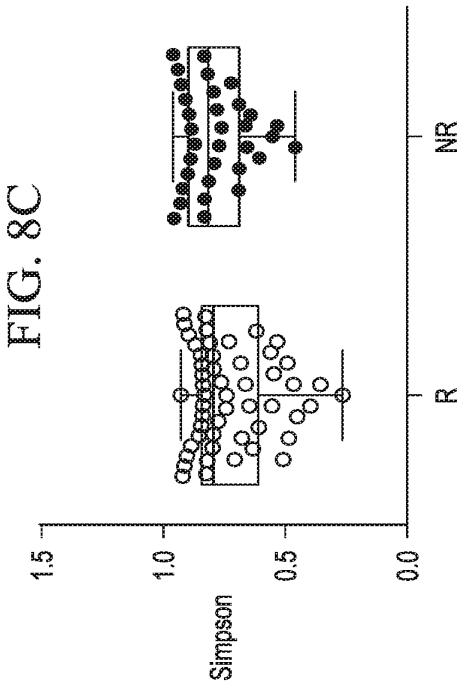


FIG. 8D

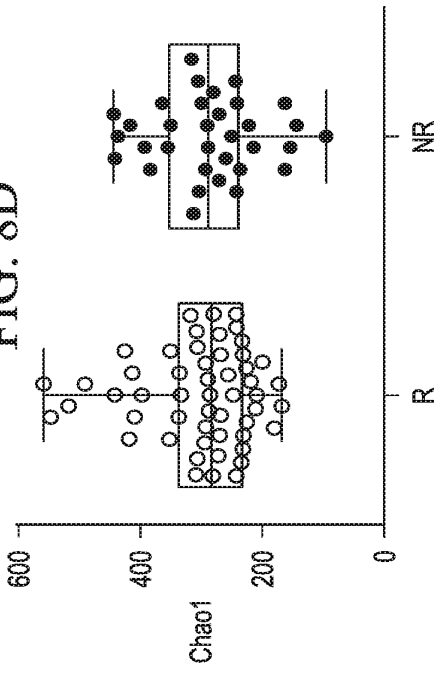


FIG. 9A

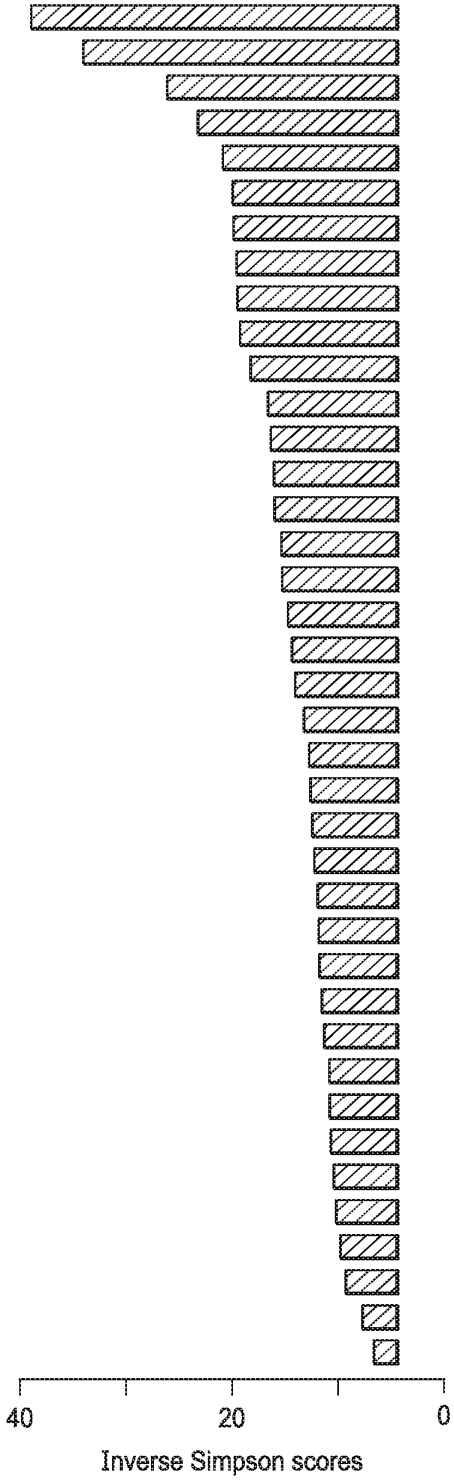
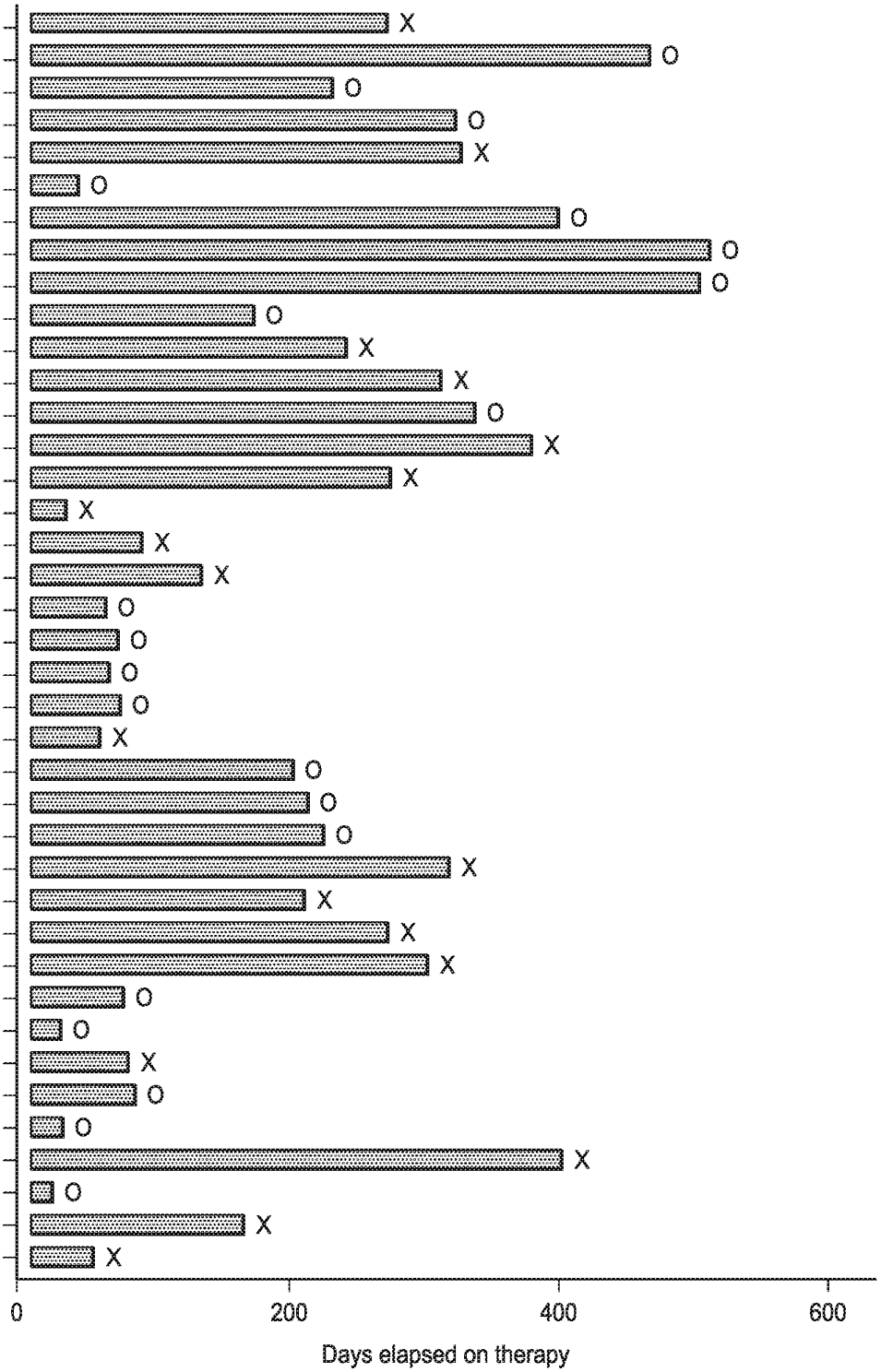


FIG. 9B


X
O
O
O
X
O
O
O
O
O
X
X
O
X
X
O
X
X
X
O
O
O
O
X
O
O
O
X
X
X
X
O
O
X
O
O
X
O
X
0
200
400
600
Days elapsed on therapy

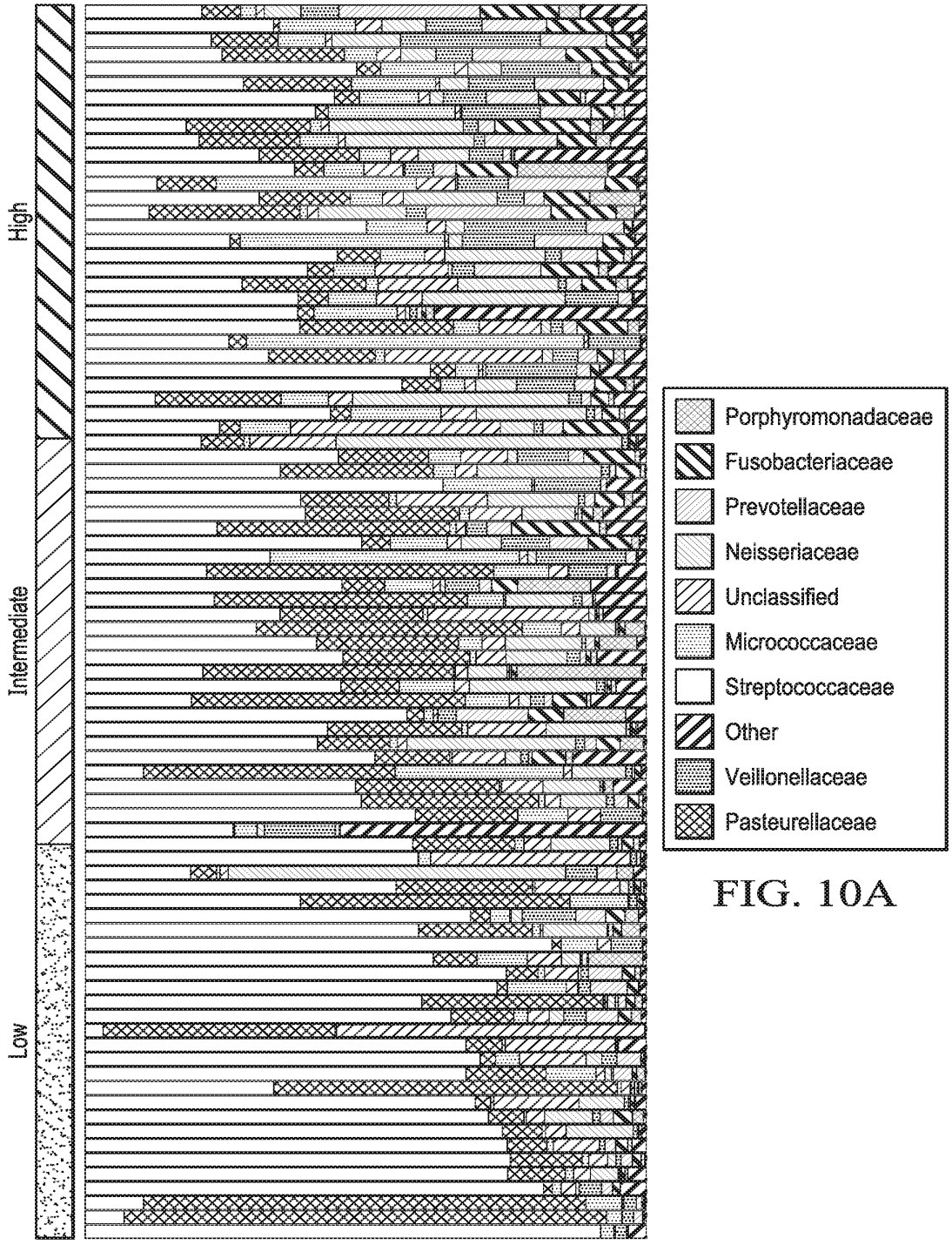

High
Intermediate
Low
Porphyromonadaceae
Fusobacteriaceae
Prevotellaceae
Neisseriaceae
Unclassified
Micrococcaceae
Streptococcaceae
Other
Veillonellaceae
Pasteurellaceae

FIG. 10A

FIG. 10B

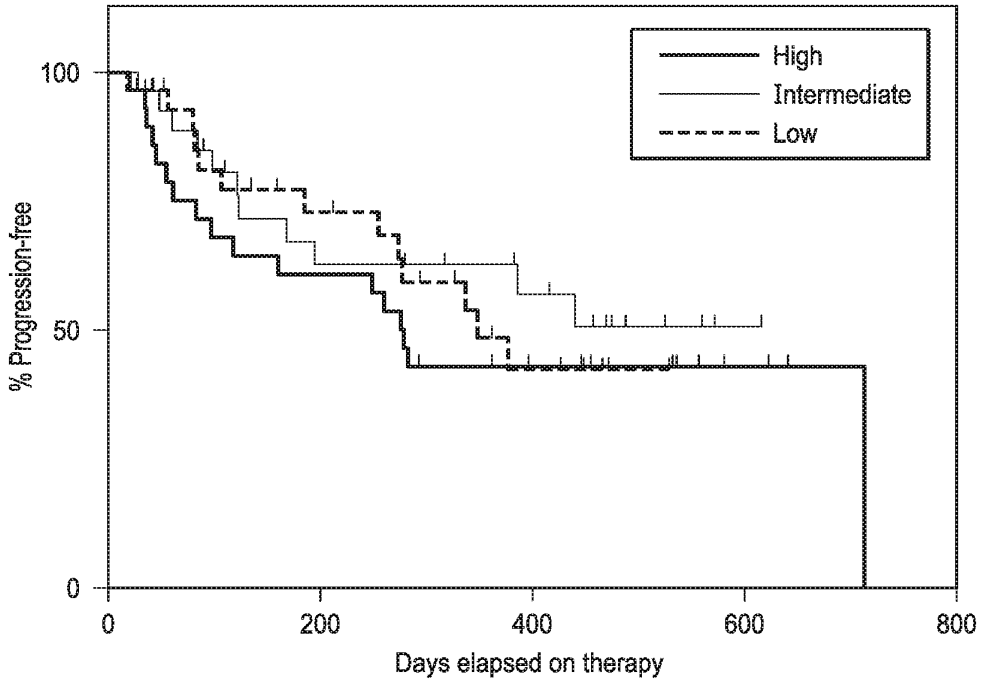

High
Intermediate
Low
100
50
0
% Progression-free
0
200
400
600
800
Days elapsed on therapy

FIG. 10C

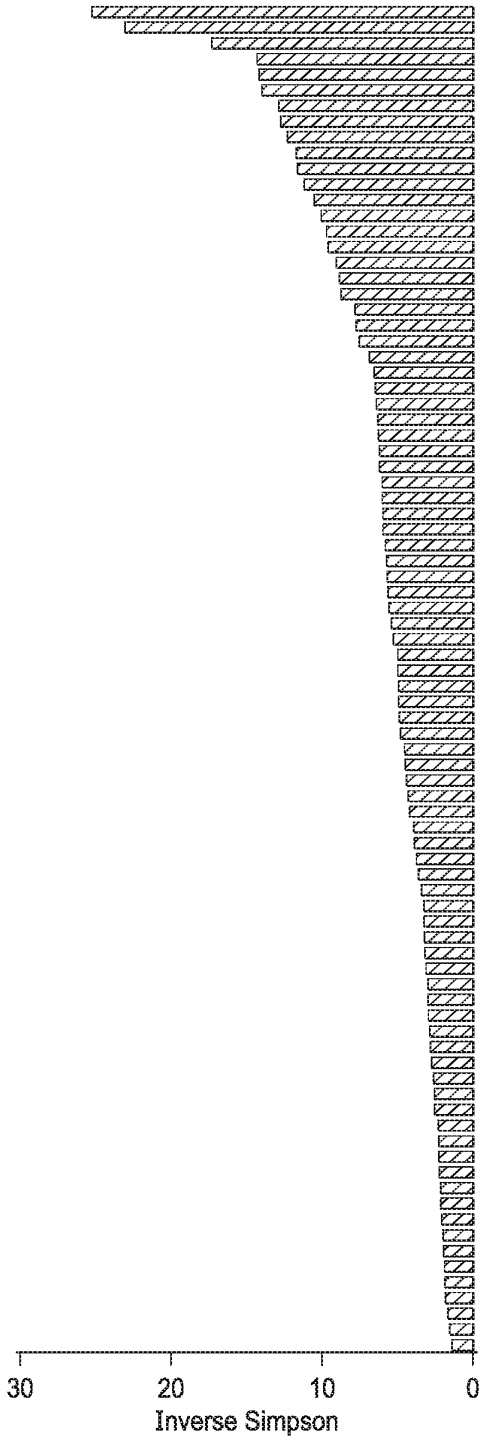


FIG. 10D

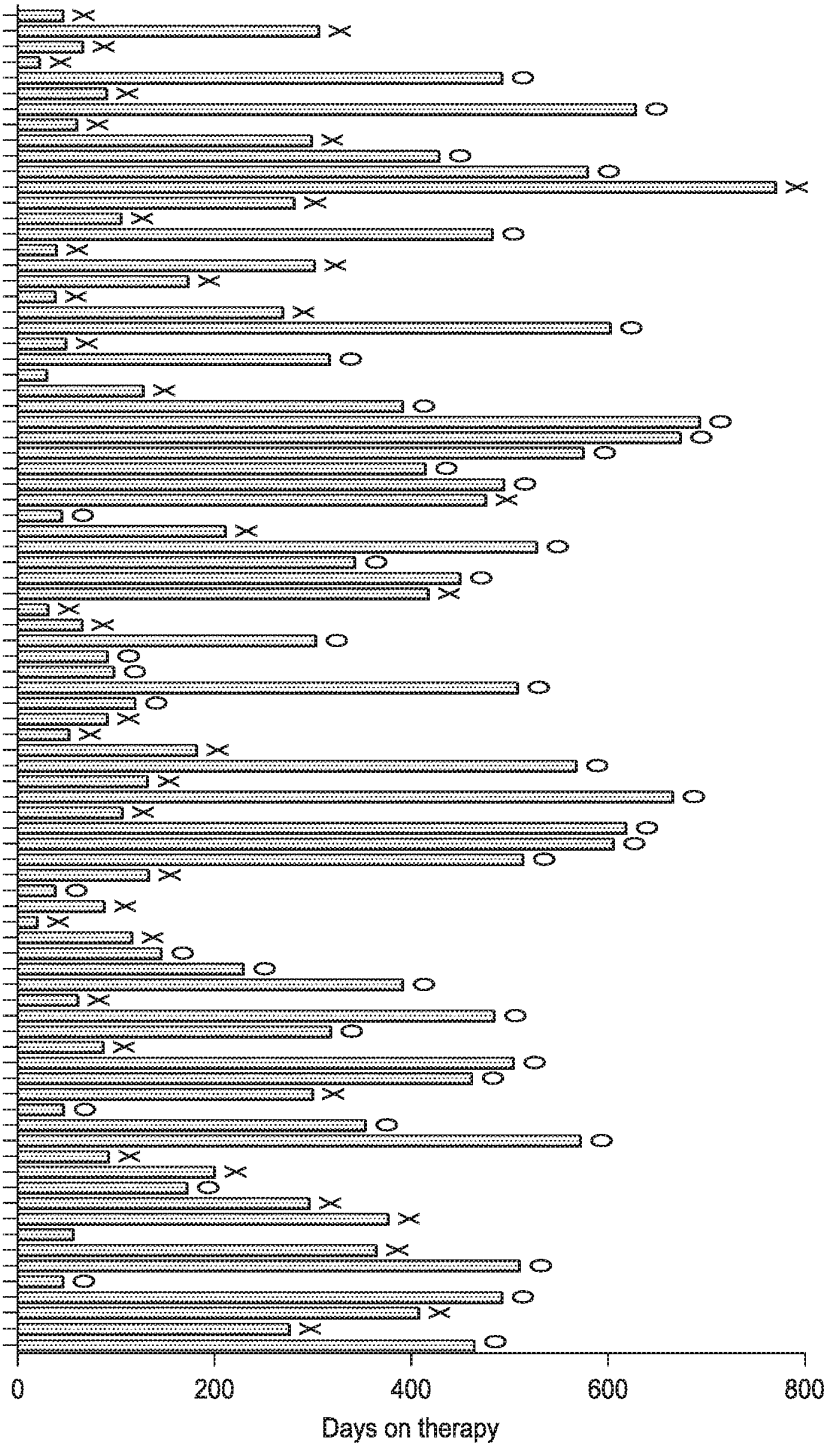


FIG. 11A

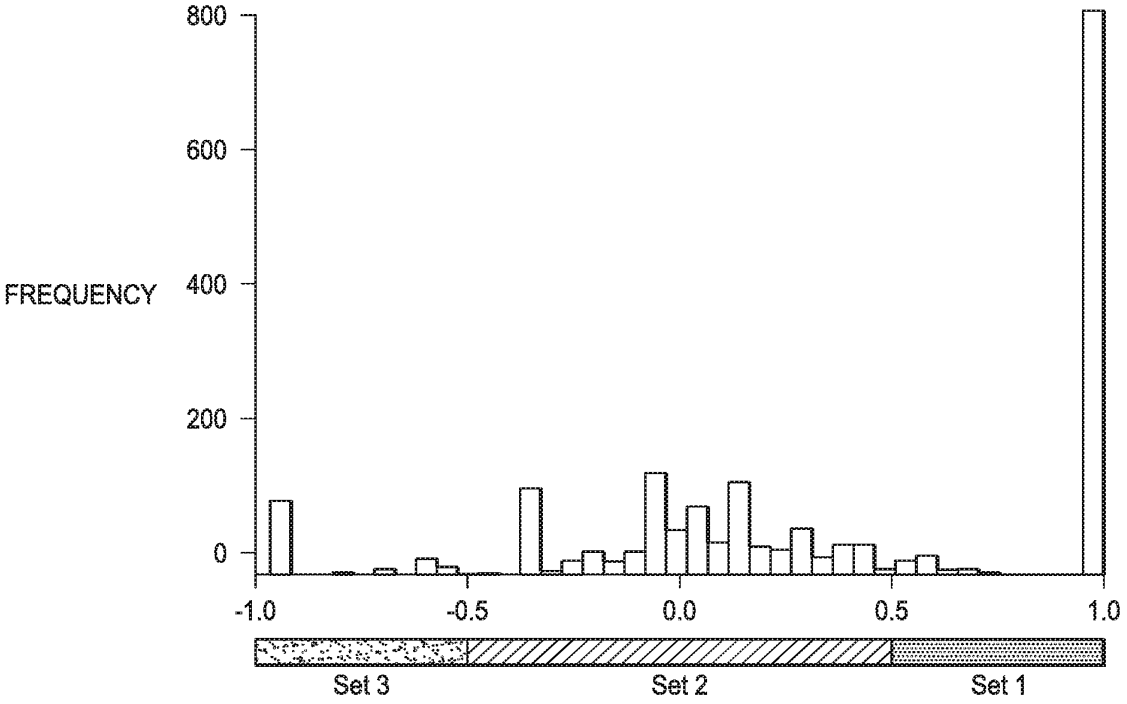


FIG. 11B

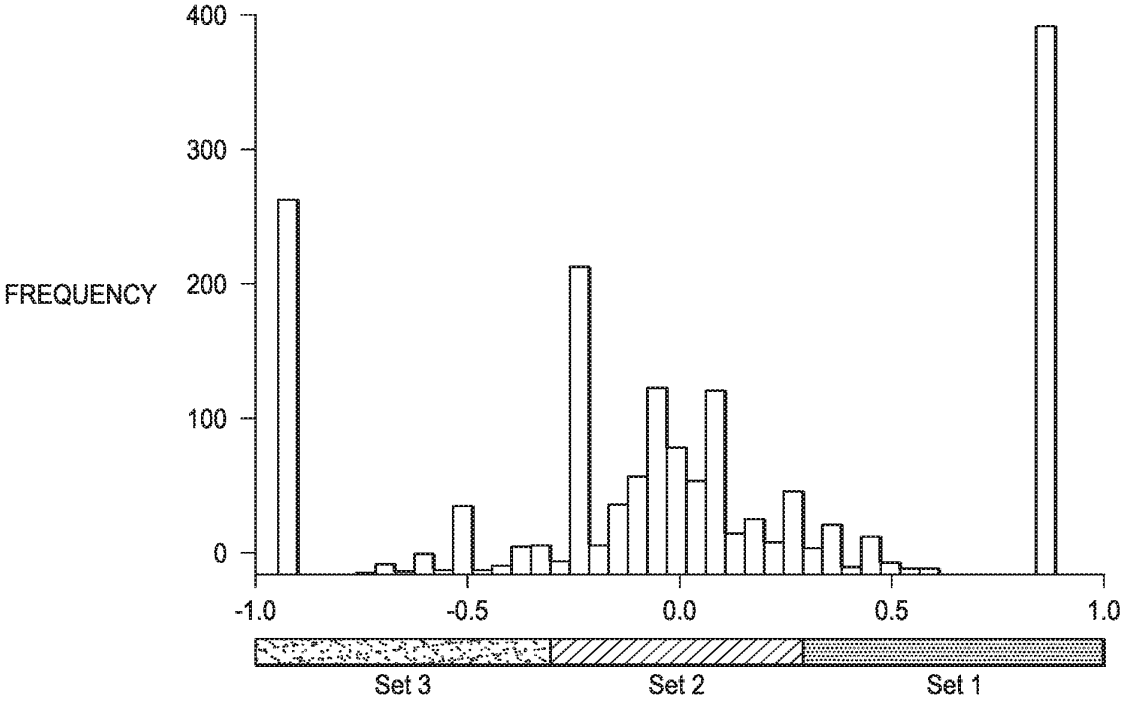


FIG. 11C

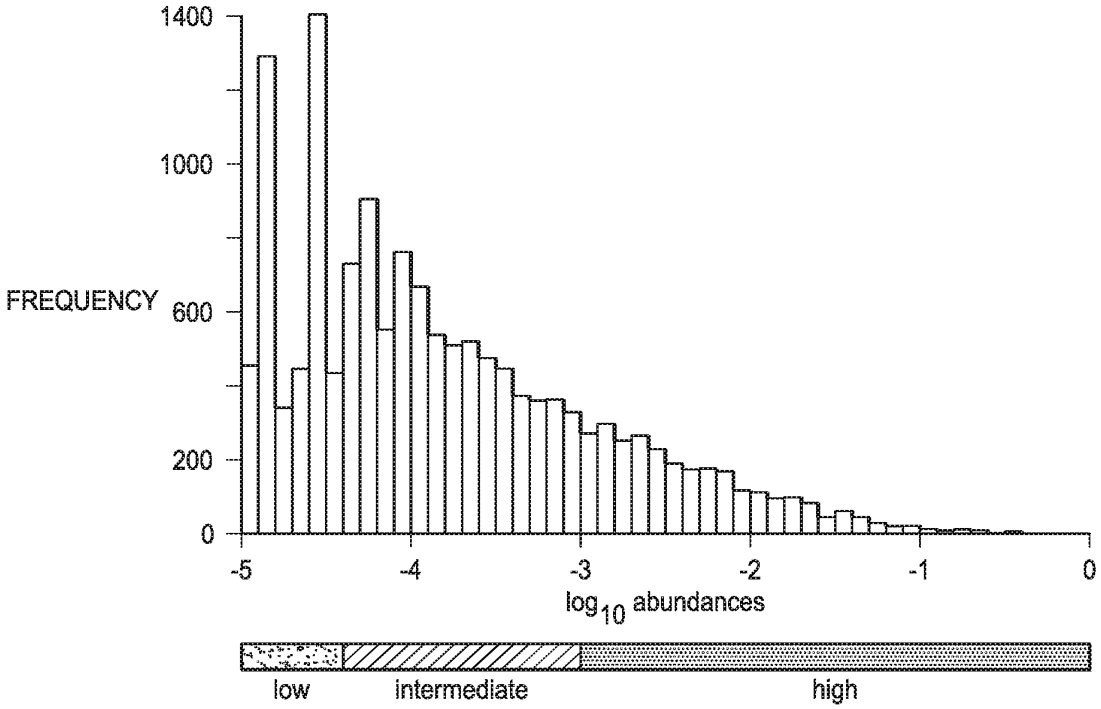
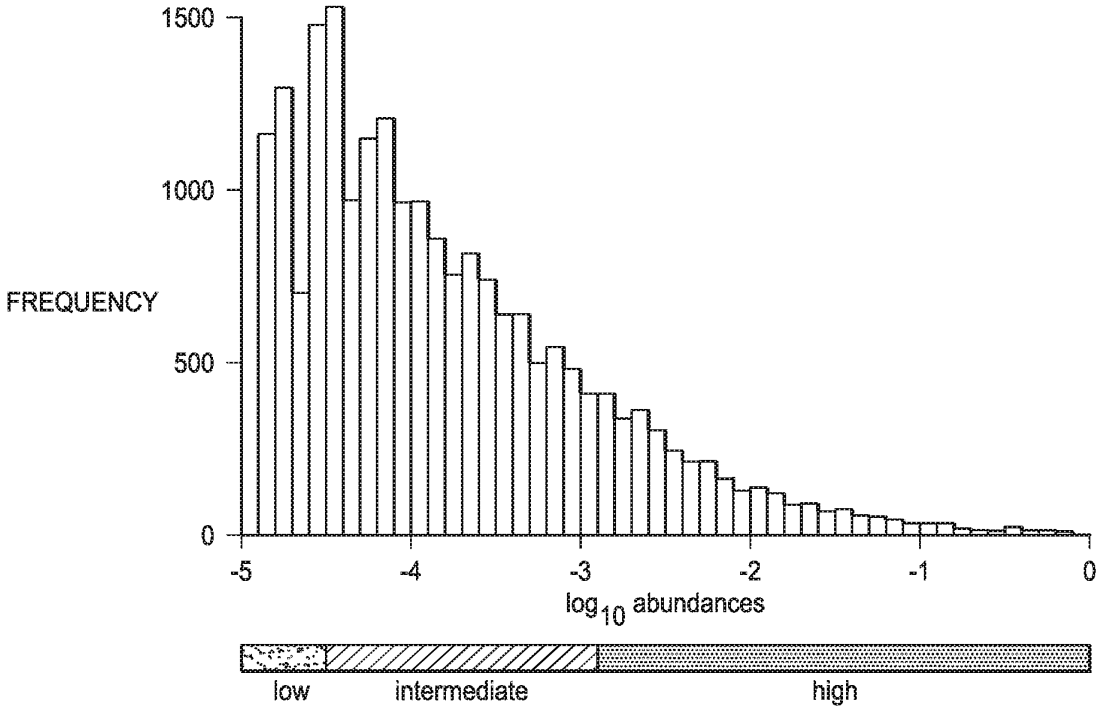


FIG. 11D



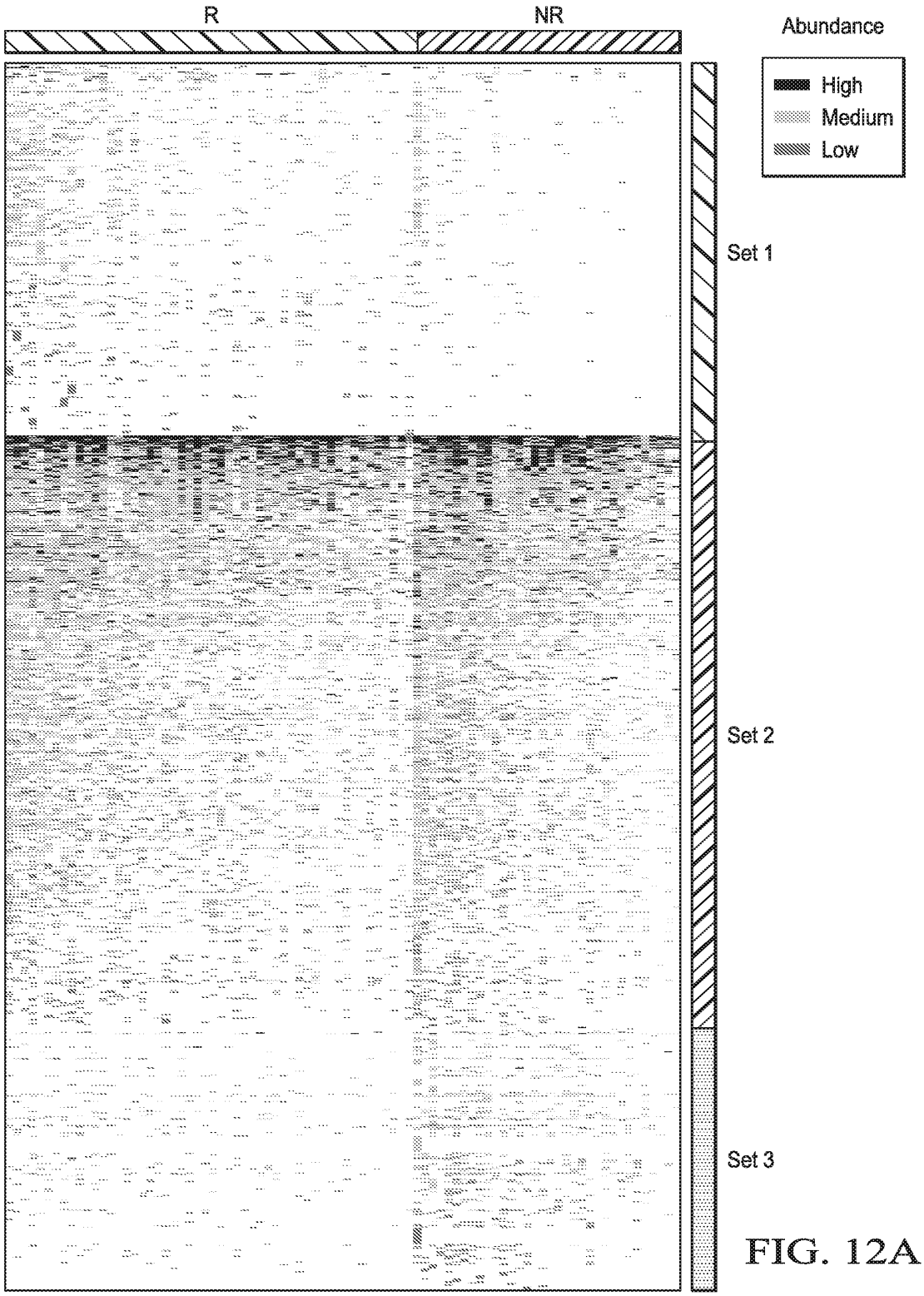


FIG. 12A

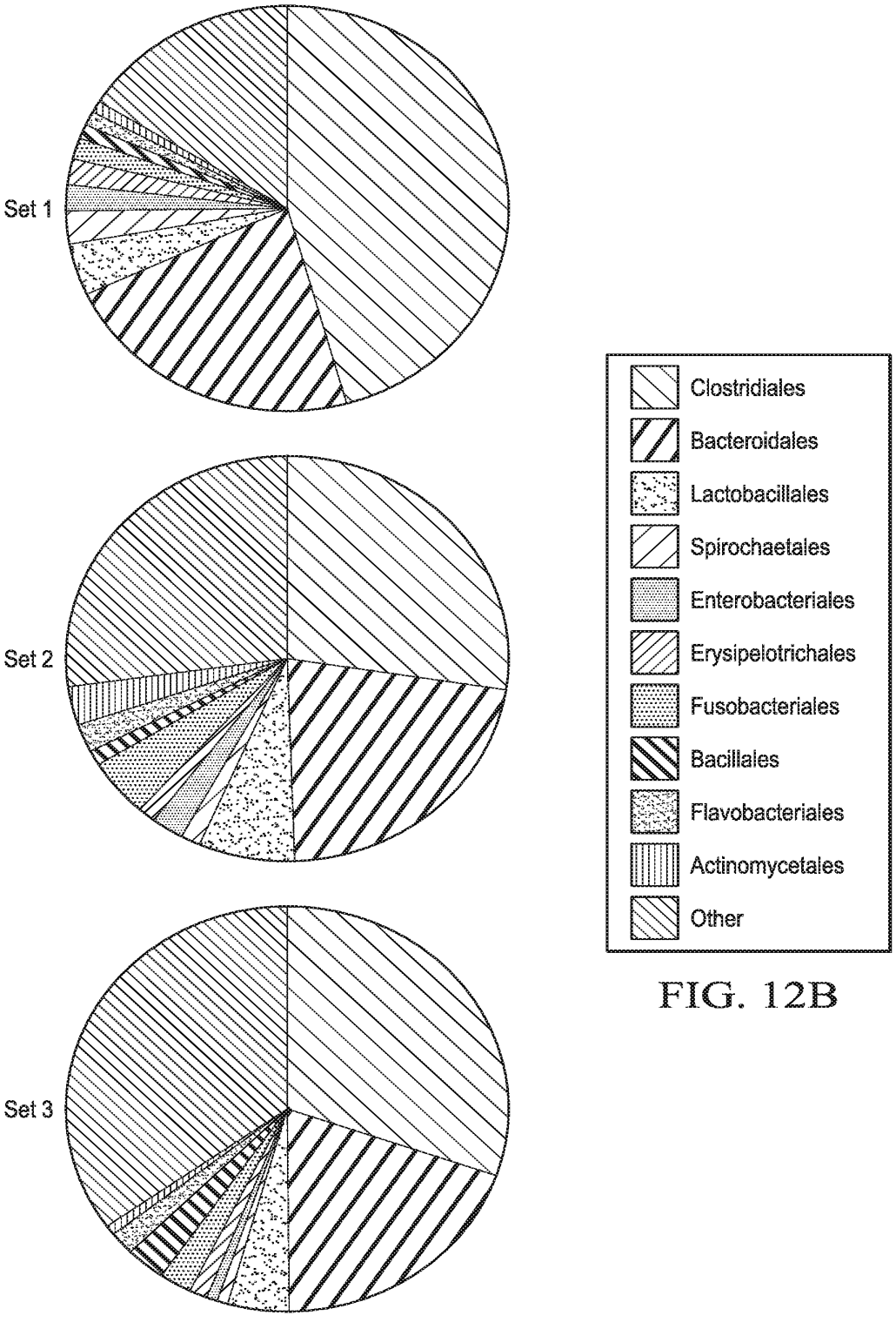

Set 1
Set 2
Set 3
Clostridiales
Bacteroidales
Lactobacillales
Spirochaetales
Enterobacteriales
Erysipelotrichales
Fusobacteriales
Bacillales
Flavobacteriales
Actinomycetales
Other

FIG. 12B

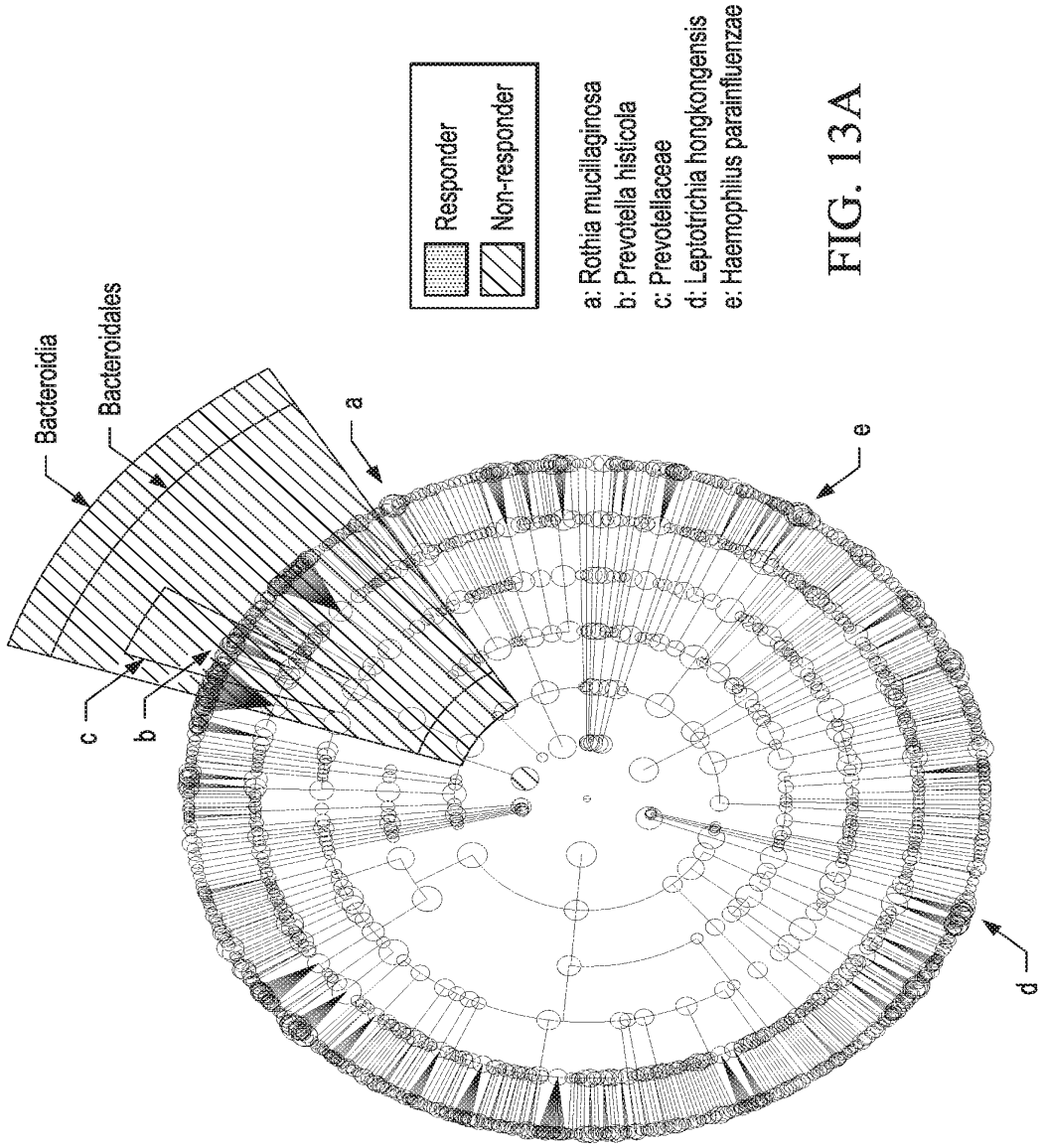

Bacteroidia
Bacteroidales
a
b
c
d
e
Responder
Non-responder
a: Rothia mucillaginosa
b: Prevotella histicola
c: Prevotellaceae
d: Leptotrichia hongkongensis
e: Haemophilus parainfluenzae

FIG. 13A

FIG. 13B

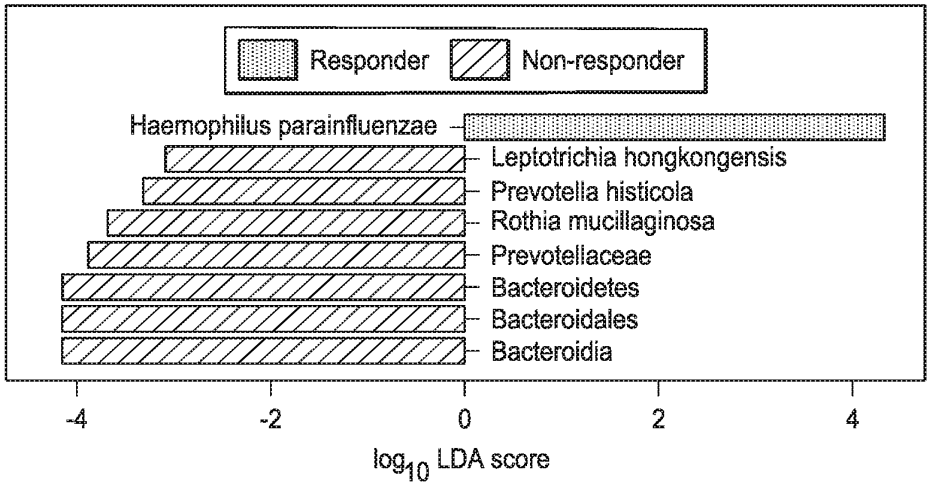


FIG. 14A

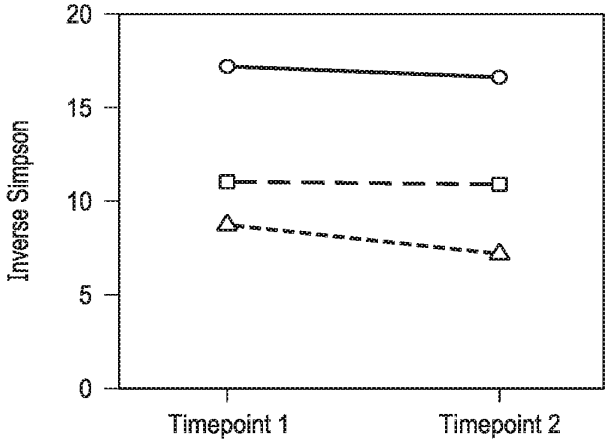
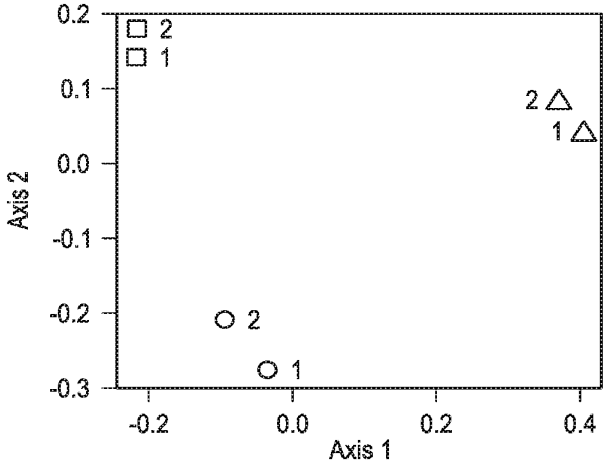


FIG. 14B



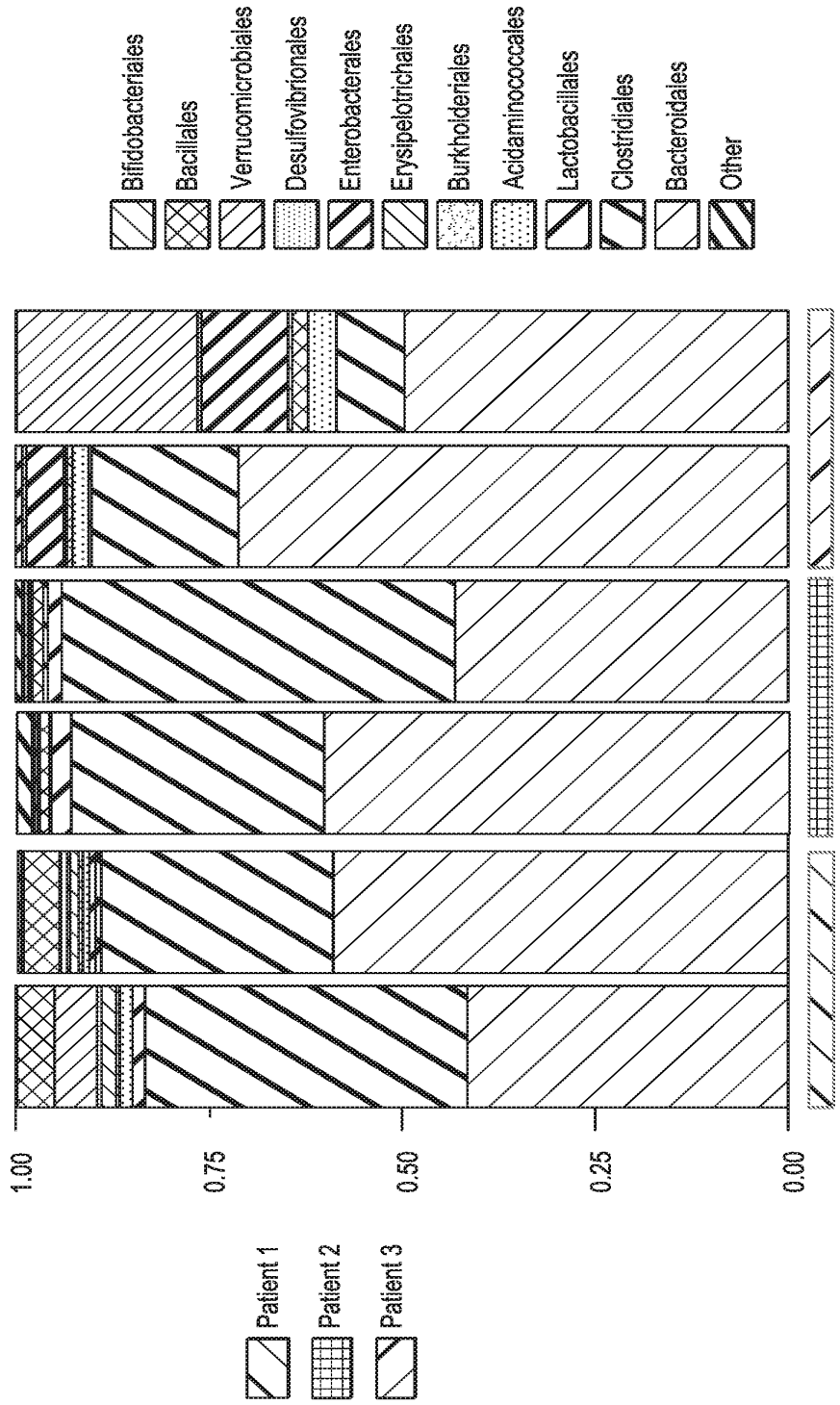

Bifidobacteriales
Bacillales
Verrucomicrobiales
Desulfovibrionales
Enterobacterales
Erysipelotrichales
Burkholderiales
Acidaminococcales
Lactobacillales
Clostridiales
Bacteroidales
Other
1.00
0.75
0.50
0.25
0.00
Patient 1
Patient 2
Patient 3

FIG. 14C

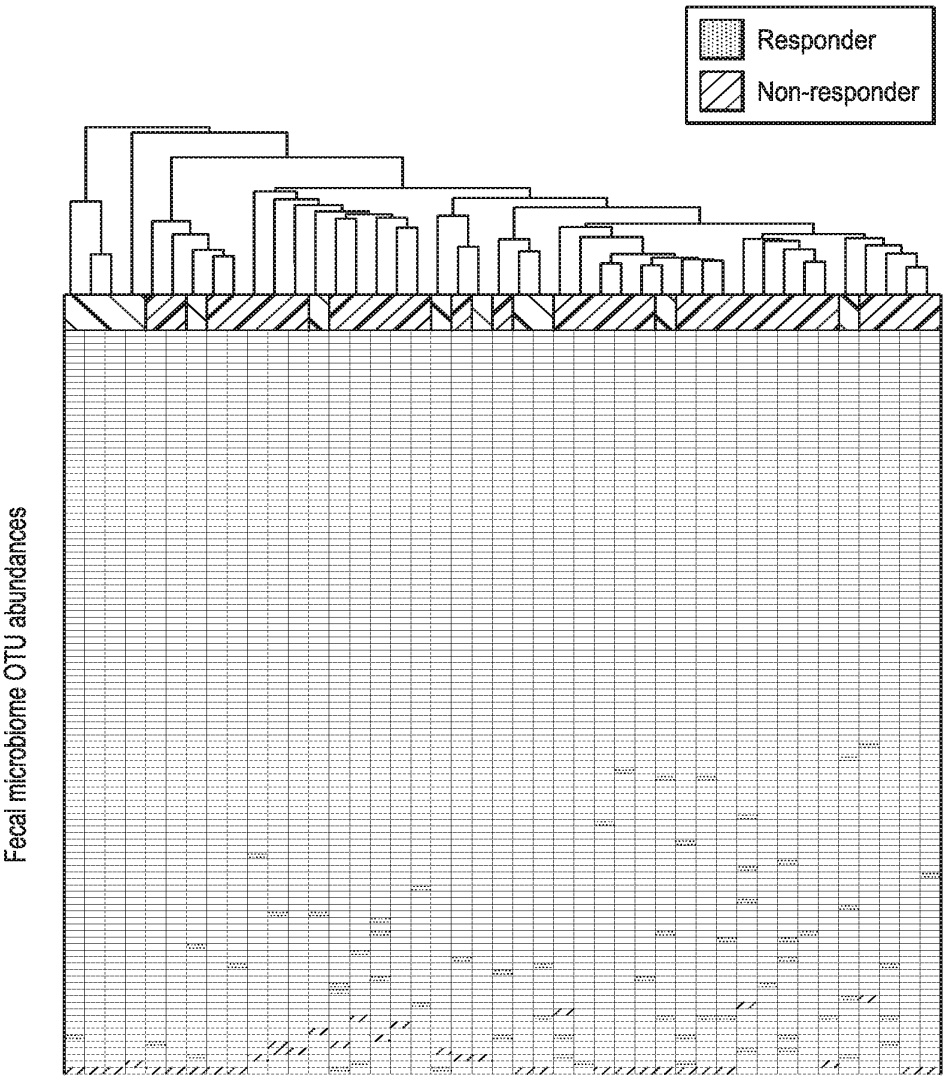


FIG. 15A

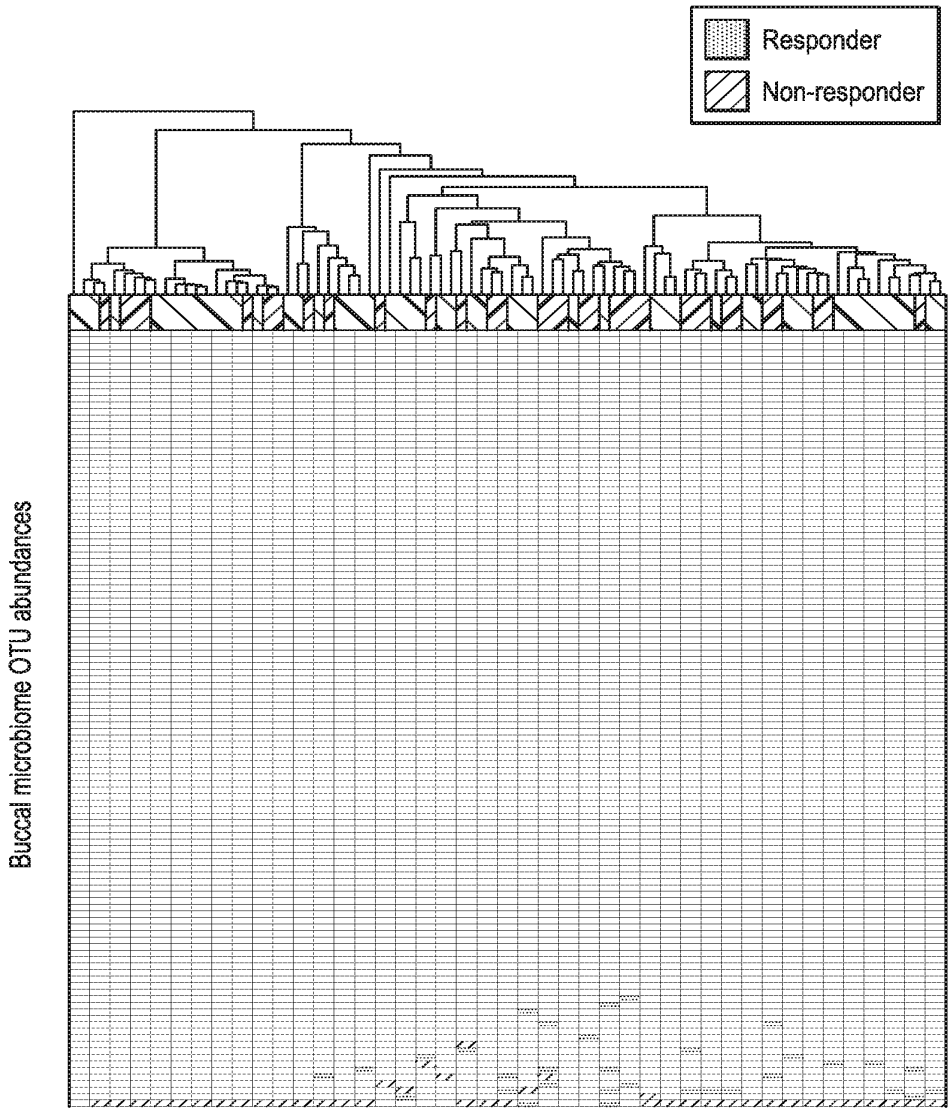

Responder
Non-responder
Buccal microbiome OTU abundances

FIG. 15B

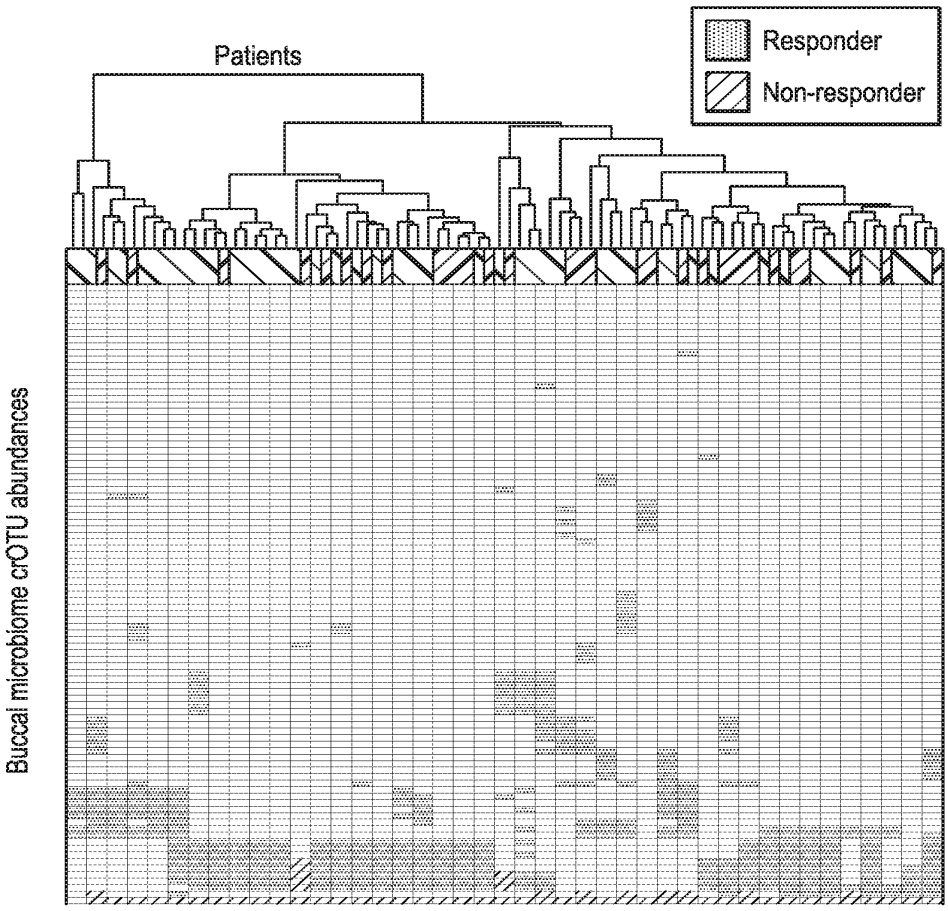


FIG. 16A

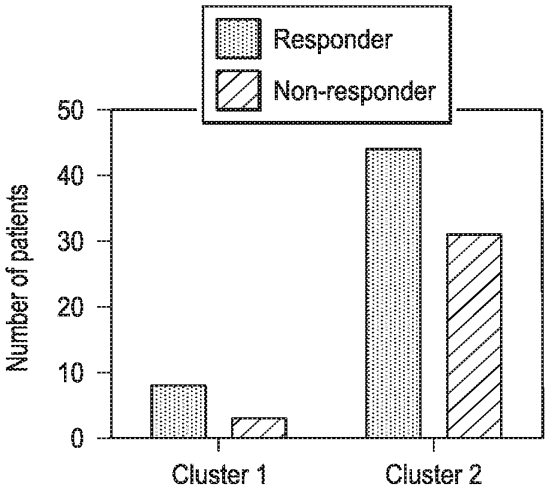
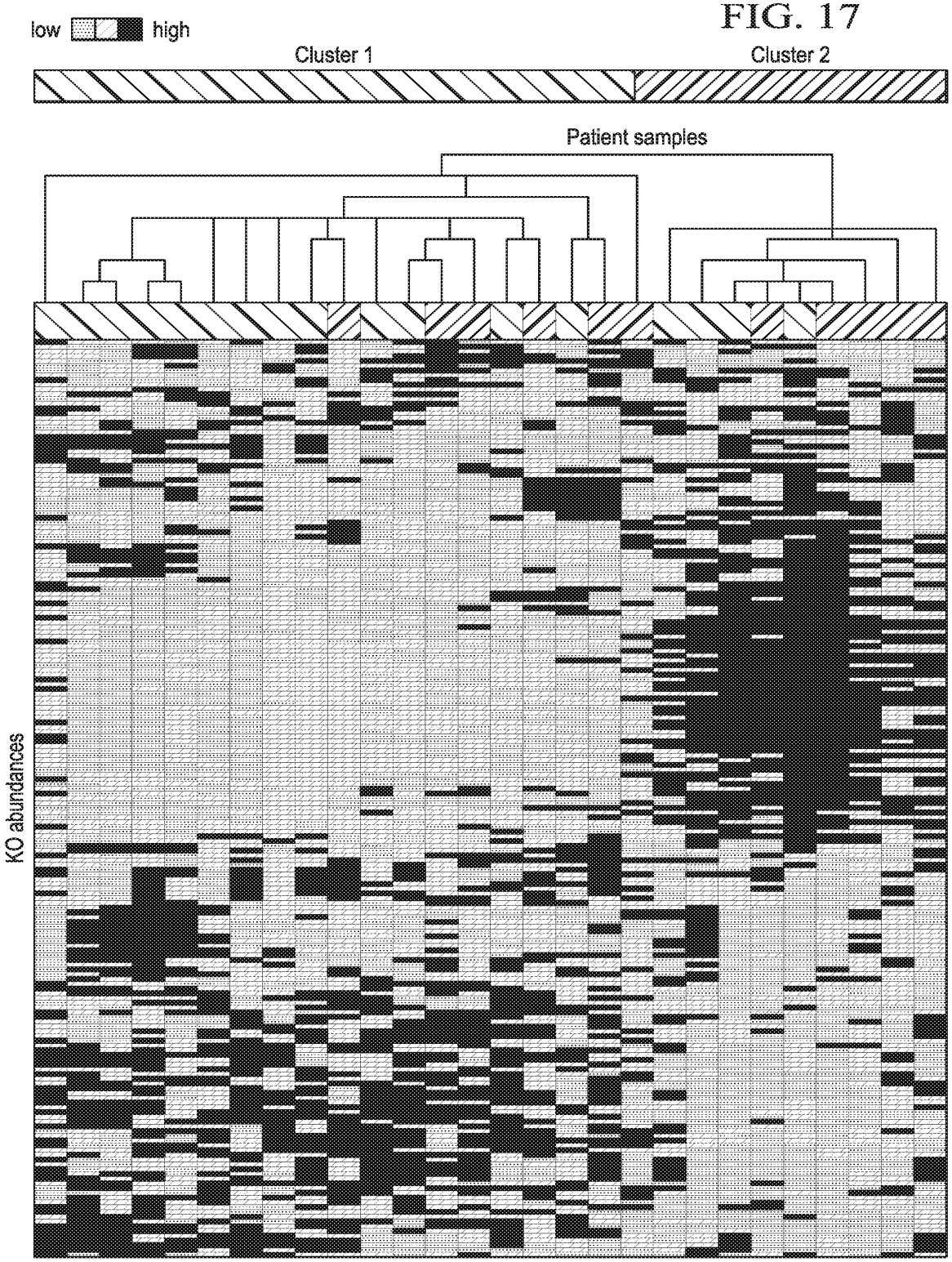


FIG. 16B

FIG. 17



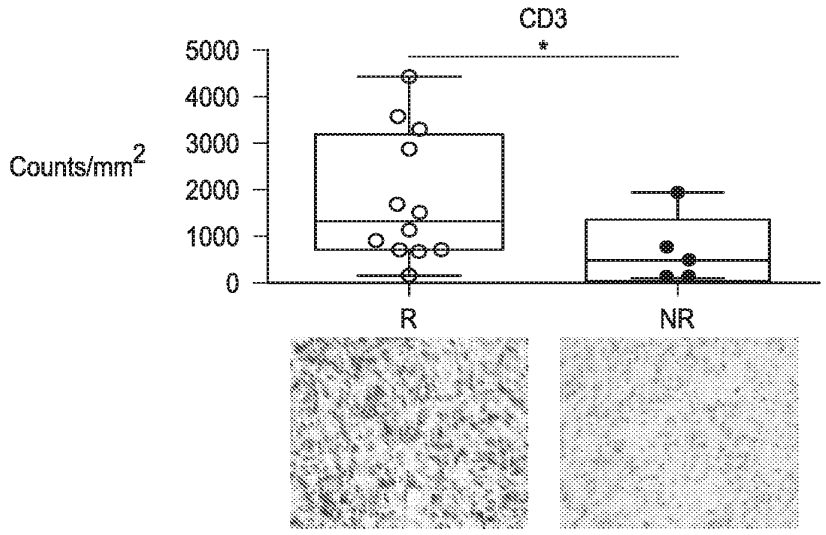


FIG. 18A

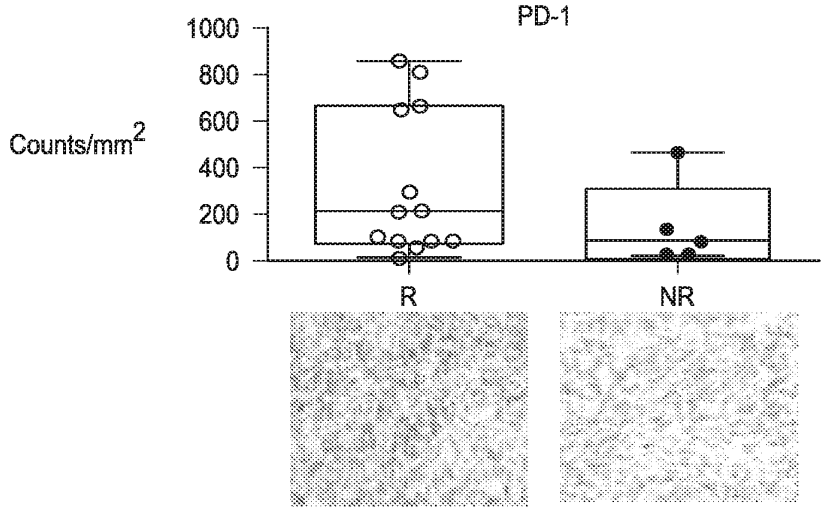


FIG. 18B

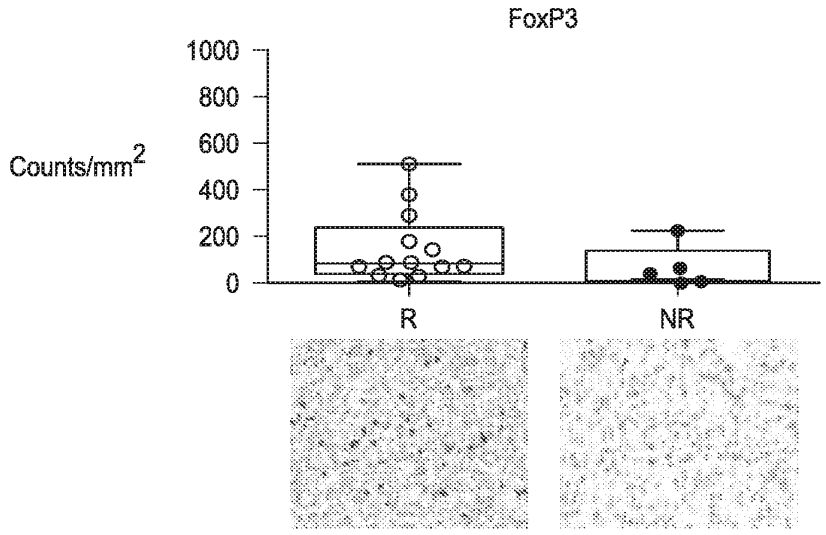


FIG. 18C

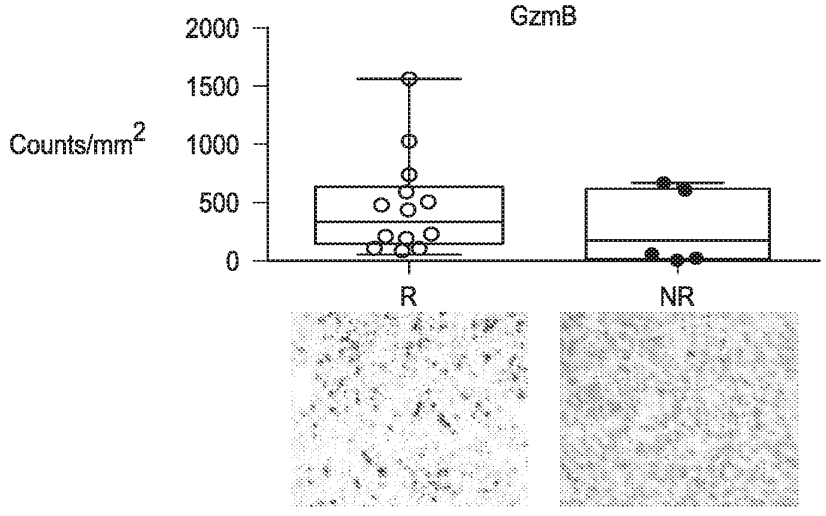


FIG. 18D

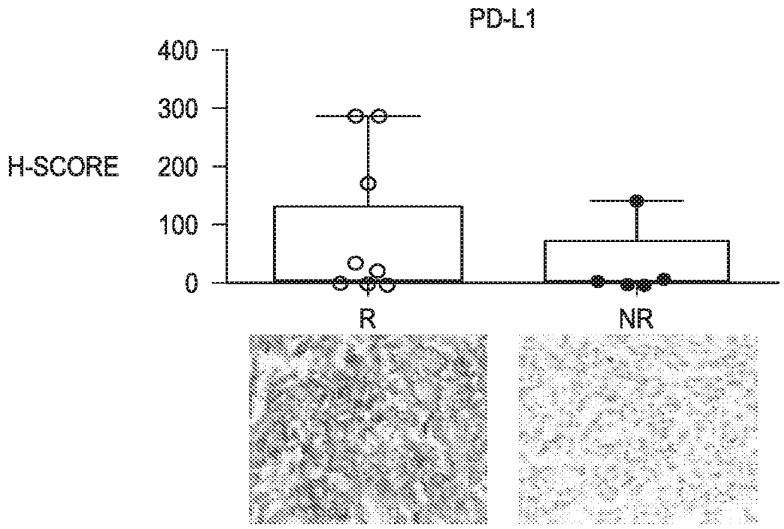


FIG. 18E

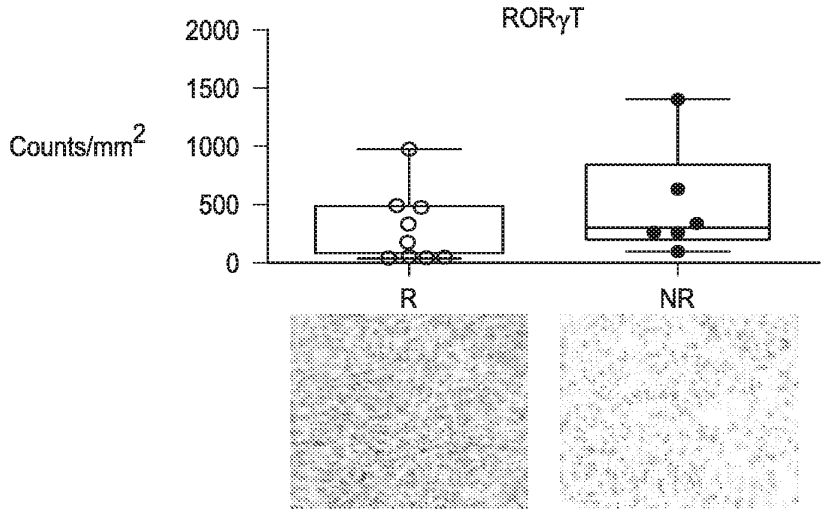
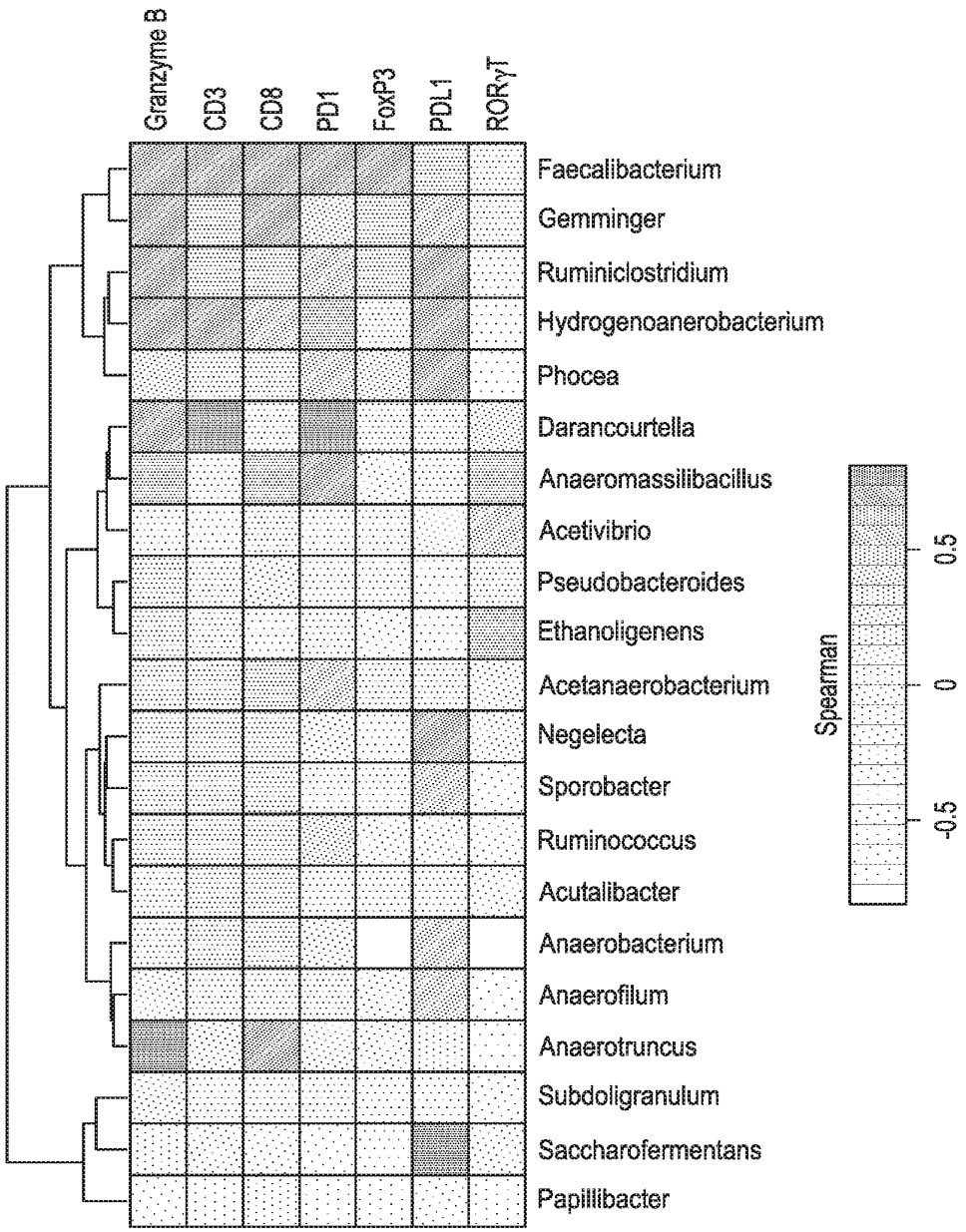


FIG. 18F

FIG. 19


Granzyme B
CD3
CD8
PD1
FoxP3
PDL1
RORγT
Faecalibacterium
Gemminger
Ruminiclostridium
Hydrogenoanerobacterium
Phocea
Darancourtella
Anaeromassilibacillus
Acetivibrio
Pseudobacteroides
Ethanoligenens
Acetanaerobacterium
Negelecta
Sporobacter
Ruminococcus
Acutalibacter
Anaerobacterium
Anaerofilum
Anaerotruncus
Subdoligranulum
Saccharofermentans
Papillibacter
Spearman
0.5
0
-0.5

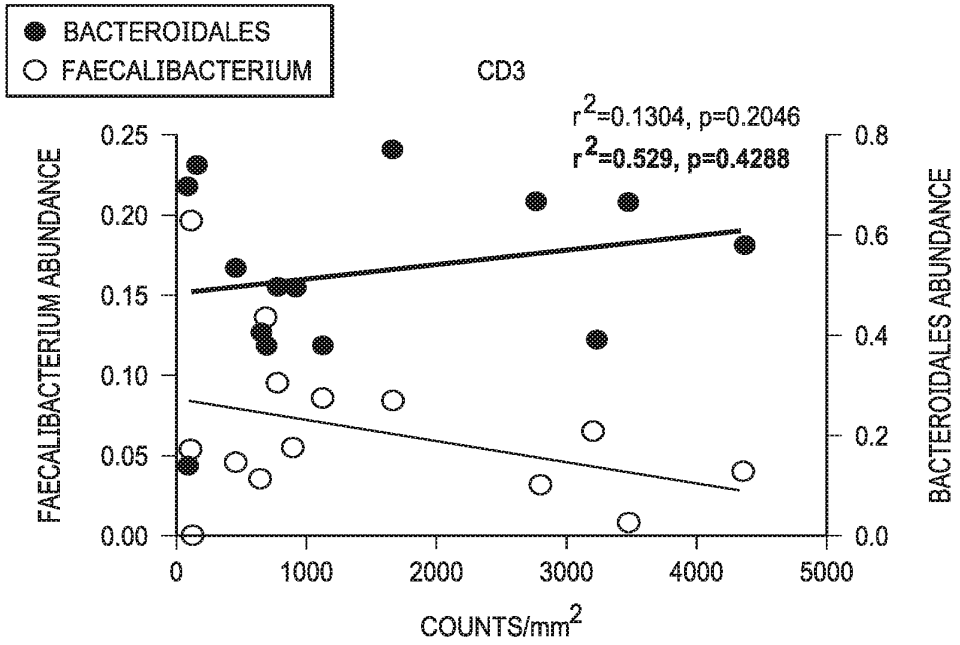


FIG. 20A

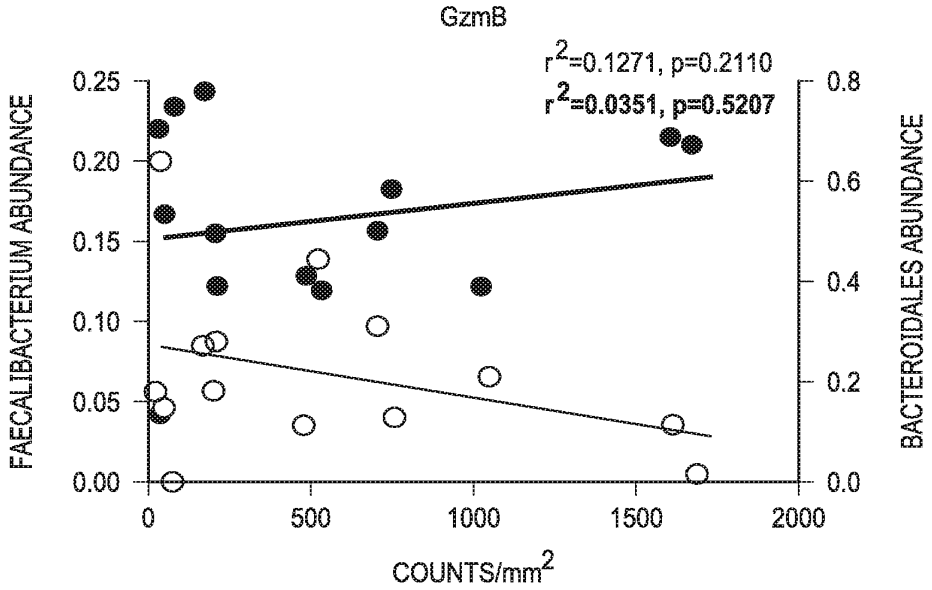


FIG. 20B

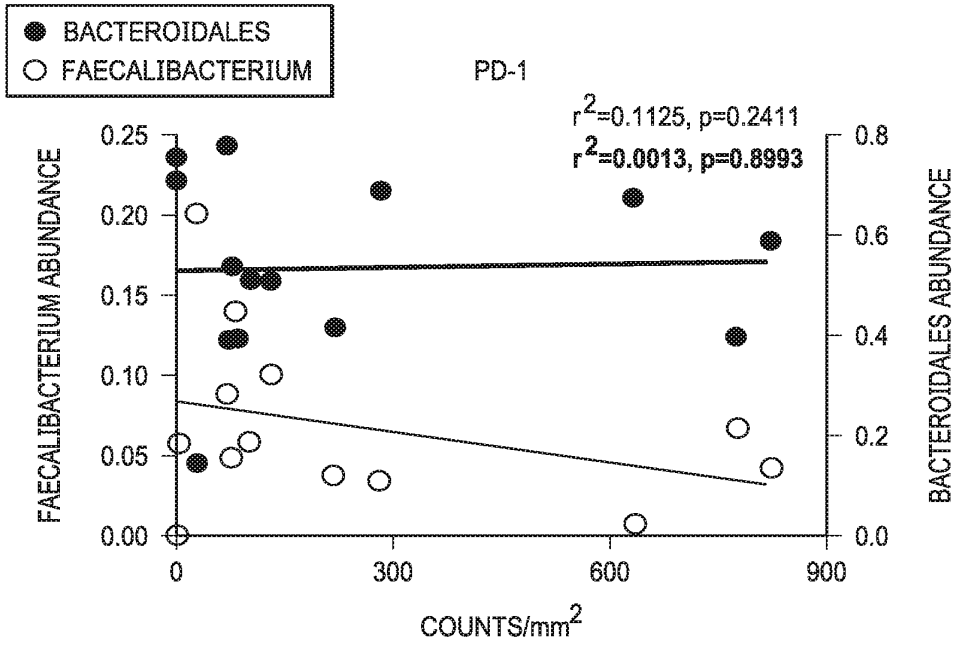


FIG. 20C

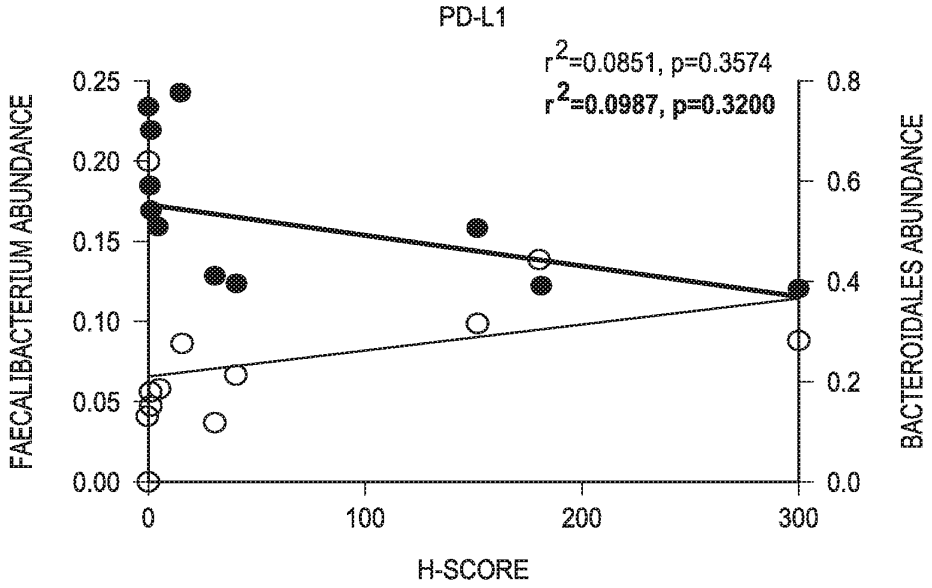


FIG. 20D

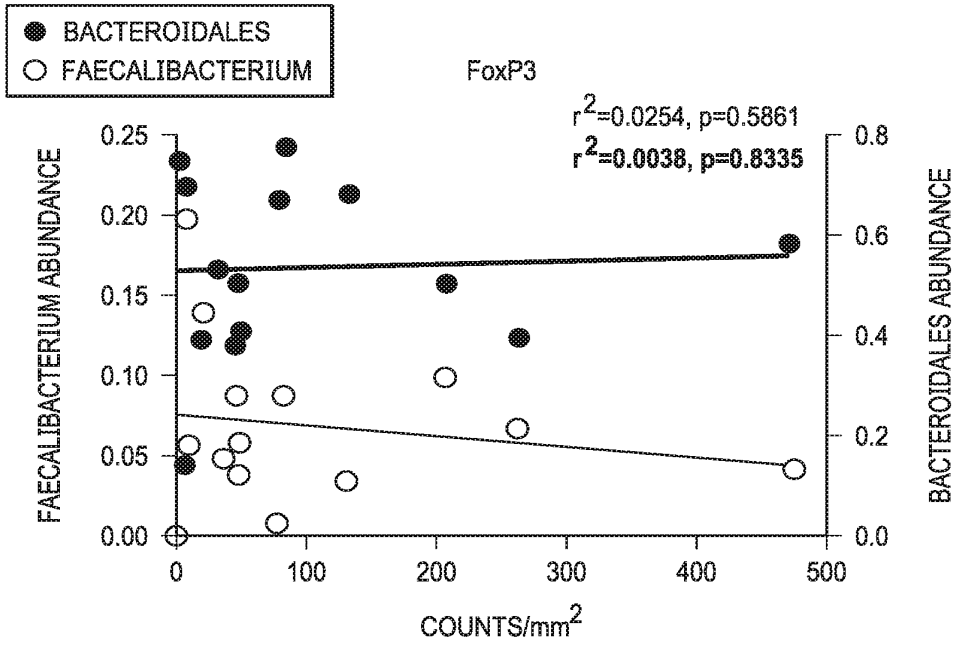


FIG. 20E

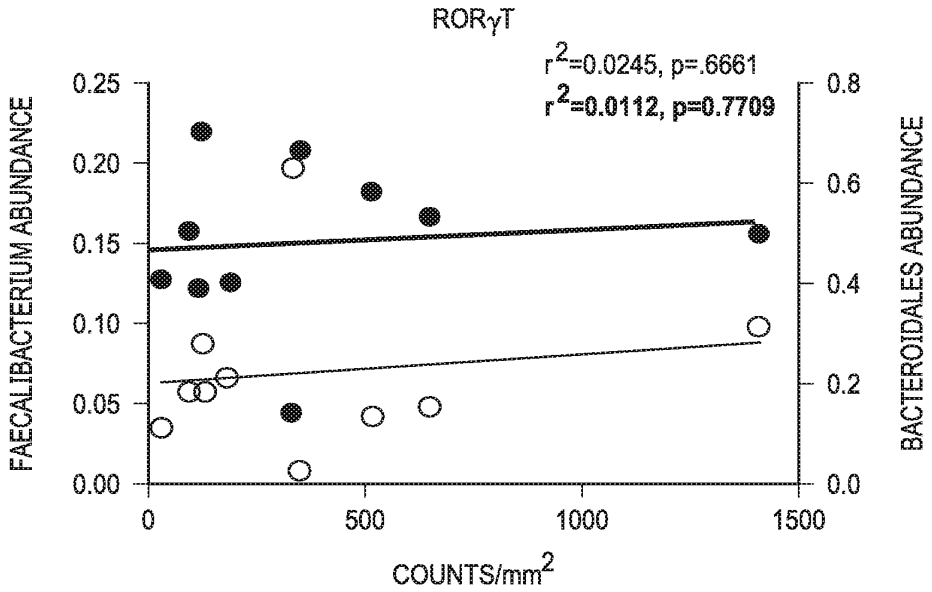


FIG. 20F

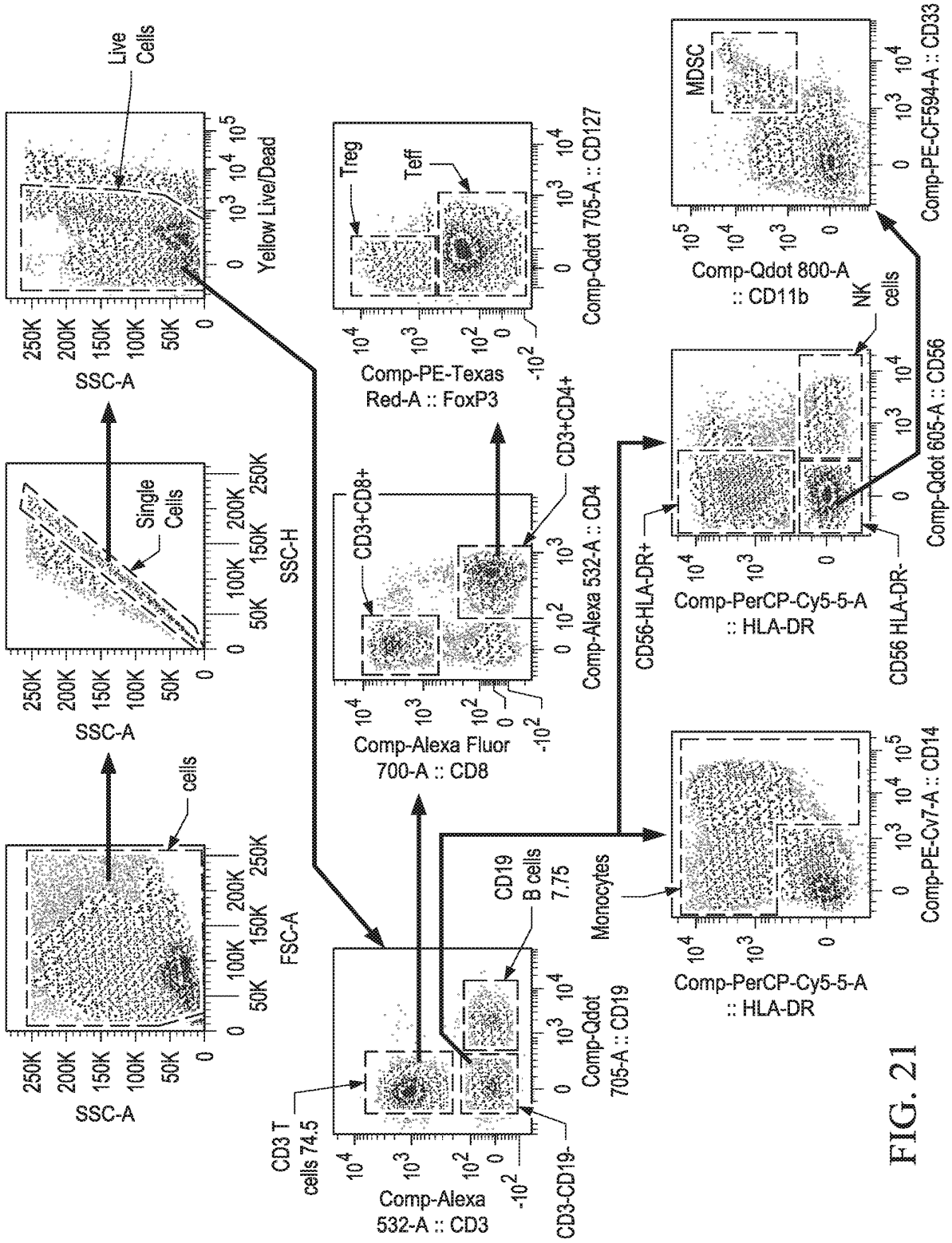

Live Cells
Yellow Live/Dead
SSC-A
Single Cells
SSC-H
cells
FSC-A
CD3 T cells 74.5
CD3-CD19-
Comp-Alexa 532-A :: CD3
CD19 B cells 7.75
Comp-Qdot 705-A :: CD19
Treg
Teff
Comp-PE-Texas Red-A :: FoxP3
Comp-Qdot 705-A :: CD127
CD3+CD8+
CD3+CD4+
Comp-Alexa Fluor 700-A :: CD8
Comp-Alexa 532-A :: CD4
Monocytes
CD56-HLA-DR+
CD56 HLA-DR-
Comp-PerCP-Cy5-5-A :: HLA-DR
NK cells
Comp-Qdot 605-A :: CD56
MDSC
Comp-Qdot 800-A :: CD11b
Comp-PE-CF594-A :: CD33
Comp-PE-Cy7-A :: CD14

FIG. 21

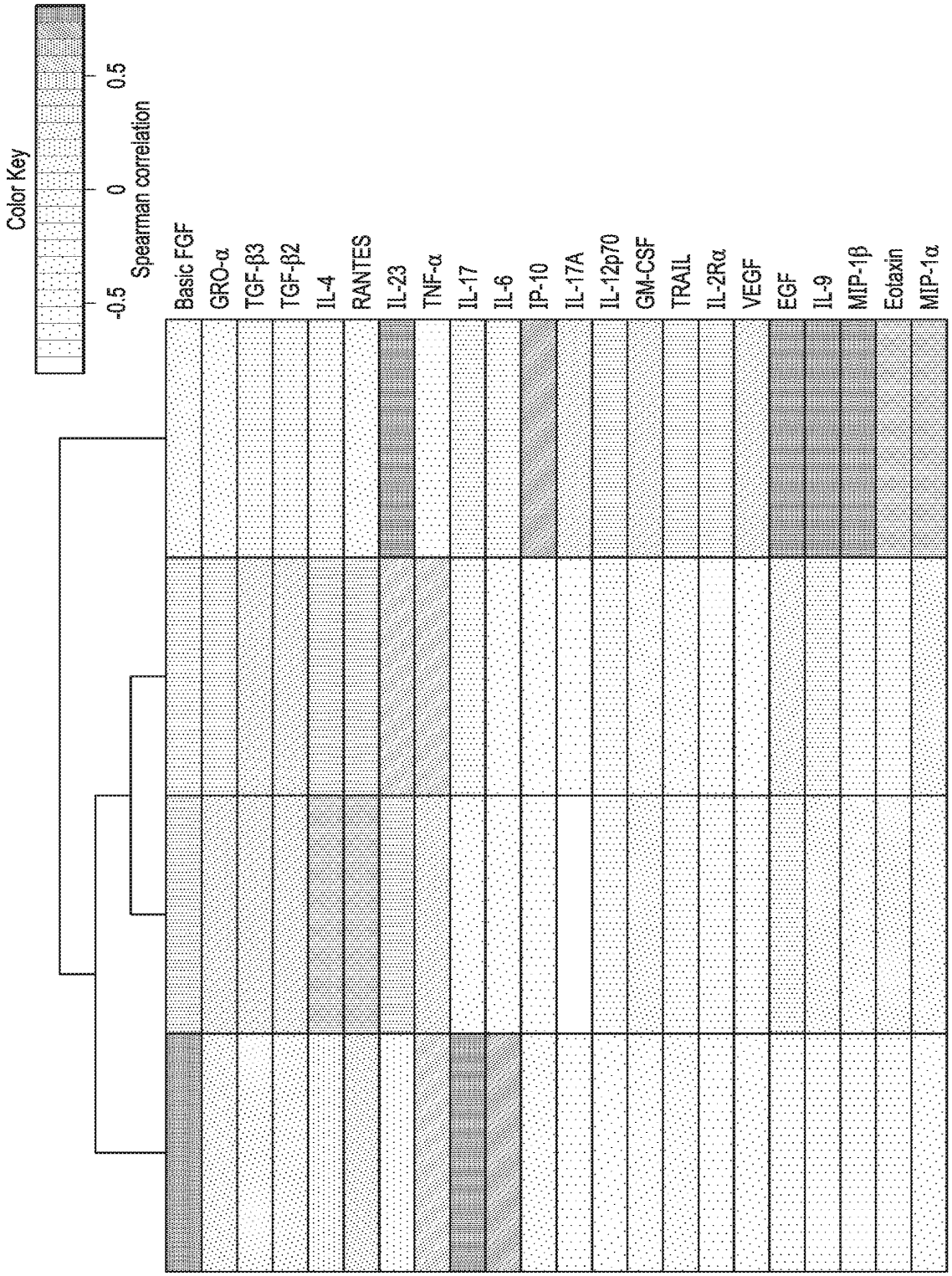

Color Key
-0.5
0
0.5
Spearman correlation
Basic FGF
GRO-α
TGF-β3
TGF-β2
IL-4
RANTES
IL-23
TNF-α
IL-17
IL-6
IP-10
IL-17A
IL-12p70
GM-CSF
TRAIL
IL-2Rα
VEGF
EGF
IL-9
MIP-1β
Eotaxin
MIP-1α
Clostridiales
Faecalibacterium
Ruminococcaceae
Bacteroidales

FIG. 22A

FIG. 22B

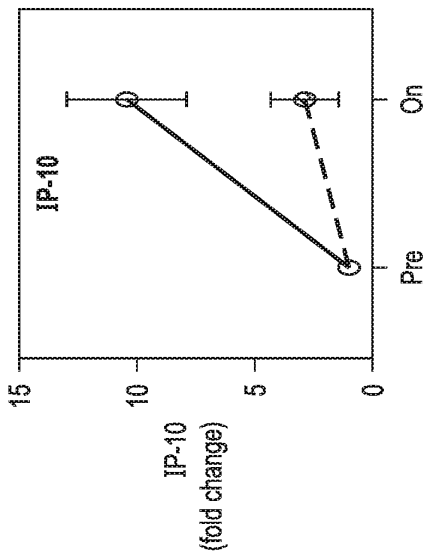


FIG. 22C

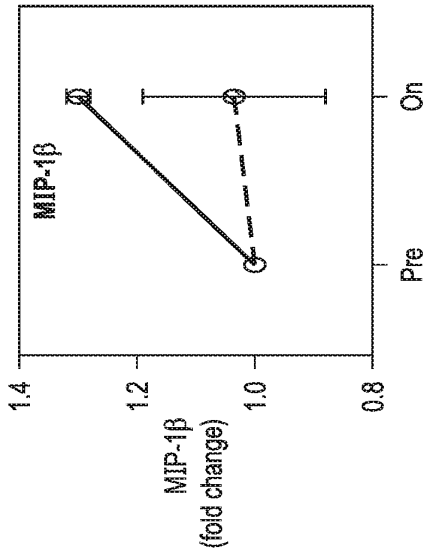
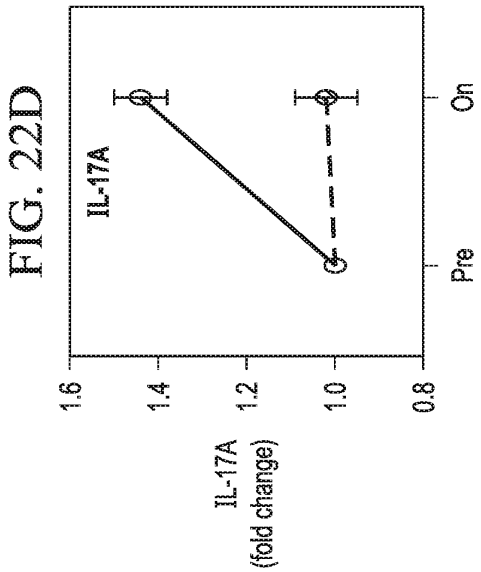


FIG. 22D



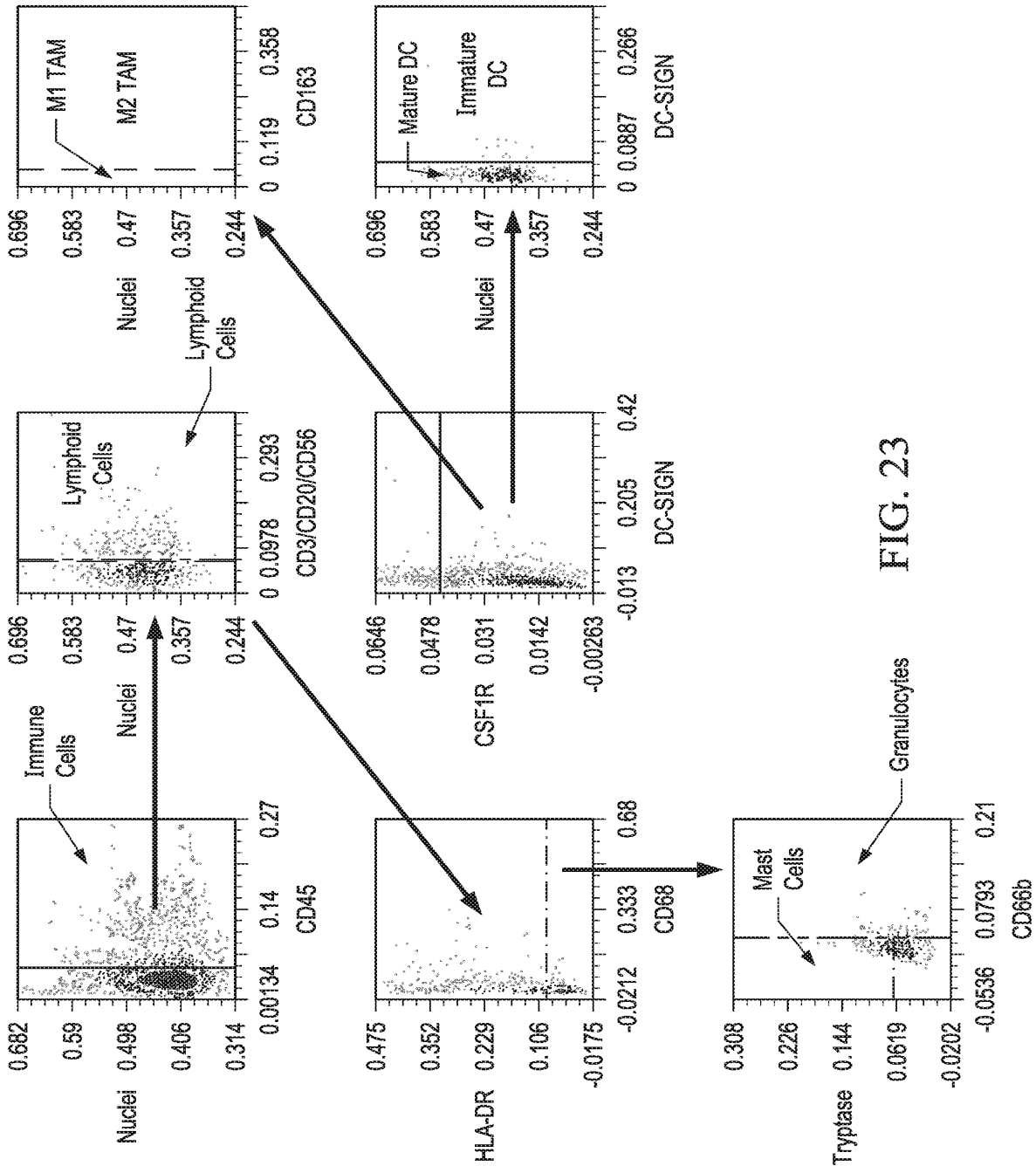

Immune Cells
Nuclei
CD45
Lymphoid Cells
CD3/CD20/CD56
M1 TAM
M2 TAM
CD163
Mature DC
Immature DC
DC-SIGN
CSF1R
DC-SIGN
HLA-DR
CD68
Granulocytes
Mast Cells
Tryptase
CD66b

FIG. 23

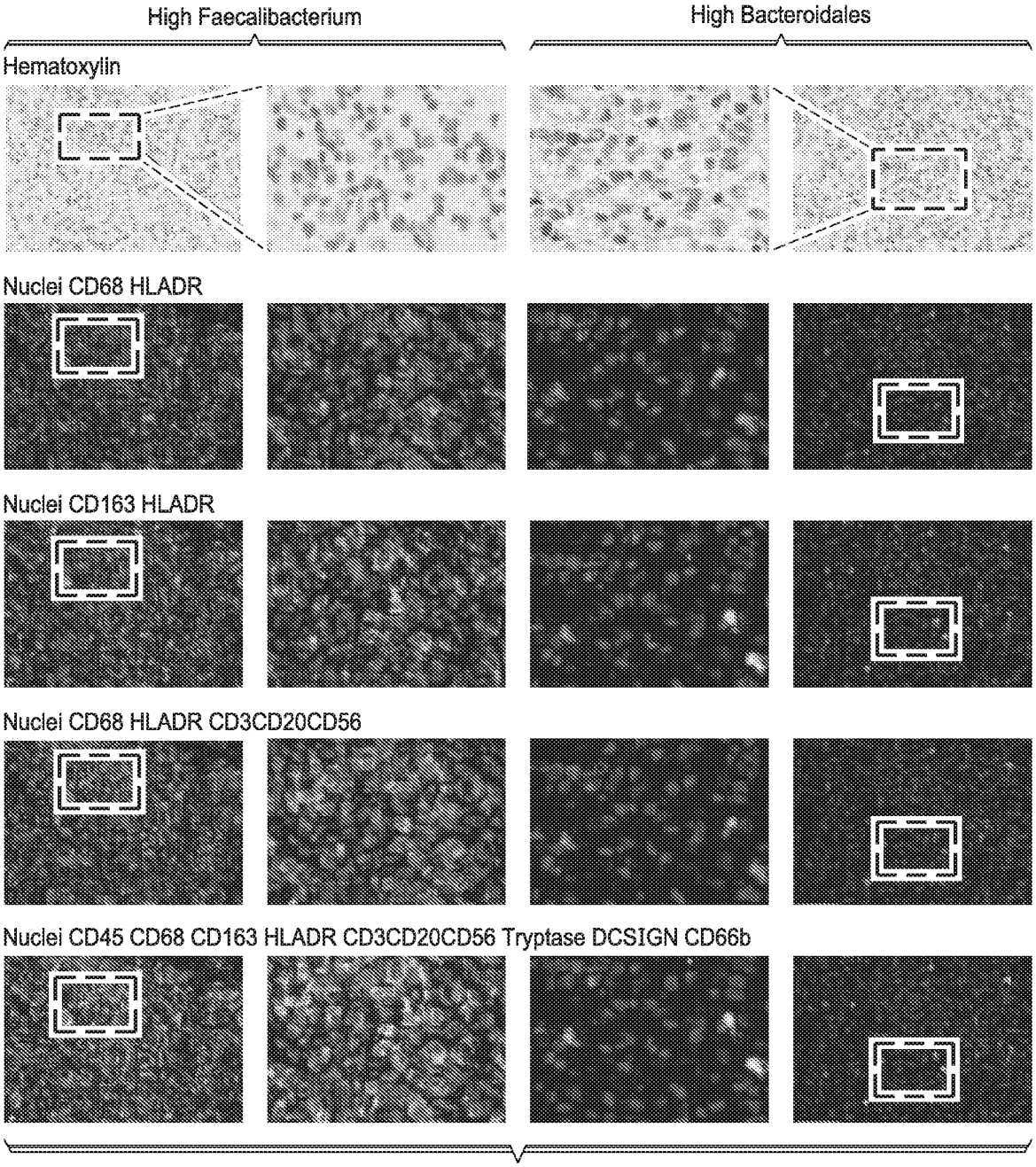

High Faecalibacterium
High Bacteroidales
Hematoxylin
Nuclei CD68 HLADR
Nuclei CD163 HLADR
Nuclei CD68 HLADR CD3CD20CD56
Nuclei CD45 CD68 CD163 HLADR CD3CD20CD56 Tryptase DCSIGN CD66b

FIG. 24A

FIG. 24C

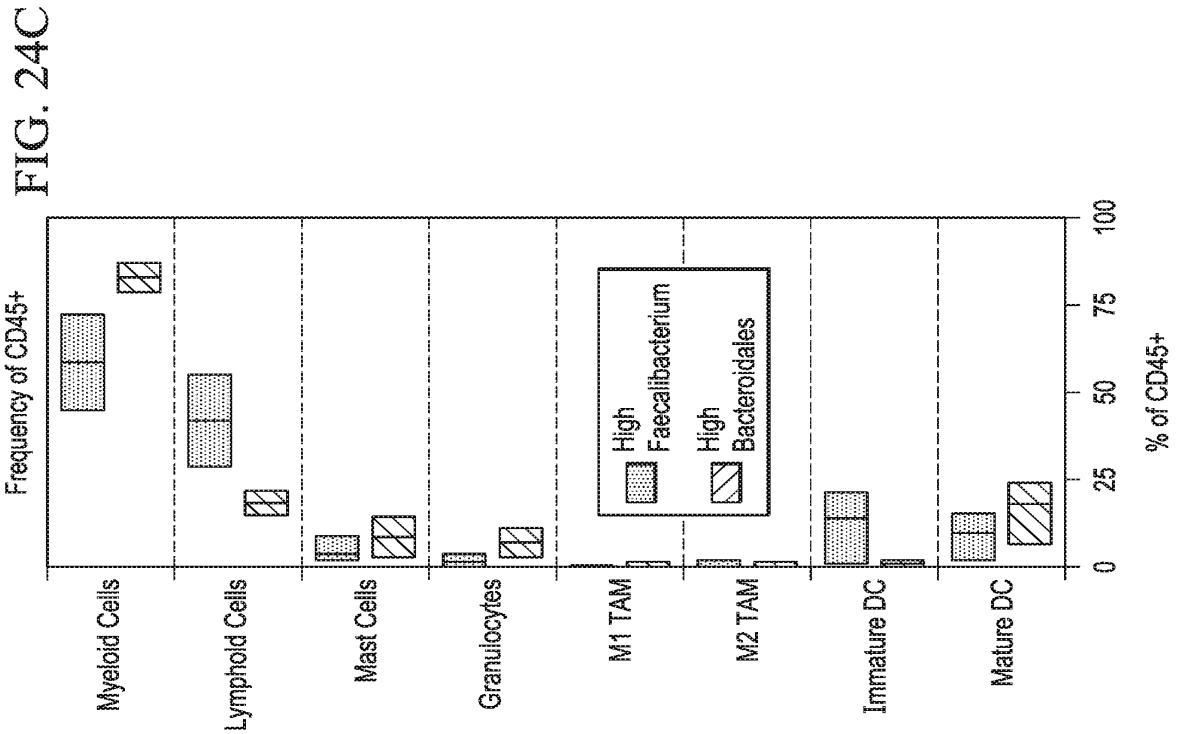
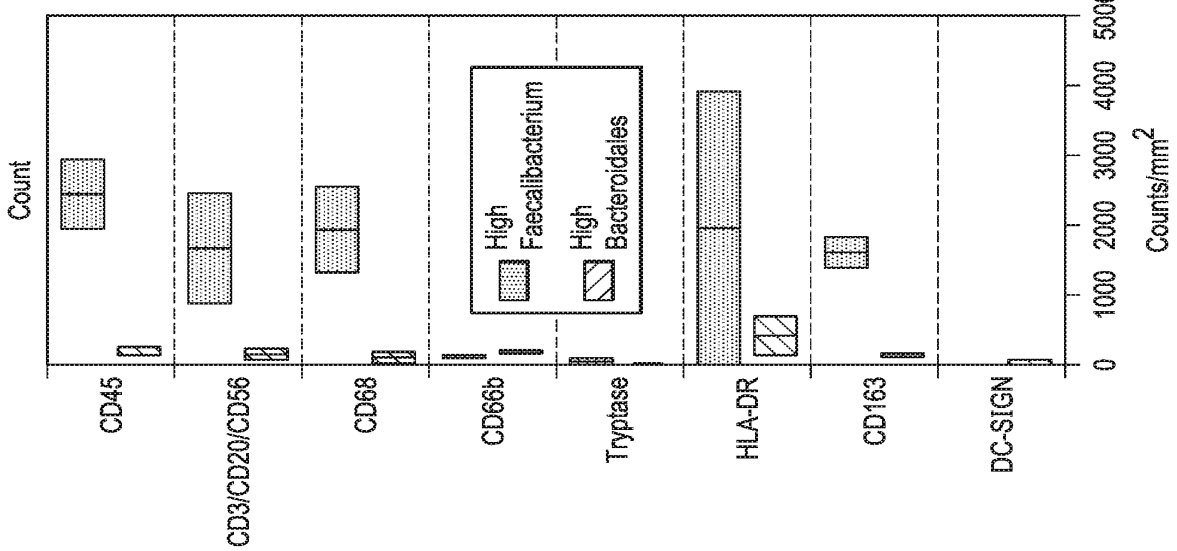


FIG. 24B



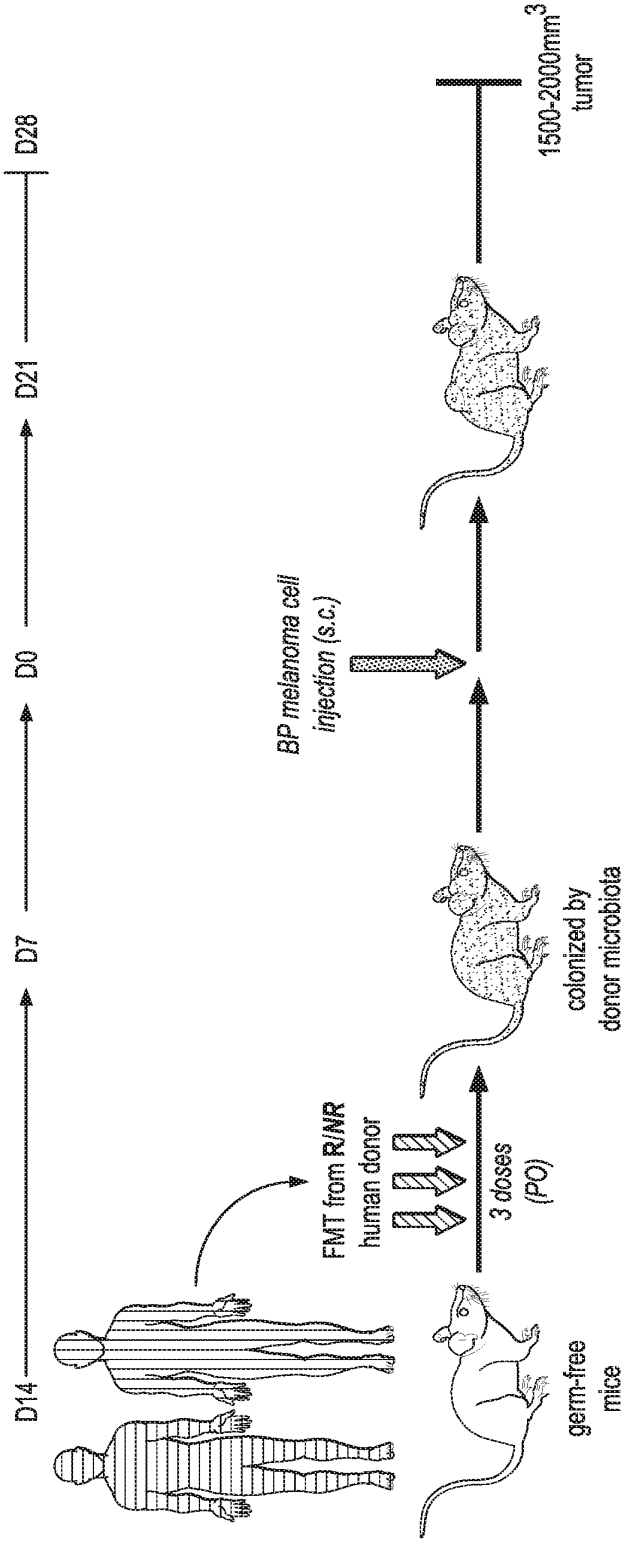

D14
D7
D0
D21
D28
FMT from R/NR human donor
3 doses (PO)
germ-free mice
colonized by donor microbiota
BP melanoma cell injection (s.c.)
1500-2000mm3 tumor

FIG. 25A

FIG. 25B

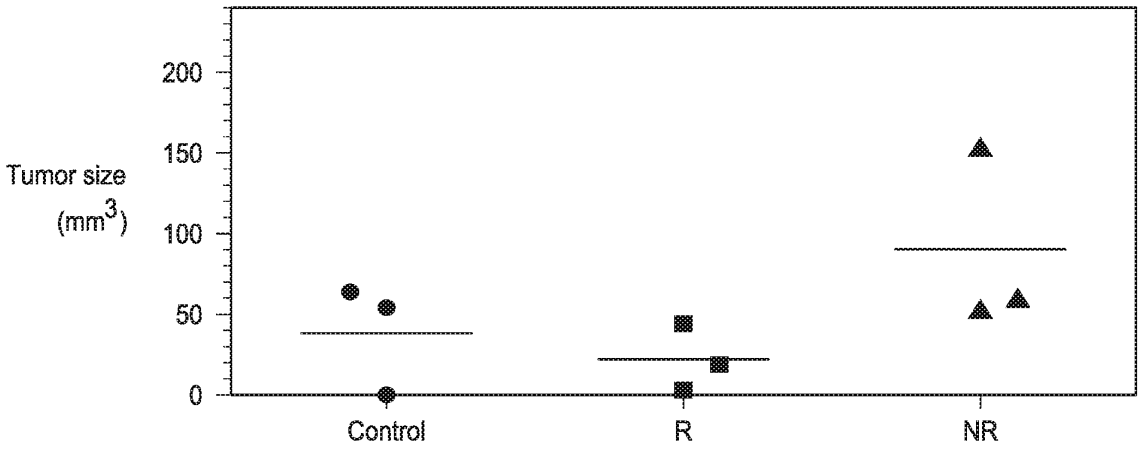


FIG. 26A

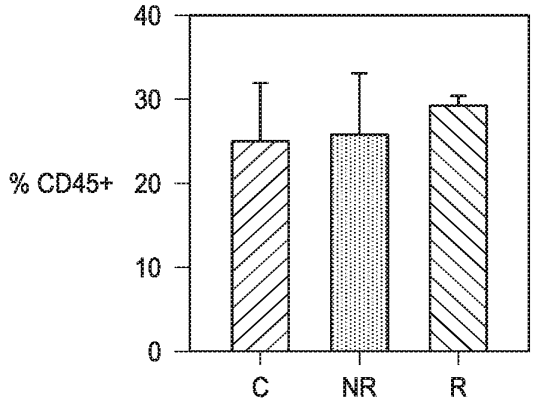


FIG. 26B

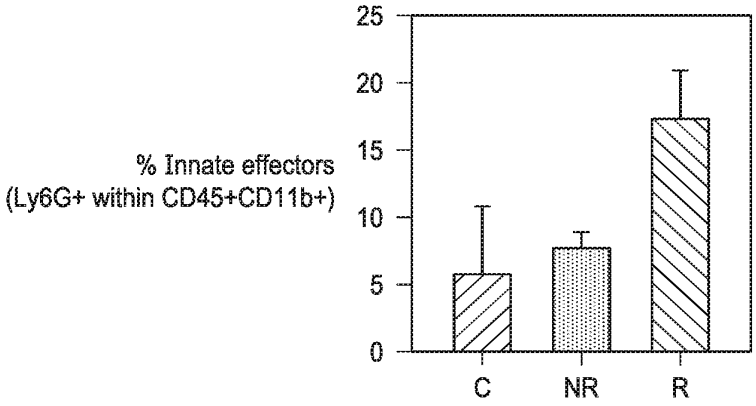
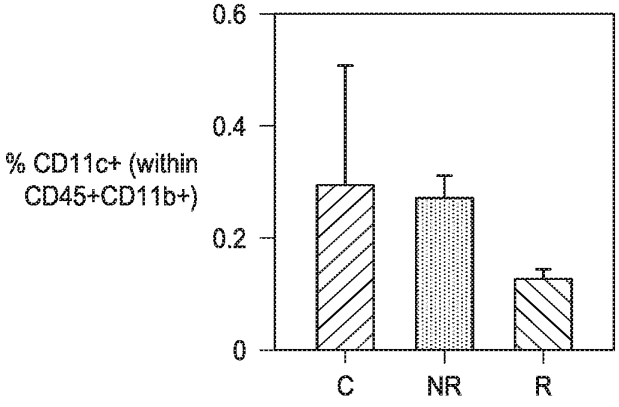


FIG. 26C



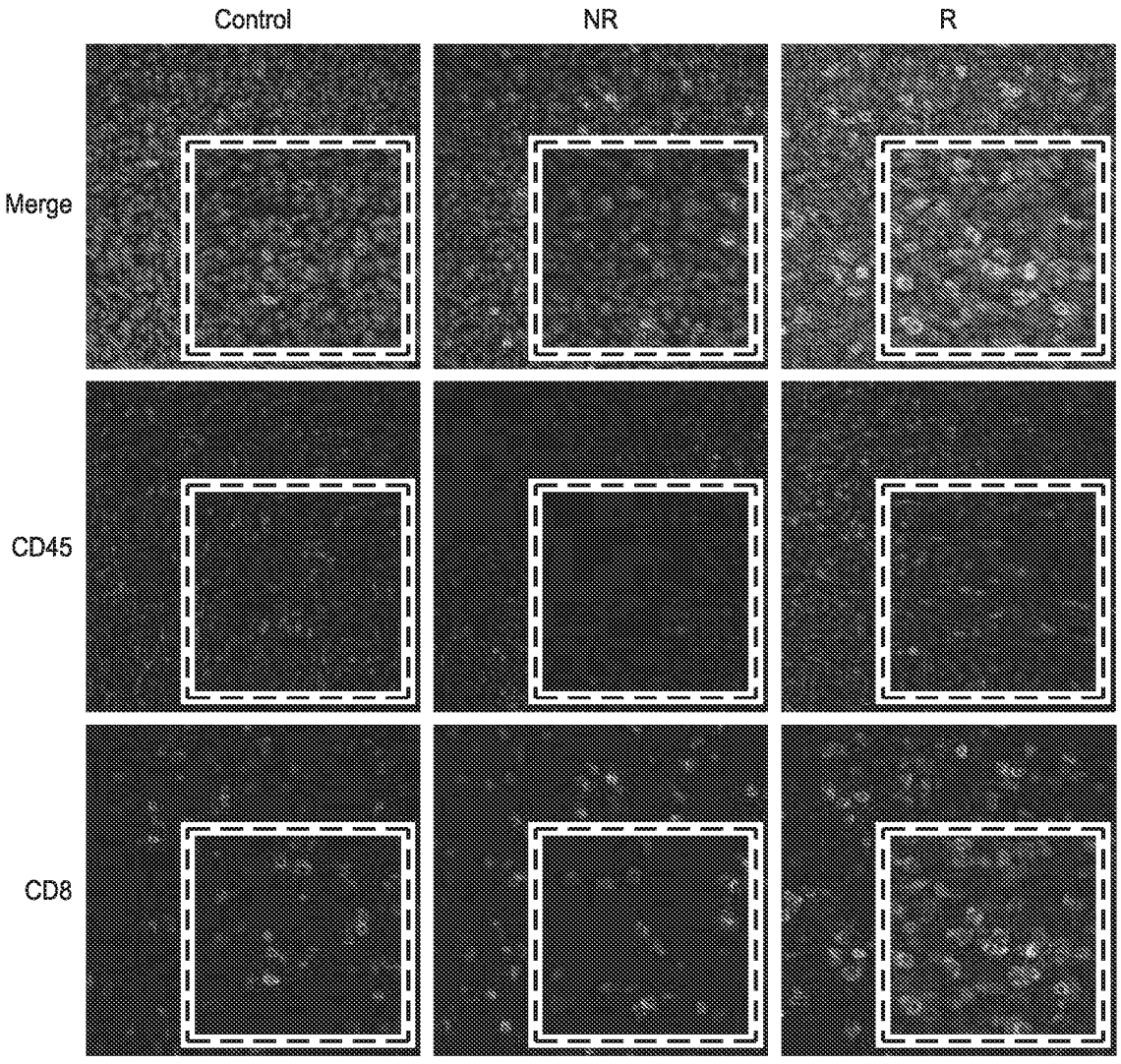


FIG. 27A

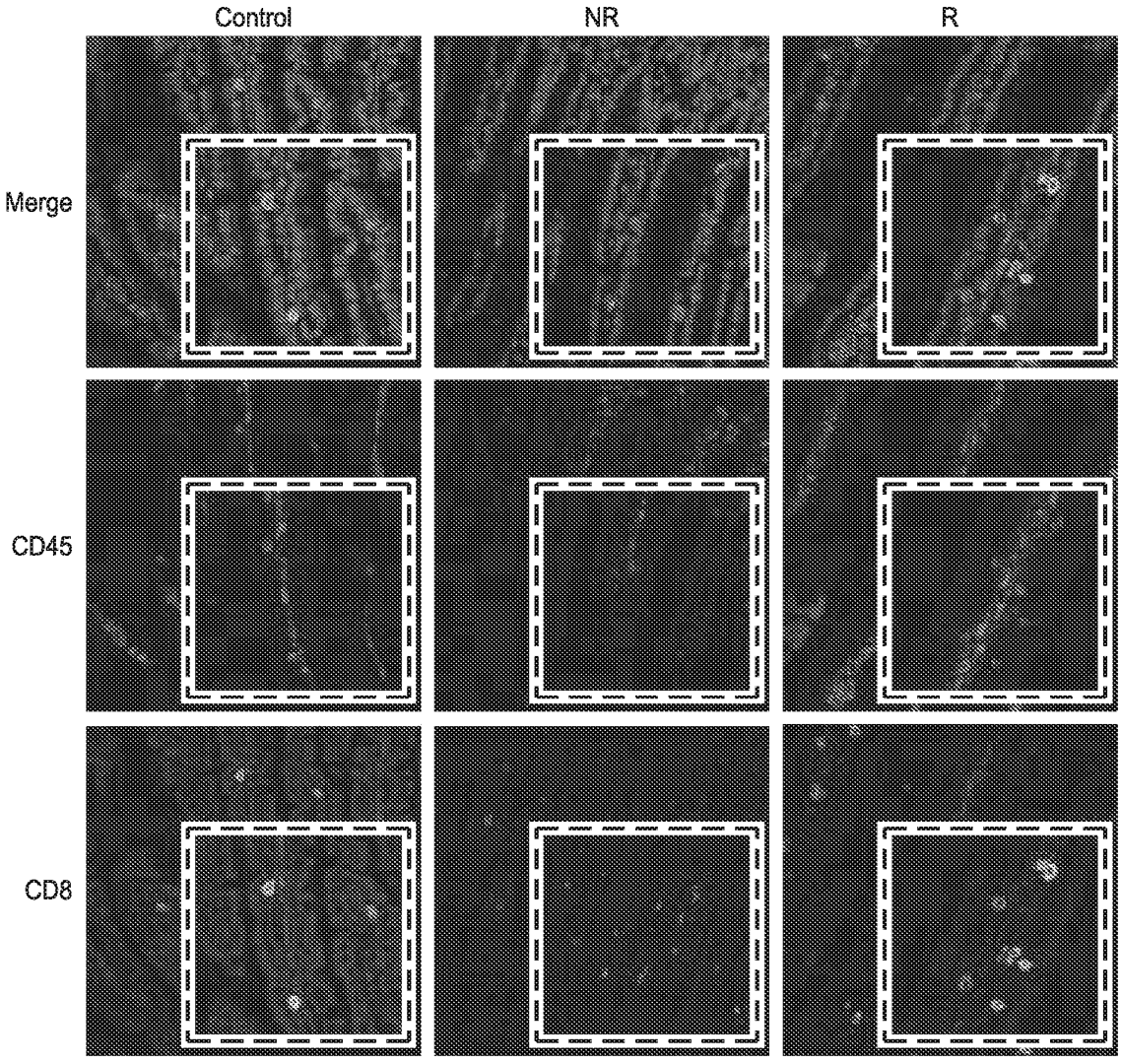


FIG. 27B

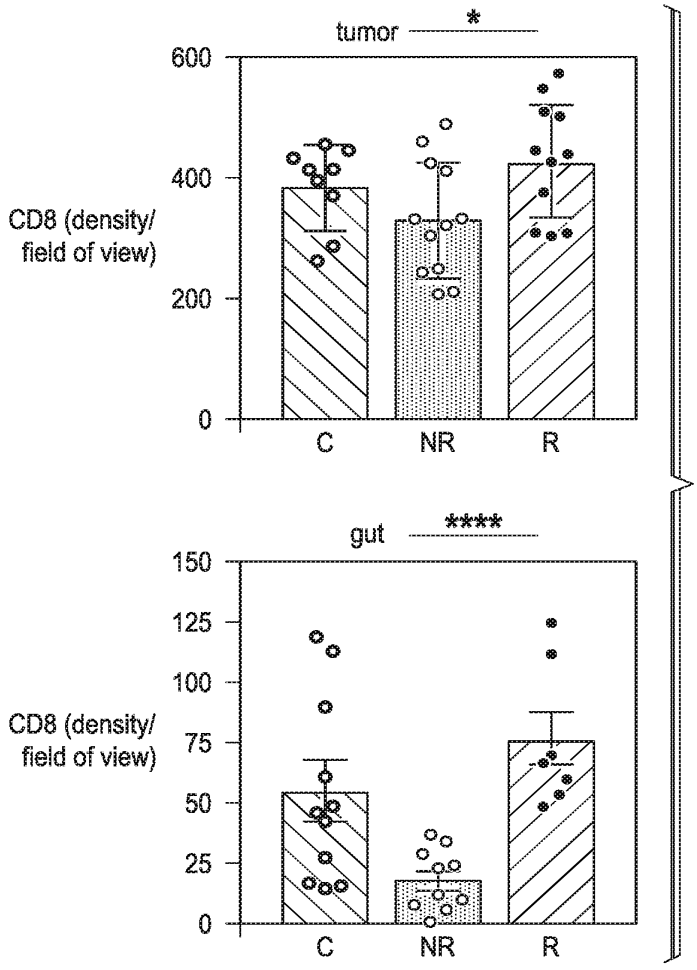

tumor
*
600
400
200
0
CD8 (density/ field of view)
C
NR
R
gut
****
150
125
100
75
50
25
0
CD8 (density/ field of view)
C
NR
R

FIG. 27C

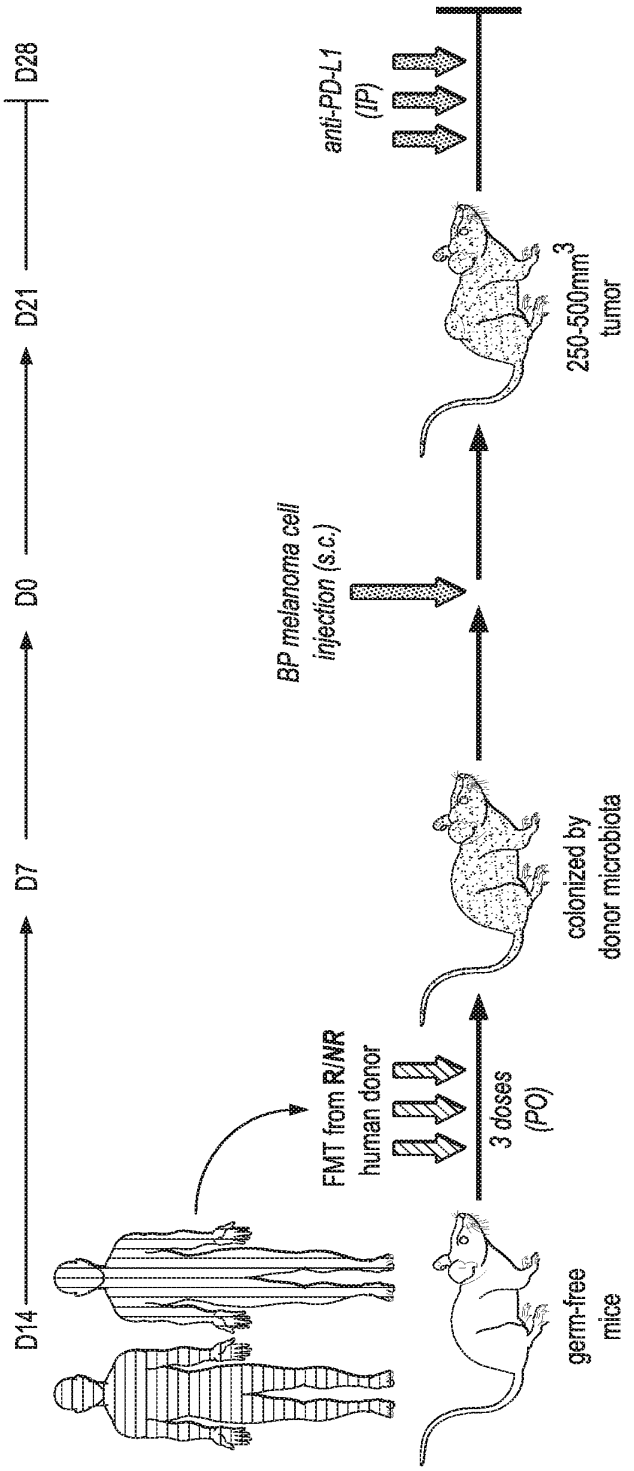

D14
D7
D0
D21
D28
germ-free mice
3 doses (PO)
FMT from R/NR human donor
colonized by donor microbiota
BP melanoma cell injection (s.c.)
250-500mm3 tumor
anti-PD-L1 (IP)

FIG. 28A

FIG. 28B

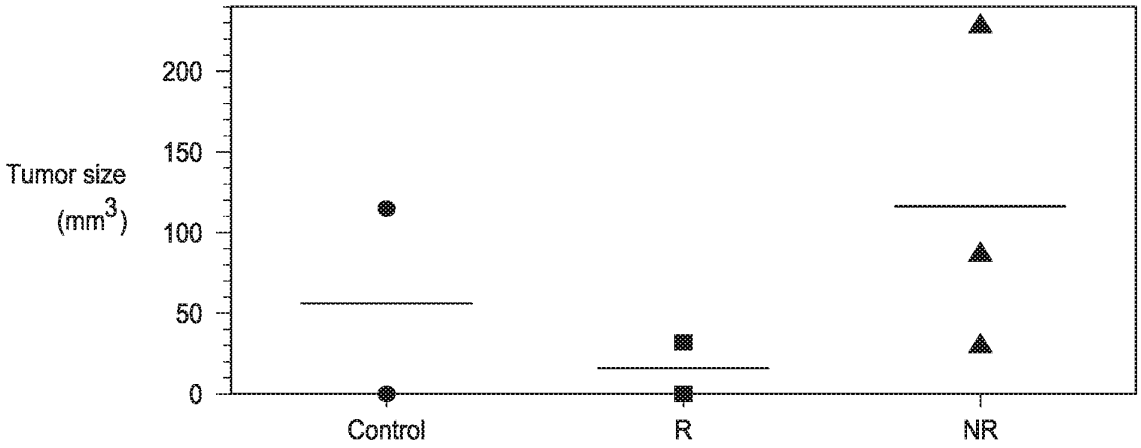


FIG. 28C

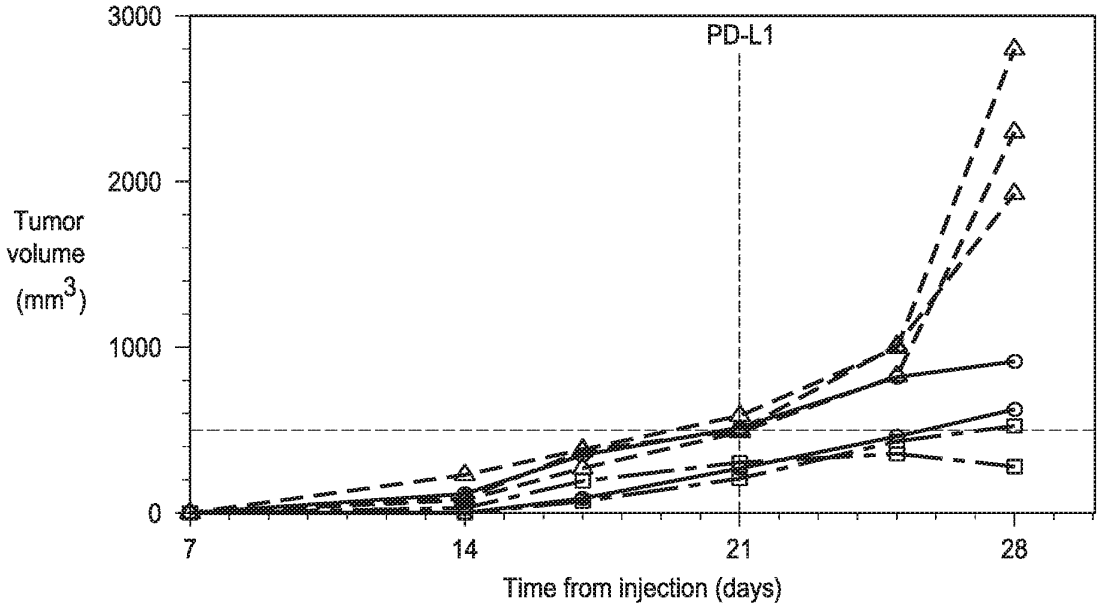


FIG. 29A

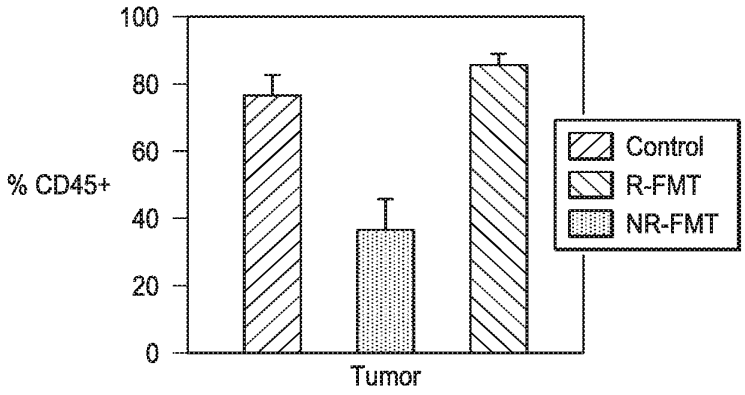


FIG. 29B

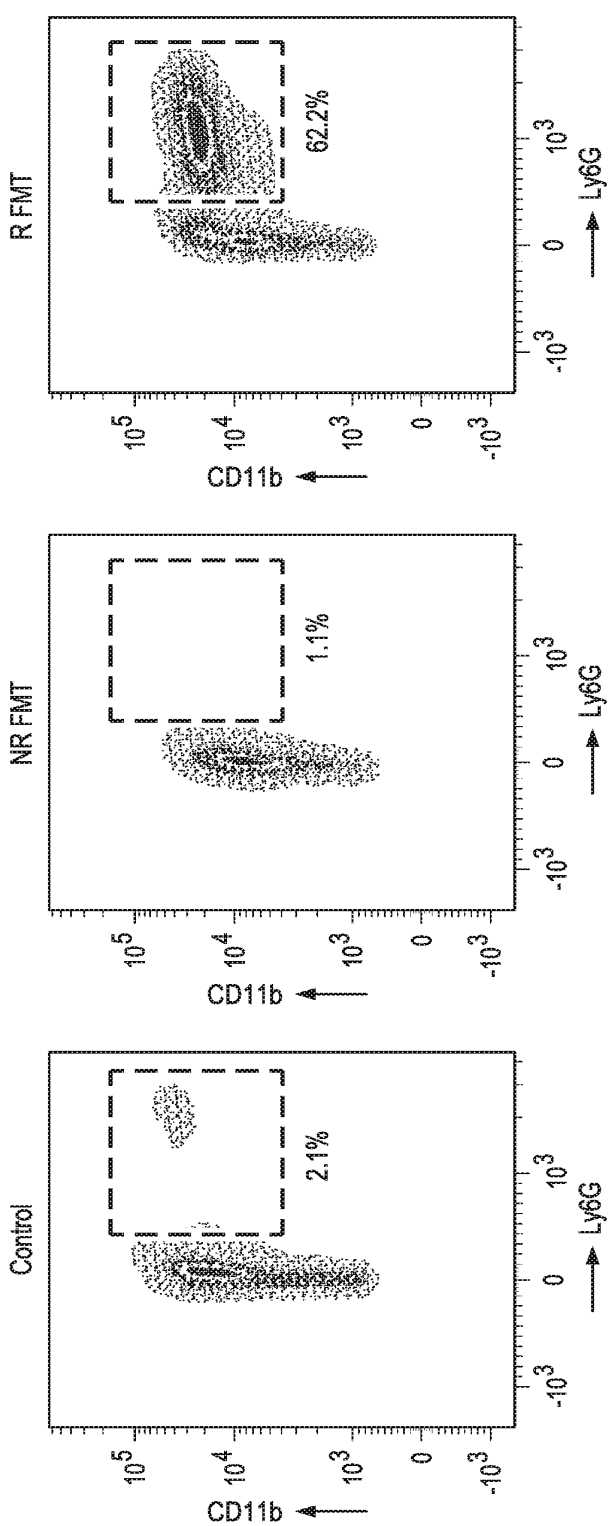
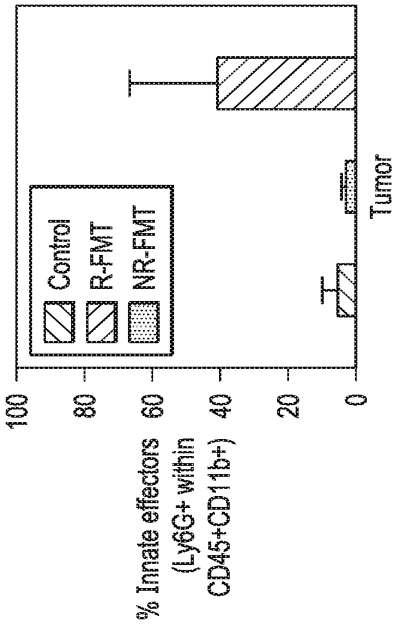


FIG. 29C



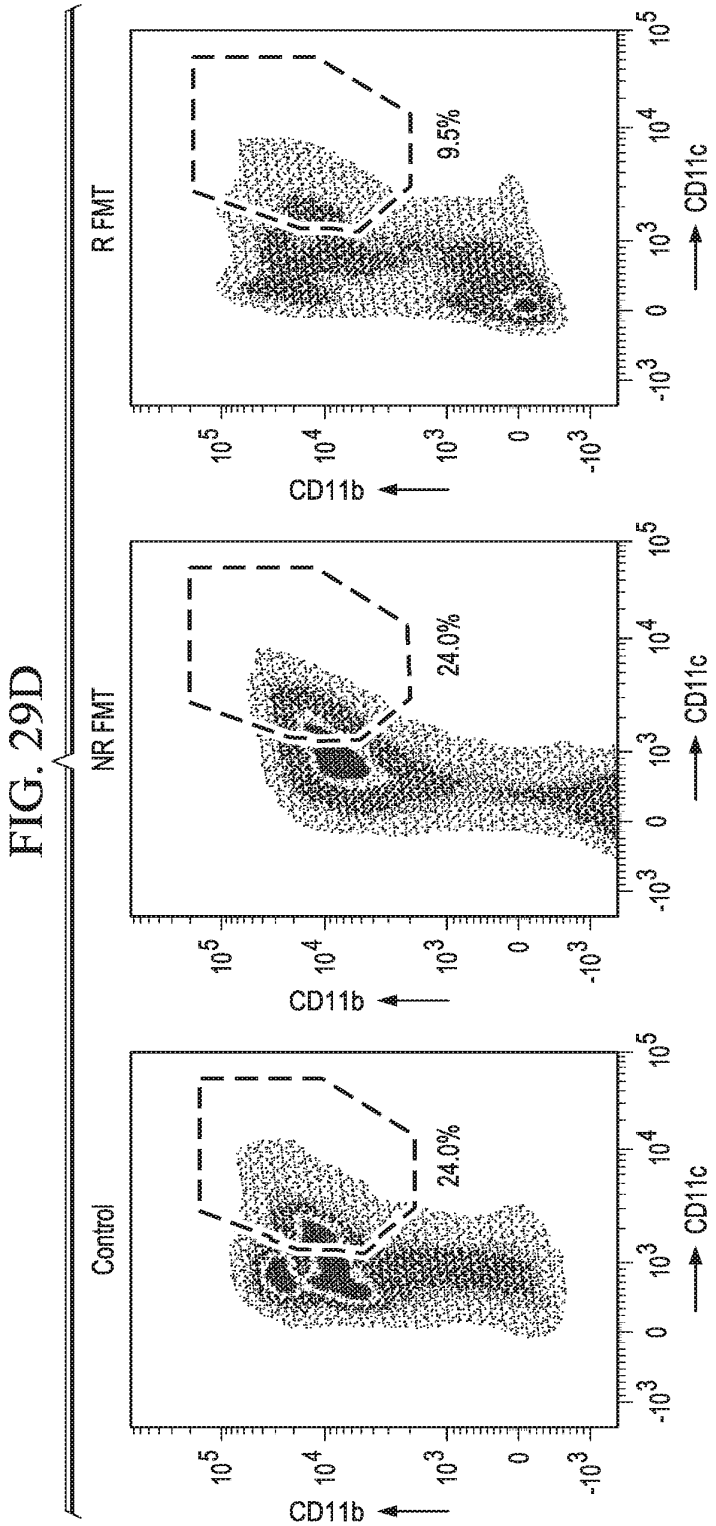


FIG. 29D

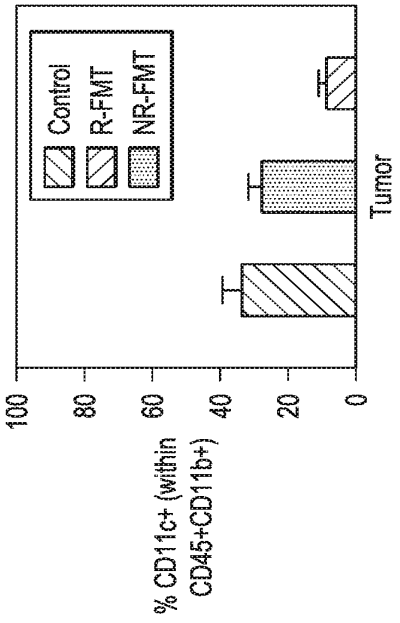


FIG. 29E

FIG. 30A

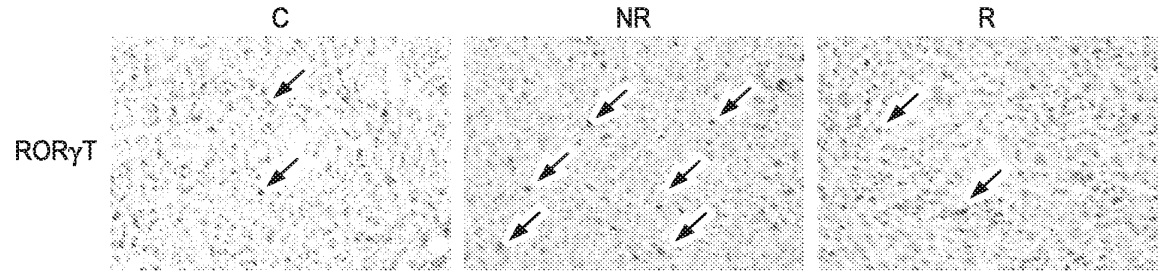


FIG. 30B

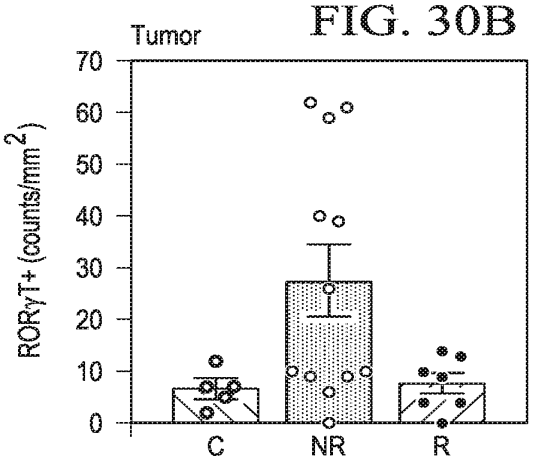


FIG. 30C

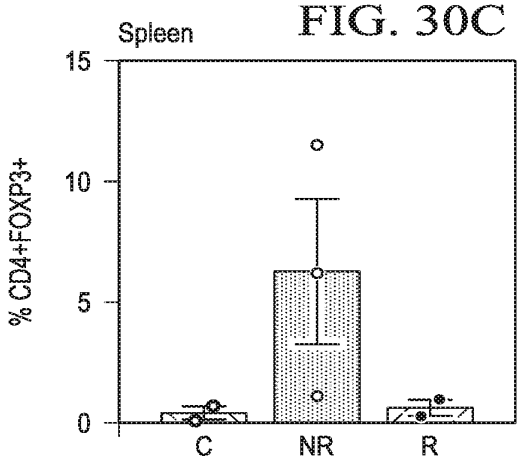
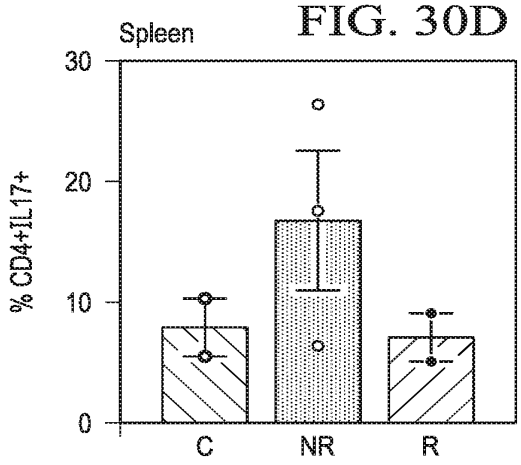


FIG. 30D



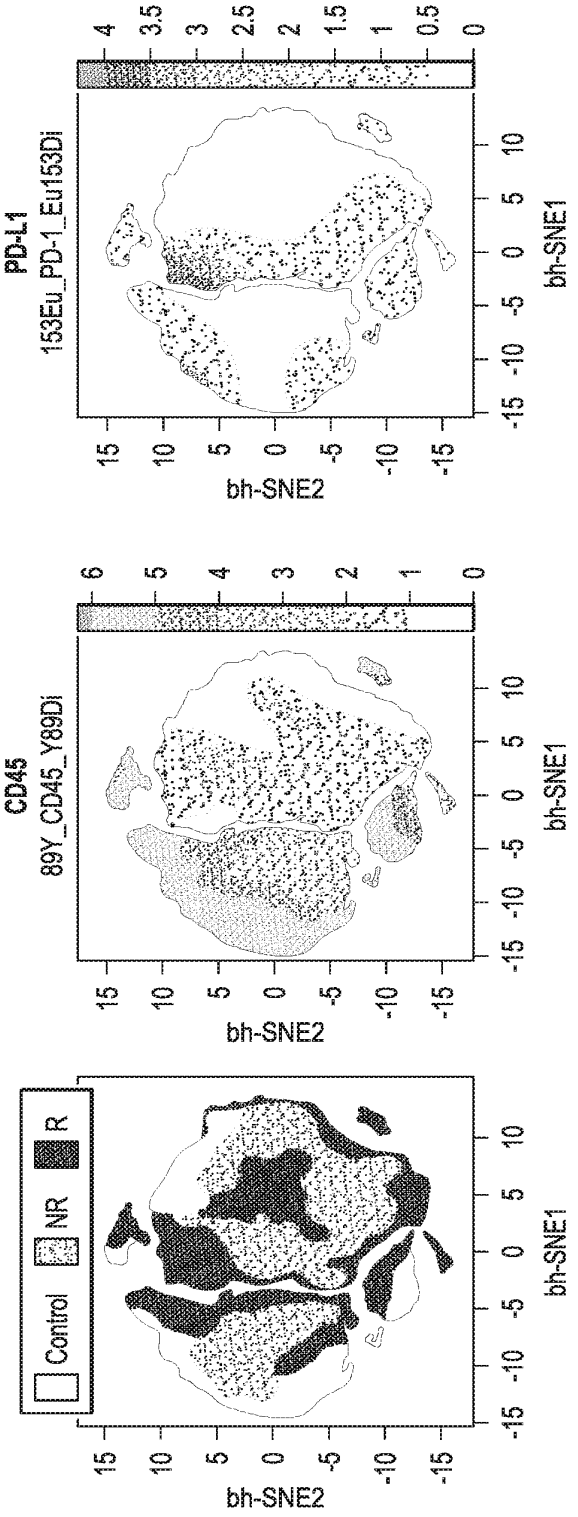

PD-L1
153Eu_PD-1_Eu153Di
CD45
89Y_CD45_Y89Di
Control
NR
R
bh-SNE1
bh-SNE2

FIG. 31A

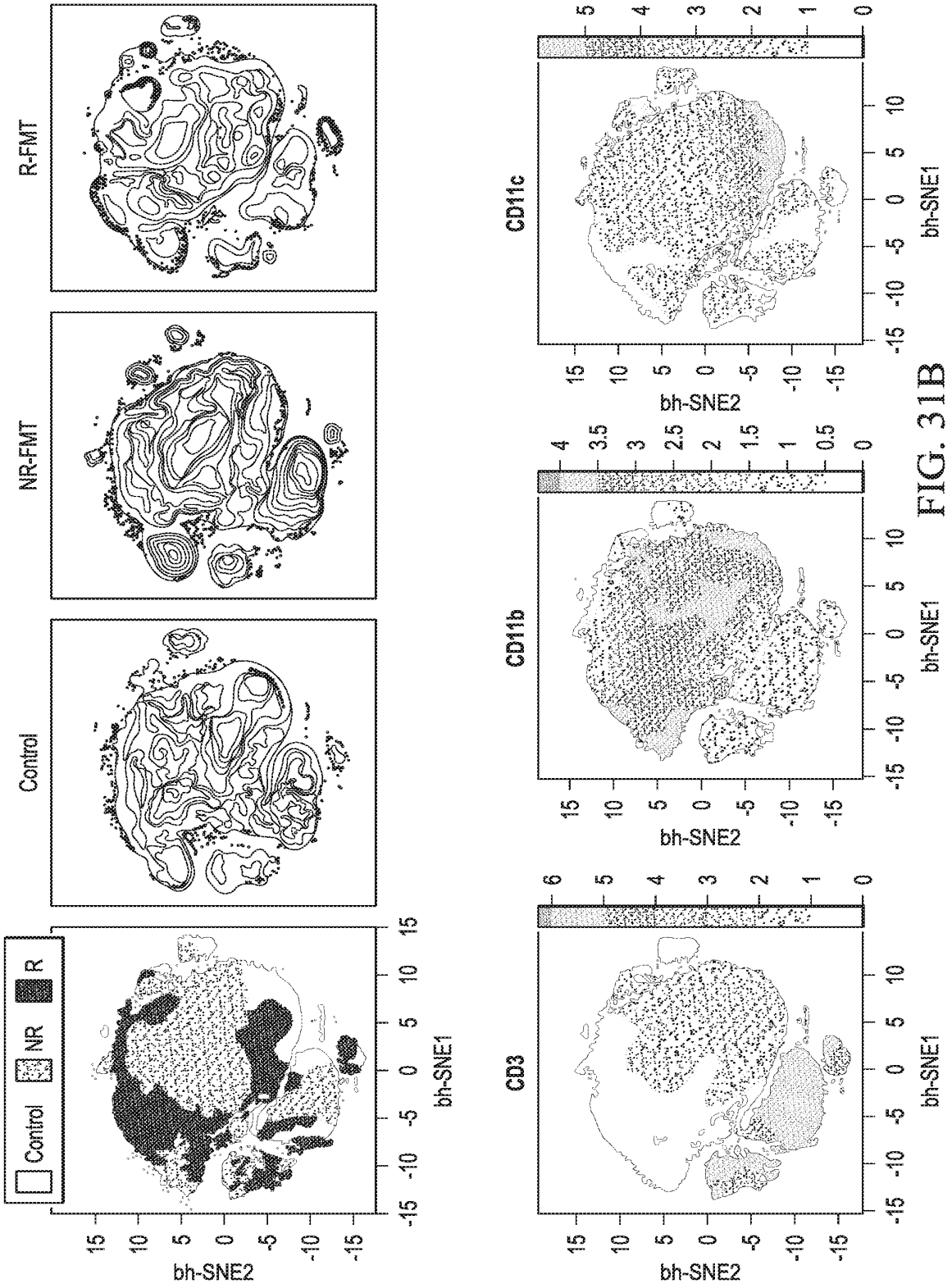

Control
NR
R
Control
NR-FMT
R-FMT
bh-SNE2
bh-SNE1
CD3
CD11b
CD11c

FIG. 31B

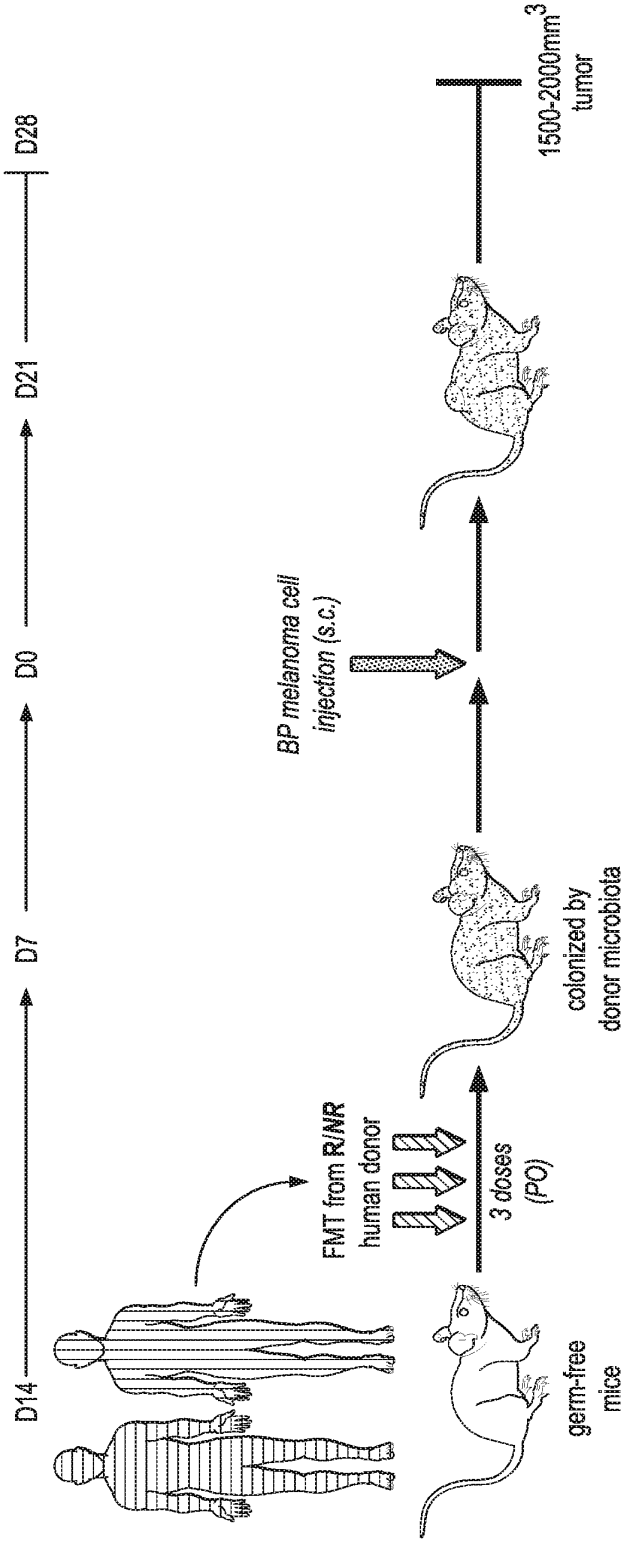

D14
D7
D0
D21
D28
germ-free mice
3 doses (PO)
FMT from R/NR human donor
colonized by donor microbiota
BP melanoma cell injection (s.c.)
1500-2000mm3 tumor

FIG. 32A

FIG. 32B

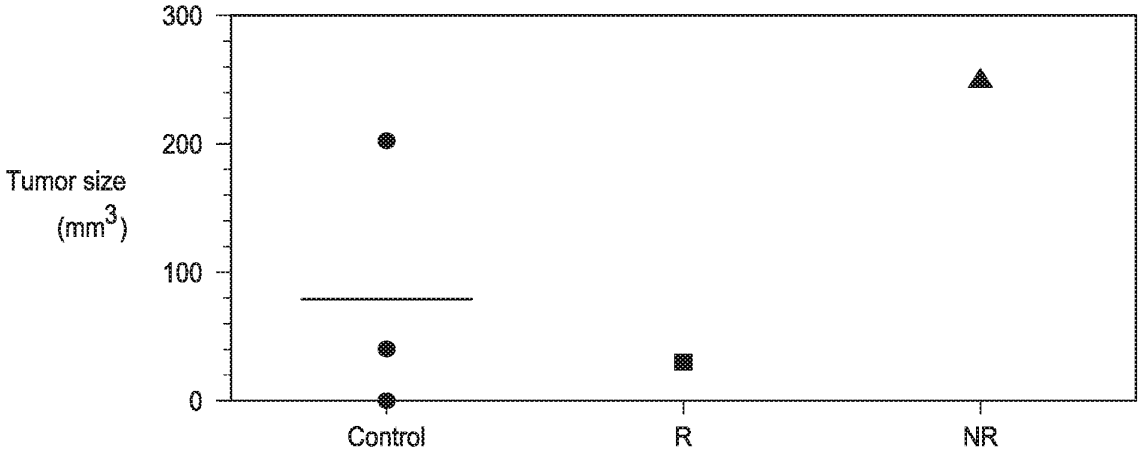


FIG. 32C

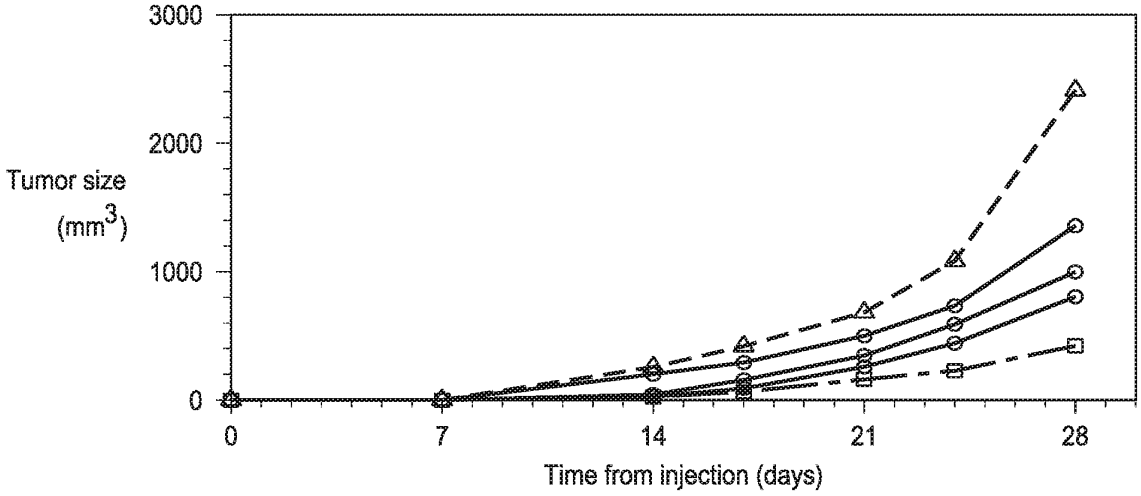


FIG. 33A

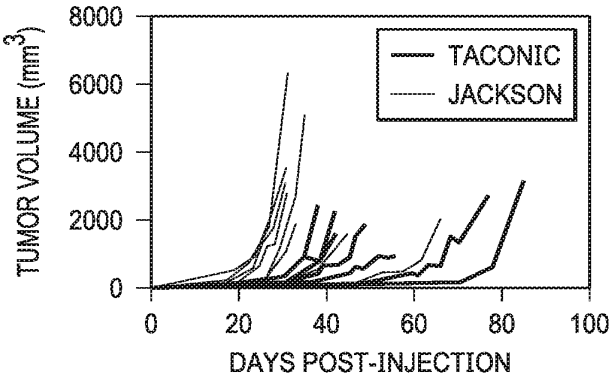


FIG. 33B

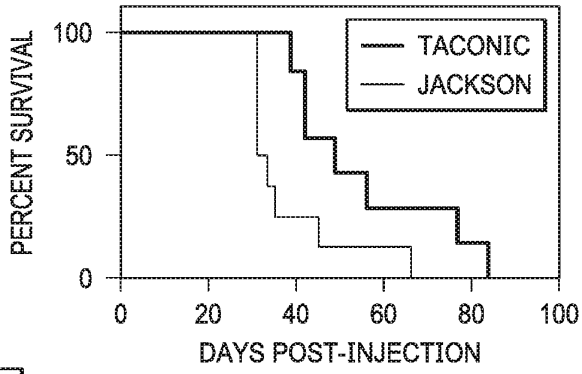


FIG. 33C

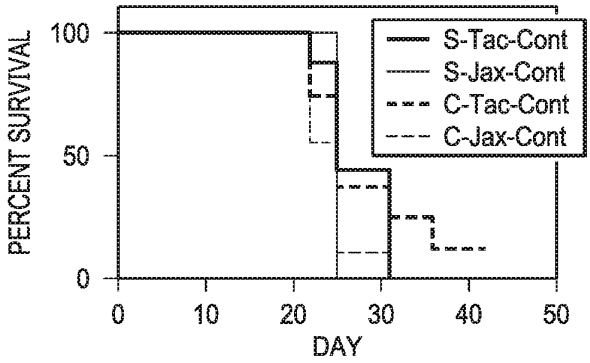


FIG. 33F

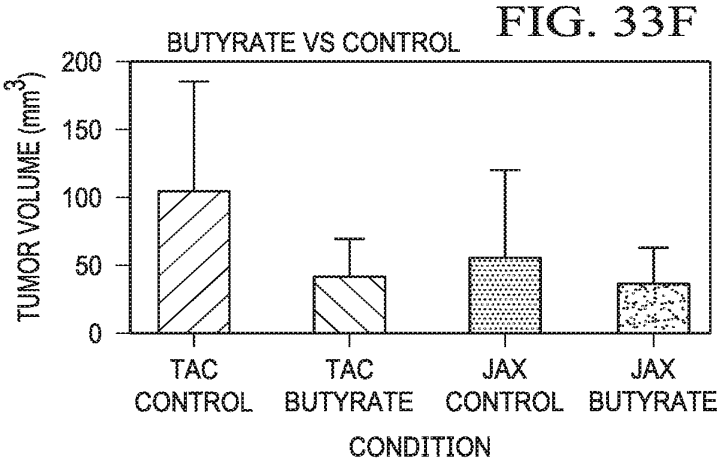
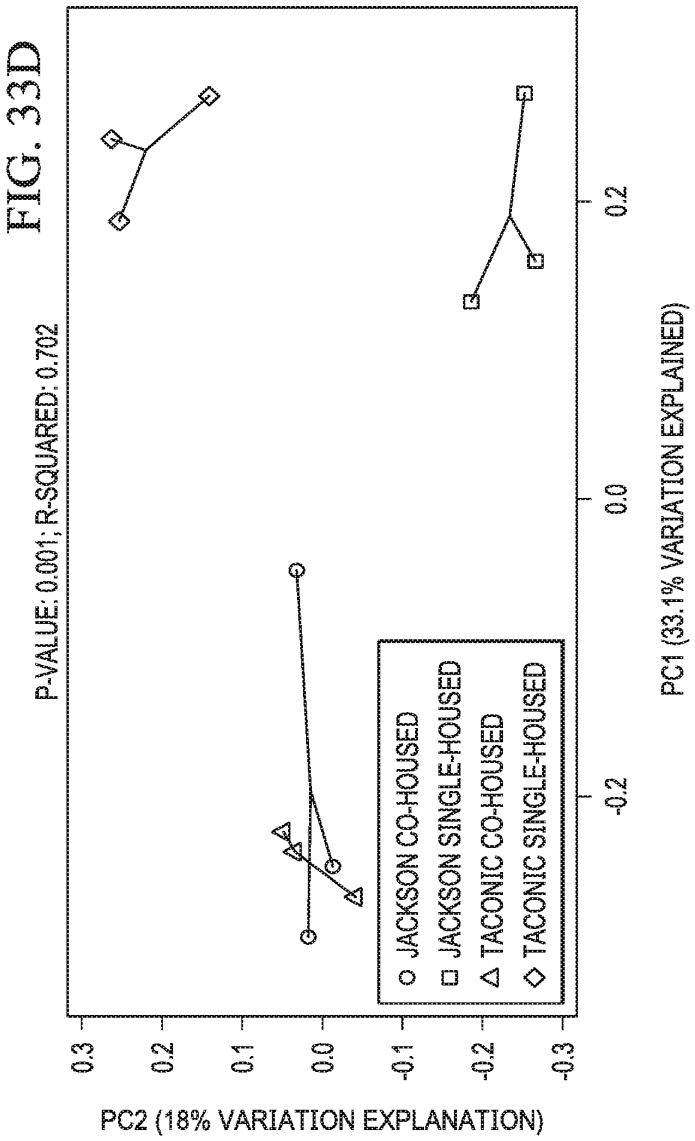


FIG. 33D


P-VALUE: 0.001; R-SQUARED: 0.702
JACKSON CO-HOUSED
JACKSON SINGLE-HOUSED
TACONIC CO-HOUSED
TACONIC SINGLE-HOUSED
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
PC2 (18% VARIATION EXPLANATION)
-0.2
0.0
0.2
PC1 (33.1% VARIATION EXPLAINED)

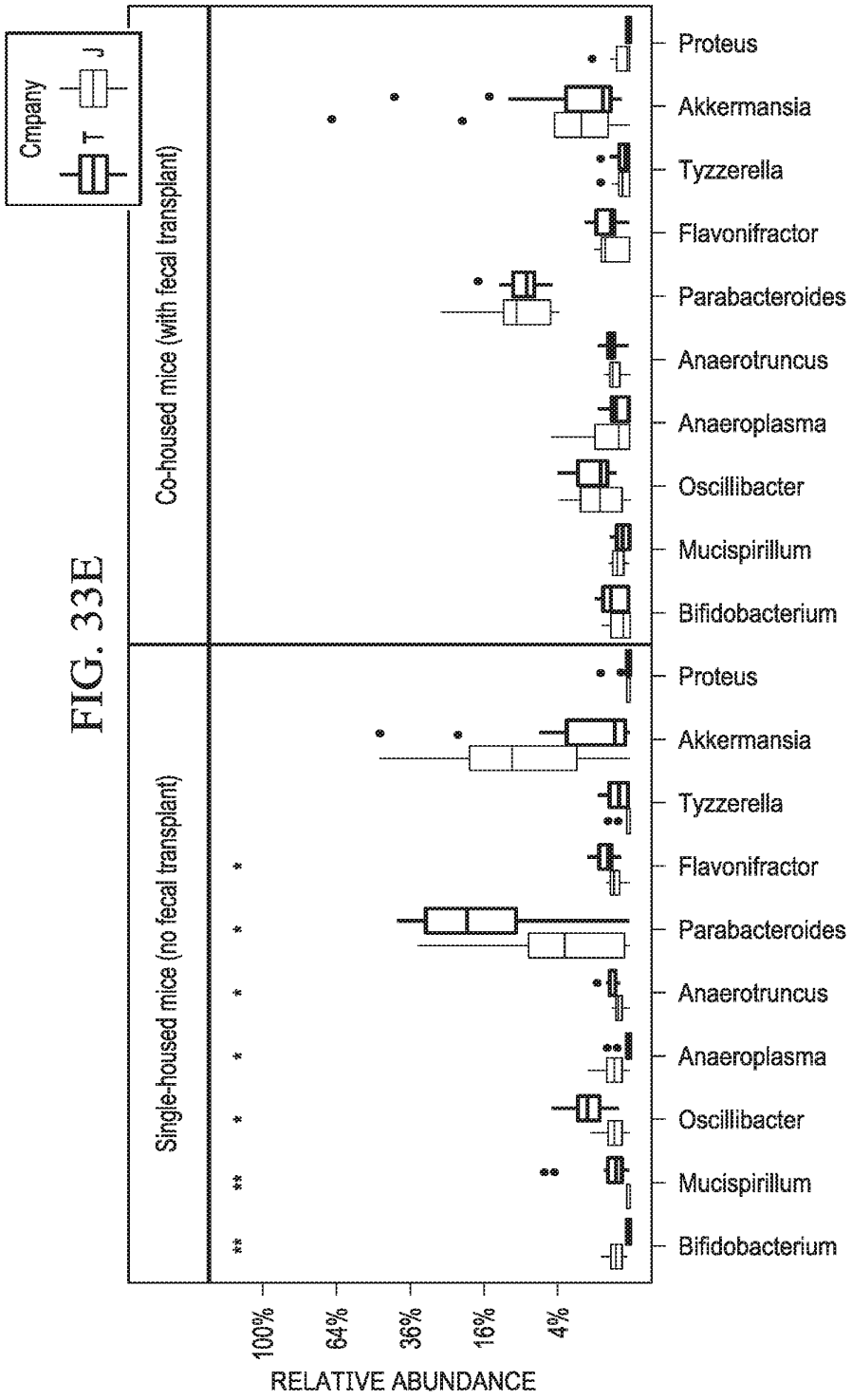

Cmpany
T
J
Co-housed mice (with fecal transplant)
Single-housed mice (no fecal transplant)
Proteus
Akkermansia
Tyzzerella
Flavonifractor
Parabacteroides
Anaerotruncus
Anaeroplasma
Oscillibacter
Mucispirillum
Bifidobacterium
100%
64%
36%
16%
4%
RELATIVE ABUNDANCE

FIG. 33E

FIG. 34A

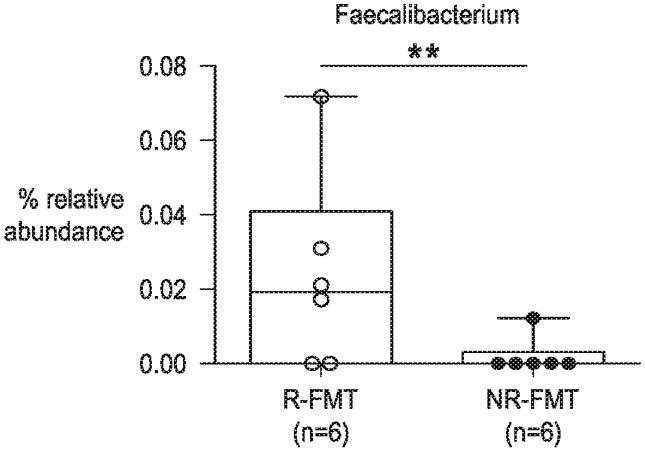


FIG. 34B

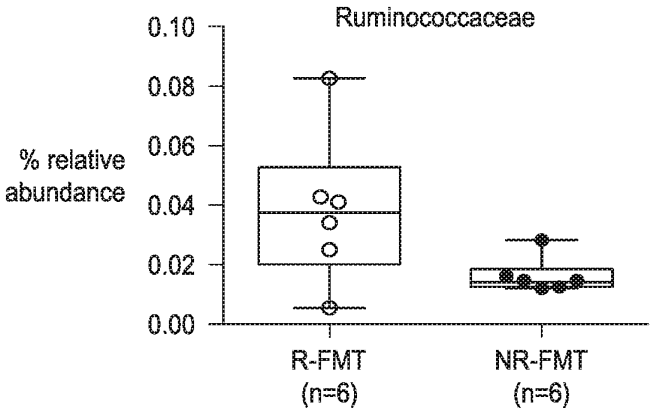
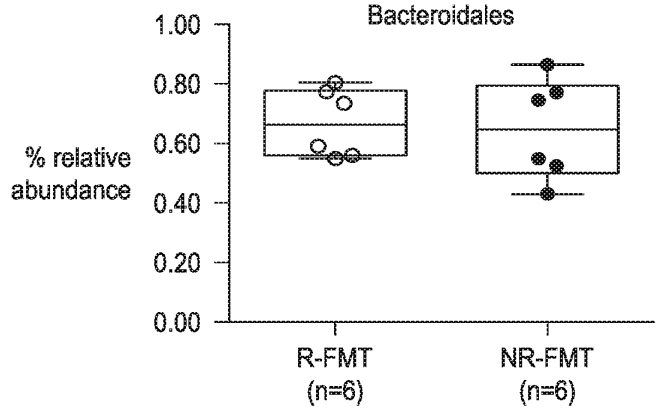


FIG. 34C



CLAIMS

WHAT IS CLAIMED IS:

1. 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. A composition comprising at least two isolated or purified populations of bacteria belonging to one or more of the families Ruminococcaceae, Clostridiaceae, Lachnospiraceae, Micrococcaceae, and/or Veilonellaceae.

3. 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. The compositon of claim 1 or claim 2, wherein the composition is a live bacterial product or a live biotherapeutic product.

5. 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. The compositon of claim 1 or claim 2, wherein the at least one population of bacteria or the at least two isolated or purified populations of bacteria belong to Clostridiales Family XII and/or Clostridiales Family XIII.

7. 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.

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8. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus *Ruminococcus.*

9. 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 the species *Ruminococcus bromii.*

10. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Ruminococcaceae is further defined as a population of bacteria belonging to the genus *Faecalibacterium.*

11. The composition of claim 10, wherein the population of bacteria belonging to the genus *Faecalibacterium* is further defined as a population of bacteria belonging to the species *Faecalibacterium prausnitzii.*

12. The composition of claim 1 or claim 2, wherein the population of bacteria belonging to the family Micrococcaceae is further defined as a population of bacteria belonging to the genus *Rothia.*

13. The composition of claim 1 or claim 2, wherein the composition further comprises a population of bacteria belonging to the species *Porphyromonas pasteri,* the species *Clostridium hungatei,* the species *Phascolarctobacterium faecium,* the genus *Peptoniphilus,* and/or the class Mollicutes.

14. The composition of claim 1 or claim 2, wherein the composition is essentially free of populations of bacteria belonging to the order Bacteroidales.

15. 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 belongs 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.

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16. 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 selected from the group consisting of the species in Table 1 with an "ei" equal to 1.

17. 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 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 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, 1737, 218205, 1121298, 684066, 433659, 52699, 204516, 706562, 253257, 328812, 1280, 147802, 58134, 1335613, 891, 585394, 1582, 235931, 308994, 1589, 1682,

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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.

18. 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% identical to the sequence of SEQ ID NO: 1-876.

19. 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 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*, *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*,

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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*, *Capnocytophaga sputigena*, *Casaltella massiliensis*, *Catabacter hongkongensis*, *Catenibacterium mitsuokai*, *Christensenella minuta*, *Christensenella timonensis*, *Chryseobacterium taklimakanense*, *Citrobacter freundii*,

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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 butyriciproducens*,

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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*

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massiliensis, *Robinsoniella peoriensis*, *Romboutsia timonensis*, *Roseburia faecis*, *Roseburia hominis A2-183*, *Roseburia intestinalis*, *Roseburia inulinivorans DSM 16841*, *Rothia dentocariosa ATCC 17931*, *Ruminiclostridium 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.*

20. 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. 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 species of bacteria are 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.

22. 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 belong to

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species, subspecies or strains comprising nucleotide sequences with at least 80 percent identity to the co-abundance gene group (CAG) sequences 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.

23. 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 selected from the group consisting of species 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, 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

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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.

24. The composition of claim 1 or claim 2, wherein the bacteria are lyophilized or freeze dried.

25. The composition of claim 1 or claim 2, wherein the composition is formulated for oral delivery.

26. The composition of claim 1 or claim 2, wherein the composition formulated for oral delivery is a tablet or capsule.

27. The composition of claim 1 or claim 2, wherein the tablet or capsule comprises an acid-resistant enteric coating.

28. The composition of claim 1 or claim 2, wherein the composition comprising the 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.

29. The composition of claim 1 or claim 2, wherein the composition is lyophilized or is frozen.

30. The composition of claim 1 or claim 2, wherein 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.

31. The composition of claim 1 or claim 2, wherein the composition is formulated for multiple administrations.

32. 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 comprise an antibiotic resistance gene.

33. 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 butyrate-producing populations of bacteria.

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34. The composition of claim 1 or claim 2, further comprising butyrate.

35. A method of treating or preventing cancer in a subject comprising administering to the subject a composition in accordance with any one of claims 1-34.

36. The method of claim 35, wherein the cancer is a skin cancer.

37. The method of claim 35, 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.

38. The method of claim 35, wherein the cancer is melanoma.

39. The method of claim 38, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

40. The method of claim 35, wherein the method further comprises administering at least one additional anticancer treatment.

41. The method of claim 40, 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.

42. The method of claim 41, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

43. The method of claim 40, 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.

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44. 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. The method of claim 44, wherein the cancer is a skin cancer.

46. The method of claim 44, 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.

47. The method of claim 44, wherein the cancer is melanoma.

48. The method of claim 47, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

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

50. 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.

51. The method of claim 50, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

52. 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.

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53. The method of claim 44, defined as method of treating a cancer wherein the subject has a tumor.

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

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

56. The method of claim 55, wherein the T lymphocytes are cytotoxic T lymphocytes.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. The method of claim 62, wherein the innate effector cells are $CD45^+CD11b^+Ly6G^+$ cells.

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64. 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.

65. The method of claim 64, wherein suppressive myeloid cells are $CD45^+CD11b^+CD11c^+$ cells.

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

67. 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 the bacterial populations of the composition of claim 1 or claim 2.

68. The method of claim 67, wherein the cancer is a skin cancer.

69. The method of claim 67, 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.

70. The method of claim 67, wherein the cancer is melanoma.

71. The method of claim 70, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

72. The method of claim 67, wherein the method further comprises administering at least one additional anticancer treatment.

73. 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.

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74. The method of claim 73, wherein the cancer is a skin cancer.

75. The method of claim 73, 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.

76. The method of claim 73, wherein the cancer is melanoma.

77. The method of claim 76, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

78. The method of claim 73, wherein the patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

79. The method of claim 73, wherein the microbial profile is a gut microbial profile.

80. 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 of claim 1 or 2 to said subject, wherein the subject has been administered an immune checkpoint inhibitor.

81. The method of claim 80, further comprising administering at least one immune checkpoint inhibitor.

82. The method of claim 81, wherein more than one checkpoint inhibitor is administered.

83. The method of claim 81, further comprising administering a prebiotic or probiotic.

84. The method of claim 80, wherein the isolated or purified butyrate-producing bacterial population comprises bacteria comprising an antibiotic resistance gene.

85. The method of claim 84, further comprising administering the butyrate-producing bacterial population comprising an antibiotic resistance gene.

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86. The method of claim 85, further comprising administering the antibiotic to which the antibiotic resistance gene confers resistance.

87. The method of claim 80, wherein the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales.

88. The method of claim 87, wherein the one or more bacterial species are from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriaceae.

89. The method of claim 87, 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.*

90. The method of claim 87, wherein the one or more bacterial species is *Faecalibacterium prausnitzii.*

91. The method of claim 80, the butyrate-producing bacterial population does not comprise bacterial species of the family Prevotellaceae.

92. The method of claim 80, wherein administering the butyrate comprises administering a butyrate prodrug or salt.

93. The method of claim 80, wherein administering butyrate comprises administering sodium butyrate, arginine butyrate, ethylbutyryl lactate, tributyrin, 4-phenyl butyrate, pivaloyloxymethyl butyrate (AN-9) or butylidenedi-butyrate (AN-10).

94. The method of claim 80, wherein the butyrate or butyrate-producing bacterial population, are administered orally, rectally, via colonoscopy, sigmoidoscopy, enema or by direct injection.

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95. The method of claim 81, wherein the at least one immune checkpoint inhibitor is administered intravenously, and the butyrate and/or the butyrate-producing bacterial population is administered orally.

96. The method of claim 81, wherein 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.

97. The method of claim 81, wherein the at least one immune checkpoint inhibitor is a human programmed cell death 1 (PD-1) axis-binding antagonist.

98. The method of claim 97, wherein 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.

99. The method of claim 98, wherein the PD-1 axis-binding antagonist is a PD-1-binding antagonist.

100. The method of claim 99, wherein the PD-1-binding antagonist inhibits the binding of PD-1 to PDL1 and/or PDL2.

101. The method of claim 99, wherein the PD-1-binding antagonist is a monoclonal antibody or antigen binding fragment thereof.

102. The method of claim 99, wherein the PD-1-binding antagonist is nivolumab, pembrolizumab, pidillizumab, KEYTRUDA®, AMP-514, REGN2810, CT-011, BMS 936559, MPDL328OA or AMP-224.

103. The method of claim 81, wherein the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody.

104. The method of claim 103, wherein the anti-CTLA-4 antibody is tremelimumab, YERVOY®, or ipilimumab.

105. The method of claim 81, wherein the at least one immune checkpoint inhibitor is an anti-killer-cell immunoglobulin-like receptor (KIR) antibody.

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106. The method of claim 105, wherein the anti-KIR antibody is lirilumab.

107. The method of claim 80, wherein the cancer is a skin cancer.

108. The method of claim 80, 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.

109. The method of claim 80, wherein the cancer is melanoma.

110. The method of claim 108, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

111. The method of claim 80, wherein the method further comprises administering at least one additional anticancer treatment.

112. The method of claim 111, 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.

113. The method of claim 112, wherein the biological therapy is a monoclonal antibody, siRNA, miRNA, antisense oligonucleotide, ribozyme or gene therapy.

114. The method of claim 111, 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.

115. 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.

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116. The method of claim 115, wherein the cancer is a skin cancer.

117. The method of claim 115, 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.

118. The method of claim 115, wherein the cancer is melanoma.

119. The method of claim 118, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

120. The method of claim 115, wherein the method further comprises administering at least one additional anticancer treatment.

121. The method of claim 115, wherein the favorable microbial profile is further defined as having (a) high alpha-diversity of the gut microbiome; (b) a high abundance of butyrate-producing bacteria in the gut microbiome; (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 in the gut microbiome; or (d) one or more of the bacteria species in Table 2 designated with a response status of responder (R) in the gut microbiome.

122. The method of claim 115, wherein the 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.

123. The method of claim 115, wherein the 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.

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124. The method of claim 115, wherein the 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.

125. The method of claim 115, wherein the favorable microbial profile is further defined as a high abundance of butyrate-producing bacteria. the butyrate-producing bacteria comprises one or more species is from the genus *Ruminococcus* or *Faecalibacterium.*

126. The method of claim 115, wherein the subject is determined to comprise a favorable microbial profile or favorable gut microbiome by analyzing the microbiome in a patient sample.

127. The method of claim 115, wherein the patient sample is a fecal sample or buccal sample.

128. The method of claim 115, wherein analyzing comprises performing 16S ribosomal sequencing and/or metagenomics whole genome sequencing.

129. 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. The method of claim 129, wherein the cancer is a skin cancer.

131. The method of claim 129, 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.

132. The method of claim 129, wherein the cancer is melanoma.

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133. The method of claim 132, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

134. The method of claim 129, wherein the patient is administered an immune checkpoint inhibitor if the patient is predicted to have a favorable response to the immune checkpoint inhibitor.

135. The method of claim 134, wherein the patient is administered a second immune checkpoint inhibitor.

136. The method of claim 129, wherein the favorable microbial profile is a favorable gut microbial profile.

137. The method of claim 129, wherein the cancer is skin cancer.

138. The method of claim 137, wherein the skin cancer is melanoma or metastatic melanoma.

139. The method of claim 129, wherein the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

140. The method of claim 129, wherein the butyrate-producing bacterial population comprises one or more bacterial species of the order Clostridiales.

141. The method of claim 140, wherein the one or more species is from the family Ruminococcaceae, Christensenellaceae, Clostridiaceae or Coriobacteriacease.

142. The method of claim 140, wherein 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, Ruminococcus productus, Ruminococcus schinkii, Ruminococcus torques, Subdoligranulum variabile, Butyrivibrio fibrisolvens, Roseburia intestinalis, Anaerostipes caccae, Blautia obeum, Eubacterium nodatum, and Eubacterium oxidoreducens.*

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143. The method of claim 140, wherein the one or more species is *Faecalibacterium prausnitzii.*

144. The method of claim 140, wherein the immune checkpoint inhibitor is an anti-PD1 monoclonal antibody or an anti-CTLA4 monoclonal antibody.

145. The method of claim 140, further comprising administering at least one additional anticancer treatment.

146. The method of claim 145, 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.

147. The method of claim 145, wherein the at least one additional anticancer treatment is butyrate and/or a butyrate-producing bacterial population.

148. The method of claim 145, further comprising administering a prebiotic or probiotic composition.

149. The method of claim 148, wherein probiotic composition is the composition of claim 1 or claim 2.

150. 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 butyrate-producing bacteria; or (b) one 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.

151. The method of claim 150, further comprising administering to the patient a probiotic composition of claim 1 or claim 2 if the patient is predicted to not have a favorable response to the immune checkpoint inhibitor.

152. The method of claim 151, wherein a patient predicted to not have a favorable response to an immune checkpoint inhibitor is administered an immune checkpoint inhibitor after administration of the composition of claim 1 or claim 2.

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153. The method of claim 150, further comprising administering at least one non-immune checkpoint inhibitor additional anticancer treatment to the subject predicted to not have a favorable response to the immune checkpoint inhibitor.

154. The method of claim 153, wherein 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.

155. The method of claim 153, wherein the at least one additional anticancer treatment is butyrate and/or a butyrate-producing bacterial population.

156. The method of claim 153, wherein the anti-cancer therapy is a prebiotic or probiotic.

157. The method of claim 156, wherein the probiotic is a composition of claim 1 or claim 2.

158. The method of claim 150, wherein the cancer is skin cancer.

159. The method of claim 158, wherein the skin cancer is melanoma.

160. The method of claim 150, 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 carcinoma, microcystic adnexal carcinoma, Paget's disease of the breast, atypical fibroxanthoma, leiomyosarcoma, or angiosarcoma.

161. The method of claim 159, wherein the melanoma is metastatic melanoma, Lentigo Maligna, Lentigo Maligna Melanoma, Superficial Spreading Melanoma, Nodular Melanoma, Acral Lentiginous Melanoma or Desmoplastic Melanoma.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US17/53717
International Application No.

27 September 2017 (27.09.2017)
International Filing Date

RO/US
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* UTFC.P1305WO

Box No. I TITLE OF INVENTION

METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Board of Regents, The University of Texas System
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Austin, TX 78701
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Telephone No.

Facsimile No.

Applicant's registration No. with the Office

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☒ all designated States ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send, notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or ☒ exclusively in electronic form (no paper notifications will be sent).

E-mail address: docket@phiplaw.com

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a) the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ JP Japan **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM AND DOCUMENT

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 27 September 2016 27.09.2016	62/400.372	US		
item (2) 19 May 2017 19.05.2017	62/508.885	US		
item (3) 12 September 2017 12.09.2017	62/557.566	US		

☐ Further priority claims are indicated in the Supplemental Box.

Furnishing the priority document(s):

☒ The **receiving Office** is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application(s) was filed with the receiving Office which, for the purposes of this international application, is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

☒ The **International Bureau** is requested to obtain from a digital library a certified copy of the earlier application(s) identified above, using, where applicable, the access code(s) indicated below *(if the earlier application(s) is available to it from a digital library)*:

☒ item (1) access code 5607 ☒ item (2) access code 1057 ☒ item (3) access code 1063 ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information **must** be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA/ US

Continuation of Box No. VII USE OF EARLIER SEARCH AND CLASSIFICATION RESULTS

1. Request by the applicant under Rule 4.12

1.1 ☐ The ISA indicated in Box No. VII **is requested to take into** account **the results of the earlier search(es)** indicated below (*see also Notes to Continuation of Box No. VII, item 1; use of results of more than one earlier search*)

Filing date *(day/month/year)*	Application Number	Country *(or regional Office)*

☐ **Statement (Rule 4.12(ii)):** this international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.

1.2 **Submission of the earlier search results, where necessary***

☐ **Availability of documents (Rules 12*bis*.1(c) and (d) and 12*bis*.2(b)):** the following documents **are available to the ISA** in a form and a manner acceptable to it, and therefore **DO NOT need** to be submitted by the applicant to the receiving Office, or to the ISA.

- ☐ a copy of the results of the earlier search,
- ☐ a copy of the earlier application,
- ☐ a translation of the earlier application into a language which is accepted by the ISA,
- ☐ a translation of the results of the earlier search into a language which is accepted by the ISA,
- ☐ a copy of any document cited in the earlier search results *(if known, please indicate below the documents available to the ISA)*:

☐ **Request from the applicant to the receiving Office to transmit to the ISA a copy of the earlier search results (Rule 12*bis*.1(b) and (d))**: (*where the earlier search **was not** carried out by the ISA indicated in Box No. VII **but** by the **same Office** as that which is acting as receiving Office; or where the earlier search results are otherwise **available** to the receiving Office*): the applicant **requests** the receiving Office **to prepare and transmit** to the ISA a copy of the earlier search results.

* The applicant **only** needs to furnish a copy of the earlier search results to the receiving Office, or the ISA, if none of the scenarios mentioned under item 1 applies. (*See item 10 in the check-list and also Notes to Continuation of Box No. VII, item 1*).

☐ Further earlier searches are indicated on a continuation sheet.

2. Transmission of the earlier search and classification results to the ISA by the receiving Office where the applicant DID NOT make a request under Rule 4.12

2.1 Where the international application claims priority of an earlier application, subject to Article 30(2)(a) and (3), **the receiving Office**:

- **shall transmit** a copy of the earlier search and classification results to the ISA (unless such copy is already available to the ISA), where the earlier application was filed with the **same Office** as that which is acting as **the receiving Office and** that Office **has carried out** the earlier search in respect of the earlier application (Rule 23*bis*.2(a));
- **may transmit** such a copy if the earlier application was filed with a different Office, but where the results of that earlier search and classification are nevertheless available to the receiving Office (Rule 23*bis*.2(c)).

However, where the applicant did not request the receiving Office to transmit to the ISA a copy of the earlier search results under Rule 4.12 (see above item 1), in respect of an earlier search carried out on the following earlier application, the priority of which is subsequently claimed in this international application, the applicant may consider (*see also Notes to Continuation of Box No. VII, item 2; use of more than one earlier search*):

Filing date *(day/month/year)*	Application Number	Country *(or regional Office)*

2.2 **Request not to transmit the earlier search results by the receiving Office to the ISA (Rule 23*bis*.2(b))**

☐ to **request** that the receiving Office **DOES NOT transmit** the results of the earlier search to the ISA (Rule 23*bis*.2(b)) (*may only be checked where the international application is filed with the following receiving Offices: DE, FI and SE*)

2.3 **Authorization to transmit the earlier search and classification results by the receiving Office to the ISA (Rule 23*bis*.2(a) and (e))**

☐ to **authorize** the receiving Office **to transmit** the results of the earlier search and classification to the ISA (Rule 23*bis*.2(e)) (*may only be checked where the international application is filed with the following receiving Offices: AU, CH, CZ, FI, HU, IL, JP, NO, SE, SG and US*)

☐ to **authorize** the receiving Office **to transmit** the results of the earlier international search and classification to the ISA (Rule 23*bis*.2(a) and Article 30(2)(a) and (3)) (*may only be checked where the earlier search concerns an **international application**, the priority of which is subsequently claimed in this international application and where the earlier international search was carried out by a **different** ISA than the ISA chosen in Box No. VII*)

☐ Further earlier searches are indicated on a continuation sheet.

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:			Number of declarations
☐	Box No. VIII (i)	Declaration as to the identity of the inventor :	
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Sheet No. 5

Box No. IX **CHECK LIST for EFS-Web filings** - this sheet is only to be used when filing an international application with RO/US via **EFS-Web**

This international application **contains** the following:	Number of sheets
(a) request form PCT/RO/101 (including any declarations and supplemental sheets) :	5
(b) description (excluding any sequence listing part of the description, see (f), below) :	213
(c) claims :	23
(d) abstract :	1
(e) drawings (if any) :	78
(f) sequence listing part of the description in the form of an **image file** (e.g. PDF) :	
Total number of sheets (including the sequence listing part of the description if **filed as an image file**) :	320

(g) sequence listing part of the description

- ☒ filed in the form of an **Annex C/ST.25 text file**
- ☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an **Annex C/ST.25 text file**

Indicate type and number of physical data carrier(s): .txt file via EFS-Web

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☐ fee calculation sheet :	
2. ☐ original separate power of attorney :	
3. ☐ original general power of attorney :	
4. ☐ copy of general power of attorney; reference number: :	
5. ☐ priority document(s) identified in Box No. VI as item(s) :	
6. ☐ Translation of international application into *(language)*: :	
7. ☐ separate indications concerning deposited microorganism or other biological material :	
8. ☐ *(only where item (f) is marked in the left column)* copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but **furnished only for the purposes of international search** under Rule 13*ter* :	
9. ☐ *(only where item (f) (in the left column) and item 8 (above) are marked)* a statement confirming that "the information recorded in electronic form submitted under Rule 13*ter* is identical to the sequence listing as contained in the international application" as filed via EFS-Web: :	
10. ☐ copy of results of earlier search(es) (Rule 12*bis*.1(a)) :	
11. ☐ other *(specify)*: :	

Figure of the drawings which should accompany the abstract:	**Language of filing** of the international application: English

Box No. X **SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

/ Marshall P. Byrd/

Marshall P. Byrd
Agent, Reg. No. 62,454

For receiving Office use only

1. Date of actual receipt of the purported international application: 27 September 2017 (27.09.2017)	2. Drawings: ☒ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA / US	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000636

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference UTFC.P1305WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2017/053717	International filing date *(day/month/year)* 27 September 2017 (27.09.2017)	Priority date *(day/month/year)* 27 September 2016 (27.09.2016)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

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

2. This REPORT consists of a total of 21 sheets, including this cover sheet.

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

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

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

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

	Date of issuance of this report 14 May 2019 (14.05.2019)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnès Wittmann-Regis e-mail: pct.team6@wipo.int

Form PCT/IB/373 (January 2004)

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)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/53717

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]).

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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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-***-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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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 γδT17 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 γδT17 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.

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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 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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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-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/53717

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.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16337820 Document Date: 03/28/2019

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

PTO-1390 (01-18)
Approved for use through 8/31/2019. OMB 0651-0021
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.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

Attorney Docket No.	
UTSC.P1149US/1001065871	
U.S. Application No. (if known, see 37 CFR 1.5)	

International Application No.	International Filing Date	Priority Date Claimed
PCT/US2017/053717	September 27, 2017	September 27, 2016

Title of Invention
METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME

First Named Inventor
Jennifer WARGO

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). NOTE: The express request under 35 U.S.C. 371(f) will not be effective unless the requirements under 35 U.S.C. 371(c)(1), (2), and (4) for payment of the basic national fee, copy of the International Application and English translation thereof (if required), and the oath or declaration of the inventor(s) have been received.
2. ☐ A copy of the International Application (35 U.S.C. 371(c)(2)) is attached hereto (not required if the International Application was previously communicated by the International Bureau or was filed in the United States Receiving Office (RO/US)).
3. An English language translation of the International Application (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
4. An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
   a. ☐ is attached.
   b. ☐ was previously filed in the international phase under PCT Rule 4.17(iv).

Items 5 to 8 below concern amendments made in the international phase.

PCT Article 19 and 34 amendments

5. ☐ Amendments to the claims under PCT Article 19 are attached (not required if communicated by the International Bureau) (35 U.S.C. 371(c)(3)).
6. ☐ English translation of the PCT Article 19 amendment is attached (35 U.S.C. 371(c)(3)).
7. ☐ English translation of annexes (Article 19 and/or 34 amendments only) of the International Preliminary Examination Report is attached (35 U.S.C. 371(c)(5)).

Cancellation of amendments made in the international phase

8a. ☐ Do not enter the amendment made in the international phase under PCT Article 19.

8b. ☐ Do not enter the amendment made in the international phase under PCT Article 34.

NOTE: A proper amendment made in English under Article 19 or 34 will be entered in the U.S. national phase application absent a clear instruction from applicant not to enter the amendment(s).

The following items 9 to 17 concern a document(s) or information included.

9. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ■ A preliminary amendment.
11. ■ An Application Data Sheet under 37 CFR 1.76.
12. ☐ A substitute specification. NOTE: A substitute specification cannot include claims. See 37 CFR 1.125(b).
13. ☐ A power of attorney and/or change of address letter.
14. ■ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821-1.825 (not required if sequence listing in text format was indicated on the PCT Request as part of the International Application and the sequence listing was published as part of the international application).
15. ☐ Assignment papers *(cover sheet and document(s))*. Name of Assignee: _____
16. ☐ 37 CFR 3.73(c) Statement *(when there is an Assignee)*.

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. 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 15 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.

U.S. APPLN. No. (if known – see 37 CFR 1.5)	INTERNATIONAL APPLICATION No.	ATTORNEY DOCKET No.

17. ☐ Other items or information:

IB308, International Search Report and Written Opinion

The following fees have been submitted.	CALCULATIONS
18. ■ Basic national fee (37 CFR 1.492(a)) **$300**	$ 300
19. ■ Examination fee (37 CFR 1.492(c)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • All other situations **$760**	$ 760
20. ■ Search fee (37 CFR 1.492(b)) • If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4)..... **$0** • Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$140** • International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB..... **$520** • All other situations **$660**	140 $
TOTAL OF 18, 19, and 20 =	$ 1200
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)). Fee for each additional 50 sheets of paper or fraction thereof **$400**	

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
- 100 =	/ 50 =		x **$400**	$

Surcharge for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).....**$140**	$ 140

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =		x **$100**	$
Independent claims	- 3 =		x **$460**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			**+ $820**	$

Fee for submission of Sequence Listing text file of 300 MB to 800 MB (37 CFR 1.21(o)(1)).....**$1,000**	$
Fee for submission of Sequence Listing text file of more than 800 MB (37 CFR 1.21(o)(2)).....**$10,000**	$
Processing fee for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)).....**$140 +**	$
TOTAL OF ABOVE CALCULATIONS =	$ 1340
■ **Applicant asserts small entity status.** See 37 CFR 1.27. Fees above are reduced by ½.	
☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Fees above are reduced by ¾. Applicant must attach form PTO/SB/15A or B or equivalent.	
TOTAL NATIONAL FEE =	$ 670
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31)..... **$50.00** per property **+**	$
TOTAL FEES ENCLOSED =	$ 670

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. ☐ The Director is hereby authorized to charge additional fees which may be required, or credit any overpayment, to Deposit Account No. _____ as follows:

i. ☐ any required fee.

ii. ☐ any required fee except for excess claims fees required under 37 CFR 1.492(d) and (e) and multiple dependent claim fee required under 37 CFR 1.492(f).

d. ■ Fees are to be charged to a credit card. **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. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended to pay fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

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 1: 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**.

NOTE 2: A U.S. national stage application may not claim priority to the international application of which it is the national phase. The filing date of a U.S. national stage application is the international filing date. See 35 U.S.C. 363.

Correspondence Address

■ The address associated with Customer Number: 32425 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone			
Email					

Signature	/Gina Shishima/	Date	March 28, 2019
Name (Print/Type)	Gina Shishima	Registration No. (Attorney/Agent)	45,104

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.

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

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)* 02 FEB 2018	
Applicant's or agent's file reference UTFC.P1305WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US17/53717	International filing date *(day/month/year)* 27 September 2017 (27.09.2017)
Applicant Board of Regents, The University of Texas System	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

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 Shane Thomas PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2017)

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.

Form PCT/ISA/210 (first sheet) (January 2015)

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)

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

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

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.

PCT Recordation of Search History

Case/PCT Application Number: PCT/US17/53717

CLIN Number/Technical Field of PCT Application: 0007 Biotechnology

Dates During Which the Search was Conducted: 14 December 2017 – 28 December 2017

Date of Completion of Recordation of Search History Form: 10 January 2018

Research Analyst Initials: ARK

Search Approval Official (SAO) Initials: DGF

Field of Search/Classification Information:

IPC(8) Classifications: A61K 35/742, 35/741, 35/747, 35/744, 35/745, 31/7105, 9/19, 35/74, 45/06; C12R 1/145 (2017.01)

CPC Classifications: A61K 35/742, 35/741, 35/747, 35/744, 35/745, 9/0053, 31/7105, 9/0019, 9/19, 35/74, 45/06; C12R 1/145

Databases Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used:

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google; EBSCO; PubMed

Search Terms: WARGO, GOPALARISHNAN, TEXAS, GAJEWSKI, SIVAN, CORRALES, ruminococcaceae, 'faecalibacterium prausnitzii', 'ruminococcus bromii', 40518, dystopia, bacteria, microbe, cell, isolate, purify, extract, population, culture, cancer, colorectal, sarcoma, granuloma, carcinoma, melanoma, tumor, 'T cell', 'T lymphocytes', administer, treat, given, cure, ameliorate, procedure, CD11b+, CD11c+, CD3+, CD8+, CD4+, CD45+

Database Search String Recordation, Including Dates of Searches:

Patent Database Search Strategy/Results:

PatSeer: 14 December 2017 – 28 December 2017

ID	Search String	De-duped	Records	Created Date
L21	TACD: ((ruminococ* or prausnitz*)^10 and (treat* or admin* or cur* or amelio* or preven*) WP (cancer)) AND (CPC:("A61K31/7105" OR "A61K35/74" OR "A61K35/741" OR "A61K35/742" OR "A61K35/744" OR "A61K35/745" OR "A61K35/747" OR "A61K45/06" OR "A61K9/0019" OR "A61K9/0053" OR "A61K9/19" OR "C12R1/145") OR IC:("A61K31/7105" OR "A61K35/74" OR "A61K35/741" OR "A61K35/742" OR "A61K35/744" OR "A61K35/745" OR "A61K35/747" OR "A61K45/06" OR "A61K9/19" OR "C12R1/145"))	SFAM	234	27-Dec-17
L20	TACD: ((ruminococ* or prausnitz*)^10 and (treat* or admin* or cur* or amelio* or preven*) WP (cancer))	SFAM	724	27-Dec-17
L19	TACD: ((ruminococ* or prausnitz*) WP (treat* or admin* or cur* or amelio* or preven*) and ((ruminococ* or prausnitz*) WP (cancer)))	SFAM	88	27-Dec-17
L18	TACD: ((ruminococ* or prausnitz*) WS (treat* or admin* or cur* or amelio* or preven*) and ((ruminococ* or prausnitz*) WS (cancer)))	SFAM	9	27-Dec-17
L17	TAC: (sarcom* OR granulom* OR carcinom* OR cancer* OR melanom*) and TACD: ((ruminococ* or prausnitz*) WS (treat* or admin* or cur* or amelio* or preven*) and ((ruminococ* or prausnitz*) WS (cancer)))	SFAM	6	27-Dec-17
L16	TAC: (sarcom* OR granulom* OR carcinom* OR cancer* OR melanom*) and TACD: ((prausnitz*) WS (treat* or admin* or cur* or amelio* or preven*))	SFAM	30	20-Dec-17
L15	TACD: ((sarcom* OR granulom* OR carcinom* OR cancer* OR melanom*) WS (prausnitz*)) and ((prausnitz*) WS (treat* or admin* or cur* or amelio* or preven*))	SFAM	7	20-Dec-17
L14	TACD: ((sarcom* OR granulom* OR carcinom* OR cancer* OR melanom*) WS (ruminococ* or Faecalibact*)) and ((ruminococ* or Faecalibact*) WS (treat* or admin* or cur* or amelio* or preven*))	SFAM	8	20-Dec-17
L13	TACD: ((isolat* or popula*) WS (bromii))	SFAM	6	20-Dec-17
L12	TAC: (("40518" OR ruminococ* or Faecalibacter*) and cancer) AND (CPC:("A61K31/7105" OR "A61K35/74" OR "A61K35/741" OR "A61K35/742" OR "A61K35/744" OR "A61K35/745" OR "A61K35/747" OR "A61K45/06" OR "A61K9/0019" OR "A61K9/0053" OR "A61K9/19" OR "C12R1/145") OR IC:("A61K31/7105" OR "A61K35/74" OR "A61K35/741" OR "A61K35/742" OR "A61K35/744" OR "A61K35/745" OR "A61K35/747" OR "A61K45/06" OR "A61K9/19" OR "C12R1/145"))	SFAM	17	19-Dec-17
L11	TAC:(((sarcoma* OR granuloma* OR carcinoma* OR cancer* OR melanoma*) WS (administer* OR treat* OR cur* OR procedure*)) AND ("40518" OR ruminococ* or Faecalibacter*))	SFAM	17	15-Dec-17
L10	TAC:((sarcoma* OR granuloma* OR carcinoma* OR cancer* OR melanoma*) AND ("40518" OR ruminococ*) AND	SFAM	1	14-Dec-17

	(administer* OR treat* OR cur* OR procedure*) AND((extract*2 OR purifi*2 OR isolat*2) WS (bacter* or popula* or cultur*)) AND (T_lymphocytes OR T_cell))			
L9	TAC:((sarcoma* OR granuloma* OR carcinoma* OR cancer* OR melanoma*) AND ("40518" OR ruminococ*) AND (administer* OR treat* OR cur* OR procedure*) AND((extract*2 OR purifi*2 OR isolat*2) WS (bacter* or popula* or cultur*)) AND (T_lymphocytes OR T_cell) AND ("CD11b+" OR "CD11c+" OR "cd3" OR "CD8+" OR "CD4+" OR "CD45+"))	SFAM	0	14-Dec-17
L8	TA:((sarcoma* OR granuloma* OR carcinoma* OR cancer* OR melanoma*) AND ("40518" OR ruminococ*) AND (administer* OR treat* OR cur* OR procedure*) AND((extract*2 OR purifi*2 OR isolat*2) WS (bacter* or popula* or cultur*)) AND (T_lymphocytes OR T_cell) AND ("CD11b+" OR "CD11c+" OR "cd3" OR "CD8+" OR "CD4+" OR "CD45+"))	SFAM	0	14-Dec-17
L7	TAC: (cancer* and (admin* WS (bacter* or microb* or cell*))) and TACD: ((ruminococ* W1 bromii) or ("R. bromii"))	SFAM	7	14-Dec-17
L6	TAC: (ruminococ* and cancer*)	SFAM	28	14-Dec-17
L5	ASN: (TEXAS) and TACD: (rumino* and cancer*)	SFAM	2	14-Dec-17
L4	ASN: (TEXAS) and TAC: (rumino*)	SFAM	1	14-Dec-17
L3	INV: (WARGO OR GOPALARISHNAN) and TACD: (rumino*)	SFAM	0	14-Dec-17
L2	INV: (WARGO OR GOPALARISHNAN) and TAC: (rumino*)	SFAM	0	14-Dec-17
L1	INV: (WARGO OR GOPALARISHNAN) and TAC: (cancer*)	SFAM	1	14-Dec-17

Non-Patent Literature (NPL) Search Strategy/Results:

EBSCO: 14 December 2017 – 28 December 2017

AU (WARGO or GOPALARISHNAN) and TX (cancer and ruminoc*)
AU (GAJEWSKI OR SIVAN OR CORRALES) and TX (cancer and ruminoc*)
TI (cancer or ruminoc*) and TX ((cancer and ruminoc*) and (ruminoc* NEAR5 (treat* or admin* or cur* or give*))
TI (cancer or ruminoc*) and TX ((cancer and ruminoc*) and (ruminoc* NEAR5 (treat* or admin* or cur* or give*))
TI (cancer and ruminoc*)
TX ((cancer or melanoma or carcinoma or sarcoma or tumor) and (ruminoc* NEAR5 (treat* or admin* or cur* or give*))
TI (cancer or "prausnitzii") and TX ((cancer or melanoma or carcinoma or sarcoma or tumor) and ("F* prausnitzii") NEAR10 (admin*))
TI (cancer or melanoma or carcinoma or sarcoma or tumor or "prausnitzii") and TX ((cancer or melanoma or carcinoma or sarcoma or tumor) and ("F* prausnitzii"))

Google: 14 December 2017 – 28 December 2017

WARGO and colorectal cancer
GOPALARISHNAN and colorectal cancer
treating cancer with ruminococcaceae
treating cancer with Faecalibacterium prausnitzii
administering ruminococcaceae to treat cancer
ruminococcus dystopia cancer
prausnitzii "skin cancer"
ruminococcus "skin cancer"
ruminococcus bromii enrichment

PubMed: 14 December 2017 – 28 December 2017

Faecalibacterium prausnitzii cancer
faecalibacterium prausnitzii cancer treatment
ruminococcus colorectal cancer
ruminococcus dystopia cancer

WO 2018/064165
PCT/US2017/053717

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

BYRD, Marshall, P.
Parker Highlander PLLC
1120 S. Capital Of Texas Highway
Bldg. One, Suite 200
Austin, TX 78746
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
31 January 2019 (31.01.2019)

Applicant's or agent's file reference
UTFC.P1305WO

IMPORTANT NOTICE

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2017/053717	27 September 2017 (27.09.2017)	27 September 2016 (27.09.2016)

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
05 April 2018 (05.04.2018)

   AZ, BY, CN, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, TM

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   AE, AG, AL, AM, AO, AP, AT, AU, BA, BB, BG, BH, BN, BR, BW, BZ, CA, CH, CL, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, ID, IL, IN, IR, IS, JO, JP, KE, KH, KN, KW, KZ, LA, LC, LK, LR, LS, LY, MA, ME, MG, MN, MW, MX, MY, NI, NO, NZ, OA, OM, PA, PE, PH, PL, PT, QA, RO, RS, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TN, TR, TT, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Agnès Wittmann-Regis

e-mail: pct.team6@wipo.int

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)

Docket Number (Optional)

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.

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

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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME
First Named Inventor/Applicant Name:	Jennifer WARGO
Filer:	Gina N. Shishima/David Edwards
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:				
BASIC NATIONAL STAGE FEE	2631	1	150	150
NATL STAGE SEARCH FEE - U.S. WAS THE ISA	2641	1	70	70
NATL STAGE EXAM FEE - ALL OTHER CASES	2633	1	380	380
Pages:				
Claims:				
Miscellaneous-Filing:				
OATH/DECL > 30 MOS FROM 371 COMMENCEMENT	2617	1	70	70
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PET. DELAY SUB OR RESTORE PRIORITY-CLAIM	2454	1	1000	1000
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1670**

Electronic Acknowledgement Receipt

EFS ID:	35564084
Application Number:	16337820
International Application Number:	PCT/US2017/053717
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/David Edwards
Filer Authorized By:	Gina N. Shishima
Attorney Docket Number:	UTSC.P1149US/1001065871
Receipt Date:	28-MAR-2019
Filing Date:	
Time Stamp:	17:24:04
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	$1670
RAM confirmation Number	032919INTEFSW17243600
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	Sequence Listing (Text File)	UTSC_P1149US-Sequence-Listing.TXT	4333059 	no	-
Warnings:					
Information:					
2	Application Data Sheet	UTSC-P1149US-ADS.pdf	112533 14763fd7957449c6fdce0d3922a8f653eabc1485	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Preliminary Amendment	UTSC-P1149US-Preliminary-Amendment.pdf	141754 4f9b01cfd0c0f48960ab915718e1bd7c07cb2121	no	3
Warnings:					
Information:					
4	Transmittal of New Application	UTSC-P1149US-371-Transmittal.pdf	181714 6ae1412fe3a9e8f9b47fecc6a33913564a4928d8	no	4
Warnings:					
Information:					
5	Documents submitted with 371 Applications	UTSC-P1149WO-ISR.pdf	690006 0162c205a7557f18053d5cf93d87eecff6b688c4	no	13
Warnings:					
Information:					
6	Documents submitted with 371 Applications	UTSC-P1149WO-IB308.pdf	67747 d0f79d95250f3b06b815592380f4d3fc69ef0e9d	no	1
Warnings:					

Information:					
7	Miscellaneous Incoming Letter	UTSC-P1149US-Petition-to-Revive.pdf	199297 9cfe29667d9847cd99e5db6023ecca658b063c41	no	3
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	38758 e79b286a2ee14e7b65d0cf512e12da9fb8b6d4b4	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	5764868	

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/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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 contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
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)
Approved for use through 11/30/2020. OMB 0651-0032
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 contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
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/1001065871	**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
	Application Number	
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)
Approved for use through 11/30/2020. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
Title of Invention	METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	UTSC.P1149US/1001065871
	Application Number	
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
First Name	Gina	Last Name	Shishima	Registration Number	45,104

Additional Signature may be generated within this form by selecting the Add button.

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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.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: THE BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	Group Art Unit: Not Yet Assigned
Serial No.: Not Yet Assigned	Examiner: Not Yet Assigned
Filed: Herewith	Atty. Dkt. No.: UTSC.P1149US/1001065871
For: METHODS FOR ENHANCING IMMUNE CHECKPOINT BLOCKADE THERAPY BY MODULATING THE MICROBIOME	Confirmation No.: Not Yet Assigned

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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:

March 28, 2019	/Gina N. Shishima/
Date	Gina N. Shishima

PRELIMINARY AMENDMENT

Commissioner:

Applicant respectfully submits this Preliminary Amendment in the above-referenced case. Consideration of this case in view of the amendments made herein is respectfully requested.

Amendment to the Specification beginning on page 2.

Remarks begin on page 3.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000694

AMENDMENT

AMENDMENT TO THE SPECIFICATION

Please replace paragraph [0001] with the following amended paragraph:

[0001] This application is a national phase application under 35 U.S.C. §371 of International Application No. PCT/US2017/053717, filed September 27, 2017 which claims the benefit of priority of United States Provisional 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.

Exhibit 1002
Microbiotica, Limited v. Board of Reagents, The University of Texas System
Page 000695

REMARKS

The specification has been amended to update the priority data; no new matter is added.

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

Respectfully submitted,

/Gina N. Shishima/

Gina N. Shishima
Reg. No. 45,104
Attorney for Applicant

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

Date: March 28, 2019

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