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(54) Title: INDUCTION OF LAMINA PROPRIA REGULATORY T CELLS

(57) Abstract: Described herein are methods and compositions for the induction of the production of regulatory T cells and for the treatment and/or prevention of diseases associated with pathological immune responses, such as inflammatory bowel diseases.



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INDUCTION OF LAMINA PROPRIA REGULATORY T CELLS

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent
5 Application serial number 62/183,019, filed June 22, 2015, and U.S. Provisional Patent
Application serial number 62/183,021, filed June 22, 2015, each of which are hereby
incorporated by reference in their entirety.

GOVERNMENT INTEREST

This invention was made with Government support under National Institutes of
10 Health Grant R01-AI51530 and R56AI110630. The Government has certain rights in the
invention.

BACKGROUND

Regulatory T cells (Tregs) are a subset of T cells that help keep the immune system
in check by suppressing immune responses, thereby reducing immune-mediated pathology,
15 such as autoimmune disease, inflammatory disease and allergies. Tregs regulate the
immune response through a number of mechanisms, such as the secretion of inhibitory
cytokines, such as IL-10 and TGF- β , the expression of inhibitory receptor CTLA-4 and
granzyme-mediated cytotoxicity.

One of the key regulators of Treg development and function is the transcription
20 factor FoxP3. Reduced numbers of FoxP3 expressing Tregs are associated with
autoimmune diseases such as systemic lupus erythematosus (SLE). Mutation of FoxP3 in
humans results IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked)
syndrome, which is characterized by a dysfunction of regulatory T cells and subsequent
autoimmunity.

Beyond their role in regulating immune activity, Tregs located in parenchymal
25 tissues, referred to as "tissue Tregs," are also involved in certain other, non-immunological,
processes. For example, tissue Tregs that reside in visceral adipose tissue regulate
metabolic parameters, while those located in muscle tissue channel tissue inflammation and
regeneration following muscle injury.

30 An important population of tissue Tregs resides in the lamina propria (LP) of the
digestive tract, and in particular in the colon. In fact, under normal conditions, compared
with all other tissues, the intestinal lamina propria has the greatest population of Tregs.
Such LP Tregs modulate responses to commensal microbes, thereby reducing the risk of

intestinal immunopathologies. LP Tregs are an unusual population, which has provoked some contradictory observations. T cell receptors expressed by LP Tregs show a marked reactivity against microbial antigens, which are important drivers of LP Treg differentiation and/or expansion (Lathrop *et al.*, *Nature* 478:250 (2011); Cebula *et al.*, *Nature* 497:258 (2013)), and some LP Tregs may arise by conversion from FoxP3⁺ conventional T cells (Tconv) (Lathrop *et al.*, *Nature* 478:250 (2011)), although arguments for a thymic origin have also been made (Cebula *et al.*, *Nature* 497:258 (2013)). Many LP Tregs express marker profiles (Nr1⁺, Helios⁺) that differ from Tregs found in peripheral lymphoid tissue (Bilate and Lafaille, *Annu. Rev. Immunol.* 30:733 (2012), though the significance of the different marker expression patterns is unclear. Generally, germ-free (GF) mice exhibit a reduced abundance of LP Tregs (Ai *et al.*, *Immunol. Rev.* 259:60 (2014)), and colonization of GF mice by pools of microbes (particularly Schadler's flora and *Clostridia* combinations) elicited the differentiation or expansion of Helios⁺Nr1⁺ LP Tregs (Geuking *et al.*, *Immunity* 34:794 (2011); Atarashi *et al.*, *Nature* 500:232 (2013); Atarashi *et al.*, *Science* 331:337 (2011)). The ability of single microbes to induce colonic Tregs has been more controversial, and the need for complex combinations has been suggested Atarashi *et al.*, *Nature* 500:232 (2013); Atarashi *et al.*, *Science* 331:337 (2011); Faith *et al.*, *Sci. Transl. Med.* 6:220ra11 (2014). Accordingly, induction of LP Tregs is a promising treatment for intestinal immunopathologies, including inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

SUMMARY

In certain aspects, provided herein are methods and compositions for inducing the production of Rorγ⁺Helios⁺ lamina propria regulatory T cells (LP Tregs) and/or for treating or preventing a disease associated with a pathological immune response (*e.g.*, an inflammatory bowel disease) in a subject.

In certain aspects provided herein is a method for inducing the production of Rorγ⁺Helios⁺ LP Tregs in a subject comprising administering to the subject a composition comprising a bacteria or a combination of bacteria that induce the production of Rorγ⁺Helios⁺ LP Tregs. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the composition is a food product supplemented with the bacteria. In some embodiments, the food product is or comprises a dairy product (*e.g.*, yogurt, frozen yogurt, ice cream, milk or cheese). In some embodiments, the food product is a non-dairy food product. In some embodiments, the food

product is a beverage. In some embodiments, the composition is administered orally. In some embodiments, the composition is administered rectally.

In certain aspects provided herein is a method of treating or preventing an inflammatory bowel disease in a subject comprising administering to the subject a composition comprising a bacteria or a combination of bacteria that induce the production of Rorγ⁺Helios⁺ LP Tregs. In some embodiments, the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease. In some embodiments, the disease is Crohn's disease or ulcerative colitis. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the composition is a food product supplemented with the bacteria. In some embodiments, the food product is or comprises a dairy product (*e.g.*, yogurt, frozen yogurt, ice cream, milk or cheese). In some embodiments, the food product is a non-dairy food product. In some embodiments, the food product is a beverage. In some embodiments, the composition is administered orally. In some embodiments, the composition is administered rectally.

In some embodiments of the methods described herein, the subject has or is predisposed to a disease associated with a pathological immune response. In some embodiments, the disease is an inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease). In some embodiments, the disease is Crohn's disease or ulcerative colitis.

In some embodiments of the methods described herein, the subject has reduced levels of bacteria present in their gut. In some embodiments, the subject had been administered an antibiotic prior to administration of the composition. In some embodiments, the antibiotic was administered less than a month, less than 30, 28, 21, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 days prior to administration of the composition.

In certain aspects, provided herein is a composition for inducing the production of Rorγ⁺Helios⁺ LP Tregs in a subject comprising a bacteria or a combination of bacteria that induce the production of Rorγ⁺Helios⁺ LP Tregs. In some embodiments, the composition

further comprises a pharmaceutically acceptable carrier. In some embodiments, the composition is a food product supplemented with the bacteria. In some embodiments, the food product is or comprises a dairy product (e.g., yogurt, frozen yogurt, ice cream, milk or cheese). In some embodiments, the food product is a non-dairy food product. In some
 5 embodiments, the food product is a beverage. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is formulated for rectal administration.

In certain aspects, provided herein is a method of making a composition for inducing the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs in a subject comprising combining a
 10 bacteria that induces the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs with a pharmaceutically acceptable carrier. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is formulated for rectal administration.

In certain aspects, provided herein is a method of making a composition for inducing the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs in a subject comprising combining a
 15 bacteria that induces the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs with a food product. In some embodiments, the food product is or comprises a dairy product (e.g., yogurt, frozen yogurt, ice cream, milk or cheese). In some embodiments, the food product is a non-dairy food product. In some embodiments, the food product is a beverage.

In some embodiments of the compositions and methods described herein, the
 20 bacteria that induces the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs is selected from a species of bacteria listed in Figure 5. In some embodiments, the bacteria that induces the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs does not belong to the Clostridia class. In some embodiments, the bacteria that induces the production of $\text{Ror}\gamma^+\text{Helios}^-$ LP Tregs is selected from the group
 25 consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides*
 30 *fingoldii* and *Bifidobacterium breve*. In some embodiments, the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,

Fusobacterium nucleatum and *Parabacteroides johnsonii*. In some embodiments, the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*. In some embodiments, the bacteria is selected from the group

5 consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*. In some embodiments, the bacteria is *Bacteroides ovatus*. In some embodiments, the bacteria is *Campylobacter jejuni*. In some embodiments, the bacteria is *Staphylococcus saprophyticus*. In some embodiments, the bacteria is *Enterococcus faecalis*. In some embodiments, the bacteria are live, replication competent bacteria.

10 In some embodiments of the compositions and methods described herein, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*,

15 *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%,

20 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*. In some

25 embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%,

30 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%,

55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria is *Bacteroides ovatus*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Campylobacter jejuni*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Staphylococcus saprophyticus*. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Enterococcus faecalis*.

10 In some embodiments of the compositions and methods described herein, the bacteria that induces the production of Ror γ ⁺Helios⁻ LP Tregs is selected from a strain of bacteria listed in Figure 5. In some embodiments, the bacteria that induces the production of Ror γ ⁺Helios⁻ LP Tregs does not belong to the Clostridia class. In some embodiments, the bacteria that induces the production of Ror γ ⁺Helios⁻ LP Tregs is selected from the group

15 consisting of *Bacteroides ovatus*_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus saprophyticus*_DLK1, *Enterococcus faecalis*_HH22, *Bacteroides thetaiotaomicron*_ATCC29741, *Bacteroides vulgatus*_ATCC8482, *Bacteroides uniformis*_ATCC8492, *Enterococcus faecalis*_TX0104, *Lactobacillus casei*_AO47, *Bacteroides fragilis*_CL03T00C08, *Acinetobacter lwoffii*_F78, *Fusobacterium*

20 *nucleatum*_F0419, *Enterococcus faecalis*_OG1RF, *Bacteroides thetaiotaomicron*_ATCC29148, *Parabacteroides johnsonii*_CL02T12C29, *Bacteroides oleiciplenus*_DSM22535, *Lactobacillus rhamnosus*_LMS2-1, *Bacteroides massiliensis*_DSM17679, *Parabacteroides merdae*_CL03T12C32, *Fusobacterium mortiferum*_AO16, *Bifidobacterium breve*_SK134, *Bacteroides finegoldii*_DSM17565 and

25 *Bacteroides fragilis*_3_1_12. In some embodiments, the bacteria is selected from the group consisting of *Bacteroides ovatus*_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus saprophyticus*_DLK1, *Enterococcus faecalis*_HH22, *Bacteroides thetaiotaomicron*_ATCC29741, *Bacteroides vulgatus*_ATCC8482, *Bacteroides uniformis*_ATCC8492, *Enterococcus faecalis*_TX0104, *Lactobacillus casei*_AO47,

30 *Bacteroides fragilis*_CL03T00C08, *Acinetobacter lwoffii*_F78, *Fusobacterium nucleatum*_F0419, *Enterococcus faecalis*_OG1RF, *Bacteroides thetaiotaomicron*_ATCC29148 and *Parabacteroides johnsonii*_CL02T12C29. In some embodiments, the bacteria is selected from the group consisting of *Bacteroides*

ovatus_CL02T12C04, Campylobacter jejuni_AS-84-79, Staphylococcus saprophyticus_DLK1, Enterococcus faecalis_HH22, Bacteroides thetaiotaomicron_ATCC29741 and Bacteroides vulgatus_ATCC8482. In some embodiments, the bacteria is selected from the group consisting of Bacteroides

5 ovatus_CL02T12C04, Campylobacter jejuni_AS-84-79, Staphylococcus saprophyticus_DLK1 and Enterococcus faecalis_HH22. In some embodiments, the bacteria is Bacteroides ovatus_CL02T12C04. In some embodiments, the bacteria is Campylobacter jejuni_AS-84-79. In some embodiments, the bacteria is Staphylococcus saprophyticus_DLK1. In some embodiments, the bacteria is Enterococcus faecalis_HH22.

10 In some embodiments, the bacteria are live, replication competent bacteria.

In some embodiments of the compositions and methods described herein, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of Bacteroides ovatus_CL02T12C04, Campylobacter jejuni_AS-

15 84-79, Staphylococcus saprophyticus_DLK1, Enterococcus faecalis_HH22, Bacteroides thetaiotaomicron_ATCC29741, Bacteroides vulgatus_ATCC8482, Bacteroides uniformis_ATCC8492, Enterococcus faecalis_TX0104, Lactobacillus casei_AO47, Bacteroides fragilis_CL03T00C08, Acinetobacter lwoffii_F78, Fusobacterium nucleatum_F0419, Enterococcus faecalis_OG1RF, Bacteroides

20 thetaiotaomicron_ATCC29148, Parabacteroides johnsonii_CL02T12C29, Bacteroides oleiciplenus_DSM22535, Lactobacillus rhamnosus_LMS2-1, Bacteroides massiliensis_DSM17679, Parabacteroides merdae_CL03T12C32, Fusobacterium mortiferum_AO16, Bifidobacterium breve_SK134, Bacteroides finegoldii_DSM17565 and Bacteroides fragilis_3_1_12. In some embodiments, at least 10%, 15%, 20%, 25%, 30%,

25 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of Bacteroides ovatus_CL02T12C04, Campylobacter jejuni_AS-84-79, Staphylococcus saprophyticus_DLK1, Enterococcus faecalis_HH22, Bacteroides

thetaiotaomicron_ATCC29741, Bacteroides vulgatus_ATCC8482, Bacteroides uniformis_ATCC8492, Enterococcus faecalis_TX0104, Lactobacillus casei_AO47, Bacteroides fragilis_CL03T00C08, Acinetobacter lwoffii_F78, Fusobacterium nucleatum_F0419, Enterococcus faecalis_OG1RF, Bacteroides

30 thetaiotaomicron_ATCC29148 and Parabacteroides johnsonii_CL02T12C29. In some

embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus saprophyticus*_DLK1, *Enterococcus* faecalis_HH22, *Bacteroides thetaiotaomicron*_ATCC29741 and *Bacteroides vulgatus*_ATCC8482. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides* ovatus_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus* saprophyticus_DLK1 and *Enterococcus* faecalis_HH22. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Bacteroides* ovatus_CL02T12C04. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Campylobacter jejuni*_AS-84-79. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Staphylococcus saprophyticus*_DLK1. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition is *Enterococcus* faecalis_HH22.

In certain aspects, provided herein are methods and compositions for inducing the production or activity of regulatory T cells in a subject. In some embodiments, the methods comprise administering to the subject an agent that activates $R\gamma$ (*i.e.*, a $R\gamma$ agonist). In some embodiments, the regulatory T cells are lamina propria regulatory T cells.

In certain aspects, provided herein are methods and compositions for treating or preventing a disease associated with a pathological immune response. In some embodiments, the methods comprise administering to the subject an agent that activates $R\gamma$ (*i.e.*, a $R\gamma$ agonist). In some embodiments, the agent is administered in an amount sufficient to induce the production or activity of regulatory T cells (*e.g.*, lamina propria regulatory T cells) in the subject. In some embodiments, the disease associated with a pathological immune response is an inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel

syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease. In some embodiments, the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

In some embodiments of the methods described herein, a Ror γ agonist is administered to a subject (*e.g.*, an effective dose of a Ror γ agonist). In some embodiments, the Ror γ agonist is a small molecule. In some embodiments, the Ror γ agonist is a sterol. In some embodiments, the sterol Ror γ agonist is selected from the group consisting of cholesterol sulfate, 25-OHC, 25-OHC sulfate, desmosterol, desmosterol sulfate, 5 α ,6 α -epoxycholestanol sulfate, 7 α ,27-diOHC, 5 α ,6 α -epoxycholestanol, 24S,25-epoxycholesterol, 7 α -OHC, 20 α -OHC, 22R-OHC, 24S-OHC, 27-OHC, 7 β ,27-OHC, 7-keto,27-OHC, 7 α ,27-OHC, 4AC4MA Δ° , Δ 7-daf, zymosterol, 4C, 7DHC, zymosterone, 4C22OH, 4,7-cholesten, 25OH, OR-12872 and OR-942

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows Ror γ , encoded by *Rorc*, is preferentially expressed in colonic Tregs. **(A)** Heatmap of gene clusters that are enriched in tissue Tregs and colonic Tregs. Top: Genes that are overrepresented or underrepresented in tissue Tregs vs. splenic Tregs (at a Fold Change>2) were clustered using hierarchical clustering (Pearson correlation). Bottom: Heatmap of colon preferential gene clusters that are biased in colonic Tregs (at a Fold Change>1.5) compared with other tissue Tregs. **(B)** Heatmap of transcription factors that are overrepresented in colonic Tregs compared with Tregs from other lymphoid and non-lymphoid tissues. *Rorc* was the most differential based on hierarchical clustering analysis. **(C)** Representative dot plots (left) and respective frequencies (right) of Ror γ^{+} Helios $^{-}$ Tregs within the Foxp3 $^{+}$ CD4 $^{+}$ TCR β^{+} population. (n=26) ***P<0.0001, paired t test. **(D)** Representative dot plots of Ror γ vs Helios, Nr1p or Il33R expression within the colonic Foxp3 $^{+}$ CD4 $^{+}$ TCR β^{+} population. Quantification of these plots is shown in FigS2 (n $\geq$ 5). **(E)** depicts representative dot plots (top) and frequency (bottom) of Ror γ^{+} Helios $^{-}$ Tregs within the Foxp3 $^{+}$ CD4 $^{+}$ TCR β^{+} population across different tissues- colon, small intestinal lamina propria (SI), Peyer's patches (PP), mesenteric lymph nodes (MLN), peripheral lymph nodes (LN), spleen (Spl), injured muscle, thymus and MC138 tumor. **(F)** Lymphocytes were treated with PMA and ionomycin and stained for Il17-A, Il17-F and FoxP3. Representative dot plots of Il17-A and Foxp3 expression (top), and frequencies of Il17-A or Il17-F

producing cells (bottom) within Foxp3⁺ Tregs or Foxp3⁻ Tconvs from the colon (n=16), SI (n=4) and spleen (n=10) are shown.

Figure 2 shows a comparison of gene expression profiles of Tregs from colon and spleen uncovered 933 differential transcripts. Colonic and splenic Tregs were sorted from Foxp3⁺ mice. Fold change difference and corresponding p values between gene expression of colonic and splenic Tregs are shown in volcano plot. Colonic signature is highlighted at a FoldChange>2 and p value <0.05.

Figure 3 shows Rorγ⁺ Tregs express low levels of Nrp1, Helios and IL33R. **(A)** Colonic lymphocytes were stained with Foxp3, Helios, Nrp1 and Rorγ. Frequencies of Helios⁺ or Nrp⁺ cells are reported within the Rorγ⁺ Tregs or Rorγ⁻ Tregs. **(B)** Representative dot plots of IL33R and Foxp3 expression within the CD4⁺TCRβ⁺ population and IL33R and Helios expression within the Foxp3⁺CD4⁺TCRβ⁺ population.

Figure 4 shows Rorγ⁺Helios⁻ Tregs are induced by gut microbacteria. **(A)** Graphical representation of colonic Rorγ⁺Helios⁻ Tregs within the Foxp3⁺CD4⁺TCRβ⁺ population from adult SPF (n=14) and germ free mice (n=26). ***P<0.0001, unpaired t test. **(B)** Induction of Rorγ in colonic Tregs during normal post-natal development in SPF mice. Left: Representative dot plots of Rorγ⁺Helios⁻ and Rorγ⁻Helios⁻ Tregs within the Foxp3⁺CD4⁺TCRβ⁺ population before (d14) during (d19) and after (d24) Rorγ induction. Right top: Frequency of Foxp3⁺ Tregs within CD4⁺TCRβ⁺ cells. Right bottom: Frequency of Rorγ⁺Helios⁻ Tregs (red) and Rorγ⁻Helios⁻ Tregs (black) within the Foxp3⁺CD4⁺TCRβ⁺ population. **(C)** Mice were treated with single (Neomycin, Vancomycin, Ampicillin, Metronidazole) or full cocktail (VMNA) of antibiotics for 4 weeks. Frequency of colonic Rorγ⁺Helios⁻ Tregs within the Foxp3⁺CD4⁺TCRβ⁺ population is shown. ***P<0.0001, unpaired t test. **(D)** Germ free mice were colonized with single bacterial species (mono-colonization) for 2 weeks. Representative dot plots (top) and frequency of Rorγ⁺Helios⁻ Tregs (bottom) within the colonic Foxp3⁺CD4⁺TCRβ⁺ population following mono-colonization are shown. Coloring corresponds to different phyla. **(E)** Mice were mono-colonized with a focused sequenced set of *Bacteroides*. The frequency of Rorγ⁺Helios⁻ Tregs within the colonic Foxp3⁺CD4⁺TCRβ⁺ population is shown (E). **(F)** Colonic Rorγ⁺Helios⁻ Tregs and Rorγ⁻Helios⁻ Tregs were compared at different points of colonization in mice colonized with *Bacteroides thetaiotaomicron* ATCC29741. Representative dot plots (top) and respective frequencies within the Foxp3⁺CD4⁺TCRβ⁺ population (bottom) are shown.

Figure 5 is a table showing the induction of colonic $Rory^+Helios^-$ Tregs by the indicated bacterial species. FDR refers to false discovery rate.

Figure 6 shows induction of $Rory^+Helios^-$ Tregs is not accompanied by inflammation and is independent of bacterial load. **(A)** Haematoxylin and eosin staining of the distal colon from mono-colonized mice and the corresponding frequency of colonic $Rory^+Helios^-$ Tregs. **(B)** Correlation between bacterial load (measured as CFU) and frequency of colonic $Rory^+Helios^-$ Tregs in mono-colonized mice. Correlation coefficient = 0.046.

Figure 7 shows characterization of Treg populations in *Foxp3-Cre. Rorc^{fl/fl}* mice. Colonic and splenic lymphocytes were isolated from WT or *Foxp3-Cre. Rorc^{fl/fl}* mice, which lack *Rory* expression specifically in Tregs. Representative dot plots (left) and frequencies of $Foxp3^+$ Tregs (middle) within the $CD4^+TCR\beta^+$ population and $Helios^-$ Tregs (right) within the $Foxp3^+CD4^+TCR\beta^+$ population are shown. *Foxp3*, ***P*=0.004; $Helios^-$ Tregs, **P*=0.03, unpaired t test.

Figure 8 shows $Rory^+$ Tregs control colitis. **(A)** Colonic and splenic lymphocytes from WT (n=7) mice and *Foxp3-Cre.Rorc^{fl/fl}* (n=8) littermates were treated with PMA and ionomycin. Frequencies of IL17-A (left) and IFN γ (right) producing cells within the $CD4^+TCR\beta^+$ population are shown. IL17-A, ****P*=0.0002; IFN γ , ***P*=0.004, unpaired t test. **(B)** TNBS-colitis score of WT (n=9) and *Foxp3-Cre.Rorc^{fl/fl}* (n=8) littermates challenged with TNBS is shown. Colitis score is calculated based on weight loss, histologic score and other physical parameters (detailed in FigS5). ***P*=0.001, paired t test. **(C)** Haematoxylin and eosin staining of the distal colon. **(D)** Correlation of TNBS-colitis score (x-axis) with $Rory^+Helios^-$ Treg frequency (y-axis) in mice monocolonized for 2 weeks with bacteria that elicit high, medium or low $Rory^+Helios^-$ Treg phenotypes prior to the induction of TNBS - colitis. Correlation coefficient= 0.82, ****P*>0.0001.

Figure 9 shows *Rory* Tregs protect from colitis. TNBS- colitis was induced in WT (n=9) and *Foxp3-Cre.Rorc^{fl/fl}* (n=8) littermates. Percent weight loss (left) and colon thickness (right) are shown. Data is representative of three independent experiments.

Figure 10 shows *Rory* contributes to colonic Treg homeostasis and determines a part of the colonic Treg signature. **(A)** Colonic $Rory^+$ or $Rory^-$ Tregs were sorted from an intercross of *Foxp3^{thy1.1}* and *Rorc^{gfp}* reporter male mice. Mean gene expression values are shown for $Rory^+$ or $Rory^-$ Tregs and colonic Treg signature, shown in FigS1, is highlighted in red (induced) or blue (repressed) (n=3). **(B)** Some of the genes (*Havcr2*, *Cxcr3*), over-

represented in Rory^+ Tregs, were validated at protein level. Representative dot plots of Cxcr3 and Tim3 encoded by *Havcr2* are shown. (C) Fold change differences in gene expression between CD4 T cells and Treg cells that are enriched for or lack Rory expression are shown. CD4 T cells were sorted from SI of germ free mice or mice
 5 monocolonized with SFB. Gene changes that are specific to Rory^+ Tregs (red), shared by both Rory^+ Tregs and TH17 cells (green) and specific to TH17 cells (blue) are highlighted.(n=3).

DETAILED DESCRIPTION

General

10 In certain aspects, provided herein are methods and compositions related to the use of bacteria that induce the production of Rory^+ Helios⁻ lamina propria regulatory T cells (LP Tregs) for the production of such LP Tregs in a subject and/or the treatment or prevention an inflammatory bowel disease in a subject.

As described herein, the present inventors discovered that Rory is expressed in a
 15 FoxP3⁺ Helios⁻ population of LP Tregs. Indeed, Rory^+ Tregs are a major subset of those Tregs elicited in response to antigens of commensal microbes in the gut. The present inventors have further identified a number of human commensal bacterial species and strains that are capable of inducing production of Rory^+ Helios⁻ LP Tregs when administered to a subject. Examples of such bacteria are provided in Figure 5 and include *Bacteroides*
 20 *ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
 25 and *Bifidobacterium breve*. Compositions comprising such bacteria are therefore useful for the induction of Rory^+ Helios⁻ LP Tregs in a subject and/or for the treatment or prevention of diseases associated with a pathological immune response, such as an inflammatory bowel disease.

In certain aspects, provided herein are methods and compositions for the induction
 30 of lamina propria regulatory T cells (LP Tregs) and/or for the treatment of a disease associated with a pathological immune response (e.g., an inflammatory bowel disease) through the induction of Rory expression or activity. Thus, in certain aspects, provided herein are compositions and methods for the treatment and/or prevention of inflammatory

bowel disease in a subject comprising administering to the subject an agent that activates Ror γ (*i.e.*, an Ror γ agonist).

Ror γ is a transcription factor encoded by the *Rorc* gene that has previously been reported to be antagonistic to FoxP3 (Korn *et al.*, *Annu. Rev. Immunol.* 27:485 (2009)). As FoxP3 is a key regulator of Treg development, inhibition of Ror γ has been proposed as a mechanism for the treatment of autoimmune diseases (*e.g.*, U.S. Pat. No. 8,912,219, U.S. Pat. Pub. 2014/0163110, each of which is hereby incorporated by reference). Mice lacking FoxP3⁺ Treg expression of Ror γ have increased disease severity in a colitis model. This role for Ror γ contrasts strongly with the previously accepted dichotomy between FoxP3 and Ror γ , a notion that stems mainly from their antagonism in the outcome of TGF β supplemented *in vitro* cultures (Zou *et al.*, *Nature* 453:236 (2008)).

As described herein, in LP Tregs, Ror γ controls a specific transcriptional signature, overlapping but mainly distinct from its transcriptional signature in conventional T cells. Notably missing are most transcripts encoding the pro-inflammatory IL-17 cytokine family, but the shared aspects of the transcriptional signature include *Il23r*. Notably, human *IL23R* genetic variants are strongly associated with inflammatory bowel disease (Abraham and Cho, *Annu. Rev. Med.* 60:97 (2009)). Ror γ ⁺ Tregs do not respond to the alarmin IL-33, and are phenotypically distinct from IL33R⁺Helios⁺ cells that congregate or expand in response to IL-33 in response to tissue damage. Mutually exclusive expression of IL-33 receptor and Ror γ in LP Tregs indicates that these molecules distinguish responses to commensal versus aggressive microbes.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The articles “*a*” and “*an*” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article.

As used herein, the term “*administering*” means providing an agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering.

The term “*agent*” is used herein to denote a chemical compound, a small molecule, a mixture of chemical compounds and/or a biological macromolecule (such as a nucleic acid, an antibody, an antibody fragment, a protein or a peptide). Agents may be identified as having a particular activity by screening assays described herein below. The activity of

such agents may render them suitable as a “therapeutic agent” which is a biologically, physiologically, or pharmacologically active substance (or substances) that acts locally or systemically in a subject.

As used herein, an “*effective amount*” is an amount effective in treating or
5 preventing a disease associated with a pathological immune response, including, for example, inflammatory bowel disease.

The phrase “*pharmaceutically-acceptable carrier*” as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or
10 transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body.

“*Small molecule*” as used herein, is meant to refer to a composition, which has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates,
15 lipids or other organic (carbon-containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays described herein.

As used herein, the term “*subject*” means a human or non-human animal selected for treatment or therapy. In certain embodiments, of the methods and compositions
20 described herein the subject is a human subject.

The phrases “*therapeutically-effective amount*” and “*effective amount*” as used herein means the amount of an agent which is effective for producing the desired therapeutic effect in at least a sub-population of cells in a subject at a reasonable benefit/risk ratio applicable to any medical treatment.

25 “*Treating*” a disease in a subject or “*treating*” a subject having a disease refers to subjecting the subject to a pharmaceutical treatment, *e.g.*, the administration of a drug, such that at least one symptom of the disease is decreased or prevented from worsening.

Bacteria that Induce LP Tregs

In certain aspects, provided herein are compositions and methods related the use of
30 bacteria that induce the production of Rorγ⁺Helios⁺ LP Tregs. Examples of such bacteria are provided in Figure 5. In some embodiments, the bacteria does not belong to the Clostridia class.

In some embodiments, the species of the bacteria that induces the production of Rorγ⁺Helios⁻ LP Tregs is *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,
 5 *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the strain of the bacteria that induces the production of Rorγ⁺Helios⁻ LP Tregs is selected from the group consisting of *Bacteroides*
 10 *ovatus*_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus saprophyticus*_DLK1, *Enterococcus faecalis*_HH22, *Bacteroides thetaiotaomicron*_ATCC29741, *Bacteroides vulgatus*_ATCC8482, *Bacteroides uniformis*_ATCC8492, *Enterococcus faecalis*_TX0104, *Lactobacillus casei*_AO47, *Bacteroides fragilis*_CL03T00C08, *Acinetobacter lwoffii*_F78, *Fusobacterium*
 15 *nucleatum*_F0419, *Enterococcus faecalis*_OG1RF, *Bacteroides thetaiotaomicron*_ATCC29148, *Parabacteroides johnsonii*_CL02T12C29, *Bacteroides oleiciplenus*_DSM22535, *Lactobacillus rhamnosus*_LMS2-1, *Bacteroides massiliensis*_DSM17679, *Parabacteroides merdae*_CL03T12C32, *Fusobacterium mortiferum*_AO16, *Bifidobacterium breve*_SK134, *Bacteroides finegoldii*_DSM17565
 20 and/or *Bacteroides fragilis*_3_1_12.

In some embodiments, the bacteria that induce the production of Rorγ⁺Helios⁻ LP Tregs do not express a heterologous gene (*i.e.*, are not recombinant). In some embodiments, the bacteria that induce the production of Rorγ⁺Helios⁻ LP Tregs are recombinant. In some
 25 embodiments, the bacteria that induce the production of Rorγ⁺Helios⁻ LP Tregs are attenuated.

In some embodiments, the bacteria that induce the production of Rorγ⁺Helios⁻ LP Tregs has a genomic sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% homology the genomic sequence of a bacteria strain described herein (*e.g.*,
 30 *Bacteroides ovatus*_CL02T12C04, *Campylobacter jejuni*_AS-84-79, *Staphylococcus saprophyticus*_DLK1, *Enterococcus faecalis*_HH22, *Bacteroides thetaiotaomicron*_ATCC29741, *Bacteroides vulgatus*_ATCC8482, *Bacteroides uniformis*_ATCC8492, *Enterococcus faecalis*_TX0104, *Lactobacillus casei*_AO47, *Bacteroides fragilis*_CL03T00C08, *Acinetobacter lwoffii*_F78, *Fusobacterium*

nucleatum_F0419, *Enterococcus faecalis*_OG1RF, *Bacteroides*
*thetaiotaomicron*_ATCC29148, *Parabacteroides johnsonii*_CL02T12C29, *Bacteroides*
*oleiciplenus*_DSM22535, *Lactobacillus rhamnosus*_LMS2-1, *Bacteroides*
*massiliensis*_DSM17679, *Parabacteroides merdae*_CL03T12C32, *Fusobacterium*
 5 *mortiferum*_AO16, *Bifidobacterium breve*_SK134, *Bacteroides finegoldii*_DSM17565
 and/or *Bacteroides fragilis*_3_1_12).

The bacteria described herein can be grown in culture using methods known in the art. For example, *Bacteroides*, *Clostridia*, *Bifidobacteria*, *Lactobacilli*, *Enterococci*, *Fusobacteria*, *Propionibacteria* and *Peptostreptococcus* can be grown in supplemented
 10 Yeast extract-peptone-glycerol (YPG) medium, Blood Brucella Agar or Blood TSA Agar plates. *Acinetobacter* can be grown in SB medium and LB Agar plates. *Lachnospiraceae*, *Veillonella*, *Coprobacillus* can be grown in chopped meat broth. Anaerobic bacteria can be cultured under strictly anaerobic conditions (80% N₂, 10% H₂, 10% CO₂) at 37 °C in an anaerobic chamber. *Staphylococcus* can be grown aerobically, at 37 °C in L-broth and on
 15 LB Agar plates.

In some embodiments, combinations of species or strains of bacteria induce the production of Rorγ⁺Helios⁺ LP Tregs (e.g., the strains and species of bacteria listed in Figure 5) are used in the methods and/or compositions provided herein. In certain
 20 embodiments, a combination of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 of species or strains of bacteria induce the production of Rorγ⁺Helios⁺ LP Tregs are used in the methods and/or compositions described herein.

In some embodiments, the combination of bacteria used in the compositions and/or methods described herein includes *Bacteroides ovatus* and one or more bacterial strains selected from the group consisting of *Campylobacter jejuni*, *Clostridia ramosum*,
 25 *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
 30 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni* and one or more bacterial strains selected from the group consisting of *Clostridia ramosum*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*,

Bacteroides thetaiotaomicron, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum* and one or more bacterial strains selected from the group consisting of *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus* and one or more bacterial strains selected from the group consisting of *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis* and one or more bacterial strains selected from the group consisting of *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*

massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group consisting of
5 *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*,
Acinetobacter lwoffii, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
Fusobacterium mortiferum, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*
10 and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*
15 and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
20 *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
25 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
30 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*,

Bacteroides massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of
5 *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of
10 *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of
15 *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of
20 *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of
Parabacteroides merdae, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

25 In some embodiments, the combination of bacteria includes *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of
30 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Campylobacter jejuni* and one or more bacterial strains selected from the group consisting of *Clostridia ramosum*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*,
 5 *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
 10 *Clostridia ramosum* and one or more bacterial strains selected from the group consisting of *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*
 15 *massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Staphylococcus saprophyticus* and one or more bacterial strains selected from the group consisting of *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides*
 20 *thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Enterococcus faecalis* and one or more bacterial strains selected from the group consisting of *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*,
 25 *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of

Bacteroides thetaiotaomicron, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
Parabacteroides johnsonii, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
5 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
Bacteroides thetaiotaomicron and one or more bacterial strains selected from the group
consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*,
Acinetobacter lwoffii, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*,
10 *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
Parabacteroides merdae, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
Bifidobacterium breve.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
Bacteroides vulgatus and one or more bacterial strains selected from the group consisting of
15 *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,
Fusobacterium nucleatum, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*,
Lactobacillus rhamnosus, *Bacteroides massiliensis*, *Parabacteroides merdae*,
Fusobacterium mortiferum, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
20 *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting
of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
Parabacteroides johnsonii, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*,
Bacteroides massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
25 *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of
Bacteroides fragilis, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*,
Bacteroides oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
Parabacteroides merdae, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
30 *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
Bacteroides fragilis and one or more bacterial strains selected from the group consisting of
Acinetobacter lwoffii, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium*
5 *nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group
10 consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group
15 consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group
20 consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides*
25 *finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides ovatus*,
5 *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Clostridia ramosum* and one or more bacterial strains selected from the group consisting of *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
10 *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*,
15 *Staphylococcus saprophyticus* and one or more bacterial strains selected from the group consisting of *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
20 *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Enterococcus faecalis* and one or more bacterial strains selected from the group consisting of *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*,
25 *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*,
30 *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*

massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

10 In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
15 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*,
20 *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
25 *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

30

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
5 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*,
10 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
15 *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*,
25 *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Parabacteroides merdae* and one or more bacterial strains selected from the group
30 consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Campylobacter jejuni*,
5 *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Staphylococcus saprophyticus* and one or more bacterial strains selected from the group consisting of *Enterococcus faecalis*, *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*,
10 *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*,
15 *Enterococcus faecalis* and one or more bacterial strains selected from the group consisting of *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
20 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
25 *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group
30 consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,

Parabacteroides merdae, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of
5 *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*,
10 *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*,
15 *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
20 *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
25 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.
30

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus*

rhamnosus, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group
5 consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group
10 consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group
15 consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group
consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
and/or *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Parabacteroides merdae* and one or more bacterial strains selected from the group
consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*,
25 *Fusobacterium mortiferum* and one or more bacterial strains selected from the group
consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridia ramosum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*
30 and one or more bacterial strains selected from the group consisting of *Clostridium histolyticum*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*

massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides*
5 *uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

10 In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
Parabacteroides johnsonii, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*
15 *massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*,
20 *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,
25 *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
30 *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*

massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides massiliensis* and one or more bacterial strains selected from the

group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Staphylococcus saprophyticus*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Clostridium histolyticum* and one or more bacterial strains selected from the group consisting of *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting

of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

5 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
10 *Bifidobacterium breve*.

 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
15 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
20 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*,
25 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
30 *Bifidobacterium breve*.

 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group

consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group
5 consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
10 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

15 In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Enterococcus faecalis*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides thetaiotaomicron* and one or more bacterial strains selected from the group consisting of *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
25 *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*,
30 *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*,
5 *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*,
10 *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*,
15 *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
20 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*,
25 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
30 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

5 In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

10 In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Clostridium histolyticum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus* and one or more bacterial strains selected from the group consisting of *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*,
25 *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,
30 *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

5 In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides thetaiotaomicron*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Bacteroides uniformis* and one or more bacterial strains selected from the group consisting of *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of
5 *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group
10 consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group
15 consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group
20 consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group
25 consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group
consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
and/or *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Parabacteroides merdae* and one or more bacterial strains selected from the group
consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides vulgatus*,
5 *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Lactobacillus casei* and one or more bacterial strains selected from the group consisting of *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
10 *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*,
15 *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*,
20 *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*,
25 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*,
30 *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group

consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group
5 consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
10 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

15 In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides uniformis*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Bacteroides fragilis* and one or more bacterial strains selected from the group consisting of *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

25 In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus*

rhamnosus, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group
5 consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group
10 consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group
15 consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group
consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
and/or *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Parabacteroides merdae* and one or more bacterial strains selected from the group
consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*,
25 *Fusobacterium mortiferum* and one or more bacterial strains selected from the group
consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus casei*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*,
30 *Acinetobacter lwoffii* and one or more bacterial strains selected from the group consisting of
Fusobacterium nucleatum, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*,
Lactobacillus rhamnosus, *Bacteroides massiliensis*, *Parabacteroides merdae*,
Fusobacterium mortiferum, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*,
5 *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or
10 *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

15 In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*,
20 *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Parabacteroides merdae* and one or more bacterial strains selected from the group
25 consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Bacteroides fragilis*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and one or more bacterial strains selected from the group

consisting of *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*,
5 *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*,
10 *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of
15 *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii*
20 and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

25 In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Acinetobacter lwoffii*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

30 In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Parabacteroides johnsonii* and one or more bacterial strains selected from the group consisting of *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides*

massiliensis, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Fusobacterium nucleatum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Bacteroides oleiciplenus* and one or more bacterial strains selected from the group consisting of *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Bacteroides massiliensis* and one or more bacterial strains selected from the

group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Parabacteroides merdae* and one or more bacterial strains selected from the
5 group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

10 In some embodiments, the combination of bacteria includes *Parabacteroides johnsonii*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus* and one or more bacterial strains selected from the group consisting of *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium*
15 *mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides oleiciplenus*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus*, *Bacteroides massiliensis* and one or more bacterial strains selected from the group consisting of *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

5 In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Lactobacillus rhamnosus*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

10 In some embodiments, the combination of bacteria includes *Bacteroides massiliensis*, *Parabacteroides merdae* and one or more bacterial strains selected from the group consisting of *Fusobacterium mortiferum*, *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides massiliensis*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Bacteroides massiliensis*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

20 In some embodiments, the combination of bacteria includes *Parabacteroides merdae*, *Fusobacterium mortiferum* and one or more bacterial strains selected from the group consisting of *Bacteroides finegoldii* and/or *Bifidobacterium breve*.

In some embodiments, the combination of bacteria includes *Parabacteroides merdae*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

25 In some embodiments, the combination of bacteria includes *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

Bacterial Compositions

In certain embodiments, provided herein is a composition (e.g., a pharmaceutical composition, a dietary supplement or a food product) containing bacteria or combinations of bacteria that induce the production of Ror γ ⁺Helios⁺ LP Tregs. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier.

In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from among the bacterial species described herein. 10%,

15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the bacteria in the composition are selected from among the bacterial strains described herein.

5 In some embodiments, the compositions described herein may include only one species of bacteria described herein or may include two or more species of the bacteria described herein. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of the species described herein, in any combination, can be included in the compositions provided herein.

10 In some embodiments, the compositions described herein may include only one strain of the bacteria described herein or may include two or more strains of the bacteria described herein. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 of the strains described herein, in any combination, can be included in the compositions provided herein.

15 In some embodiments, the composition described herein may be a pharmaceutical composition, a dietary supplement, or a food product (*e.g.*, a food or beverage). In some embodiments, the food product is an animal feed.

As described in detail below, the pharmaceutical compositions disclosed herein may be specially formulated for administration in solid or liquid form, including those adapted for oral or rectal administration.

20 In certain embodiments, the pharmaceutical composition for oral administration described herein comprises an additional component that enables efficient delivery of the bacteria to the colon, in order to more efficiently induce the production of LP Tregs in the colon. In some embodiments, pharmaceutical preparation that enables the delivery of the bacteria to the colon can be used. Examples of such formulations include pH sensitive
25 compositions, such as buffered sachet formulations or enteric polymers that release their contents when the pH becomes alkaline after the enteric polymers pass through the stomach. When a pH sensitive composition is used for formulating the pharmaceutical preparation, the pH sensitive composition can be a polymer whose pH threshold of the decomposition of the composition is between about 6.8 and about 7.5.

30 Another embodiment of a pharmaceutical composition useful for delivery of the bacteria to the colon is one that ensures the delivery to the colon by delaying the release of the bacteria by approximately 3 to 5 hours, which corresponds to the small intestinal transit time. In some embodiments, the pharmaceutical composition for delayed release includes a

hydrogel shell. The hydrogel is hydrated and swells upon contact with gastrointestinal fluid, with the result that the contents are effectively released (released predominantly in the colon). Delayed release dosage units include bacteria-containing compositions having a material which coats or selectively coats the bacteria. Examples of such a selective coating material include in vivo degradable polymers, gradually hydrolyzable polymers, gradually water-soluble polymers, and/or enzyme degradable polymers. A wide variety of coating materials for efficiently delaying the release is available and includes, for example, cellulose-based polymers such as hydroxypropyl cellulose, acrylic acid polymers and copolymers such as methacrylic acid polymers and copolymers, and vinyl polymers and copolymers such as polyvinylpyrrolidone.

Examples of composition enabling the delivery to the colon further include bioadhesive compositions which specifically adhere to the colonic mucosal membrane (for example, a polymer described in the specification of U.S. Pat. No. 6,368,586, hereby incorporated by reference) and compositions into which a protease inhibitor is incorporated for protecting particularly a biopharmaceutical preparation in the gastrointestinal tracts from decomposition due to an activity of a protease.

An example of a system enabling the delivery to the colon is a system of delivering a composition to the colon by pressure change in such a way that the contents are released by utilizing pressure change caused by generation of gas in bacterial fermentation at a distal portion of the stomach. Such a system is not particularly limited, and a more specific example thereof is a capsule which has contents dispersed in a suppository base and which is coated with a hydrophobic polymer (for example, ethyl cellulose).

Another example of the system enabling the delivery to the colon is a system of delivering a composition to the colon, the system being specifically decomposed by an enzyme (for example, a carbohydrate hydrolase or a carbohydrate reductase) present in the colon. Such a system is not particularly limited, and more specific examples thereof include systems which use food components such as non-starch polysaccharides, amylose, xanthan gum, and azopolymers.

In some embodiments, the compositions described herein further comprise an immunosuppressive agent. Examples of immunosuppressive agents include, but are not limited to, corticosteroids, mesalazine, mesalamine, sulfasalazine, sulfasalazine derivatives, immunosuppressive drugs, cyclosporin A, mercaptopurine, azathiopurine, prednisone, methotrexate, antihistamines, glucocorticoids, epinephrine, theophylline, cromolyn sodium,

anti-leukotrienes, anti-cholinergic drugs for rhinitis, anti-cholinergic decongestants, mast-cell stabilizers, monoclonal anti-IgE antibodies, vaccines (*e.g.*, vaccines used for vaccination where the amount of an allergen is gradually increased), cytokine inhibitors, such as anti-IL-6 antibodies, TNF inhibitors such as infliximab, adalimumab, certolizumab
5 pegol, golimumab, or etanercept, and combinations thereof.

In some embodiments, the composition is a food product (*e.g.*, a food or beverage) such as a health food or beverage, a food or beverage for infants, a food or beverage for pregnant women, athletes, senior citizens or other specified group, a functional food, a beverage, a food or beverage for specified health use, a dietary supplement, a food or
10 beverage for patients, or an animal feed. Specific examples of the foods and beverages include various beverages such as juices, refreshing beverages, tea beverages, drink preparations, jelly beverages, and functional beverages; alcoholic beverages such as beers; carbohydrate-containing foods such as rice food products, noodles, breads, and pastas; paste products such as fish hams, sausages, paste products of seafood; retort pouch products such
15 as curries, food dressed with a thick starchy sauces, and Chinese soups; soups; dairy products such as milk, dairy beverages, ice creams, cheeses, and yogurts; fermented products such as fermented soybean pastes, yogurts, fermented beverages, and pickles; bean products; various confectionery products, including biscuits, cookies, and the like, candies, chewing gums, gummies, cold desserts including jellies, cream caramels, and frozen
20 desserts; instant foods such as instant soups and instant soy-bean soups; microwavable foods; and the like. Further, the examples also include health foods and beverages prepared in the forms of powders, granules, tablets, capsules, liquids, pastes, and jellies.

In some embodiments the composition is a food product for animals, including humans. The animals, other than humans, are not particularly limited, and the composition
25 can be used for various livestock, poultry, pets, experimental animals, and the like. Specific examples of the animals include pigs, cattle, horses, sheep, goats, chickens, wild ducks, ostriches, domestic ducks, dogs, cats, rabbits, hamsters, mice, rats, monkeys, and the like, but the animals are not limited thereto.

Rory

30 In certain embodiments, provided herein are methods inducing LP Tregs and/or treating a disease or disorder associated with a pathological immune response, such as an inflammatory bowel disease, by inducing Rory. Activation of Rory can, for example, be via an increase in Rory protein activity or Rory protein amount. For example, agents that induce

Ror γ include agents that increase Ror γ protein activity, agents that decrease Ror γ protein degradation, agents that increase Ror γ mRNA stability, and agents that increase transcription and/or translation of nucleic acids encoding Ror γ protein.

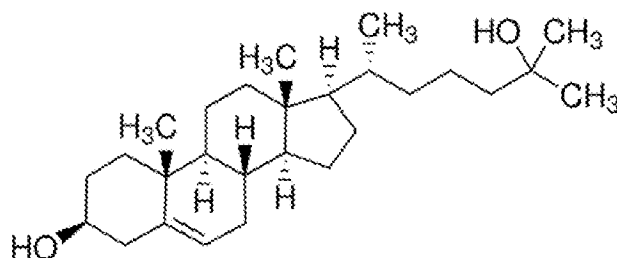
Ror γ is a DNA-binding transcription factor and is a member of the NR1 subfamily of nuclear hormone receptors. Ror γ is encoded by the *Rorc* gene. While Ror γ has previously been reported to be antagonistic to Treg inducing transcription factor FoxP3, as disclosed herein, Ror γ is expressed in a major population of LP Tregs. The amino acid sequence human Ror γ is available at NCBI accession number XP_006711547.2, which is incorporated by reference herein. The nucleic acid sequence of the human Ror γ isoform mRNA is available at NCBI accession numbers XM_006711484.2, which is incorporated by reference herein.

Ror γ Agonists

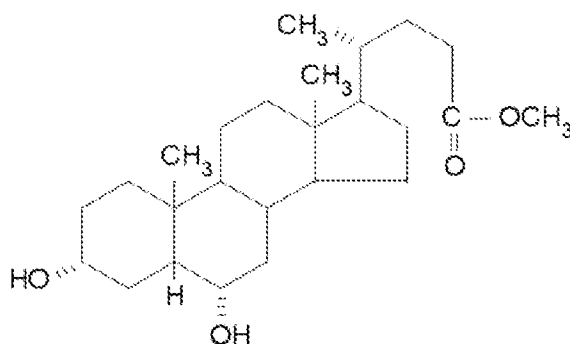
In certain embodiments, provided herein are compositions and methods for inducing Tregs and/or for treating inflammatory bowel disease. These methods include administering an agent that activates Ror γ (*i.e.*, a Ror γ agonist). Such agents include those disclosed below, those known in the art and those identified using the screening assays described herein. In some embodiments, any agent that activates Ror γ can be used to practice the methods disclosed herein. Ror γ agonists may be small molecules, proteins, peptides, nucleic acids, carbohydrates or antibodies. In some embodiments, the Ror γ agonist is a sterol. Exemplary Ror γ agonists are described in Hu *et al.*, *Nature Chemical Biology* 11:141-147 (2015), Soroosh *et al.*, *Proc. Natl. Acad. Sci. USA* 111:12163-12168 (2014) and Santori *et al.*, *Cell Metabolism* 21:286-297 (2015) and U.S. Pat. 8,389,739, each of which is hereby incorporated by reference.

In some embodiments, the Ror γ agonist is a sterol selected from the group consisting of cholesterol sulfate, 25-OHC, 25-OHC sulfate, desmosterol, desmosterol sulfate, 5 α ,6 α -epoxycholestanol sulfate, 7 α ,27-diOHC, 5 α ,6 α -epoxycholestanol, 24S,25-epoxycholesterol, 7 α -OHC, 20 α -OHC, 22R-OHC, 24S-OHC, 27-OHC, 7 β ,27-OHC, 7-keto,27-OHC, 7 α ,27-OHC, 4AC4M Δ° , Δ^7 -daf, zymosterol, 4C, 7DHC, zymosterone, 4C22OH, 4,7-cholesten, 25OH, OR-12872, OR-942, or a prodrug, active derivative or pharmaceutically acceptable salt thereof.

In some embodiments, the Ror γ agonist is 25-OHC, a 25-OHC prodrug, an active derivative of 25-OHC or a pharmaceutically acceptable salt thereof. 25-OHC has the following chemical structure:



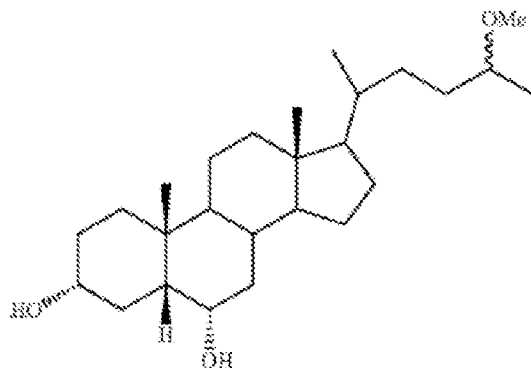
In some embodiments, the Ror γ agonist is hyodeoxycholic acid methyl ester (OR-942), a hyodeoxycholic acid methyl ester prodrug, an active derivative of hyodeoxycholic acid methyl ester or a pharmaceutically acceptable salt thereof. hyodeoxycholic acid methyl ester has the following chemical structure:



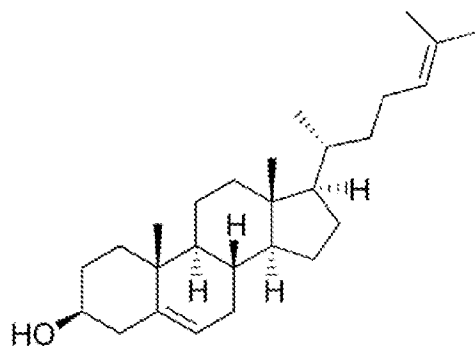
10

In some embodiments, the Ror γ agonist is OR-12872 (4R-[3R,6R-Bis-(tert-butyl-dimethyl-silanyloxy)-10R,13R-dimethyl-5R-8S-9S-14S-hexadecahydrocyclopenta[a]phenanthren-17R-yl]-pentanoic acid methyl ester), an OR-12872 prodrug, an active derivative of OR-12872 or a pharmaceutically acceptable salt thereof. Synthesis of OR-12872 is described in U.S. Pat. 8,389,739, which is hereby incorporated by reference in its entirety. OR-12872 has the following chemical structure:

15

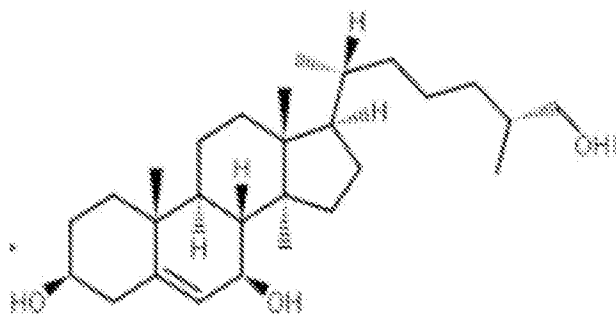


In some embodiments, the Ror γ agonist is desmosterol, a desmosterol prodrug, an active derivative of desmosterol or a pharmaceutically acceptable salt thereof. Desmosterol has the following chemical structure:



5

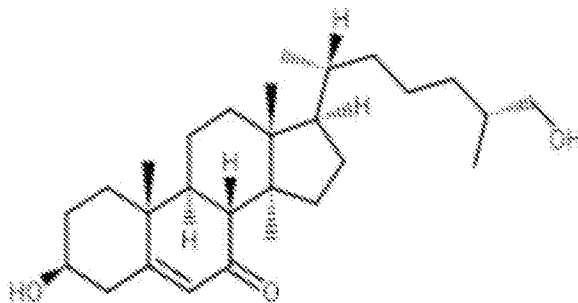
In some embodiments, the Ror γ agonist is 7 β ,27-OHC, a 7 β ,27-OHC prodrug, an active derivative of 7 β ,27-OHC or a pharmaceutically acceptable salt thereof. 7 β ,27-OHC has the following chemical structure:



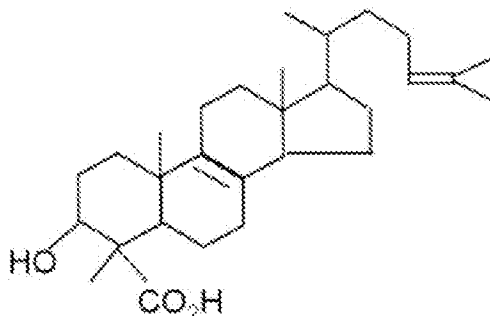
10

In some embodiments, the Ror γ agonist is 7keto,27-OHC, a 7keto,27-OHC prodrug, an active derivative of 7keto,27-OHC or a pharmaceutically acceptable salt thereof. 7keto,27-OHC has the following chemical structure:

15



In some embodiments, the Rory agonist is 4 α -carboxy,4 β -methyl-zymosterol (4ACD8), a 4ACD8 prodrug, an active derivative of 4ACD8 or a pharmaceutically acceptable salt thereof. 4ACD8 has the following chemical structure:



In some embodiments, agents useful in the methods described herein can be identified by screening compound libraries (including sterol libraries) to identify compounds that induce Rory activity (*e.g.*, in a reporter assay, such as those described in Hu *et al.*, *Nature Chemical Biology* 11:141-147 (2015), Soroosh *et al.*, *Proc. Natl. Acad. Sci. USA* 111:12163-12168 (2014) and Santori *et al.*, *Cell Metabolism* 21:286-297 (2015) and U.S. Pat. 8,389,739, each of which is hereby incorporated by reference).

Agents useful in the methods disclosed herein may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Agents may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide

oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.*

- 5 (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

- Libraries of agents may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al.*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

15 Pharmaceutical Compositions

In certain embodiments, provided herein is a composition, *e.g.*, a pharmaceutical composition, containing at least one agent described herein together with a pharmaceutically acceptable carrier. In one embodiment, the composition includes a combination of multiple (*e.g.*, two or more) agents described herein.

- 20 As described in detail below, the pharmaceutical compositions disclosed herein may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; or (2)
- 25 parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation.

- Methods of preparing these formulations or compositions include the step of bringing into association an agent described herein with the carrier and, optionally, one or
- 30 more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association an agent described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Pharmaceutical compositions suitable for parenteral administration comprise one or more agents described herein in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions
5 just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol,
10 propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

15 Regardless of the route of administration selected, the agents provided herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions disclosed herein, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Methods

20 In certain aspects, provided herein are methods for inducing production of Rory⁺Helios⁺ LP Tregs and/or for treating or preventing a disease or disorder associated a pathological immune response, such as an autoimmune disease, an allergic reaction and/or an inflammatory disease. In some embodiments, the disease or disorder is an inflammatory bowel disease (*e.g.*, Crohn's disease or ulcerative colitis).

25 The methods described herein can be used to treat any subject in need thereof. As used herein, a "*subject in need thereof*" includes any subject that has a disease or disorder associated with a pathological immune response (*e.g.*, an inflammatory bowel disease), as well as any subject with an increased likelihood of acquiring a such a disease or disorder.

The compositions described herein can be used, for example, as a composition for
30 preventing or treating (reducing, partially or completely, the adverse effects of) an autoimmune disease. such as chronic inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, or Hashimoto's disease; an allergic disease, such as a food allergy, pollenosis, or asthma; an infectious disease, such as an

infection with *Clostridium difficile*; an inflammatory disease such as a TNF-mediated inflammatory disease (*e.g.*, an inflammatory disease of the gastrointestinal tract, such as pouchitis, a cardiovascular inflammatory condition, such as atherosclerosis, or an inflammatory lung disease, such as chronic obstructive pulmonary disease); a

- 5 pharmaceutical composition for suppressing rejection in organ transplantation or other situations in which tissue rejection might occur; a supplement, food, or beverage for improving immune functions; or a reagent for suppressing the proliferation or function of effector T-cells.

In some embodiments, provided herein are methods of treating an inflammatory
10 bowel disease. Inflammatory bowel diseases include, for example, certain art-recognized forms of a group of related conditions. Several major forms of inflammatory bowel diseases are known, with Crohn's disease (regional bowel disease, *e.g.*, inactive and active forms) and ulcerative colitis (*e.g.*, inactive and active forms) the most common of these disorders. In addition, the inflammatory bowel disease encompasses irritable bowel syndrome,
15 microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis. Other less common forms of IBD include indeterminate colitis, pseudomembranous colitis (necrotizing colitis), ischemic inflammatory bowel disease, Behcet's disease, sarcoidosis, scleroderma, IBD-associated dysplasia, dysplasia associated masses or lesions, and primary sclerosing cholangitis.

20 In some embodiments, administration is in combination with administration of at least one prebiotic substance (*e.g.*, a prebiotic substance that favors the growth of the bacterial species in the composition over the growth of other human commensal bacterial species). In some embodiments, the prebiotic substance is a nondigestible oligosaccharide. In some embodiments, the prebiotic substance is almond skin, inulin, oligofructose,
25 raffinose, lactulose, pectin, hemicellulose, amylopectin, acetyl-Co A, biotin, beet molasses, yeast extracts, and resistant starch.

In some embodiments, the compositions described herein are administered in combination with an immunosuppressive agent. Examples of immunosuppressive agents include corticosteroids, mesalazine, mesalamine, sulfasalazine, sulfasalazine derivatives,
30 immunosuppressive drugs, cyclosporin A, mercaptopurine, azathiopurine, prednisone, methotrexate, antihistamines, glucocorticoids, epinephrine, theophylline, cromolyn sodium, anti-leukotrienes, anti-cholinergic drugs for rhinitis, anti-cholinergic decongestants, mast-cell stabilizers, monoclonal anti-IgE antibodies, vaccines, anti-TNF inhibitors such as

infliximab, adalimumab, certolizumab pegol, golimumab, or etanercept, and combinations thereof. Also described herein is a composition that comprises the bacterial composition and at least one substance selected from the group consisting of corticosteroids, mesalazine, mesalamine, sulfasalazine, sulfasalazine derivatives, immunosuppressive drugs, cyclosporin
5 A, mercaptopurine, azathiopurine, prednisone, methotrexate, antihistamines, glucocorticoids, epinephrine, theophylline, cromolyn sodium, anti-leukotrienes, anti-cholinergic drugs for rhinitis, anti-cholinergic decongestants, mast-cell stabilizers, monoclonal anti-IgE antibodies, vaccines, anti-TNF inhibitors such as infliximab, adalimumab, certolizumab pegol, golimumab, or etanercept, and combinations thereof.

10 In some embodiments, the methods provided herein include the step of administering at least one antibiotic before or in combination with, the administration of a composition described herein.

In some embodiments, the methods provided herein include the step of determining the subject's microbiome prior to the administration of a composition described herein. In
15 some embodiments, the selection of the bacteria or combination of bacteria administered to the subject is determined based upon the make-up of the subject's microbiome.

Actual dosage levels of the bacteria in the compositions described herein may be varied so as to obtain an amount of the bacteria which is effective to achieve the desired therapeutic response for a particular patient. A physician or veterinarian having ordinary
20 skill in the art can readily determine and prescribe the effective amount of the composition required.

The pharmaceutical compositions disclosed herein may be delivered by any suitable route of administration, including orally and parenterally. In certain embodiments the pharmaceutical compositions are delivered generally (e.g., via oral or parenteral
25 administration).

EXEMPLIFICATION

Experimental Procedures

Mice

Mice were bred in a pathogen-free facility or in germ-free isolators. For IL-33
30 administration, recombinant mouse IL-33 (BioLegend) was administered i.p. at 2 µg/ injection every other day for 7 days.

Preparation of lymphocytes and flow cytometry

Intestinal tissues were treated with RPMI containing 1 mM dithiothreitol, 20 mM EDTA and 2% FBS at 37°C for 15 min to remove epithelial cells. The tissues were then minced and dissociated in collagenase solution containing 1.5 mg/ml collagenase II (Gibco) 0.5 mg/ml, dispase and 1% FBS containing RPMI solution constantly stirring at 37 °C for 5 45 min. Single cell suspensions were then filtered and washed with 4% RPMI solution. The Peyer's Patches were treated in a similar fashion except for the first step of removal of epithelial cells. Lymph nodes and spleens were mechanically disrupted.

Single-cell suspensions were stained with antibodies against CD4, CD8, TCR-b, CD45, IL-17A, IFN γ , Helios (Biolegend), Ror γ , Foxp3, ST2((eBioscience), Nr1(R&D Systems), anti-ST2 conjugated to biotin (mdBioproducts). For cytokine analysis, cells were 10 treated with RMPI containing 10% FBS, 10 ng/ml phorbol 12-myristate 13-acetate (Sigma), 1 μ M Ionomycin (Sigma) in presence of GolgiStop (BD Biosciences) for 3.5 hours. For intracellular staining of cytokines and transcription factors, cells were stained for surface markers and fixed in eBioscience Fix/Perm buffer overnight, followed by permeabilization 15 in eBioscience permeabilization buffer for 45 min in the presence of antibodies. Cells were acquired with a BD LSRII and analysis was performed with FlowJo (Tree Star) software.

Gene expression profiling

Cells were double-sorted into TRIzol (Invitrogen) using a MoFlo sorter. All samples were generated in duplicate or triplicate. Sample processing and data analysis were 20 performed on GeneChip Mouse Genome M1.0 ST chip arrays (Affymetrix) as described in D. Cipolletta *et al.*, *Nature* 486, 549 (2012), which is hereby incorporated by reference.

TNBS Colitis

Mice were desensitized via administration of 1% TNBS (prepared in 4:1 acetone: olive oil solution) on shaven skin between the shoulders. A week later, colitis was induced 25 by intrarectal administration of 150-200 μ g TNBS per gram of mouse (Sigma) in 50% ethanol into anaesthetized mice via a thin round-tip needle. The TNBS concentration was optimized for each batch of TNBS used in both germ free and SPF mice. The tip of the needle was inserted 4 cm proximal to the anal verge, and mice were held in a vertical position for at least 1 min after the injection. All the mice were observed and weighed daily 30 and were sacrificed on day 4 after intrarectal TNBS administration at the peak of the disease. A combined colitis score was calculated based on weight loss, histology, diameter of the colon, and the appearance of the stool. For TNBS induction in gnotobiotic mice, mice were colonized with single bacterial species for 2 weeks, as described earlier, prior to

TNBS administration. Weight loss was scored as follows: 0, 0-4% weight loss or weight gain; 1, 4-10% weight loss; 2, 10-15% weight loss; 3, 15-20% weight loss; 4, more than 20% weight loss. The appearance of the stool was assessed as follows: 0, hard; 1, softened stool; 2, diarrhea; 3, bloody diarrhea. The thickness of the colon was assessed based on differential in diameter (Δ diameter=diameter of TNBS treated colon- diameter of untreated colon): 0, no change; 1, Δ diameter <1mm; 2, Δ diameter= 1-2mm; 3, Δ diameter= 2-3mm; 4, Δ diameter>3mm.

Histology

Colons were fixed with Bouin's fixative, sectioned, and stained with haematoxylin and eosin. The degree of inflammation in the distal part of colon was graded from 0 to 4 as follows: 0, normal intact structure; 1, mild inflammation with intact structure; 2, infiltration of leukocytes and some damage to structure; 3, severe inflammation accompanied by complete loss of structure; 4, necrosis of the tissue.

Bioinformatic and statistical analysis

Significance was assessed by the Student's t test. When necessary paired t test was used and a p value of < 0.05 was deemed statistically significant.

Microarray data were background-corrected and normalized using the robust multi-array average (RMA) algorithm implemented in the GenePattern software package and replicates were averaged. Genes that have a mean expression value of at least 120 in any of the samples with a coefficient of variance set for >0.25 were analyzed. Genes that over- or under-represented in colonic Tregs compared with splenic Tregs or in $Rory^+$ Tregs compared with $Rory^-$ Tregs were determined by at least 2-fold or 1.5-fold differential expression respectively. Colon-preferential and tissue-specific gene clusters were determined by clustering genes that are over or under-expressed by 2-fold or higher in any of the tissues compared with spleen. Hierarchical clustering analysis used Pearson correlation in all comparisons. Genes that were over- or under-represented by 1.5 fold or higher in colonic Tregs compared with all non-lymphoid tissues were considered colon-preferential. Genes that have p values >0.05 at and FDR of 0.1 were deemed significant.

Example 1: Expression of *Rory* by colonic regulatory T cells

Comparison of gene expression profiles of highly purified $CD4^+FoxP3^+$ Tregs (from *Foxp3^{igfp}* reporter mice, described Bettelli *et al.*, *Nature* **441**, 235 (2006), which is hereby incorporated by reference) from colon or spleen uncovered 933 differential transcripts (at a FoldChange > 2 and FDR < 0.1; Fig. 1A (top), Fig. 2). Among these differential transcripts,

several important signaling and effector pathways (including *Icos*, *Gzmb*, *Lag3*, *Areg*, *IL1rl1*; Fig. 1A (top)), were shared in patchwork manner by other tissue Tregs, but ~39% (at a colon specific bias > 1.5 fold compared to other tissues) had preferential expression in colonic Tregs (including *Il10*, *Ctla4*, *Havcr2*, *Ccl20*, *Jak2*, *Fosl2*; Fig. 1A (bottom)).

- 5 Correspondingly, several transcription factors were over-expressed in colon, including *Ahr*, *Epas1*, *Hey1*, *Bcl6*, *Npas2*, *Nr1d1*, and *Maf*. The most differential of these transcription factors was *Rorc* (gene that encodes Ror γ ; Fig. 1B, 1C). Ror γ controls many aspects of innate and adaptive immunocyte differentiation, and is known as the key regulator of IL17 producing CD4⁺ T cells (Th17), and as a reciprocal antagonist of FoxP3 during in vitro
- 10 differentiation in which iTreg and Th17 represent alternative cell fates (reviewed in Korn *et al.*, *Annu. Rev. Immunol.* **27**, 485 (2009), which is hereby incorporated by reference).

- Flow cytometry confirmed that a large proportion of colonic CD4⁺FoxP3⁺ Tregs indeed expressed Ror γ (40-60% in adult SPF mice), a phenotype largely absent in spleen or lymph node (LN) (Fig. 1C). Helios and Nr1d1, which are considered markers of thymus-
- 15 derived Tregs (reviewed in Bilate and Lafaille, *Annu. Rev. Immunol.* **30**, 733 (2012), which is hereby incorporated by reference), were absent on colonic Ror γ ⁺ Tregs (Fig. 1D, Fig. 3A). The combination of Ror γ and Helios demarcated three distinct subsets of colonic Tregs, Ror γ ⁺ representing the majority of Helios⁻ cells (Fig. 1D, 3A left). This pattern was also seen for Treg cells in other tissues, and consistent with the RNA data. Ror γ ⁺ Tregs
- 20 were also detected in the small intestine and in the regenerating muscle, albeit at lower frequencies (Fig. 1E). Ror γ ⁺ Tregs were distinct from those expressing the IL-33 receptor, most of which were Helios⁺ (Fig. 1D, Fig. 3B). Rare Tregs expressing IL-17 and Ror γ have been observed during chronic inflammation or cancer, usually with high levels of Helios suggestive of a thymic origin (reviewed in Du *et al.*, *J. Leukoc. Biol.* **96**, 39 (2014), hereby
- 25 incorporated by reference). IL-17 production in colonic Ror γ ⁺ Tregs was tested. In contrast to the clear subset of IL-17 expressing Tregs in the small intestine LP, colonic Ror γ ⁺ Tregs did not secrete IL-17A or F (Fig. 1F).

Example 2: Certain Species of Gut Microbacteria Induce Ror γ ⁺ Regulatory T cells

- The properties of colonic Ror γ ⁺ Treg population suggested a link to the gut
- 30 microbiota. Germ free (GF) mice had a far lower proportion of Ror γ ⁺ Tregs than their conventionally-raised specific-pathogen-free (SPF) counterparts (Fig. 4A). During normal maturation of SPF mice, Ror γ ⁺ Tregs appeared between 15 and 25 days of age (Fig. 4B), coincident with the radical changes in the gut microbiota that accompany the transition to

solid food. Interestingly, Ror γ^+ Tregs appeared a few days after cells with a Ror γ^+ Helios $^-$ phenotype. Oral antibiotic treatment of adult mice strongly affected Ror γ^+ Tregs (Fig. 4C), a large reduction following a broad-spectrum combination (vancomycin, neomycin, metronidazole, ampicillin “VMNA”) while individual antibiotics have less or no effect
 5 suggested the contribution of several microbes.

A panel of bacterial species selected from the microbiota of the human gastrointestinal tract were tested for their ability to induce the production of Ror γ^+ Tregs. Bacteria were obtained from the ATCC, BEI Resources, or the German Collection of Microorganisms and Cell Cultures (DSMZ), or from the laboratory collections at Harvard
 10 Medical School. Anaerobic bacteria were cultured under strictly anaerobic conditions (80% N₂, 10% H₂, 10% CO₂) at 37°C in an anaerobic chamber.

Germfree C57BL/6J were maintained in sterile isolators, and were inoculated by gavage with single bacterial species at 4 weeks of age, then housed in gnotobiotic isolators. After 2 weeks, mice were sacrificed, colon tissue was harvested, cleaned of luminal content
 15 and treated with RPMI containing 1 mM DTT, 20 mM EDTA and 2% FBS at 37°C for 15 min to remove epithelial cells. The colon tissue was then minced and dissociated in collagenase solution (1.5mg/ml collagenase II (Gibco), 0.5mg/ml dispase and 1%FBS in RPMI) with constantly stirring at 37°C for 45min. Single cell suspensions were then filtered and washed in RPMI buffer, and stained with antibodies against CD4, CD8, TCR- β , CD45,
 20 then fixed in eBioscience Fix/Perm buffer overnight, followed by permeabilization in eBioscience permeabilization buffer for 45 min in the presence of conjugated anti-Foxp3 and anti-Ror γ antibodies. Cells were analyzed with a BD LSRII flow cytometer, and data analysis was performed with FlowJo (Tree Star) software. The proportion of Ror γ^+ Tregs was determined within the total population of CD4 $^+$ FoxP3 $^+$ Treg cells, and the significance
 25 of the difference relative to unmanipulated germfree mice determined using a two-tailed Student’s T-test. False-discovery rates were estimated using the Benjamini–Hochberg procedure.

A number of microbes elicited colonic Ror γ^+ Tregs, with a reproducible gradient of responses, and for some at frequencies comparable with those of SPF mice (Fig. 4D and 5).
 30 This restoration of Ror γ^+ Tregs was independent of bacterial load and not accompanied by inflammation (Fig. 6). Bacteria able to induce Ror γ^+ Treg (and FoxP3 $^+$ Tregs more generally) belonged to several phyla and genera. The ability to promote colonic Treg production within the *Bacteroides* genus varied (high proportions with *B. thetaiotaomicron*,

low with *B. fragilis*). A wider *Bacteroides* panel was assessed (Fig. 4E and 5). Here again, a range of abilities to induce colonic Ror γ^+ Tregs was observed. Colonic Ror γ^+ Tregs did not appear immediately after GF colonization, but only after a few days. Here again, Ror γ^+ Helios $^-$ Tregs appeared to follow Ror γ^+ Helios $^-$ cells (Fig. 4F), suggesting that the Ror γ^+ Helios $^-$ cells are a first differentiation intermediate, prior to the induction of Ror γ .

Example 3: Reduced gut regulatory T cells in Ror γ deficient mice

Foxp3-cre Rorc^{fl/fl} mice were generated. Such mice have a Treg-selective deficiency in *Rorc*. These mice do not show systemic Treg deficiency or *scurfy*-like pathology, but the amount of total colonic Tregs, and more specifically that of Helios $^-$ Tregs, was reduced (Fig. 7). The loss of Ror γ^+ Tregs in *Foxp3-cre Rorc^{fl/fl}* mice was accompanied by an increase of IL-17 and IFN γ production among FoxP3 $^-$ conventional CD4 $^+$ T cells (Fig. 8A), suggesting a decreased regulatory activity of colonic Tregs in the absence of Ror γ . To verify this point, *Foxp3-cre Rorc^{fl/fl}* mice were assessed in the Trinitrobenzenesulfonic acid- (TNBS) induced colitis model. *Foxp3-cre.Rorc^{fl/fl}* mice showed significant exacerbation of disease severity, reflected in the overall colitis score and the histopathology (Figs. 8B and 8C, Fig. 9). In GF mice monocolonized with microbes that induce different levels of Ror γ^+ Tregs, and challenged in the TNBS sensitization model, a significant correlation between the frequency of Ror γ^+ Tregs and the colitis score was observed (Fig. 8D). These results demonstrate a non-redundant role for Ror γ^+ Tregs in colonic homeostasis.

Example 4: Ror γ function in Ror γ^+ regulatory T cells

What transcripts Ror γ controls in Ror γ^+ Tregs, and whether it is necessary to specify this particular Treg lineage was also examined. Gene expression profiles of Ror γ^+ and Ror γ^- colonic Tregs (from an intercross of *Foxp3^{thy1.1}* and *Rorc^{gfp}* reporter mice) were compared. Ror γ^+ Tregs were enriched relative to Ror γ^- Tregs in some, but not all, transcripts of the colonic Treg signature (Fig. 10A), notably *Il23r*, *Cxcr3*, *Tbx21* and *Havcr2*. Preferential expression of some of the corresponding proteins, including Cxcr3, was validated (Fig. 10B). *Il1rl1* (encodes IL-33R), *Nrp1* and *Ikzf2* were underrepresented in Ror γ^+ Tregs.

It was next examined how the transcripts associated with Ror γ in colonic Tregs relate to the Ror γ -dependent signature in conventional Th17 cells, as defined from a comparison of CD4 $^+$ T cells from the small intestine of mice colonized, or not, with Segmented Filamentous Bacteria, classic inducers of Ror γ^- dependent Th17 cells (Fig. 10C). Much of the classic Th17 signature did not correlate with Ror γ in colonic Tregs (Fig. 10C), and there was only a minority of shared transcripts (*e.g.* *Rorc* itself, *Il23r*, *Ccl20*, as

well as *Il17a*). In contrast, Rorγ in colonic Tregs was specifically associated with Treg preferential transcripts (Fig. 10C, *e.g. Havrc2, Lag3, Tbx21*).

Incorporation by Reference

5 All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method of inducing the production of Ror γ ⁺Helios⁺ lamina propria regulatory T cells in a subject comprising administering to the subject a composition comprising a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
2. The method of claim 1, wherein the composition does not comprise a bacterium of the Clostridia class.
3. The method of claim 1 or claim 2, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
4. The method of claim 3, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
5. The method of claim 3, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

6. The method of claim 3, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
7. The method of claim 3, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
8. The method of claim 3, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
9. The method of any one of claims 1 to 8, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.
10. The method of any one of claims 1 to 8, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.
11. The method of any one of claims 1 to 8, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.

12. The method of any one of claims 1 to 8, wherein the bacteria is *Bacteroides ovatus*.
13. The method of any one of claims 1 to 8, wherein the bacteria is *Campylobacter jejuni*.
14. The method of any one of claims 1 to 8, wherein the bacteria is *Staphylococcus saprophyticus*.
15. The method of any one of claims 1 to 8, wherein the bacteria is *Enterococcus faecalis*.
16. The method of any one of claims 1 to 15, wherein the composition further comprises a pharmaceutically acceptable carrier.
17. The method of any one of claims 1 to 15, wherein the composition is a food product supplemented with the bacteria.
18. The method of any one of claims 1 to 17, wherein the subject has or is predisposed to a disease associated with a pathological immune response.
19. The method of any one of claims 1 or 18, wherein the subject has or is predisposed to an inflammatory bowel disease.
20. The method of claim 19, wherein the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease.
21. The method of claim 20, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.
22. The method of any one of claims 1 to 21, wherein the composition is administered orally.
23. The method of any one of claims 1 to 16 or 18 to 21, wherein the composition is administered rectally.
24. The method of any one of claims 1 to 23, wherein the bacteria are live, replication competent bacteria.
25. The method of any one of claims 1 to 24, wherein the subject had been administered an antibiotic less than a week prior to administration of the composition.
26. The method of claim 25, wherein the subject had been administered an antibiotic less than 3 days prior to administration of the composition.

27. The method of any one of claims 1 to 26, wherein the subject has reduced levels of commensal bacteria present in their gut.
28. A method of treating or preventing an inflammatory bowel disease in a subject comprising administering to the subject a composition comprising a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
29. The method of claim 28, wherein the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmacytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease.
30. The method of claim 29, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.
31. The method of any one of claims 28 to 30, wherein the administration of the composition induces the production of Ror γ ⁺Helios⁺ lamina propria regulatory T cells in the subject.
32. The method any one of claims 28 to 31, wherein the composition does not comprise a bacterium of the Clostridia class.
33. The method of any one of claims 28 to 32, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
34. The method of claim 33, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*,

Bacteroides vulgatus, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

35. The method of claim 33, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

36. The method of claim 33, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

37. The method of claim 33, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

38. The method of claim 33, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

39. The method of any one of claims 28 to 38, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.
40. The method of any one of claims 28 to 38, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.
41. The method of any one of claims 28 to 38, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.
42. The method of any one of claims 28 to 38, wherein the bacteria is *Bacteroides ovatus*.
43. The method of any one of claims 28 to 38, wherein the bacteria is *Campylobacter jejuni*.
44. The method of any one of claims 28 to 38, wherein the bacteria is *Staphylococcus saprophyticus*.
45. The method of any one of claims 28 to 38, wherein the bacteria is *Enterococcus faecalis*.
46. The method of any one of claims 28 to 45, wherein the composition further comprises a pharmaceutically acceptable carrier.
47. The method of any one of claims 28 to 45, wherein the composition is a food product supplemented with the bacteria.
48. The method of any one of claims 28 to 47, wherein the composition is administered orally.
49. The method of any one of claims 28 to 46, wherein the composition is administered rectally.
50. The method of any one of claims 28 to 49, wherein the bacteria are live, replication competent bacteria.
51. A composition for inducing the production of Ror γ ⁺Helios⁺ lamina propria regulatory T cells in a subject comprising a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus*

faecalis, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

52. The composition of claim 51, wherein the composition does not comprise a bacterium of the Clostridia class.

53. The composition of claim 51 or claim 52, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

54. The composition of claim 53, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

55. The composition of claim 53, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

56. The composition of claim 53, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

57. The composition of claim 53, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

58. The composition of claim 53, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

59. The composition of any one of claims 51 to 58, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.

60. The composition of any one of claims 51 to 58, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.

61. The composition of any one of claims 51 to 58, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.

62. The composition of any one of claims 51 to 58, wherein the bacteria is *Bacteroides ovatus*.

63. The composition of any one of claims 51 to 58, wherein the bacteria is *Campylobacter jejuni*.

64. The composition of any one of claims 51 to 58, wherein the bacteria is *Staphylococcus saprophyticus*.
65. The composition of any one of claims 51 to 58, wherein the bacteria is *Enterococcus faecalis*.
66. The composition of any one of claims 51 to 65, wherein the composition further comprises a pharmaceutically acceptable carrier.
67. The composition of any one of claims 51 to 65, wherein the composition is a food product supplemented with the bacteria.
68. The composition of any one of claims 51 to 67, wherein the composition is formulated for oral administration.
69. The composition of any one of claims 51 to 66, wherein the composition is formulated for rectal administration.
70. The composition of any one of claims 51 to 69, wherein the bacteria are live, replication competent bacteria.
71. A method of making a composition for inducing the production of Rorγ⁺Helios⁺ lamina propria regulatory T cells in a subject comprising combining a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve* with a pharmaceutically acceptable carrier.
72. The method of claim 71, wherein the composition does not comprise a bacterium of the Clostridia class.
73. The method of claim 71 or claim 72, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

74. The method of claim 73, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

75. The method of claim 73, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

76. The method of claim 73, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

77. The method of claim 73, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

78. The method of claim 73, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

79. The method of any one of claims 71 to 78, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.

80. The method of any one of claims 71 to 78, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.

81. The method of any one of claims 71 to 78, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.

82. The method of any one of claims 71 to 78, wherein the bacteria is *Bacteroides ovatus*.

83. The method of any one of claims 71 to 78, wherein the bacteria is *Campylobacter jejuni*.

84. The method of any one of claims 71 to 78, wherein the bacteria is *Staphylococcus saprophyticus*.

85. The method of any one of claims 71 to 78, wherein the bacteria is *Enterococcus faecalis*.

86. The method of any one of claims 71 to 85, wherein the composition is formulated for oral administration.

87. The method of any one of claims 71 to 85, wherein the composition is formulated for rectal administration.

88. The method of any one of claims 71 to 87, wherein the bacteria are live, replication competent bacteria.

89. A method of making a composition for inducing the production of Ror γ ⁺Helios⁺ lamina propria regulatory T cells in a subject comprising combining a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*,

Fusobacterium nucleatum, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve* with a food product.

90. The method of claim 89, wherein the composition does not comprise a bacterium of the Clostridia class.

91. The method of claim 89 or 90, wherein the food product comprises a dairy product.

92. The method of claim 91, wherein the dairy product is yogurt, frozen yogurt, ice cream, milk or cheese.

93. The method of claim 89 or 90, wherein the food product is a non-dairy food product.

94. The method of any one of claims 89 to 93, wherein the food product is a beverage.

95. The method of any one of claims 89 to 94, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

96. The method of claim 95, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

97. The method of claim 95, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

98. The method of claim 95, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

99. The method of claim 95, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

100. The method of claim 95, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

101. The method of any one of claims 89 to 100, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.

102. The method of any one of claims 89 to 100, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.

103. The method of any one of claims 89 to 100, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.
104. The method of any one of claims 89 to 100, wherein the bacteria is *Bacteroides ovatus*.
105. The method of any one of claims 89 to 100, wherein the bacteria is *Campylobacter jejuni*.
106. The method of any one of claims 89 to 100, wherein the bacteria is *Staphylococcus saprophyticus*.
107. The method of any one of claims 89 to 100, wherein the bacteria is *Enterococcus faecalis*.
108. The method of any one of claims 89 to 107, wherein the bacteria are live, replication competent bacteria.
109. A composition for inducing the production of Ror γ ⁺Helios⁺ lamina propria regulatory T cells in a subject comprising a food product supplemented with a bacteria selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
110. The composition of claim 109, wherein the composition does not comprise a bacterium of the Clostridia class.
111. The composition of claim 109 or 110, wherein the food product comprises a dairy product.
112. The composition of claim 111, wherein the dairy product is yogurt, frozen yogurt, ice cream, milk or cheese.
113. The composition of claim 109 or 110, wherein the food product is a non-dairy food product.
114. The composition of any one of claims 109 to 113, wherein the food product is a beverage.
115. The composition of any one of claims 109 to 114, wherein at least 10% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*,

Campylobacter jejuni, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

116. The composition of claim 115, wherein at least 25% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

117. The composition of claim 115, wherein at least 50% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

118. The composition of claim 115, wherein at least 75% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

119. The composition of claim 115, wherein at least 90% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides*

oleiciplenus, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

120. The composition of claim 115, wherein at least 99% of the bacteria in the composition are selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

121. The composition of any one of claims 109 to 120, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum* and *Parabacteroides johnsonii*.

122. The composition of any one of claims 109 to 120, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron* and *Bacteroides vulgatus*.

123. The composition of any one of claims 109 to 120, wherein the bacteria is selected from the group consisting of *Bacteroides ovatus*, *Campylobacter jejuni*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*.

124. The composition of any one of claims 109 to 120, wherein the bacteria is *Bacteroides ovatus*.

125. The composition of any one of claims 109 to 120, wherein the bacteria is *Campylobacter jejuni*.

126. The composition of any one of claims 109 to 120, wherein the bacteria is *Staphylococcus saprophyticus*.

127. The composition of any one of claims 109 to 120, wherein the bacteria is *Enterococcus faecalis*.

128. The composition of any one of claims 109 to 127, wherein the bacteria are live, replication competent bacteria.

129. The method or composition of any one of claims 1, 28, 51, 71, 89 or 109, wherein *Bacteroides ovatus* is present in combination with one or more of *Campylobacter jejuni*,

Staphylococcus saprophyticus, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

130. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 wherein *Campylobacter jejuni* is present in combination with one or more of

Staphylococcus saprophyticus, *Enterococcus faecalis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

131. The method or composition of any one of claims 1, 28, 51, 71, 89, 109, 129 and 130 wherein *Staphylococcus saprophyticus* is present in combination with one or more of

Enterococcus faecalis, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

132. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 131, wherein *Enterococcus faecalis* is present in combination with one or more of

Bacteroides thetaiotaomicron, *Bacteroides vulgatus*, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

133. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 132, wherein *Bacteroides thetaiotaomicron* is present in combination with one or more

Bacteroides vulgatus, *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

134. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 133, wherein *Bacteroides vulgatus* is present in combination with one or more *Bacteroides uniformis*, *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
135. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 134, wherein *Bacteroides uniformis* is present in combination with one or more *Lactobacillus casei*, *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
136. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 135, wherein *Lactobacillus casei* is present in combination with one or more *Bacteroides fragilis*, *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
137. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 136, wherein *Bacteroides fragilis* is present in combination with one or more *Acinetobacter lwoffii*, *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
138. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 137, wherein *Acinetobacter lwoffii* is present in combination with one or more *Fusobacterium nucleatum*, *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
139. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 138, wherein *Fusobacterium nucleatum* is present in combination with one or more *Parabacteroides johnsonii*, *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.

140. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 139, wherein *Parabacteroides johnsonii* is present in combination with one or more *Bacteroides oleiciplenus*, *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
141. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 140, wherein *Bacteroides oleiciplenus* is present in combination with one or more *Lactobacillus rhamnosus*, *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
142. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 141, wherein *Lactobacillus rhamnosus* is present in combination with one or more *Bacteroides massiliensis*, *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
143. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 142, wherein *Bacteroides massiliensis* is present in combination with one or more *Parabacteroides merdae*, *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
144. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 143, wherein *Parabacteroides merdae* is present in combination with one or more *Fusobacterium mortiferum*, *Bacteroides finegoldii* and *Bifidobacterium breve*.
145. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 144, wherein *Fusobacterium mortiferum* is present in combination with one or more *Bacteroides finegoldii* and *Bifidobacterium breve*.
146. The method or composition of any one of claims 1, 28, 51, 71, 89, 109 and 129 to 145, wherein *Bacteroides finegoldii* is present in combination with *Bifidobacterium breve*.
147. The method or composition of any one of claims 129 to 146, wherein *Clostridia ramosum* is also present.
148. The method or composition of any one of claims 129 to 147, wherein *Clostridia histolyticum* is also present.
149. A method of inducing the production or activity of regulatory T cells in a subject comprising administering to the subject an agent that activates Ror γ .
150. The method of claim 149, wherein the regulatory T cells are lamina propria regulatory T cells.

151. The method of claim 149 or claim 150, wherein the subject has or is predisposed to a disease associated with a pathological immune response.
152. The method of claim 149 or 150, wherein the subject has or is predisposed to an inflammatory bowel disease.
153. The method of claim 152, wherein the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease.
154. The method of claim 152, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.
155. The method of any one of claims 149 to 154, wherein the agent is a small molecule.
156. The method of any one of claims 149 to 154, wherein the agent is a sterol.
157. The method of claim 156, wherein the sterol is selected from the group consisting of cholesterol sulfate, 25-OHC, 25-OHC sulfate, desmosterol, desmosterol sulfate, 5 α ,6 α -epoxycholestanol sulfate, 7 α ,27-diOHC, 5 α ,6 α -epoxycholestanol, 24S,25-epoxycholesterol, 7 α -OHC, 20 α -OHC, 22R-OHC, 24S-OHC, 27-OHC, 7 β ,27-OHC, 7-keto,27-OHC, 7 α ,27-OHC, 4AC4M Δ° , Δ^7 -daf, zymosterol, 4C, 7DHC, zymosterone, 4C22OH, 4,7-cholesten, 25OH, OR-12872 and OR-942.
158. The method of claim 156, wherein the sterol is 25-OHC, desmosterol or 7 β ,27-OHC.
159. A method of treating or preventing a disease associated with a pathological immune response in a subject comprising administering to the subject an agent that activates Ror γ .
160. The method of claim 159, wherein the disease associated with a pathological immune response is an inflammatory bowel disease.
161. The method of claim 160, wherein the inflammatory bowel disease is Crohn's disease, ulcerative colitis, irritable bowel syndrome, microscopic colitis, lymphocytic-plasmocytic enteritis, coeliac disease, collagenous colitis, lymphocytic colitis and eosinophilic enterocolitis, indeterminate colitis, infectious colitis, pseudomembranous colitis, ischemic inflammatory bowel disease or Behcet's disease.
162. The method of claim 161, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

163. The method of any one of claims 149 to 162, wherein the agent is administered in an amount sufficient to induce the production or activity of regulatory T cells in the subject.
164. The method of claim 163, wherein the regulatory T cells are lamina propria regulatory T cells.
165. The method of any one of claims 159 to 164, wherein the agent is a small molecule.
166. The method of any one of claims 159 to 164, wherein the agent is a sterol.
167. The method of claim 166, wherein the sterol is selected from the group consisting of cholesterol sulfate, 25-OHC, 25-OHC sulfate, desmosterol, desmosterol sulfate, 5 α ,6 α -epoxycholestanol sulfate, 7 α ,27-diOHC, 5 α ,6 α -epoxycholestanol, 24S,25-epoxycholesterol, 7 α -OHC, 20 α -OHC, 22R-OHC, 24S-OHC, 27-OHC, 7 β ,27-OHC, 7-keto,27-OHC, 7 α ,27-OHC, 4AC4M Δ° , Δ 7-daf, zymosterol, 4C, 7DHC, zymosterone, 4C22OH, 4,7-cholesten, 25OH, OR-12872 and OR-942.
168. The method of claim 166, wherein the sterol is 25-OHC, desmosterol or 7 β ,27-OH.

Figure 1

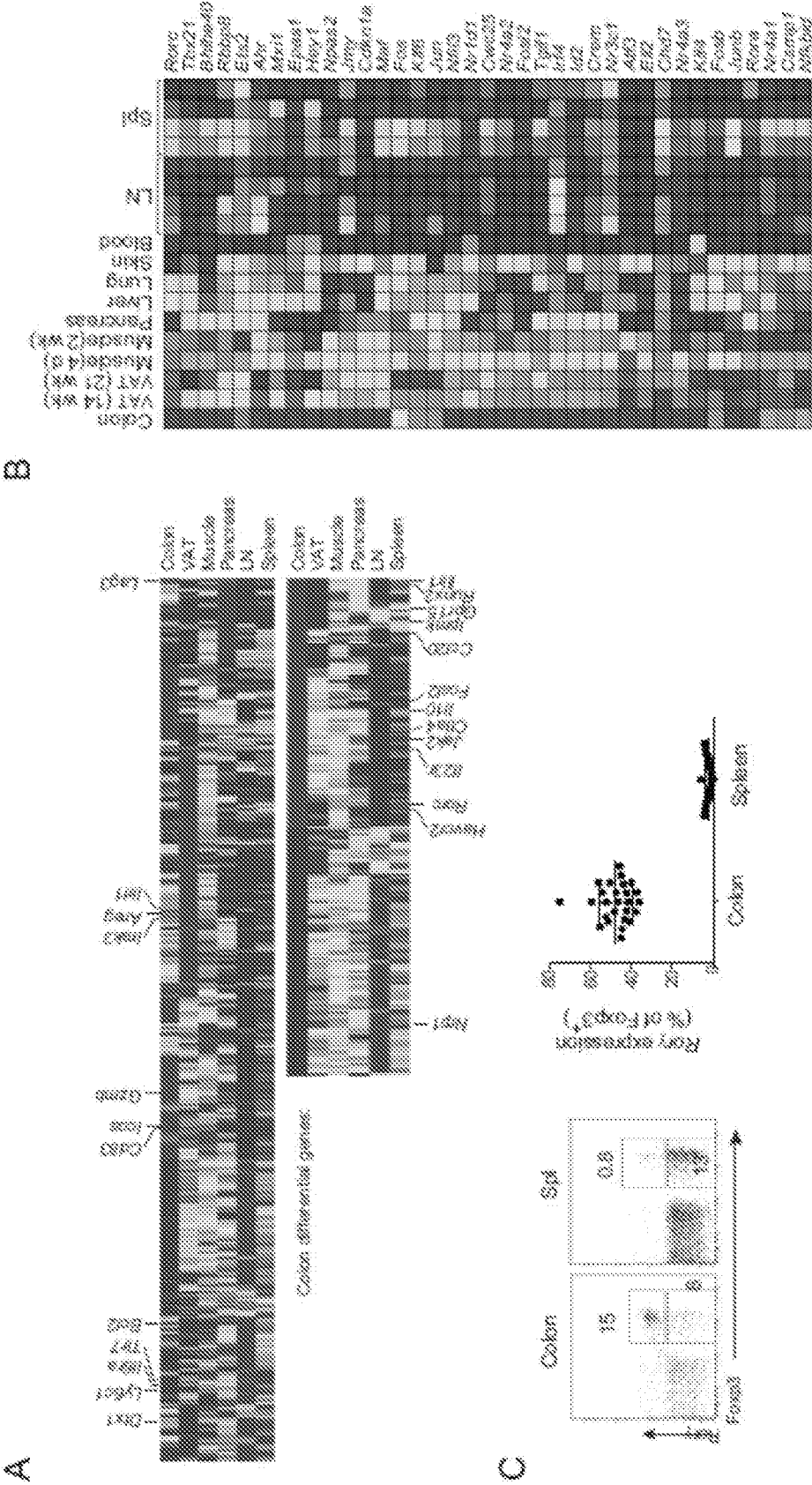


Figure 1 (Continued)

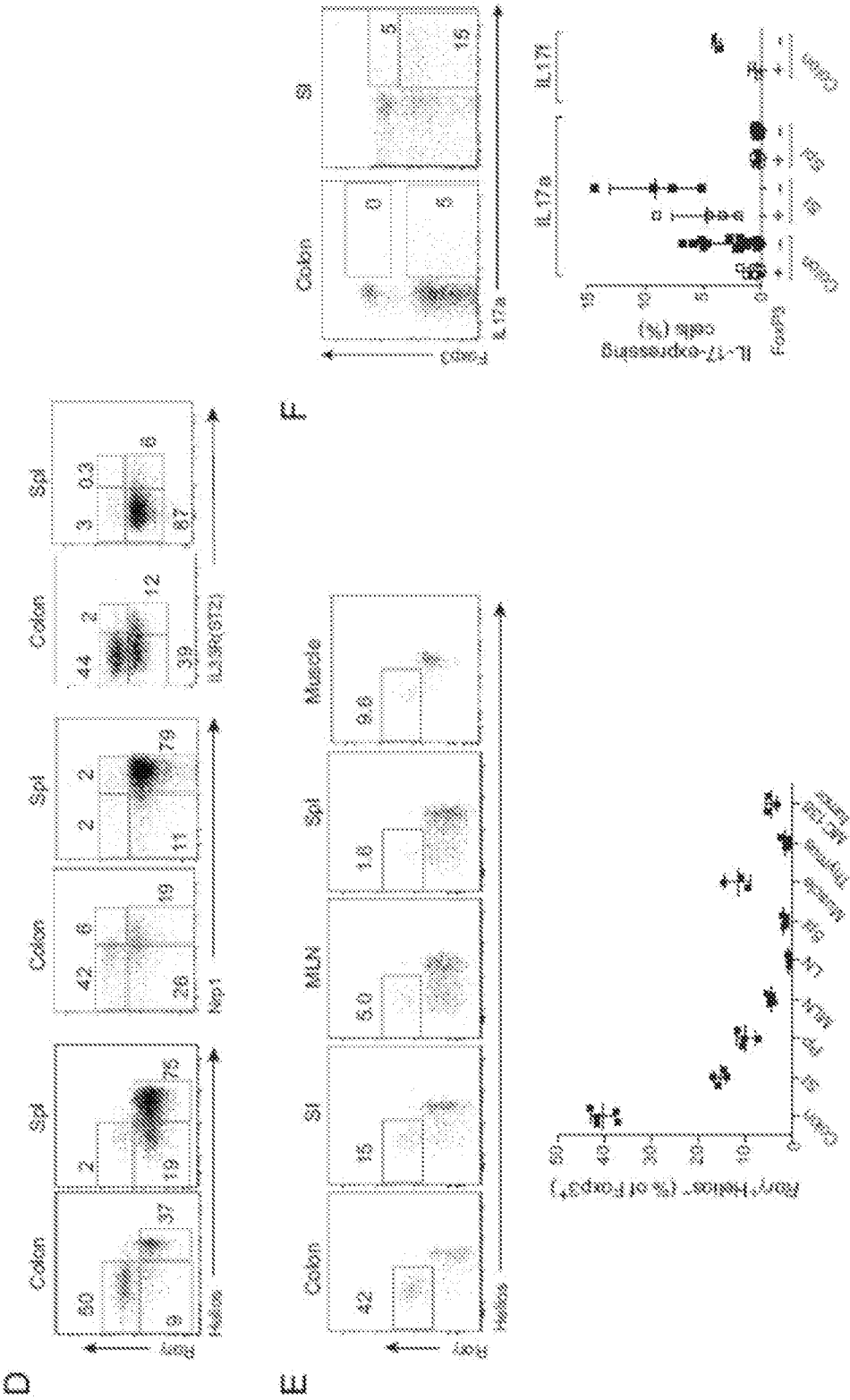


Figure 2

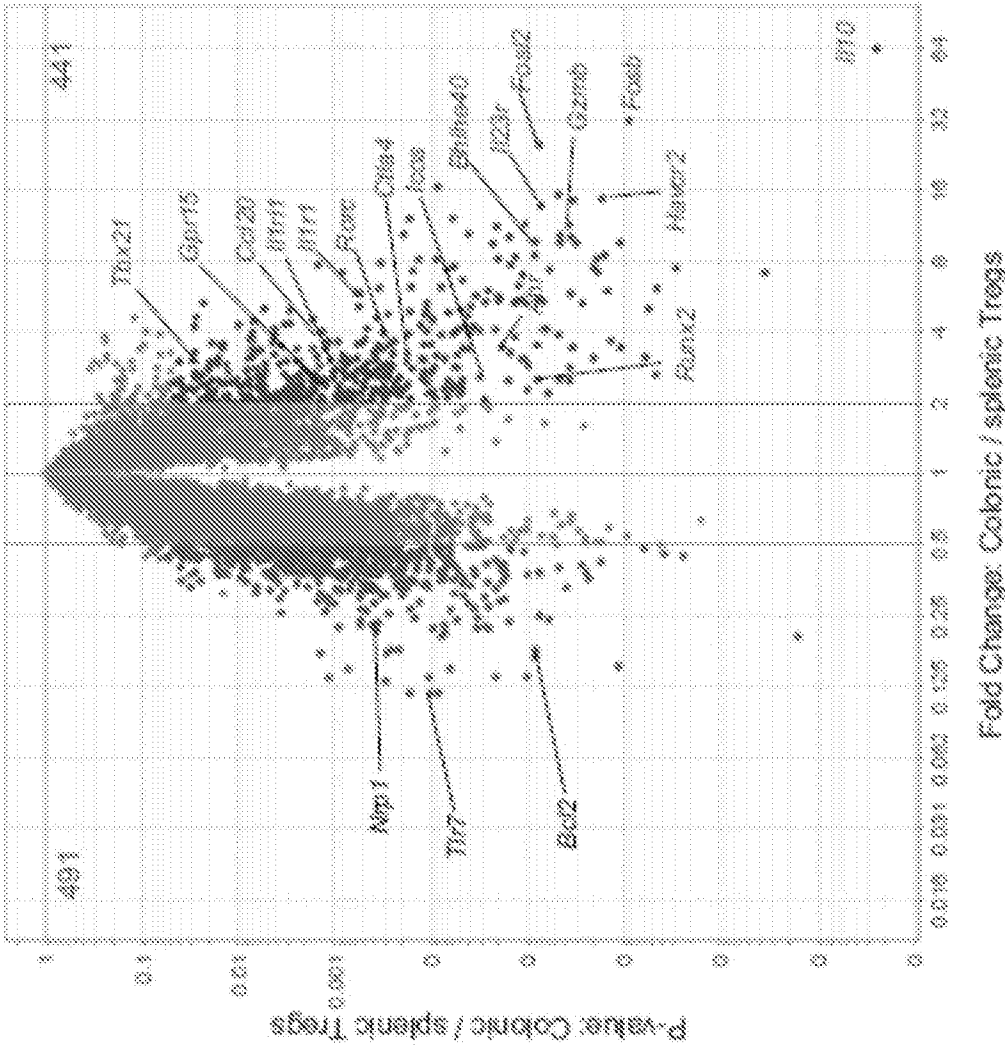
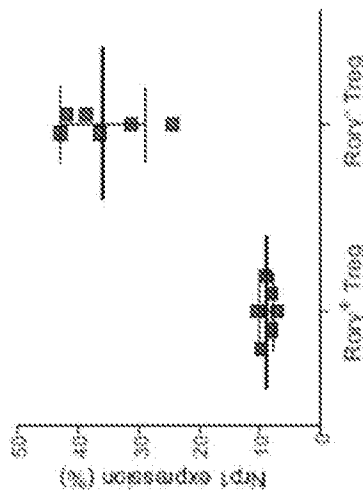
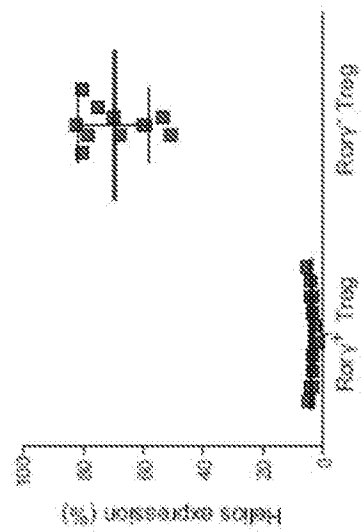


Figure 3

A



B

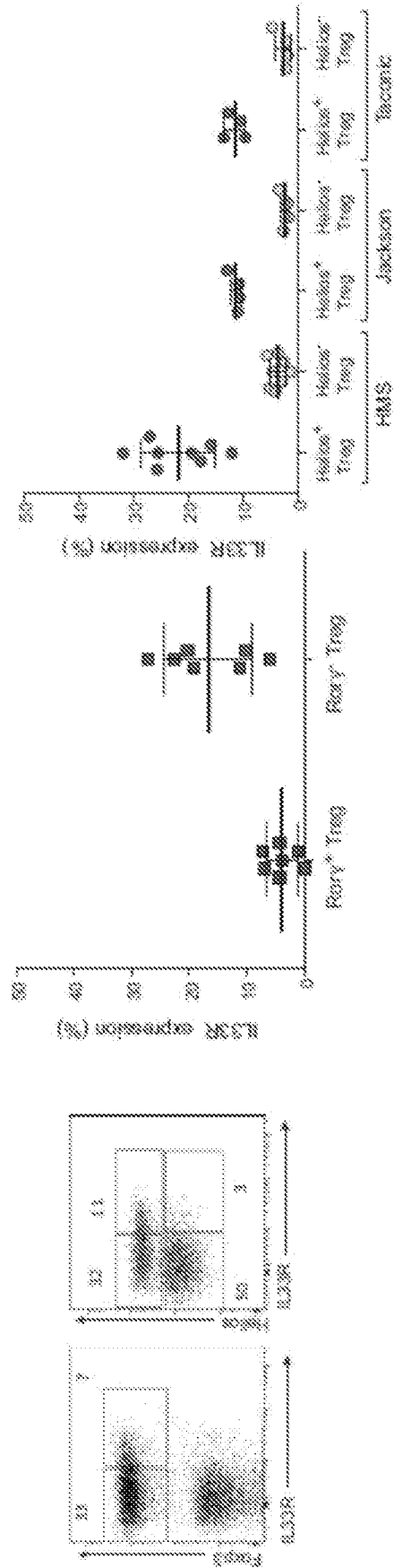
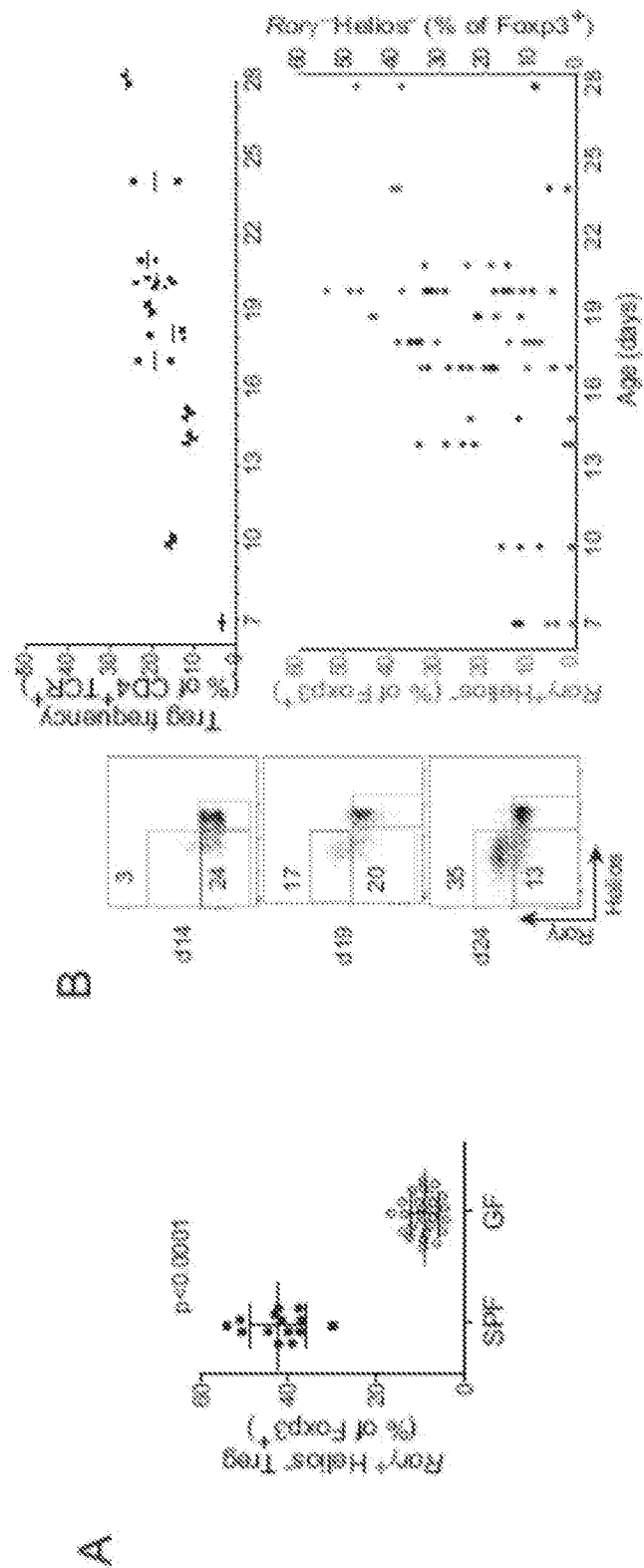


Figure 4



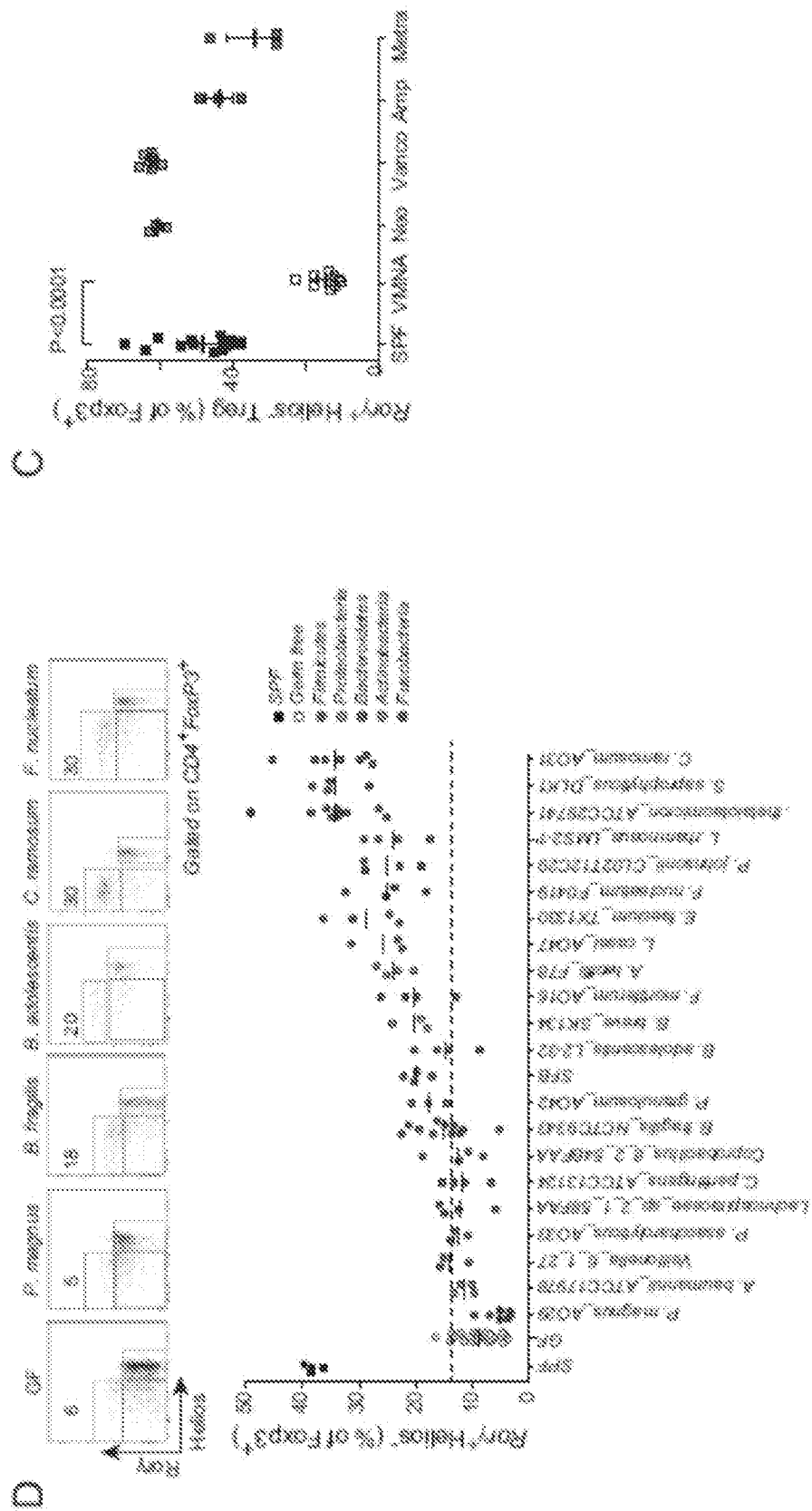


Figure 4 (Continued)

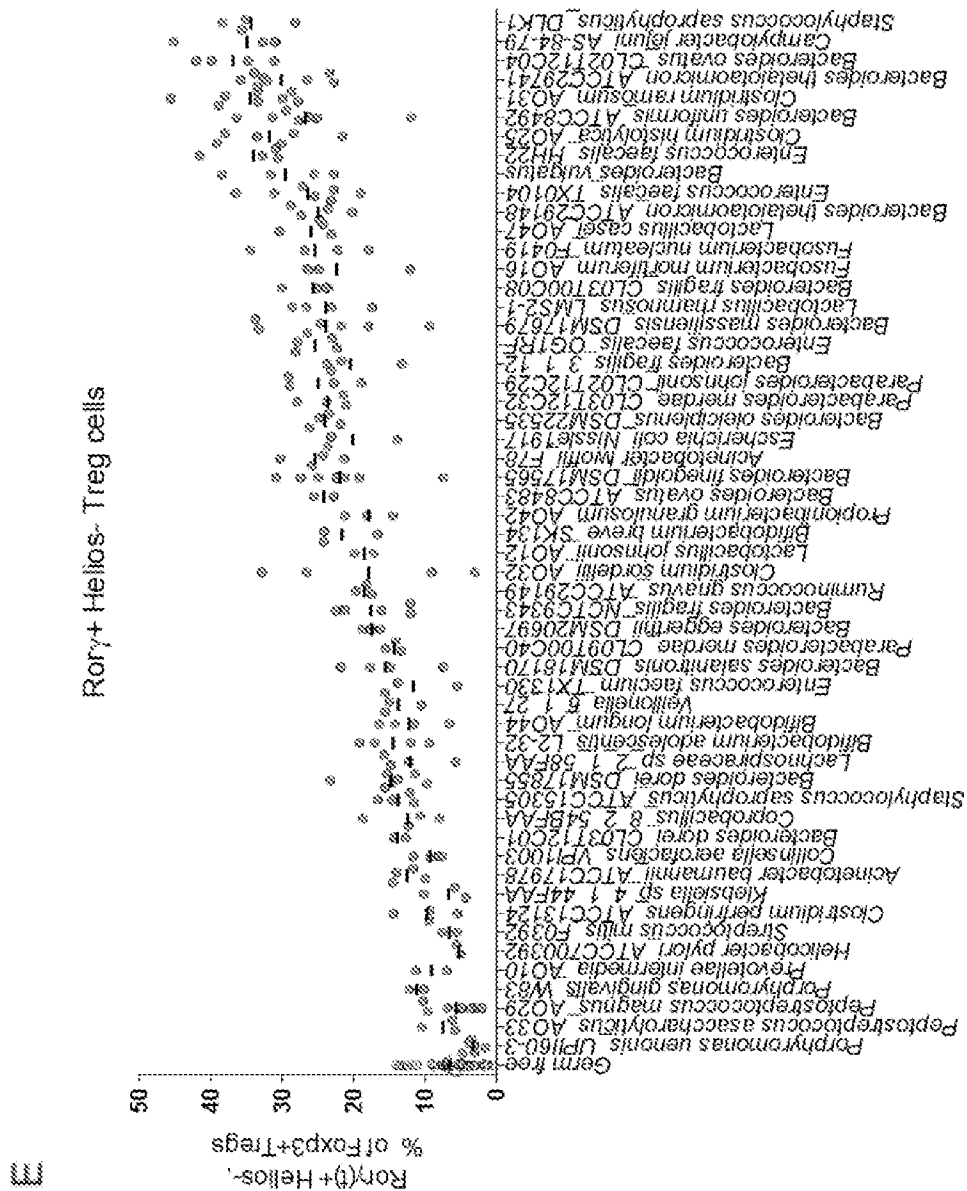


Figure 4 (Continued)

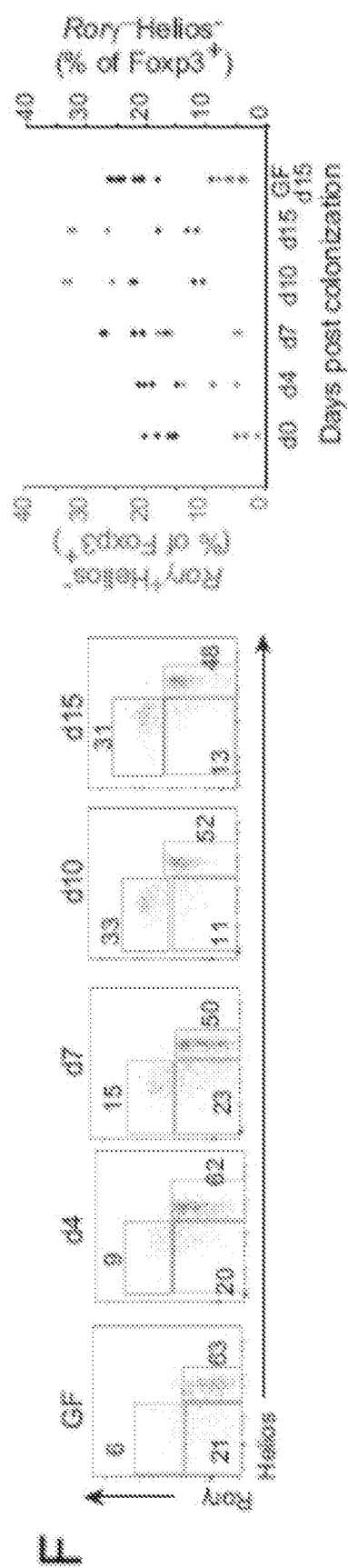


Figure 5

Bacterial Species	Strain	Rory ⁺ Helios ⁺ Tregs (%)	p-value	FDR
Bacteroides ovatus	Bacteroides ovatus CL02T12C04	36.93	0.001	0.02
Campylobacter jejuni	Campylobacter jejuni AS-84-79	34.98	0.004	0.025
Clostridia ramosum	Clostridium ramosum AO31	34.45	0.000	0.005
Staphylococcus saprophyticus	Staphylococcus saprophyticus DLK1	34.32	0.000	0.012
Enterococcus faecalis	Enterococcus faecalis HH22	33.95	0.002	0.023
Clostridium histolyticum	Clostridium histolytica AO25	31.77	0.009	0.029
Bacteroides thetaiotaomicron	Bacteroides thetaiotaomicron ATCC29741	30.09	0.000	0.002
Bacteroides vulgatus	Bacteroides vulgatus ATCC8482	29.58	0.007	0.028
Bacteroides uniformis	Bacteroides uniformis ATCC8492	26.68	0.000	0.009
Enterococcus faecalis	Enterococcus faecalis TX0104	26.46	0.000	0.011
Lactobacillus casei	Lactobacillus casei AO47	25.93	0.014	0.033
Bacteroides fragilis	Bacteroides fragilis CL03T00C08	25.63	0.000	0.014
Acinetobacter lwoffii	Acinetobacter lwoffii F78	25.42	0.001	0.018
Fusobacterium nucleatum	Fusobacterium nucleatum F0419	25.35	0.014	0.032
Enterococcus faecalis	Enterococcus faecalis OG1RF	25.32	0.000	0.015
Bacteroides thetaiotaomicron	Bacteroides thetaiotaomicron ATCC29148	24.94	0.000	0.007
Parabacteroides johnsonii	Parabacteroides johnsonii CL02T12C29	24.92	0.006	0.026
Bacteroides oleiciplenus	Bacteroides oleiciplenus DSM22535	24.07	0.000	0.003
Lactobacillus rhamnosus	Lactobacillus rhamnosus LMS2-1	23.93	0.006	0.027
Bacteroides massiliensis	Bacteroides massiliensis DSM17679	23.90	0.001	0.019
Parabacteroides merdae	Parabacteroides merdae CL03T12C32	23.55	0.001	0.017
Fusobacterium mortiferum	Fusobacterium mortiferum AO16	22.40	0.020	0.034
Bacteroides finegoldii	Bacteroides finegoldii DSM17565	21.97	0.000	0.013
Bifidobacterium breve	Bifidobacterium breve SK134	21.67	0.028	0.036
Bacteroides fragilis	Bacteroides fragilis 3_1_12	20.45	0.012	0.031
Escherichia coli	Escherichia coli Nissle1917	20.20	0.051	0.039

Figure 5 (Continued)

Bacterial Species	Strain	Rory ⁺ Helios ⁺ Tregs (%)	p-value	FDR
Candidatus Arthromitus	Segmented Filamentous Bacteria	19.38	0.000	0.01
Ruminococcus gnavus	Ruminococcus gnavus ATCC29149	18.47	0.000	0.004
Propionibacterium granulosum	Propionibacterium granulosum AO42	17.93	0.011	0.03
Clostridium sordellii	Clostridium sordellii AO32	17.88	0.208	0.045
Bacteroides fragilis	Bacteroides fragilis NCTC9343	17.58	0.002	0.022
Bacteroides eggerthii	Bacteroides eggerthii DSM20697	17.53	0.000	0.001
Bacteroides salanitronis	Bacteroides salanitronis DSM18170	15.47	0.062	0.04
Bacteroides dorei	Bacteroides dorei DSM17855	14.80	0.002	0.021
Bifidobacterium adolescentis	Bifidobacterium adolescentis L2-32	14.43	0.028	0.037
Parabacteroides merdae	Parabacteroides merdae CL09T00C40	14.30	0.000	0.008
Bacteroides dorei	Bacteroides dorei CL03T12C01	13.80	0.000	0.006
Veillonella	Veillonella 6_1_27	13.70	0.026	0.035
Acinetobacter baumannii	Acinetobacter baumannii ATCC17978	12.53	0.003	0.024
Coprobacillus	Coprobacillus 8_2_54BFAA	12.40	0.069	0.042
Bifidobacterium longum	Bifidobacterium longum AO44	12.18	0.062	0.041
Lachnospiraceae sp.	Lachnospiraceae sp_2_1_58FAA	12.14	0.074	0.043
Enterococcus faecium	Enterococcus faecium TX1330	11.62	0.250	0.046
Clostridium perfringens	Clostridium perfringens ATCC13124	9.70	0.176	0.044
Collinsella aerofaciens	Collinsella aerofaciens VPI1003	9.19	0.049	0.038
Peptostreptococcus asaccharolyticus	Peptostreptococcus asaccharolyticus AO33	7.44	0.605	0.048
Klebsiella	Klebsiella sp_4_1_44FAA	6.75	0.906	0.049
Streptococcus mitis	Streptococcus mitis F0392	6.60	0.947	0.05
Peptostreptococcus magnus	Peptostreptococcus magnus AO29	5.67	0.524	0.047
Porphyromonas uenonis	Porphyromonas uenonis UPII60-3	3.30	0.000	0.016
	Germ free	6.50		

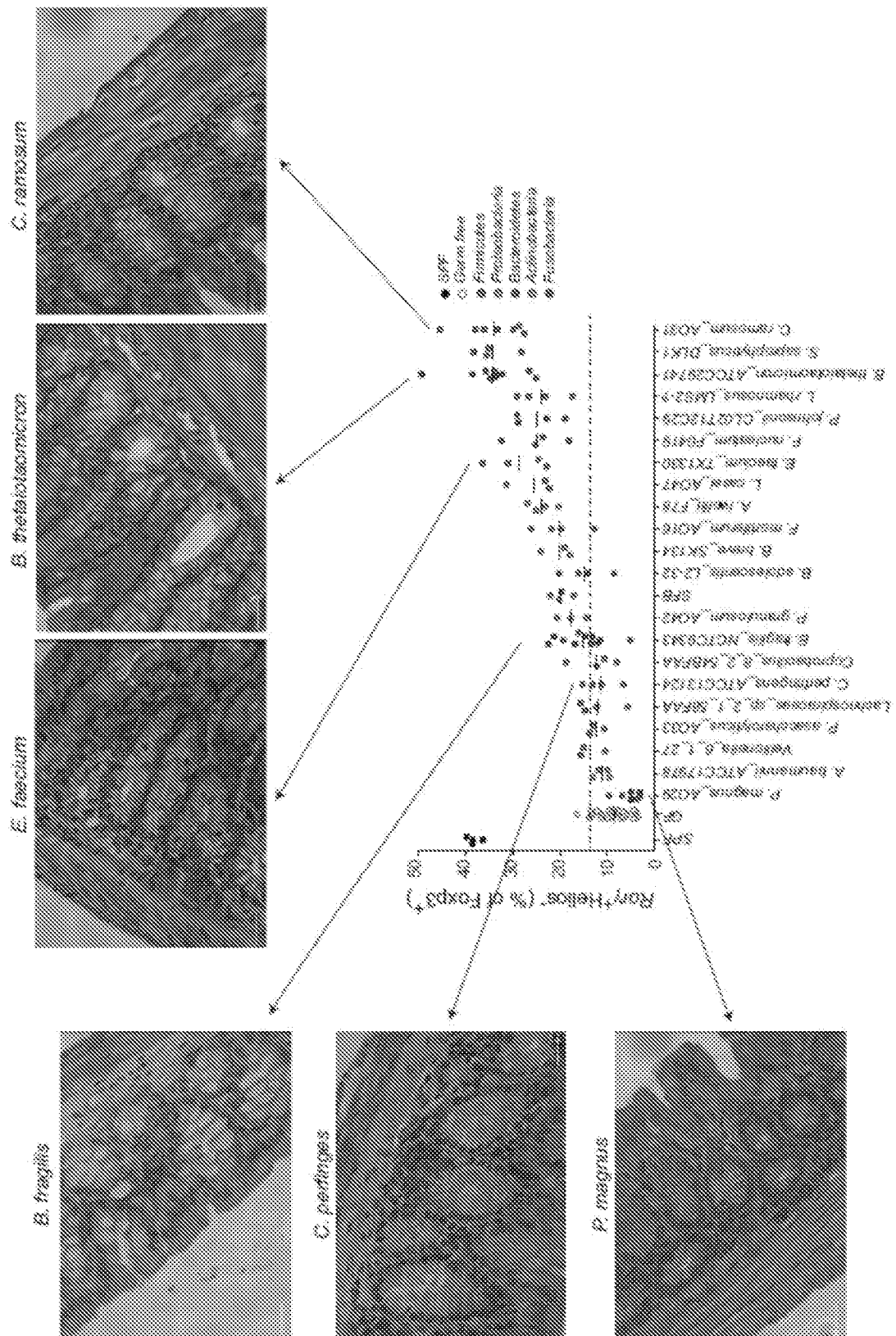


Figure 6

Figure 6 (Continued)

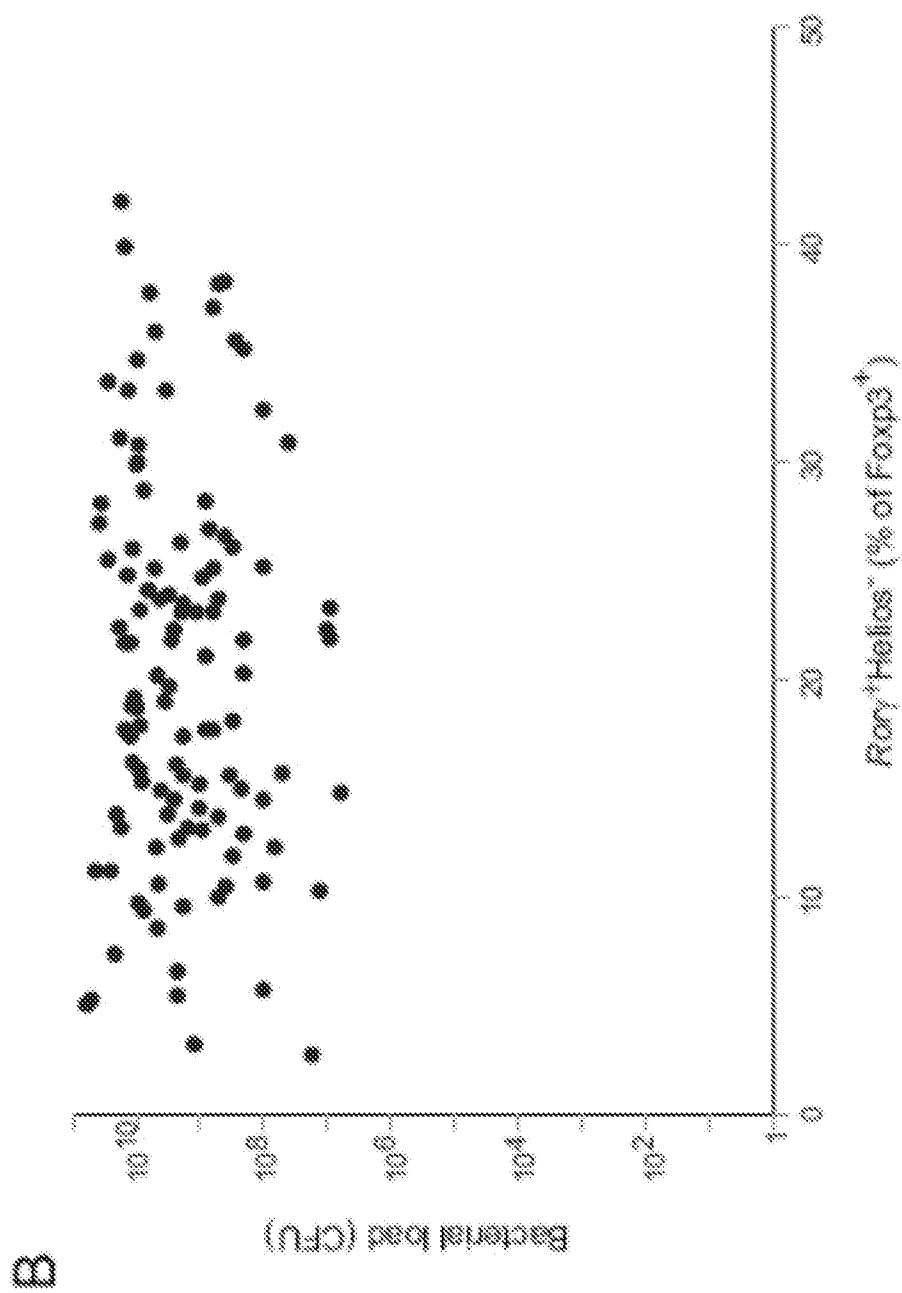


Figure 7

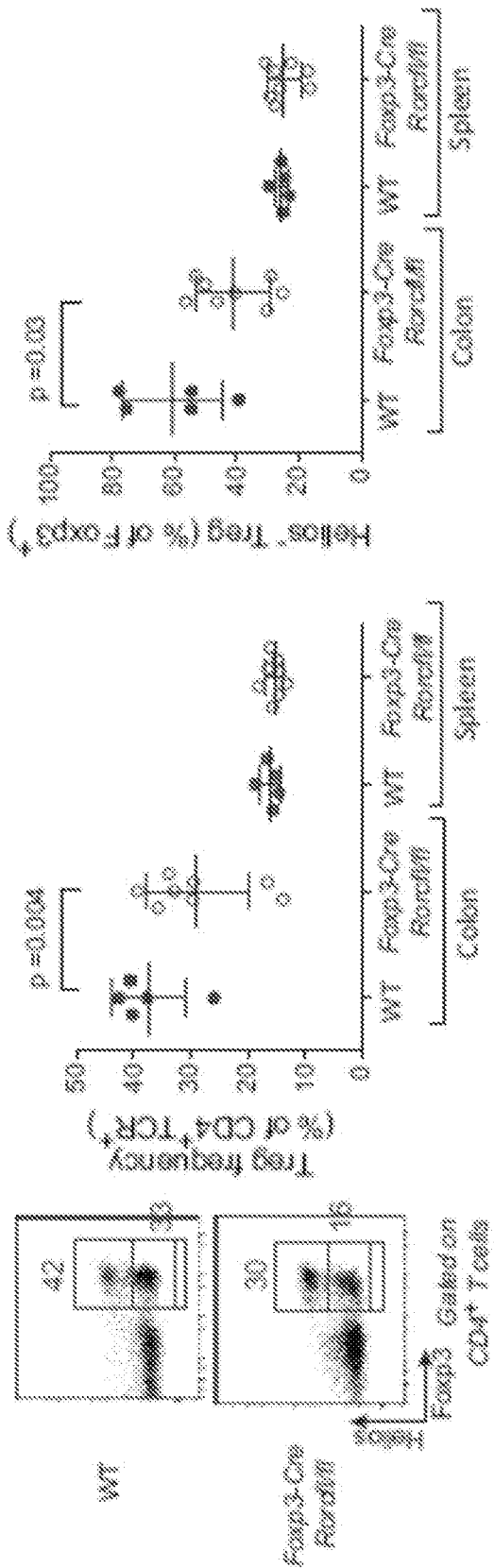


Figure 8

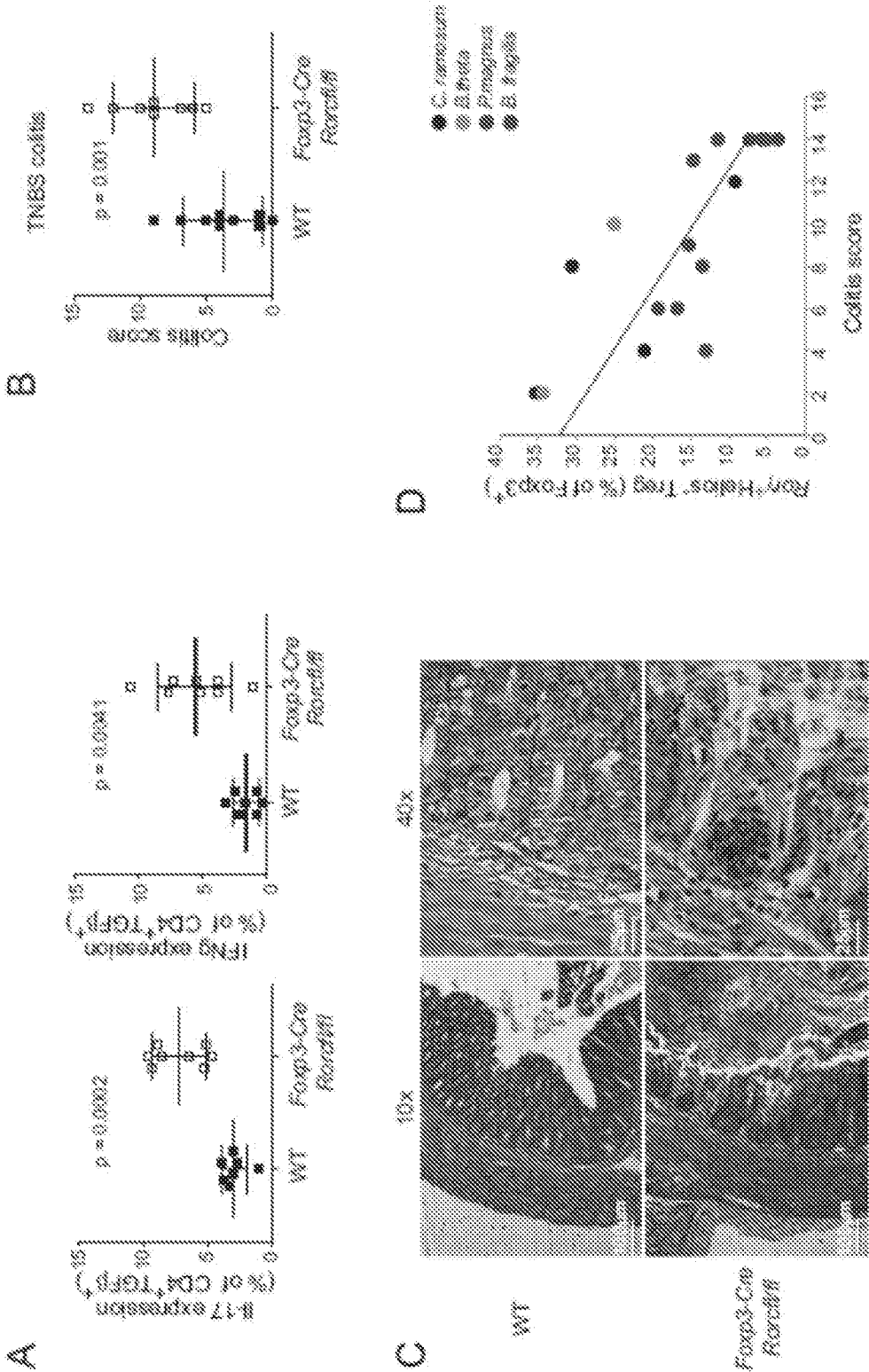


Figure 9

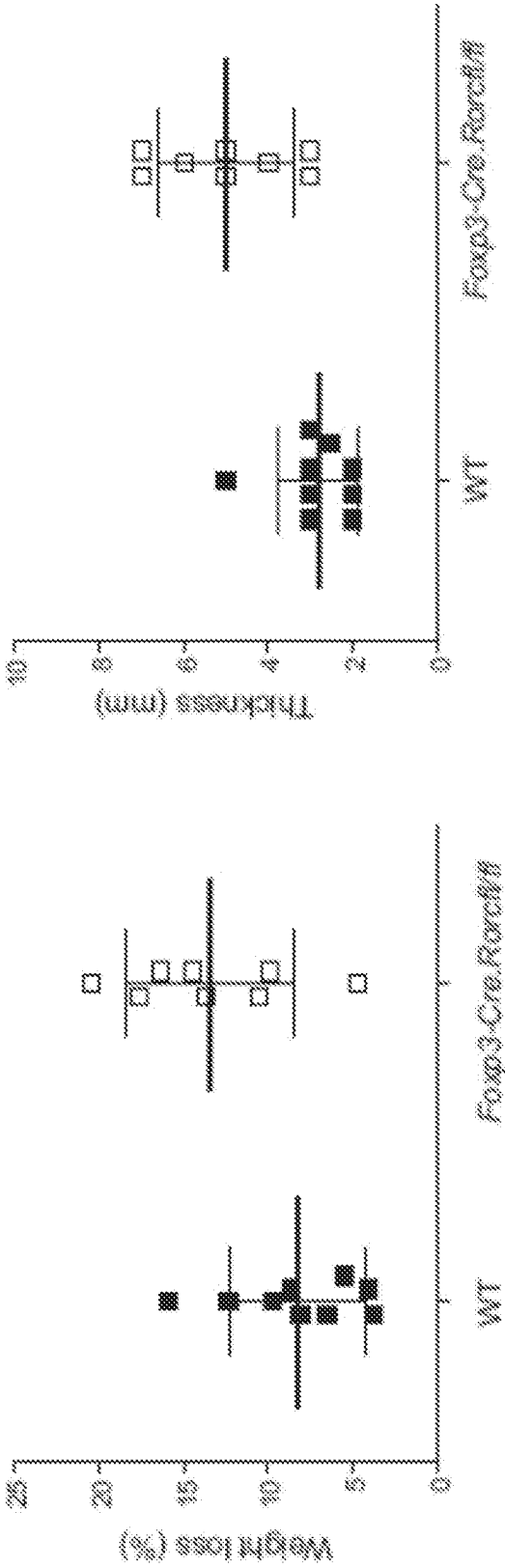


Figure 10

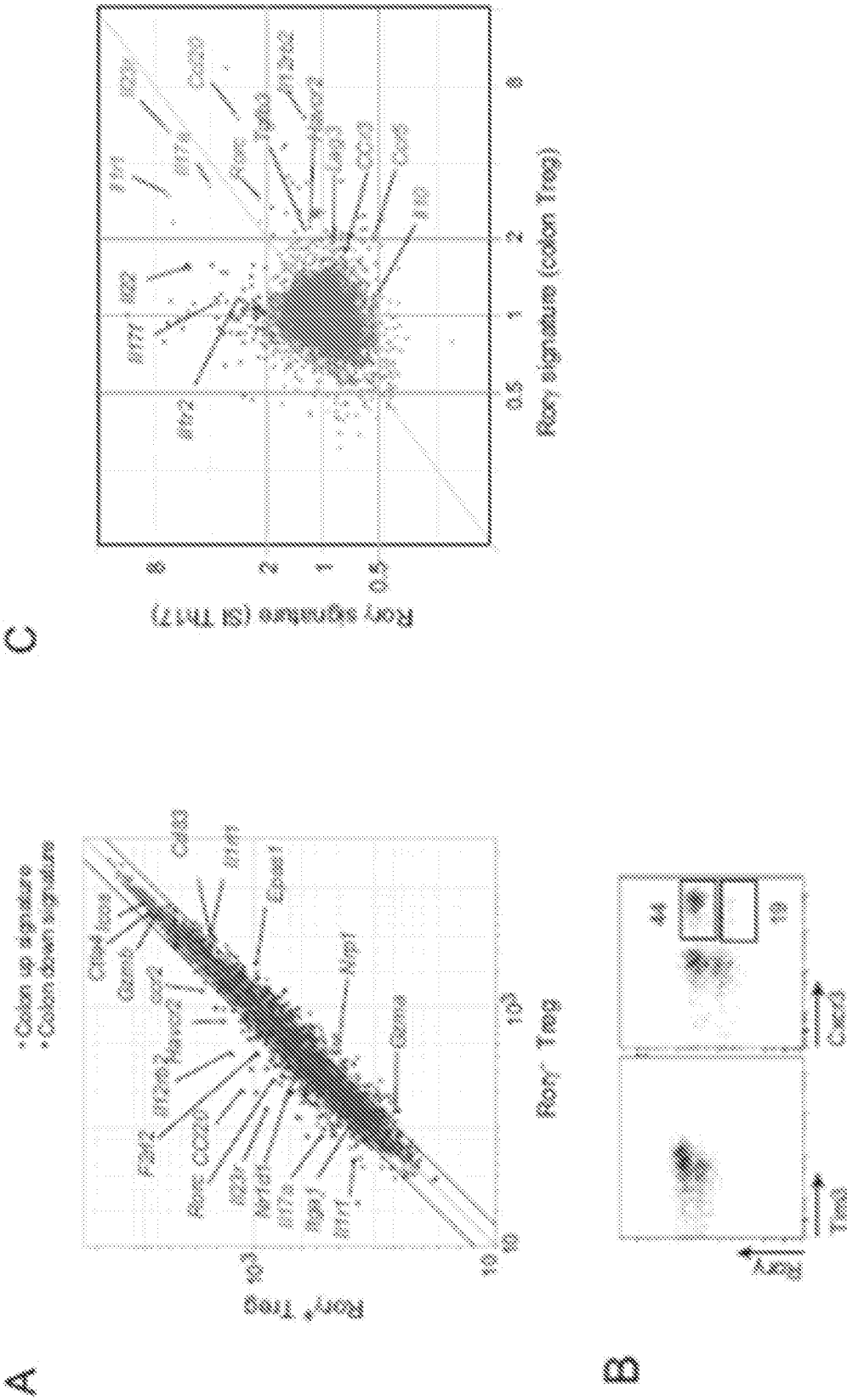
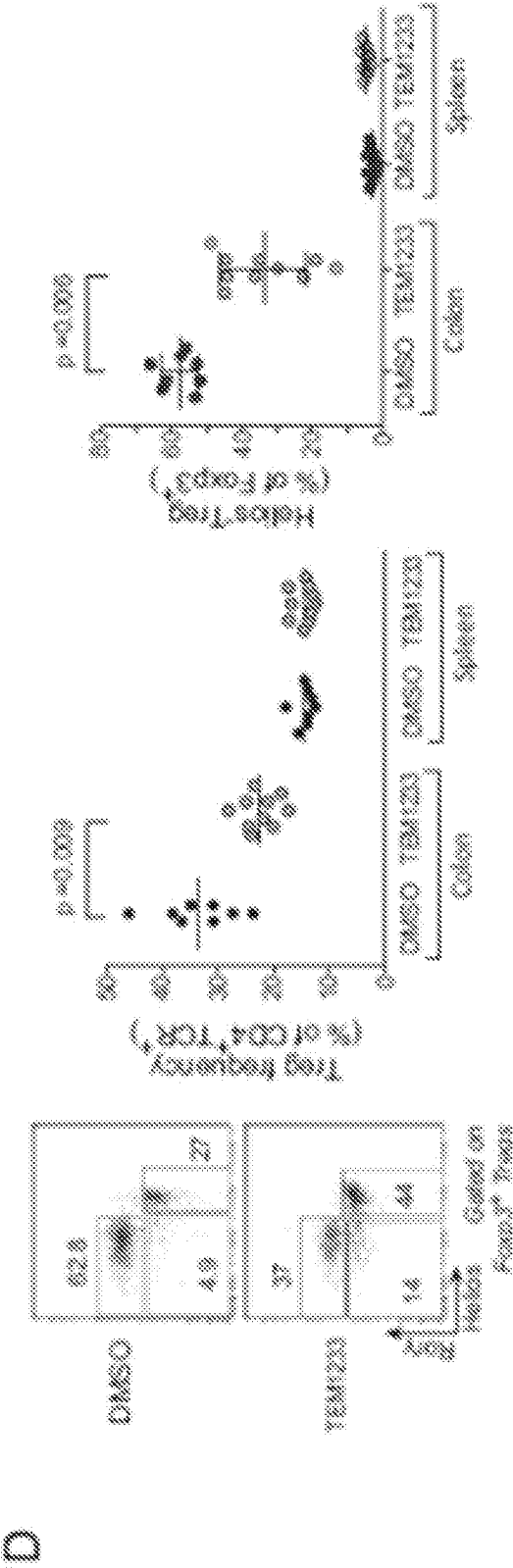


Figure 10 (Continued)



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/038502

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 35/74; A61P 1/04; C12N 1/20 (2016.01) CPC - A61K 35/74; A61K 35/741; A61K 2035/11; A61K 2035/115; C12N 1/20 (2016.08) 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) IPC - A61K 35/74; A61P 1/04; C12N 1/20 CPC - A61K 35/74; A61K 35/741; A61K 2035/11; A61K 2035/115; C12N 1/20 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 424/93.4; 424/184.1; 424/282.1; 424/780; 435/252.1 (keyword delimited) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Google Patents, Google Scholar. Search terms used: microbiota, microbiome, bacteria, regulatory, T cells, Treg, Rory, ROR, gamma, Helios, IKZF2, ANF1A2, ZNF1A2, ZNFN1A2, IKAROS, colon, lamina, bacteroides, ovatus, jejuni, saprophyticus, faecalis, thetaiotaomicron, vulgatus, uniformis, casei, fragilis, lwoffii, nucleatum, johnsonii, oleiciplenus, rhamnosus, massiliensis, merdae, mortiferum, finegoldii, breve		
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 2013/080561 A1 (UNIVERSITY OF TOKYO et al) 06 June 2013 (06.06.2013) entire document	28-30 1-8, 31, 51-58, 71-78, 89-93, 109-113, 129, 149-154, 159-162
Y	LOCHNER et al. "Restricted microbiota and absence of cognate TCR antigen leads to an unbalanced generation of Th17 cells," J Immunol, 22 December 2010 (22.12.2010), Vol. 186, No. 3, Pgs. 1531-7. entire document	1-8, 31, 51-58, 71-78, 89-93, 109-113, 129, 149-154, 159-162
A	US 2011/0229498 A1 (DRAKE et al) 22 September 2011 (22.09.2011) entire document	1-8, 28-31, 51-58, 71-78, 89-93, 109-113, 129, 149-154, 159-162
P, X	OHNMACHT et al. "The microbiota regulates type 2 immunity through RORγt+ T cells," Science, 09 July 2015 (09.07.2015), Vol. 349, Pgs. 989-993. entire document	1-8, 28-31, 51-58, 71-78, 89-93, 109-113, 129, 149-154, 159-162
P, X	SEFIK et al. "Individual intestinal symbionts induce a distinct population of RORγt+ regulatory T cells," Science, 13 August 2015 (13.08.2015), Vol. 349, Pgs. 993-997 and Supplemental Materials. entire document	1-8, 28-31, 51-58, 71-78, 89-93, 109-113, 129, 149-154, 159-162
☐ 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 14 September 2016		Date of mailing of the international search report 07 OCT 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300		Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/038502

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.: 9-27, 32-50, 59-70, 79-88, 94-108, 114-128, 130-148, 155-158, 163-168
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:

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.:

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.